Multiple Sclerosis

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key points

- Multiple sclerosis (MS) is an immune-mediated, multiphasic, mutifocal disease of the central nervous system.

- The primary etiology of MS is unknown; however, the disease has features of inflammation, demyelination, axonal injury, and neurodegeneration.

- Visual dysfunction, sensory disturbances, and gait impairment are very common presenting symptoms.

- MRI is the single most useful test in confirming the diagnosis of MS.

- Early and accurate diagnosis is paramount.

- Initiating early disease-modifying treatment can influence the clinical course.

- Symptomatic therapy can greatly improve MS patients' quality of life.

ultiple sclerosis (MS) is a neurodegenerative disease with early intense inflammation of the central nervous system (CNS). The primary etiology of MS remains unknown and is likely multifactorial. The disease is characterized pathologically by inflammatory infiltrates and demyelination, followed by varying degrees of secondary axonal degeneration.

■ **SPECIAL CLINICAL POINT: Multiple sclerosis is the most common nontraumatic cause of neurologic disability in young adults and affects approximately 400,000 people in the United States. An estimated 200 people per week are newly diagnosed.**

MS affects women two to three times more commonly than men. Most patients start with a period of unpredictable relapses and remissions, which in the majority is followed by an accumulation of neurologic dysfunction and a chronic progressive course. The life expectancy has been shown to be only 6 to 7 years less than that for a control population without MS, but the emotional and economic cost to society as a result of the disability is enormous.

HISTORY

The earliest account of a disease that appears likely to have been MS is found in writings from the 14th century, describing the illness of a Dutch nun, "Blessed Lidwina of Schiedam." The earliest pathologic descriptions by Carswell and Cruveilhier date to between 1838 and

1845. Charcot is generally credited with the first comprehensive account of the clinical and pathologic features of MS, which was published in 1868.

EPIDEMIOLOGY

Epidemiologic studies have shown that MS has an unequal geographic distribution, with large regional and ethnic variations in the prevalence of disease (Fig. 11.1). MS is rare in the tropics and increases in frequency at higher latitudes north and south of the equator. The prevalence in the United States is reported at 57.8 per 100,000 and is almost twice as common in the Northern as compared to the Southern United States. The prevalence rate has been increasing, probably because of better recognition of MS and improved treatment of complications with a correspondingly increased longevity of those affected. Prevalence rates of less than 5 per 100,000 are found in Asia, Africa (except English-speaking whites in South Africa), and northern South America. MS is also said to be much less common among Eskimos, Gypsies, and African Americans. However, these patterns may be changing with increased travel; cases of MS have been reported in native Africans who have not traveled out of the country, and the prevalence of African Americans with MS has not been reexamined adequately in the magnetic resonance imaging (MRI) era of diagnosis.

Migration studies suggest that the risk of acquiring MS is related to the location in which one has lived before puberty. Individuals migrating from high- to low-risk areas decreased their expected risk of developing MS, as determined from their area of birth. Conversely, migration from low- to high-risk areas increased the risk of acquiring MS. The reliability of migration studies has been questioned, and no definite conclusions can be made from these data.

Numerous instances of MS clusters have been reported. Several clusters have been related to exposure to heavy metals and canine distemper virus, but no conclusive link has been established. Genetic studies strongly suggest that the disease is polygenic and that genetic factors may have a stronger influence in determining susceptibility to MS than environmental factors.

PATHOLOGY OF MULTIPLE SCLEROSIS

Classic descriptions of the MS lesion as predominantly demyelinating with relative sparing of axons still hold true today. Modern tools


FIGURE 11.1 Map of the world depicting areas of high prevalence (30+/100,000, *solid*), medium prevalence (5–29/100,000, *dotted*), and low prevalence (0–4/100,000, *dashed*). White areas are regions without data or people. (From Kurtzke JF, Wallin MT. Epidemiology. In: Burks JS, Johnson KP, eds. Multiple sclerosis: diagnosis, medical management, and rehabilitation. New York: Demos Medical Publishing; 2000. Reproduced with permission from Demos Medical Publishing.)
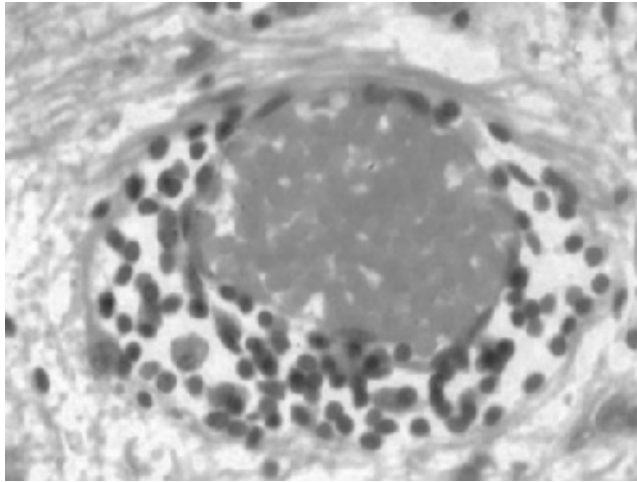
FIGURE 11.2 Perivenular infiltrate typical of the early acute inflammatory event in an active lesion.

have afforded more detailed descriptions of the immunologic and structural events occurring within lesions and have reemphasized the secondary axonal degenerative stage of the lesion. Major advances in the classification of MS pathology have been made from biopsy and rapid autopsy material. Clinicopathologic correlations using MRI and spectroscopy provide hope that advances in our understanding of the pathologic state will allow guided therapeutic interventions.

The MS plaque appears to begin with the migration of lymphocytes and macrophages across the blood–brain barrier into the perivenular space (Fig. 11.2). This is followed by diffuse parenchymal infiltration by inflammatory cells, edema, and active stripping of myelin from axons by macrophages, leading to multifocal areas of demyelination (Fig. 11.3). Subsequently, astrocytic hyperplasia and the accumulation of lipid-laden macrophages ensue. As plaques enlarge and coalesce, the initial perivenular
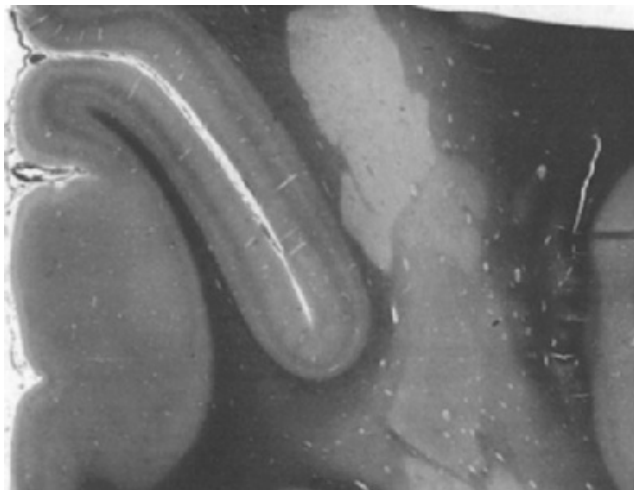
FIGURE 11.3 Luxol fast blue stain revealing loss of myelin in several irregular geographic lesions.

distribution of the lesions becomes less apparent. The inflammatory reaction is usually less pronounced in grey matter, probably because of the smaller amount of myelin in these areas. The extent of axonal loss in the demyelinated areas is highly variable. The sparing of axons is relative, and some axonal loss occurs in almost all lesions and can become substantial in severe cases. Axonal loss can also occur very early and even be present during the first clinical attack.

Plaquelike areas of pale myelin staining are called shadow plaques and are generally regarded as evidence of partial remyelination. Several studies have confirmed a remarkable potential for oligodendrocyte proliferation and partial remyelination, which seems to be impeded by as-yet-unknown local factors.

Myelin and Nerve Conduction

Proteolipid protein (PLP), myelin basic protein (MBP), and their isoforms make up 80% to 90% of the myelin sheath with 2′,3′-cyclic nucleotide 3′-phosphohydrolase (CNPase), myelin-associated glycoprotein (MAG), myelin oligodendrocyte protein (MOG), and other minor proteins making up the rest. Both PLP and CN-Pase are restricted to CNS myelin, whereas MBP constitutes about 10% of the protein in PNS myelin. Lipids constitute 80% of the dry weight of myelin. Cultured oligodendroglial cells contain a family of gangliosides of which GM_3 and GM_1 are the principal components.

One oligodendrocyte usually forms internodal segments of myelin on several different nerve fibers. This differs from the peripheral nervous system, where one Schwann cell contributes myelin to only one internodal segment. This difference may account, in part, for the much greater efficiency of regeneration in peripheral myelin. The nodes of Ranvier have a high concentration of sodium channels concentrated in the nodal membrane, which are required for saltatory conduction. During an episode of inflammatory demyelination, conduction may be transiently impaired as a result of edema, loss of myelin, and some degree of metabolic dysfunction of the nerve axon. Conduction can recover acutely on resolution of edema, subacutely with redistribution of sodium channels along the internodal membrane, or chronically after partial remyelination.

Pathologic Correlations with Magnetic Resonance Imaging

■ **SPECIAL CLINICAL POINT: The profound impact of modern imaging technologies, particularly MRI, is evident from its expanding role in the diagnosis and prognosis of MS.**

High signal (bright) T2-weighted lesions correlate well with the presence of lesions on gross pathology. However, T2 lesions lack specificity for microscopic tissue pathology and seem to represent a composite of factors including edema, demyelination, remyelination, gliosis, and axonal loss. Therefore, the T2-lesion burden does not correlate strongly with clinical disability even in clinically eloquent areas of the CNS (brainstem and spinal cord) because not all T2 lesions purport the destructive axonal pathology. Indeed, this is exactly what the T2-weighted lesion volume studies show—a weak but significant correlation with clinical disability (Expanded Disability Status Scale, or EDSS, and cognitive impairment). Because of the imprecise specificity of T2 images, more emphasis is being placed on T1-weighted images in which persistent low signal (black holes) seems to correlate better with axonal dropout and clinical disability. However, one must be cautious because during the acute enhancing phase of a lesion, and perhaps for several months thereafter, low signal T1 lesions may represent extracellular edema that can resolve.

Another misunderstood aspect of imaging is that there is a temporal sequence of lesion pathology such that acute contrast-enhanced lesions correlate well with the perivenular infiltrate and the likelihood of a clinical exacerbation but also predict future formation of black holes and brain atrophy. Indeed in a clinical trial of interferon beta (IFNβ), the drug suppressed inflammation on the MRI in the first year of

treatment but did not slow brain atrophy until the second year. This suggests that those axons that were already demyelinated prior to treatment may follow an inexorable course of degeneration during the first year of treatment, but the axons that were salvaged from demyelination by suppression of the inflammatory attack in the first year are spared degeneration in the second year. This also would explain why in two recent short-term trials of potent immunosuppressive drugs used for 12 months or one dose, contrast-enhancing lesions were reduced, but there was no effect on progression of disability or brain atrophy. Newer methods such as magnetization transfer imaging, diffusion tensor imaging, and proton magnetic resonance spectroscopy (^{1}H-MRS) may be more sensitive measures of underlying structural pathology.

ETIOLOGY AND IMMUNOPATHOGENESIS

Although the cause of MS remains uncertain, our understanding of the underlying mechanisms and pathology has grown enormously.

■ SPECIAL CLINICAL POINT: The best formulation of the pathogenesis of MS is that the disease is an autoimmune process that occurs in a genetically susceptible individual after an environmental exposure.

This hypothesis is supported by an extensive and diverse literature but is based on three seminal discoveries. The recognition by Rivers that the acute paralytic encephalitis that occasionally followed rabies and small pox vaccination was an autoimmune reaction to contaminating self-proteins led him to the discovery of experimental allergic encephalomyelitis (EAE), which has since been studied extensively as an animal model for MS. The discoveries that genes influence disease susceptibility and specifically that the human leukocyte antigen class II region on the short arm of chromosome 6 is associated with the risk of developing MS have led to a multitude of studies suggesting that polygenetic influences predispose certain individuals to acquiring MS. Finally, the

observations made regarding latitudinal gradient, migration, and disease clustering have strongly suggested an environmental role in the disease. Although no specific microbial agent has stood the test of time, modern molecular immunology has provided numerous potential mechanisms through which numerous infections could mediate autoimmunity.

Genetics

Genetic susceptibility to MS has long been suspected, based on widely differing prevalence in different ethnic populations. Family studies have found that first-degree relatives of patients are at 20-fold increased risk of developing MS. Furthermore, monozygotic twins are more likely to be concordant for MS (20% to 40%) than dizygotic twins (3% to 4%). Nonbiologic first-degree (adopted) relatives are no more likely to develop MS than the population at large, which further supports the notion that familial clustering for MS is largely genetic in origin. However, unless one invokes incomplete penetrance of genes, the twin studies also suggest a strong environmental component because no more than 40% of monozygotic twins are concordant for MS. Widely different MS prevalence among similar high-susceptibility genetic groups that inhabit different environments (such as Anglo-Saxons in England versus in South Africa) presumably must be tied to this second, environmental element of disease etiology. Studies of candidate genes and whole-genome screens suggest that multiple weakly acting genes interact epistatically to determine risk toward MS, as suspected from epidemiologic studies. Recently, various single-nucleotide polymorphisms (SNPs) associated with a higher risk of developing MS were identified on the interleukin-2 receptor α gene, interleukin-7 receptor α gene, and confirmed in the HLA-DRA locus.

Immunology of Multiple Sclerosis

The inflammatory reaction in MS is of unknown origin. Although no infectious agent has

been proved to be the cause of MS, it is hypothesized that many common viruses can trigger autoimmune-mediated demyelination in susceptible individuals through molecular mimicry (cross-reactivity between microbial proteins and myelin). In addition, there is evidence that quiescent autoreactive T cells that are present in healthy individuals may be activated through bystander activation by cytokine or polyclonal T-cell activation mediated by bacteria or viruses.

■ **SPECIAL CLINICAL POINT: It remains uncertain how tissue injury (to myelin, oligodendroglia, axons, and neurons) occurs in MS, but the inflammatory events surrounding the vast majority of acute MS lesions seem to suggest a direct immune-mediated pathology.**

The MS lesion resembles a delayed-type hypersensitivity (DTH) reaction, containing activated T cells, B cells, numerous mononuclear phagocytes, inflammatory cytokines, and adhesion molecules. Electron microscopy studies suggest the macrophage may play a major role in the direct stripping of myelin from axons, although this could be a secondary phagocytic response to excitotoxic injury of oligodendrocytes or neurons. There has been more emphasis recently on the role of innate immune cells in MS, specifically, dendritic cells and microglia. These cells seem to help facilitate the proinflammatory immune response in MS and direct autoreactive T-cell function within the CNS through antigen presentation. Therapies directed toward these cells could prove to be very beneficial.
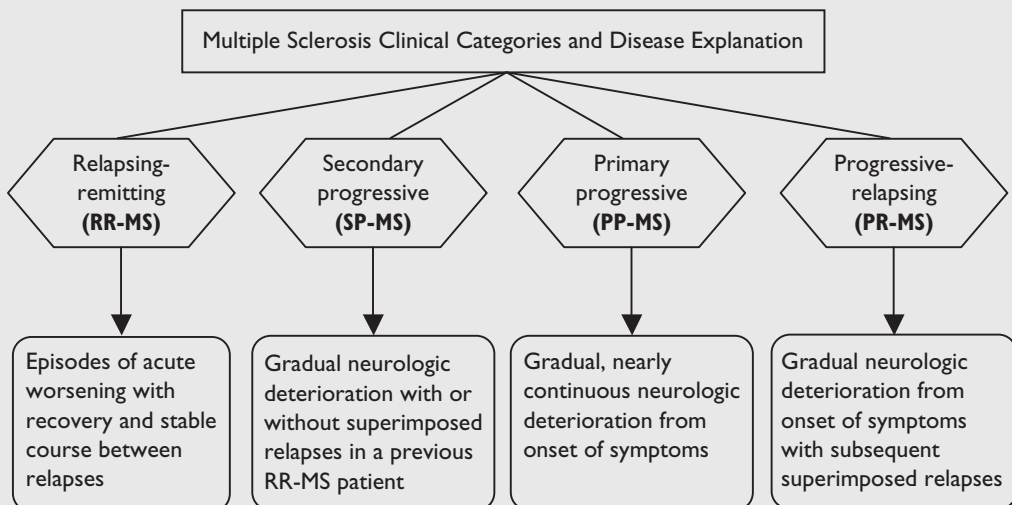
DISEASE COURSE AND CLINICAL PATTERNS

The clinical course of MS is divided into categories according to neurologic symptoms as they develop over time. A new classification for MS categories was developed by consensus among MS experts (Table 11.1).

Relapsing–Remitting Multiple Sclerosis

Relapsing–remitting MS (RR-MS) is the most common form in patients younger than age 40 years. Patients may develop focal neurologic symptoms and signs acutely or over a few days.

TABLE 11.1 | **Multiple Sclerosis Clinical Categories**

Multiple Sclerosis Clinical Categories and Disease Explanation

Relapsing-remitting **(RR-MS)**	Secondary progressive **(SP-MS)**	Primary progressive **(PP-MS)**	Progressive-relapsing **(PR-MS)**
Episodes of acute worsening with recovery and stable course between relapses	Gradual neurologic deterioration with or without superimposed relapses in a previous RR-MS patient	Gradual, nearly continuous neurologic deterioration from onset of symptoms	Gradual neurologic deterioration from onset of symptoms with subsequent superimposed relapses

Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology*. 1996;46:907–911.

These exacerbations or attacks are remarkably unpredictable and heterogeneous in character, probably because they result from varying degrees of inflammation that can occur in any part of the brain or spinal cord.

■ **SPECIAL CLINICAL POINT: Common presentations of multiple sclerosis include blurred or double vision, sensory symptoms (numbness, tingling, or pain), weakness, vertigo, or impaired balance.**

A new symptom will commonly present over 24 to 72 hours, stabilize for a few days or weeks, and then improve spontaneously over 4 to 12 weeks. Subsequent new focal symptoms or signs typically follow the initial attack months or years later and again remit partially or completely. It is very common for old symptoms to persist or reoccur, especially in response to periods of stress such as infections or prolonged elevations of core body temperature. Over time, it becomes difficult to determine whether the symptom flare represents a new exacerbation or worsening symptoms referable to past disease. Recovery from relapses is often incomplete, and permanent disability can accumulate in a stepwise fashion at this stage of the disease.

Secondary Progressive Multiple Sclerosis

Secondary progressive MS (SP-MS) refers to the patient with an initial RR-MS course who then progressively worsens over months (at least 6) to years. Natural history studies have shown that with time most patients with RR-MS convert to SP-MS. This usually occurs after 10 to 20 years from onset or after the age of 40. A patient with SP-MS may still experience relapses but does not stabilize between relapses. The predominant clinical pattern is one of continued clinical worsening. As time passes, relapses become less discrete, and the pattern becomes one of continued worsening without relapses. Conversion to SP-MS is considered a poor prognostic sign because this stage of the disease is much more refractory to the presently available immunomodulatory therapies. Some

patients with SP-MS spontaneously stabilize for considerable periods, although they only rarely recover after deficits have persisted for 6 months. The pathogenic mechanisms underlying conversion from RR-MS to SP-MS may relate to failure of remyelination and progressive axonal injury.

Primary Progressive Multiple Sclerosis

Primary progressive MS (PP-MS) accounts for approximately 10% to 15% of patients and is characterized by progressive worsening from the onset of symptoms without interposed relapses. Patients with PP-MS are more likely to be men and older than 40 years of age at symptom onset. This form of the disease often presents with progressive gait disorder as a result of leg weakness, spasticity, and impaired coordination. In cases of progressive neurologic dysfunction, it is extremely important to rule out structural pathology, infections, and hereditary and other neurodegenerative diseases. Patients with PP-MS have fewer gadolinium-enhancing brain lesions on MRI, less tissue inflammation on histopathologic assessment, and less cerebrospinal fluid (CSF) inflammation than typical for SP-MS; pathologic studies have suggested this form of the disease may represent a primary problem with the oligodendrocyte.

Progressive-Relapsing Multiple Sclerosis

According to the new classification, progressive-relapsing MS (PR-MS) refers to the rare patient with progressive disease from symptom onset, who subsequently experiences one or more relapses. In all likelihood, this is another form of SP-MS without clinically apparent relapses in the early stages of disease, and if considered separately, this group comprises only 6% or fewer of all patients with MS.

Disease patterns change over time, and it may be difficult at a given time to clearly categorize a patient's disease. The problem is particularly difficult when a patient is converting from a purely relapsing–remitting disease course to a purely progressive disease course. This has been

termed "relapsing progressive MS" by some and "transitional MS" by others, but these disease categories cannot be defined precisely by current methods. Observation for as long as 1 year may be required to categorize such a patient with confidence.

Clinically Isolated Syndromes and Prognosis

■ **SPECIAL CLINICAL POINT: In the era of partially effective prophylactic MS therapies, there has been increased emphasis on making a diagnosis early in the course of the disease to initiate appropriate preventative treatment.**

The use of MRI as a diagnostic tool is discussed later. T2-lesion burden at the time of first MS symptoms (optic neuritis, transverse myelitis, etc.) not only determines the likelihood of converting to clinically definite MS but is also predictive of future disability. For example, a patient with a single episode of optic neuritis and an abnormal brain MRI has a 50% to 80% risk of subsequently being diagnosed with MS in 5 to 10 years. The frequency of gadolinium-enhancing lesions correlates with the likelihood of having a clinical exacerbation and predicts future brain atrophy. However, because T2-weighted lesions lack specificity for tissue pathology and gadolinium enhancement is transient (2 to 8 weeks), T1 hypointense lesions (black holes) and brain atrophy may be a better measure of axonal loss and have been shown to correlate more strongly with both present and future disability. The presence of mild atrophy or persistent T1 black holes early in the course of MS should alert the physician to a potentially aggressive form of the disease.

OTHER VARIANTS OF MULTIPLE SCLEROSIS AND IMPORTANT MIMICKERS

Several other variants of MS have been described and are important to recognize.

Marburg Disease

An acute rapidly progressive form of MS, often called Marburg disease, is characterized by a person who develops acute or subacute progressive neurologic deterioration, leading to severe disability within days to months. The disease may progress steadily to a quadriplegic obtunded state with death as a result of intercurrent infection, aspiration, or respiratory failure from brainstem involvement. Postmortem studies have documented inflammation in the optic nerves, optic chiasm, cerebral hemispheres, and spinal cord. The pathology reveals a pronounced mononuclear cell infiltrate with severe axonal damage and tissue necrosis.

Neuromyelitis Optica

Neuromyelitis optica (NMO) or Devic disease refers to the patient who presents with both optic neuritis and transverse myelitis, occurring either simultaneously or separated by a few months to years. Several features differentiate this disease from classical MS, including older age of onset, higher female to male incidence (9:1), limited white matter lesions on a brain MRI, multilevel contiguous typically central spinal cord lesions (three or more vertebral levels), and severe disability and death as a result of respiratory failure in one third of all patients. NMO also seems to be more common than MS in non-Caucasians. Pathologically, the syndrome is variable with some lesions characterized by inflammation and demyelination, but it is invariable with severe necrosis and many patients having cavitary lesions in the spinal cord. Those patients who survive the acute attack commonly follow a course with features indistinguishable from RR-MS but have a worse prognosis. An NMO serum biomarker (NMO-IgG) has recently become commercially available, which can help differentiate this disease from MS. This distinction is of utmost importance since the therapeutic interventions are different for NMO and MS. While

the NMO-IgG blood test is highly specific and the majority of clinically diagnosed NMO patients will be NMO-IgG positive, a negative blood test does not exclude the diagnosis.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) and its hyperacute form, acute necrotizing hemorrhagic encephalopathy (ANHE), are thought to be forms of immune-mediated inflammatory demyelination. They differ from MS in that they are typically monophasic, whereas MS is by definition multiphasic or chronically progressive. Patients with ADEM or ANHE usually present with fever, headache, meningeal signs, and altered consciousness, which are exceedingly rare in MS. Multiple reports of clinical and pathologic overlap have been published. Some authors have suggested that the MRI can be used to differentiate MS from ADEM, but no reliable clinical criteria to differentiate the two processes exist.

PRECIPITATING FACTORS

Exposure to viruses and bacteria has been associated with precipitating disease exacerbations. The risk of an exacerbation decreases during pregnancy, with the rate being decreased by approximately two thirds in the third trimester. The risk of an acute attack in the first 3 months postpartum is increased and has been estimated that 20% to 40% of postpartum patients with MS will have an exacerbation. The decreased relapse rate during pregnancy is probably related to a family of immunosuppressive hormones and Th2. Overall, pregnancy probably has little overall effect on the course of the disease, and therefore remains a realistic possibility for woman with MS. There is increasing evidence that vitamin D deficiency may play an important role in MS. Recent studies have suggested that higher serum vitamin D levels correspond to a decreased risk of developing MS. It is well established that vitamin D receptors are present within immune cells and may promote immune regulation. The anti-inflammatory cytokine, transforming growth factor-β_1 (TGF-β_1), is typically decreased in MS and increases upon vitamin D supplementation. This association further supports the contributions of environmental factors, especially since sunlight exposure provides a major source for vitamin D. This could also explain the unusual geographical distribution of MS.

SYMPTOMS AND SIGNS

See Tables 11.2 and 11.3.

Optic Neuritis

Multiple sclerosis commonly affects the optic nerves and chiasm, and approximately 30% of patients present with visual symptoms. In acute optic neuritis, the patient experiences monocular loss of central vision and often has eye or brow pain, which worsens on lateral eye movement. The symptoms may present over a few hours to 7 days, with a few cases progressing over several weeks. Loss of visual acuity and color perception are often considerable. Most patients will recover significantly after 2 to 3 months, although continued improvement

TABLE 11.2	Initial Symptoms in Patients with Multiple Sclerosis

Symptom	Percentage
Sensory disturbance in one or more limbs	33
Disturbance of balance and gait	18
Vision loss in one eye	17
Diplopia	13
Progressive weakness	10
Acute myelitis	6
Lhermitte's symptom	3
Sensory disturbance in face	3
Pain	2

Paty DW, Poser CM. Clinical symptoms and signs of multiple sclerosis. In: Poser CM, ed. *The Diagnosis of Multiple Sclerosis.* New York: Thieme & Stratton; 1984:27.

TABLE 11.3 Common Symptoms and Signs in Patients with Multiple Sclerosis

Symptom	Sign	Comment
Visual blurring (central)	Diminished acuity (central)	Syndrome of optic neuritis seen usually early in disease
Vision loss/eye pain	Scotoma/deafferented pupil	
Diplopia	Internuclear ophthalmoplegia	May be associated with nausea, vertigo, or other brainstem signs
Oscillopsia	Rarely other oculomotor weakness, flutter, or dysmetria	
Loss of dexterity	Upper motor neuron signs often affecting legs early and arms later	Develops in many MS patients over time
Weakness		
Tightness and pain		
Shaking	Intention tremor, dysmetria, dysarthria, truncal or head titubation	Occurs in 30% of patients; may be the predominant manifestations in some patients
Imbalance		
Paresthesias	Decreased vibration and position sense in legs > hands	Sensory symptoms are often painful and distressing
Loss of sensation	Decreased fine sensation in hands	
Bandlike disturbance	Sensory level	
Falls	Wide-based gait	Gait disturbances are common in MS and can cause severe disability
Lack of coordination	Ataxic and unsteady gait	
Inability to concentrate or learn	Diminished concentration, processing speed, or verbal learning on neuropsychologic testing	May be subtle or have severe impact on patient and family; severe dementia in <10% of patients
Easily distractible		
Emotional lability	Episodic crying or laughing	Distressing to patient; generally not related to patients' actual emotions
Depression	—	Commonly underrecognized or underestimated
Fatigue	—	Disabling in many patients with MS; does not correlate with severity of motor signs
Pain	—	Numerous etiologies (see text)
Urinary urgency, hesitancy, frequency, and incontinence	Requires urodynamic testing to fully characterize type of bladder dysfunction	Often complicated by intercurrent UTI

MS, multiple sclerosis; UTI, urinary tract infection.

can occur as long as a year later; however, some patients sustain permanent damage and can become blind. Acuity is variably diminished in the affected eye. A central or centrocecal scotoma (marked enlargement of the blind spot to involve central vision) can be documented at the bedside with an Amsler grid, and red desaturation can be demonstrated with color plates or with a red-tipped hat pin. Using the swinging flashlight test in a darkened room, one can demonstrate a defect in the afferent pathway such that pupillary constriction in the affected eye is greater with contralateral than with direct light stimulus. A positive test reveals a relative afferent pupillary defect, sometimes called a Marcus Gunn pupil. Funduscopic examination is usually normal in acute retrobulbar neuritis. When the optic nerve is affected anteriorly, the disc may be congested and swollen, thus resembling papilledema. Several months after an optic neuritis, the disc often appears pale, especially at the temporal border, and this can provide evidence of a previous attack. Occasionally, optic nerve demyelination and axonal damage can manifest silently and is noticed only in the setting of other symptoms suggestive of MS.

A novel noninvasive eye scan called optical coherence tomography (OCT) is now being used to assess MS patients. The scan provides high-resolution quantifiable images of the retinal nerve fiber layer that have been shown in recent studies to reflect optic nerve damage even in asymptomatic eyes. OCT scans may prove to be a very important biomarker for disease monitoring and therapeutic effectiveness; however, since OCT scans are not specific for MS/optic nerve pathology, they are not considered a diagnostic test to the exclusion of a thorough eye exam.

Oculomotor Syndromes

Eye movement abnormalities are also extremely common in MS and include broken (saccadic) smooth pursuits, nystagmus, ocular dysmetria (overshooting target), isolated extraocular muscle palsies, and the classical internuclear ophthalmoplegia (INO).

■ **SPECIAL CLINICAL POINT: An INO results from damage to the medial longitudinal fasciculus, and its presence in a young adult, particularly when bilateral, is highly suggestive of MS.**

In its complete form, one eye is unable to adduct and the other has abducting nystagmus. More commonly one observes varying degrees of adduction lag with dysconjugate nystagmus. The patient is asked to make a rapid saccade from midline to a laterally situated target, and the examiner focuses on whether the eyes move in a conjugate manner. The condition is frequently bilateral, with one eye being more involved than the other. Quantitative infrared oculography has demonstrated that the frequency of subtle INOs is probably much greater than can be clinically appreciated.

Motor Dysfunction

Weakness, spasticity, hyperreflexia, and Babinski's sign (upgoing toe) are common manifestations of damage to the pyramidal tracts (corticospinal tracts) in patients with MS. This most commonly presents in the legs (spastic paraparesis) because of the relative length that these fibers have to travel, which makes them more susceptible to numerous areas of demyelination and noticeable conduction delays. It is not uncommon for cervical lesions to manifest first in the lower extremities. Concomitant symptoms include stiffness, spasms, and pain. Extreme hyperreflexia causes clonus, which is usually described by the patient as a shaking or tremor.

Cerebellar Signs

End-point tremor (dysmetria) on finger to nose testing is most noticeable in the upper extremities, probably because of their important role in fine movement tasks. Lower extremity and midline truncal ataxia result in gait

impairment, and some patients with MS are mistaken for being intoxicated. Head or truncal titubation or scanning dysarthria (impaired prosody) can become disabling aspects of the disease.

Sensory Symptoms

Approximately one third of patients with MS present initially with sensory disturbance involving the limbs, and the majority of patients will have paresthesias as the disease progresses. Symptoms are usually described as "pins and needles" and less commonly as a loss of sensation. Paresthesias can be painful burning or electrical sensations. The sensory symptoms follow a spinal cord pattern, often with an incomplete loss of sensation to either vibration (posterior columns) or pinprick (spinothalamic) pathways. It is important to distinguish the spinal pattern from peripheral or root lesions, which follow cutaneous or dermatomal patterns of sensory loss. Occasionally, patients will describe patches of numbness or symptoms in an apparently nonanatomic distribution, which presumably could relate to multifocal areas of demyelination or may be a manifestation of psychiatric disease.

Lhermitte's phenomenon refers to an electric tingling sensation that is precipitated by neck flexion, usually into the arms or down the back. Lhermitte's phenomenon suggests cervical spinal cord disease. It is very common in patients with MS with cervical spinal cord involvement but is not specific for MS.

Pain

Pain is very common in MS and may be caused directly by abnormal firing of sensory nerves, as a result of severe spasticity, or because of secondary orthopedic injuries. Trigeminal neuralgia (TN) or atypical facial pain are common causes of severe pain in MS. Younger patients who present with TN should be evaluated for MS as this pain syndrome is more common above the age of 50.

Cognitive and Memory Symptoms

■ **SPECIAL CLINICAL POINT: Approximately 50% of patients with MS exhibit significant short-term memory loss or difficulty with concentration, attention, and processing speed.**

Cortical deficits relating to language and visual spatial function are much less common. In only a minority of patients is dementia an incapacitating aspect of the disease. Correlations between the severity of cognitive impairment and the extent of MRI changes have been found.

Psychiatric Manifestations

Inappropriate laughing and weeping, often in response to minor provocation, occurs in more than 10% of patients with MS. Approximately 50% of patients with MS will have an episode of major depression during the course of their illness, and many patients will have chronic low-level depressive symptoms. MRI studies have confirmed an association with lesion load or atrophy, especially in the frontal and temporal lobes, and depression in MS. The health care provider should have a heightened awareness of the risk of suicide in patients with MS. Depression may also be part of a bipolar illness, which is more common in patients with MS than in control populations.

Fatigue

Fatigue may be the most common single complaint of patients with MS and can be disabling. Fatigue usually comes on late in the afternoon or may occur with strenuous activity or with exposure to heat. Short rest periods usually restore function. A less specific and more generalized fatigue is also seen and may take the form of overwhelming lassitude, which can be disabling. Episodic fatigue may herald clinical disease exacerbation. The mechanisms underlying MS fatigue are unknown.

Bladder, Bowel, and Sexual Dysfunction

Bladder dysfunction is common and can be divided into two categories. Patients may fail to

empty urine adequately, causing urinary hesitancy, postvoid fullness or dribbling, or frank inability to initiate urination despite a feeling of fullness. Alternatively, patients may fail to properly store urine, causing urgency, urge incontinence, dysuria, frequency, and nocturia. The correlation between bladder symptoms and the underlying pathophysiology is often imperfect; therefore, objective testing by cystometrogram is often necessary to characterize the problem and to guide management.

Constipation is also common in MS and should be managed aggressively to prevent complications. Fortunately, fecal incontinence is relatively rare but when present is socially devastating.

Sexual dysfunction is reported by 50% to 75% of patients with MS and is exacerbated by a variety of problems, including fatigue, decreased sensation, decreased libido, erectile dysfunction, spasticity, impaired lubrication, body image disorder, and depression.

Other Manifestations

Paroxysmal disorders in MS include dystonic spasms, tic douloureux, episodic paresthesias, seizures, ataxia, and dysarthria. Sleep disorders and sleep-related movement disorders (restless leg syndrome) are common in MS and can contribute to daytime fatigue. Various other disease manifestations occur more rarely, including hearing loss, spasms, aphasia, homonymous hemianopsia, gait apraxia, movement disorders (myoclonus and chorea), and autonomic dysfunction (sweating, feeling hot and cold, edema, and postural hypotension).

DIAGNOSIS OF MULTIPLE SCLEROSIS

■ **SPECIAL CLINICAL POINT: MS is diagnosed clinically through the demonstration of CNS lesions disseminated in time and space and with no better explanation for the disease process.**

There is no single diagnostic test, and several other diseases can mimic MS. Therefore, diagnostic criteria based on clinical features supplemented by laboratory tests have been used. The original and recently revised McDonald criteria were developed by a panel of MS experts and were based on review of extensive supportive scientific studies focusing on the sensitivity and specificity of MRI diagnostic criteria (Table 11.4). The major change associated with the latest criteria is that a diagnosis of MS can be made early after a clinically isolated syndrome if a follow-up MRI performed 1 month later demonstrates the formation of a new T2 lesion that is of sufficient size and location (Tables 11.5 and 11.6). These criteria also define MRI lesion characteristics that increase the likelihood of MS: number (>9), abutting the ventricles, juxtacortical, infratentorial, spinal, and contrast enhancing. As with all the criteria, the clause that "there must be no better explanation" remains a critical part of the definition of MS. Critics of these criteria have complained they are too restrictive, whereas purists remain unconvinced of the utility of MRI for diagnosis. The lack of specificity for MS of white matter lesions seen on MRI must also be remembered, and overreliance on imaging to the exclusion of the clinical picture can lead to diagnostic errors. Ultimately, how one defines the clinical syndrome of MS, within the recognized spectrum of multifocal demyelination discovered at autopsy to hyperacute demyelinating syndromes, remains an ongoing debate. The revised McDonald criteria provide an important update and have been adopted for the incorporation of patients in research studies.

Important Radiologic and Laboratory Features

Magnetic Resonance Imaging

■ **SPECIAL CLINICAL POINT: MRI is the single most useful test in confirming the diagnosis of MS.**

A brain MRI performed on a high field (>1.5 Tesla) magnet is abnormal in 95% of patients

TABLE 11.4

McDonald Diagnostic Criteria

	Paraclinical Tests Needed	
Clinical Presentation	**Space**	**Time**
Two attacks; two locations	No	No
Two attacks; one location	MRI abnormal or two MRI lesions + CSF	No
One attack; two locations	No	MRI criteria or second attack
One attack; one location (CIS)	MRI abnormal or two MRI lesions + CSF	MRI criteria or second attack
PP-MS (progression for 1 year)	Need two of the following: Nine MRI brain lesions or four to eight brain lesions + VEP Two MRI cord lesions Positive CSF[a]	

CSF, cerebrospinal fluid; CIS, clinically isolated syndromes; PP-MS, primary progressive multiple sclerosis; VEP, visual-evoked potential.
[a]Evidence of oligoclonal bands or increased IgG index or both.
Modified from Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." *Ann Neurol.* 2005;58:840–846.

with clinically definite MS, and the absence of high signal abnormalities in either the brain or spinal cord is strong evidence against the diagnosis of MS. MS lesions appear as areas of high signal usually in the cerebral white matter on T2-weighted images (Figs. 11.4 and 11.5). They are typically round or ovoid but may appear as fingerlike projections extending perpendicularly from the ventricular wall that is visualized best on sagittal imaging (Dawson's fingers). Typical locations include the corpus callosum, abutting the walls of the ventricles, in the juxtacortical lesions (grey–white junction), in the posterior fossa (pons and cerebellar peduncles), and in the spinal cord (cervical twice as commonly as thoracic). Fluid-attenuated inversion recovery (FLAIR) is more sensitive than conventional T2-weighted imaging for cerebral lesions but is less useful in the posterior fossa or spinal cord. Short tau inversion recovery (STIR) images have the highest sensitivity for detecting

TABLE 11.5

MRI Criteria for Brain Abnormality

Three of the following[a]:
One Gd-enhancing lesion or nine T2-hyperintense lesions if there is no Gd-enhancing lesion
At least one infratentorial lesion
At least one juxtacortical lesion
At least three periventricular lesions

Gd, gadolinium.
[a]One spinal cord lesion can be substituted for one infratentorial brain lesion. An enhancing cord lesion can substitute for an enhancing brain lesion and count twice in the MRI criteria for diagnosis (one enhancing lesion and one infratentorial lesion).
Polman CH, Reingold SC, Edan G, et al. *Ann Neurol.* 2005;58:840–846.

TABLE 11.6

Dissemination in Time

Two possible ways to demonstrate imaging dissemination in time:
(1) Scan 3 months after clinical event showing a Gd-positive lesion not at same site of original event
(2) New T2W lesion at least 30 days after initial clinical event scan

Gd, gadolinium; T2W, T2-weighted.
Polman CH, Reingold SC, Edan G, et al. *Ann Neurol.* 2005;58:840–846.
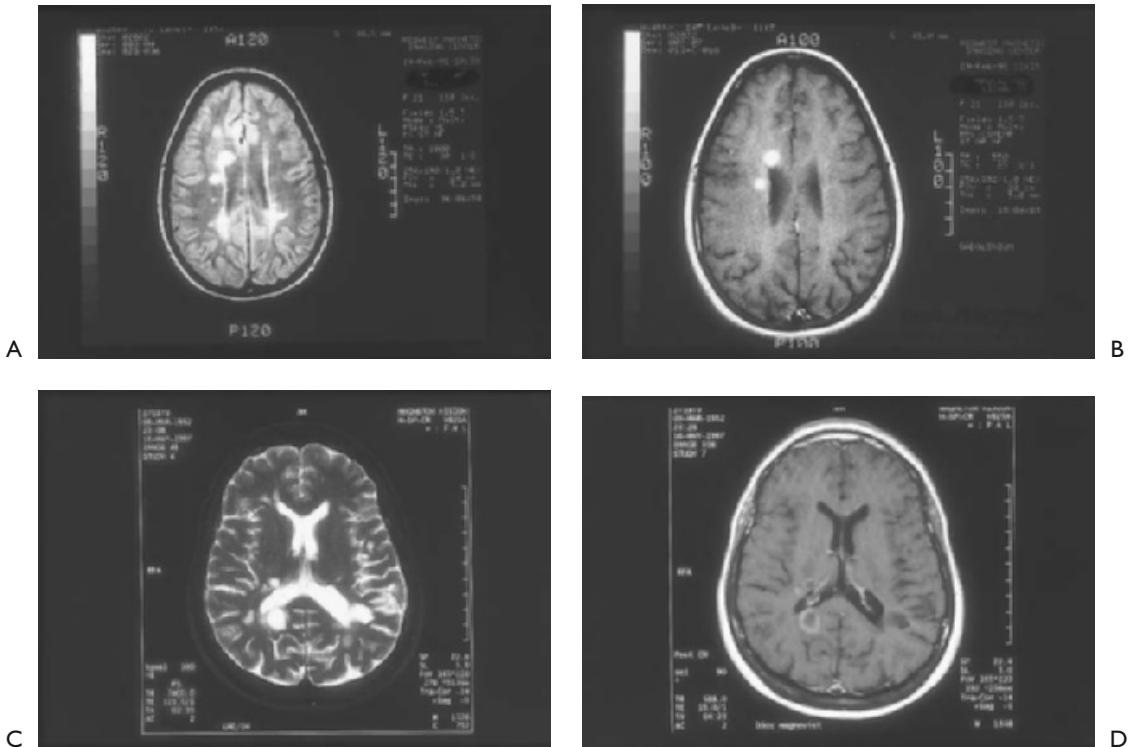
FIGURE 11.4 Magnetic resonance imaging scans of the brain of a patient with multiple sclerosis.
**A:** Fluid-attenuated inversion recovery (FLAIR) sequence demonstrating typical periventricular white matter lesions. **B:** On T1-weighted image with contrast only two of these lesions appear active. **C:** In a separate patient, T2-weighted scan demonstrating two demyelinating lesions of apparent equal intensity. **D:** The T1-weighted images with contrast reveal one lesion is active and the other is hypointense, suggesting formation of a T1 black hole. Persistence of T1 holes correlates with axonal dropout.

demyelination in the spinal cord. All MRIs performed in suspected or definite patients with MS should be done before and after intravenous (IV) administration of the paramagnetic agent gadolinium diethylenetriaminepentaacetic acid (GdDTPA). Lesions that enhance after GdDTPA have been shown to represent acute inflammatory lesions and as such increase the likelihood that a lesion is related to MS as opposed to a nonspecific small-vessel disease process. Enhancing lesions are also used as a measure of disease activity in clinical trials. Enhancing lesions last only for 2 to 8 weeks and therefore can be missed easily, so FLAIR is a more reliable measure of the total burden of disease or for infrequent serial scanning. MRI is also useful for ruling out non-MS–related structural lesions such as spinal tumors, syrinxes, Chiari malformations, and herniated disc material.

CSF Analysis

CSF studies to rule out infectious and neoplastic etiologies and to look for the presence of intrathecal immunoglobulin (Ig) synthesis are an important part of laboratory testing in cases in which the clinical picture and MRI are not diagnostic. The presence of more than 50 mononuclear cells/mm3, any neutrophils, or a CSF protein of greater than 100 mg/dL should raise concern about a diagnosis of MS. Depending on the laboratory and technique, approximately 80% to 90% of patients with clinically definite
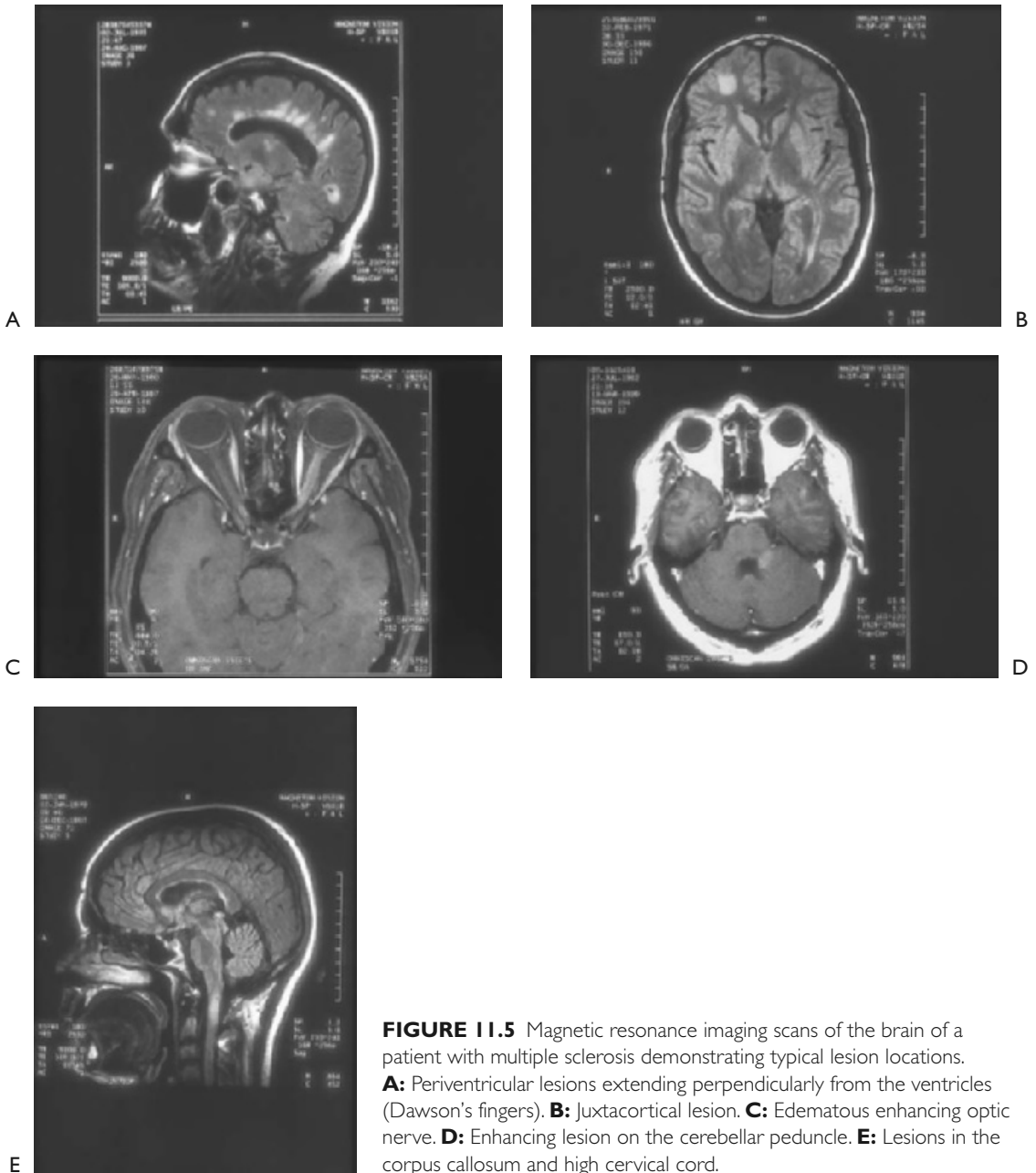
FIGURE 11.5 Magnetic resonance imaging scans of the brain of a patient with multiple sclerosis demonstrating typical lesion locations. **A:** Periventricular lesions extending perpendicularly from the ventricles (Dawson's fingers). **B:** Juxtacortical lesion. **C:** Edematous enhancing optic nerve. **D:** Enhancing lesion on the cerebellar peduncle. **E:** Lesions in the corpus callosum and high cervical cord.

MS will have two or more IgG bands present on a CSF gel electrophoresis and not in a matched serum sample (oligoclonal bands). Quantitative increases in the CSF IgG index provide similar information but do not always correlate with the presence of oligoclonal bands and should therefore also be ordered as part of CSF analysis. The sensitivity of these tests in clinically isolated syndromes is lower. In addition, oligoclonal bands are not specific for MS and have been observed in 50% of patients with infectious diseases of the nervous

system and in about 15% of patients with non-inflammatory diseases such as tumors and infarctions. MBP is released after CNS tissue injury from many processes, and other than documenting an organic etiology to the clinical presentation, the test is not helpful.

Evoked Potentials

Sensory evoked potentials are used in MS to provide objective evidence to supplement subjective sensory symptoms or occasionally to reveal clinically silent lesions. This can be particularly valuable if a psychiatric basis for the symptoms is being considered or in early cases in which MRIs are inconclusive. Of the three types of evoked potentials, brainstem auditory evoked response (BAER), somatosensory evoked potential (SSEP), and visual evoked potential (VEP), the latter is the most useful because remote optic nerve disease is common and not well visualized on MRI. VEPs can also be helpful in supporting a diagnosis of PP-MS based on the McDonald criteria.

Serologic Testing

As part of excluding other disease processes, it is often prudent to obtain peripheral blood to test: vitamin B_{12}, methylmalonic acid, 25-OH vitamin D, thyroid-stimulating hormone, erythrocyte sedimentation rate, antinuclear antibodies, Lyme titer, and rapid plasma reagin. In unusual cases, more extensive testing may include antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, anti-dsDNA antibodies, anti-Smith antibodies, Sjögren syndrome A and B antibodies, hepatitis profile, copper levels, ceruloplasmin, NMO-IgG, and angiotensin-converting enzyme. Rarely, human immunodeficiency virus and opportunistic infection can mimic MS. Some risk exists of obtaining false-positive tests, and some experts have questioned the cost-effectiveness of extensive serologic testing.

Errors in Diagnosing Multiple Sclerosis

Conditions commonly misdiagnosed for MS are listed in Tables 11.7 and 11.8.

TABLE 11.7 | **Conditions Commonly Mistaken for Multiple Sclerosis**
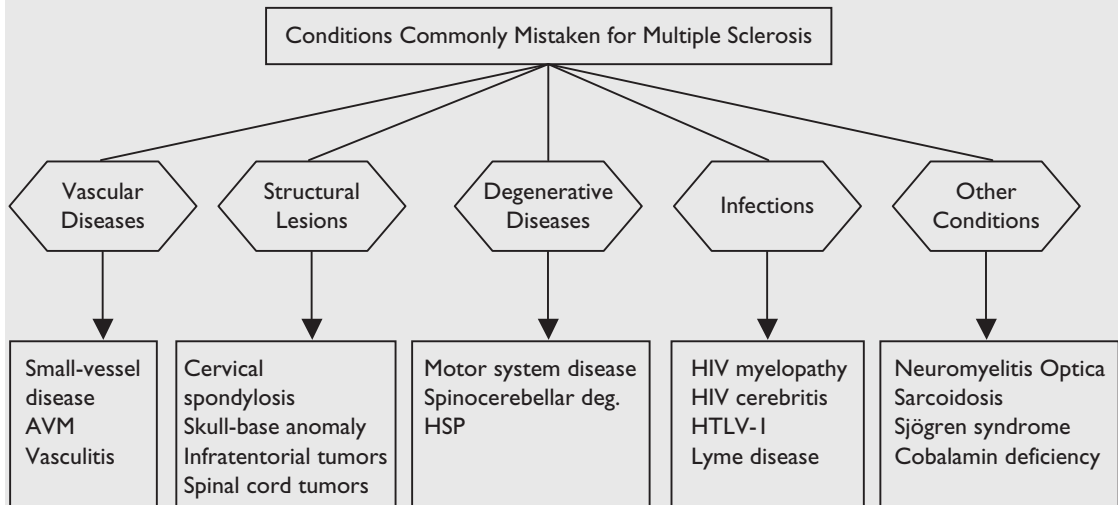
AVM, arteriovenous malformation; Deg., degeneration; HSP, hereditary spastic paraparesis; HIV, human immunodeficiency virus; HTLV-1, human T-cell lymphotrophic virus type-1.

TABLE 11.8	Diseases That Mimic Multiple Sclerosis on MRI
ADEM	Histiocytosis
HTN/small-vessel disease	HTLV-1
CADASIL	Lyme disease
Sarcoidosis	Leukodystrophies
Vasculitis	Mitochondrial disease
Migraine	Lupus
Aging-related changes	Behçet disease
Organic aciduria	HIV

ADEM, acute disseminated encephalomyelitis; HTN, hypertension; HTLV-1, human T-cell lymphotrophic virus type-1; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

■ **SPECIAL CLINICAL POINT: The rules of dissemination in time and space are critical to making an accurate diagnosis of MS.**

ADEM can appear clinically and radiographically like MS but is usually a monophasic disease process. Similarly, the presence of a cervicomedullary lesion such as with a Chiari malformation can cause multiple symptoms emanating from one location in the nervous system, so careful attention to documenting a clear second location is critical. In both situations, MRI has proved extremely useful; however, T2-weighted lesions are not specific for MS, and therefore vascular, infectious, and neoplastic etiologies of multifocal disease must be considered. The extent of exclusionary testing is usually dictated by the clinical presentation. In a case of RR-MS with typical findings and confirmatory brain MRI, little other testing is necessary. In atypical presentations with unusual historical features (fever, altered level of consciousness, exposures, no relapses), strong family history, no eye findings, purely progressive disease, or very aggressive disease from onset (NMO), more extensive testing is mandatory. Finally, psychiatric disease must be considered in the patient with numerous symptoms and little objective evidence for disease. The experienced clinician, however, recognizes that early in the course of MS, objective evidence

may be lacking and comorbid psychiatric disease can be the primary symptom. The level of confidence in the diagnosis of MS increases with time, and the physician should always be alert to alternative or coexistent disease processes even in patients who carry a diagnosis of MS.

When to Refer a Patient to a Neurologist

MS is a complicated neurologic disease, and the approaches to diagnosis and treatment are changing rapidly.

■ **SPECIAL CLINICAL POINT: It is appropriate to refer any patient suspected of having MS to a neurologist with MS experience, even if the patient has had only a single clinical event.**

Symptoms that are suspicious for MS include unexplained numbness/tingling, fatigue, urinary urgency, loss of vision in one eye, or impaired coordination. Although many of these symptoms occur commonly in healthy people, it is the persistence of a symptom or multiple symptoms that should provoke further evaluation. The non-neurologist should not be dissuaded by concomitant emotionality or psychiatric disease because this can be part of the presentation of MS. A brain MRI is a good first step in screening for MS. The presence of any high signal lesions in a young person warrants neurologic consultation.

THERAPY OF MULTIPLE SCLEROSIS

Disease-Modifying Therapies

Four partially effective disease-modifying therapies (DMT) for the initial management of MS are available in the United States: IFNb-1a (Avonex), IFNb-1a (Rebif), IFNb-1b (Betaseron), and glatiramer acetate (Copaxone). Mitoxantrone (Novantrone) was approved in the United States for the treatment of worsening forms of RR-MS, PR-MS, and SP-MS. A sixth novel agent, Natalizumab (Tysabri), was reapproved for use in the United States for patients

TABLE 11.9

Pharmacologic Treatments: Immunomodulating and Acute Relapses

Drug Name	Indication	Starting Dose	Stable Dose	Comments
Avonex (Interferon beta-1a)	Relapsing MS CIS	30 mcg IM q.d.	30 mcg IM q.d.	Flulike side effects
Rebif (Interferon beta-1a)	Relapsing MS CIS	22 mcg SC t.i.w.	44 mcg t.i.w.	Flulike side effects
Betaseron (Interferon beta-1b)	Relapsing MS CIS	0.0625 mg SC q.o.d.	0.25 mg SC q.o.d.	Flulike side effects
Copaxone (Glatiramer acetate)	Relapsing MS CIS	20 mg SC q.d.	20 mg SC q.d.	Idiosyncratic chest pain/palpitations
Tysabri (Natalizumab)	Relapsing MS	300 mg IV q4 weeks	300 mg IV q4 weeks	PML and other infections reported
Mitoxantrone (Novantrone)	Worsening forms of relapsing MS and SPMS	5–12 mg/m^2 IV	5–12 mg/m^2 IV q3 months for 2–3 years	Maximum lifetime dose 140 mg/m^2 Cardiotoxicity and leukemia reported Contraindicated in avascular necrosis
Methylprednisolone	Acute relapses	1,000 mg IV q.a.m. × 3–5 days	1,000 mg IV q.a.m. × 3–5 days	

MS, multiple sclerosis; CIS, clinically isolated syndrome; IM, intramuscularly; SC, subcutaneous; IV, intravenous; SPMS, secondary progressive multiple sclerosis.

with RR-MS who have either inadequate response to first-line therapies or are intolerant to them. Table 11.9 lists these immunomodulating pharmacologic treatments.

Beta Interferons Beta interferons (IFNα) are naturally occurring cytokines with a variety of immunomodulating and antiviral activities that may account for their therapeutic utility. IFNα may act through several mechanisms including modulation of major histocompatibility complex (MHC) expression, suppressor T-cell function, adhesion molecules, and matrix metalloproteinases. All three IFNα drugs have been shown to reduce relapses by about one third in double-blind placebo-controlled trials and are recommended either as first-line therapies or for glatiramer acetate intolerant patients with RR-MS. In addition, in each of these trials, IFNβ resulted in a 50% to 80% reduction of the inflammatory lesions visualized on brain MRI. Evidence also exists that these drugs improve quality of life and cognitive function.

The major difference between the IFNβ drugs is that Avonex is given weekly intramuscularly (IM), Rebif is given three times a week subcutaneously (SC), and Betaseron is given every other day SC. The adequacy of IFNβ-1a weekly dosing has been questioned. Studies appear to support a modest dose–response effect for IFNβ; however, one study of double dose (60 mg IM) Avonex, once a week, found no benefit over the single-dose regimen. Whether the benefit of more frequent dosing is sustained for periods longer than 2 years remains unclear, and the increased incidence of neutralizing antibodies (NAbs) with the more frequent SC dosing must also be considered.

Flulike symptoms, including fever, chills, malaise, muscle aches, and fatigue, occur in approximately 60% of patients treated with either IFNβ-1a or IFNβ-1b and usually dissipate with continued use and premedication with

nonsteroidal anti-inflammatory drugs (NSAIDs). Other side effects include injection-site reactions, worsening of preexisting spasticity, depression, mild anemia, thrombocytopenia, and elevations in transaminases, which are usually not severe and rarely lead to treatment discontinuation.

Development of NAbs can occur with any of the IFNβ products. Although the results are variable, IFNβ-1a weekly IM (Avonex) is reported to have the lowest incidence. The effect of NAbs on long-term efficacy remains to be fully defined. Some experts recommend that the results of an NAb assay in patients who exhibit insufficient treatment response may guide decisions for alternative therapy.

Glatiramer Acetate Glatiramer acetate (Copaxone) is a polypeptide mixture that was originally designed to mimic MBP. The mechanism of action of glatiramer acetate is distinct from that of IFNβ; therefore, patients may respond differently to this drug. Glatiramer acetate (20 mg SC q.d.) has also been shown to reduce the frequency of relapses by approximately one third and therefore is also recommended as a first-line treatment for RR-MS or for patients who are IFNβ intolerant. Glatiramer acetate results in a one-third reduction in the inflammatory activity seen on MRI.

Glatiramer acetate is generally well tolerated and unassociated with flulike symptoms. Immediate postinjection reactions associated with administration of glatiramer acetate include a local inflammatory reaction and an uncommon idiosyncratic reaction consisting of flushing, chest tightness with palpitations, anxiety, or dyspnea, which resolves spontaneously without sequelae. Routine laboratory monitoring is not considered necessary in patients treated with glatiramer acetate, and the development of binding antibodies does not interfere with the therapeutic efficacy of glatiramer acetate.

Mitoxantrone Mitoxantrone (Novantrone) is an anthracenedione antineoplastic agent that was shown in a phase III, randomized,

placebo-controlled, multicenter trial to reduce the number of treated relapses by 67% and slowed progression on EDSS, ambulation index, and MRI measures of disease activity. It is therefore recommended for worsening forms of MS. Acute side effects of mitoxantrone include nausea and alopecia. The lifetime use of this drug is limited to 2 to 3 years (or a cumulative dose of 120 to 140 mg/m^2) because of its cumulative cardiotoxicity. Since a more rapid cardiotoxicity can occur, a new black box warning was added recommending patients to have their baseline left ventricular ejection fraction checked prior to the start of therapy and retested before each subsequent dose. There is also increasing awareness and concern about treatment-related leukemias with this drug. More cases have been identified over the last year suggesting that the risk is higher than once suspected. Mitoxantrone is a chemotherapeutic agent that should be prescribed and administered only by experienced physicians.

Natalizumab Natalizumab (Tysabri) is a novel monoclonal antibody (mAb) directed against the adhesion molecule very late antigen-4 (VLA-4) that is expressed on leukocytes (except neutrophils). This agent is the first and currently the only mAb approved for use in MS. Natalizumab prevents leukocytes from binding to the vascular endothelium, especially during inflammation and ultimately prevents their transmigration into the CNS. Natalizumab had promising results in a phase II trial and two phase III clinical trials. In the phase III trial, AFFIRM, sustained progression of disability was reduced by 42%, clinical relapse rate was reduced by 68%, and MRI activity (enhancing lesions) was reduced by 92% in the natalizumab-treated group compared to placebo. Natalizumab was removed from the market in early 2005 after two MS patients from the second phase III trial (SENTINEL) developed a rare, deadly viral infection of the brain called progressive multifocal leukoencephalopathy (PML). Both patients were on combination therapy, Avonex plus natalizumab.

One patient eventually died and the other suffered major sustained disability. Natalizumab was subsequently reintroduced to the market in 2006 with a restricted indication for use as a second-line monotherapy treatment in RR-MS. It was initially thought that PML might occur only in the setting of combination therapy; however, since reapproval, at least four more cases of PML have been confirmed. There are now a total of seven known cases of PML as of December 2008 (one case was identified postmortem in a Crohn disease clinical trial after natalizumab treatment). The absolute risk of PML associated with natalizumab use is unknown, but an estimated risk of 0.1% is quoted and based on the previous clinical trial data. Natalizumab is only available in the United States through the TOUCH program, which was implemented for careful monitoring of potential drug-related side effects (specifically PML). TYGRIS is a worldwide phase IV safety study that is monitoring the use of natalizumab abroad. Natalizumab is given intravenously every 4 weeks under the care and supervision of an experienced infusion center staff. Serious allergic reactions can occur and typically happen within 2 hours from the start of infusion. Other more common side effects include infusion-related reactions, rashes, elevated transaminases, leucopenia, reactivation of various herpetic infections, sinusitis, and bladder/bowel infections. Two cases of melanoma were recently reported after natalizumab use; however, it is unclear whether a true association exists. Close neurologic monitoring is required during natalizumab use along with frequent blood work monitoring. Natalizumab is a potent monoclonal antibody that should be prescribed and administered only by experienced physicians.

Other Drugs Used in Multiple Sclerosis Several other drugs are commonly used in MS despite the lack of U.S. Food and Drug Administration approval and definitive evidence of efficacy. Numerous small clinical trials support the modest effect of intravenous immunoglobulin G (IVIg), azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide.

Initiation of Early Therapy

■ **SPECIAL CLINICAL POINT: Evidence is accumulating that the best time to initiate disease-modifying treatment is early in the course of the disease.**

Data indicate that irreversible axon damage may occur early in the course of RR-MS and that available therapies appear to be most effective at preventing new lesion formation but do not repair old lesions. With disease progression, the autoimmune response of MS may become more difficult to suppress. Weekly IM IFNβ-1a (Avonex) has been proved to reduce the cumulative probability of developing clinically definite MS in patients who present with a first clinical demyelinating episode and have two or more brain lesions on MRI (CHAMPS trial). High-dose interferon and glatiramer acetate therapy have further supported earlier treatment in clinical trials (ETOMS, BENEFIT, and PRECISE). Based on these data, the National Multiple Sclerosis Society (NMSS) recommends initiation of immunomodulating treatment at the time of diagnosis. The clinician must weigh these considerations against the practical concerns of young patients, for whom the prospect of starting a therapy that requires self-injection may be frightening and burdensome. There are also few long-term (more than 10 years) data regarding the safety and sustained efficacy of disease-modifying drugs. Some patients will opt to defer therapy, hoping to be among the minority of patients with benign MS, but certain MRI and clinical features should prompt the physician and patient to reconsider this approach. An MRI with contrast-enhancing lesions, large burden of white matter disease, or presence of any T1 low signal lesions (black holes) suggests a relatively poor prognosis. It may be useful to repeat the brain MRI in 6 months or 1 year to determine how quickly the disease process is evolving. The
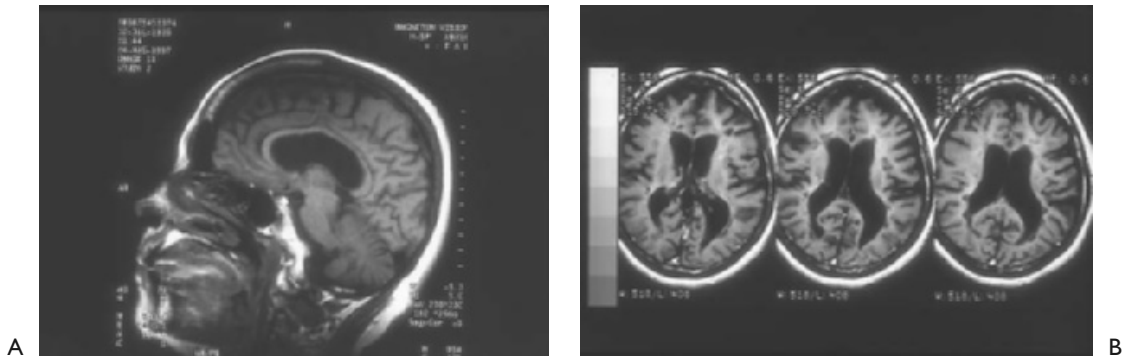
FIGURE 11.6 T1-weighted magnetic resonance imaging scans of the brain of a patient with multiple sclerosis demonstrating atrophy. **A:** Sagittal image revealing thinned corpus callosum and ventriculomegaly. **B:** Axial image with extensive ventriculomegaly and T1 black hole formation.

presence of spinal cord lesions or atrophy also suggests a poor prognosis (Figs. 11.6 and 11.7). Clinical features may be less useful for assessing prognosis, and once definite disability develops, it may be too late to treat that component of the disease.

Combination Therapy

Several trials are studying the addition of oral immunosuppressive drugs, IVIg, glatiramer acetate to IFNβ, and other agents in patients who continue to have disease activity. The rationale for this approach is based on experience with

FIGURE 11.7 Magnetic resonance imaging scans of the spinal cord of a patient with multiple sclerosis revealing multiple high signal lesions best seen using the short tau inversion recovery (STIR) sequence.
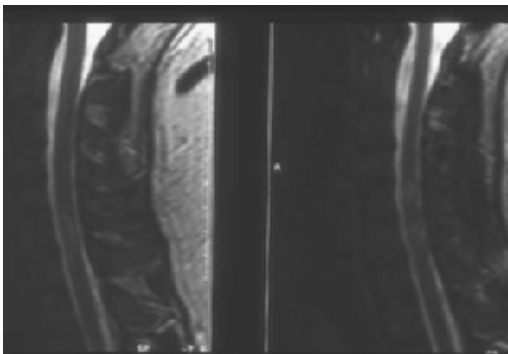
other diseases, but further testing is required both to ensure its safety and to ensure that the mechanism of action of one drug does not interfere with that of the other drug. Recently, a lack of clinical efficacy was observed in the Avonex Combination Trial (Avonex and oral methotrexate) despite being well tolerated. Combination therapies may increase the risk of serious complications due to excessive immunosuppression or decreased immune surveillance, so caution is advised when considering this treatment paradigm.

Symptomatic Therapy

■ **SPECIAL CLINICAL POINT: Appropriate recognition and treatment of ongoing symptoms can greatly improve quality of life in patients with MS (Table 11.10).**

Despite the recent advances in immunomodulating therapies to decrease new disease activity, many patients continue to suffer from ongoing symptoms related to preestablished lesions.

■ **SPECIAL CLINICAL POINT: Corticosteroids are the mainstay of acute relapse treatment and are discussed as a symptomatic therapy because at this time no conclusive evidence exists that they have any effect on the natural history or long-term outcome of a disease exacerbation.**

TABLE 11.10

Pharmacologic Treatments: Symptomatic

Drug	Indication	Starting Dose	Stable Dose	Comments
Baclofen	Spasticity	5 mg t.i.d.	10–40 mg t.i.d./q.i.d.	Severe withdrawal reaction
Tizanidine	Spasticity	2 mg q.h.s.	4–8 mg t.i.d.	—
Diazepam	Spasticity, anxiety, insomnia, vertigo	2–5 mg q.h.s.	5–10 mg t.i.d.	—
Meclizine	Vertigo	12.5 mg t.i.d.	25 mg t.i.d.	—
Oxybutynin	Urinary urgency	5 mg q.d.	5–10 mg b.i.d.	Anticholinergic effects may be contraindicated with glaucoma
Tolterodine	Urinary urgency	1 mg q.d.	1–2 mg b.i.d.	Anticholinergic effects may be contraindicated with glaucoma
Sildenafil	Erectile dysfunction	50 mg 0.5–4 hours prior to intercourse	25–100 mg	Contraindicated in macular degeneration and with nitrates
Modafinil	Fatigue	200 mg q.a.m.	100–200 mg q.d./b.i.d.	Contraindicated with certain heart conditions
Amantadine	Fatigue	100 mg b.i.d.	100 mg b.i.d.	—
Gabapentin	Pain, dystonic spasms	300 mg q.h.s.	300–900 mg t.i.d./q.i.d.	—
Carbamazepine	Pain, dystonic spasms	100 mg q.d.	100–600 mg t.i.d./q.i.d.	Contraindicated in patients with preexisting cytopenias

Corticosteroids There is evidence that corticosteroids shorten the duration and severity of an exacerbation. Intravenous methylprednisolone (IVMP), 1,000 mg, is administered daily for 3 to 5 days in the office or at home by a visiting nurse. On completion of the IVMP, prednisone may be started, 60 mg orally in the morning and reduced by 10 mg every other day until tapered off. The prednisone taper is not necessary but helps reduce withdrawal symptoms in some patients. An H2 blocker or proton pump inhibitor may be coadministered in patients with a history of ulcer or heartburn. Metoclopramide may be useful in patients who develop singultus (hiccups). The effects of steroids appear to diminish with repeated usage, and many patients reach a stage of unresponsiveness to steroids. It is unclear whether that stage can be delayed or prevented by restricting the use of steroids, but this appears to be a wise approach. Patients who become refractory to a short course of IVMP may respond to higher doses (2 g/day), longer courses (10 days), or plasma exchange.

The most common side effects of treatment are irritability, difficulty sleeping, and fluid retention. Additional well-recognized risks include hypokalemia, gastrointestinal side effects, and osteoporosis. Fluid retention can be minimized by salt restriction during the therapy, and diuretic use is discouraged because of the exaggerated risk of hypokalemia. Ankle edema can be minimized by wearing elastic stockings and elevating the leg. Hypokalemia is usually not a problem in the absence of concurrent potassium wasting, such as with diuretic therapy, but in the presence of heart disease or with concurrent diuretic therapy, oral potassium replacement should be administered and electrolyte

levels should be monitored during therapy. Anxiety and difficulty sleeping are usually minor problems. Patients may on rare occasions develop significant depression or mania during corticosteroid therapy.

In the Optic Neuritis Treatment Trial (ONTT), the rate of visual recovery was significantly faster in the IVMP group than in patients treated with placebo or oral prednisone, but no significant differences in visual outcome were found between groups at 6 months. Prednisone therapy alone increased the risk of new episodes of optic neuritis in either eye; however, the oral dose used was not equivalent to the IV dose. The ONTT results have led to widespread use of IVMP for patients with optic neuritis and an abnormal brain MRI, although equivalent doses of oral prednisone may be just as efficacious. Hints of a neuroprotective effect of steroids in other studies await confirmation.

Spasticity Mild spasticity may be managed by stretching and exercise programs such as aqua therapy and yoga. Drug therapy is indicated when stiffness, spasms, or clonus interfere with function or sleep. Baclofen is a good first choice for monotherapy. It exerts an antispastic effect by stimulating receptors for the inhibitory neurotransmitter, GABA. The initial dosage is 5 to 10 mg three times a day with intermittent upward dosage adjustments to achieve a therapeutic response or maximum tolerated dose, which may exceed 100 mg in some patients. Some patients may only require bedtime dosing to control nocturnal spasms. The principal limiting side effects of baclofen are confusion, sedation, or increased muscle weakness, and careful attention must be given to not overmedicate patients who are dependent on their muscle tone to ambulate. Baclofen may also unpredictably improve or worsen bladder function. Patients should never abruptly discontinue baclofen from doses greater than 30 mg/day because a withdrawal syndrome can occur consisting of confusion, seizures, or both. Tizanidine is an α-adrenergic agonist that exerts an antispastic effect by stimulating central pathways that provide descending inhibitory input to the spinal cord. Tizanidine is best initiated very slowly, starting with 2 mg at bedtime, with gradual dosage adjustment by 2- to 4-mg increments to a maximum of 12 mg three times a day. The principal side effects are sleepiness, orthostatic hypotension, and dry mouth. Tizanidine is said to be less likely to cause motor weakness than baclofen, but its efficacy is often limited by somnolence. It can be used alone but is often successful in low doses combined with baclofen. Gabapentin and benzodiazepines also have muscle-relaxant properties. In cases of extreme spasticity, continuous intrathecal baclofen can be delivered through an implantable infusion pump placed in an abdominal subcutaneous pocket and connected to a plastic catheter that is tethered in the lumbar subarachnoid space. Occasionally, botulinum toxin injections can be used for spasticity; however, it is less effective for larger muscle groups (hamstrings) and can be technically difficult with varying success.

Pain and Spasms Patients with disagreeable paresthesias, atypical facial pain, or tic douloureux often respond to antiepileptic drugs such as carbamazepine, oxcarbamazepine, phenytoin, gabapentin, or pregabalin. Occasionally, amitriptyline can be helpful. Narcotic analgesics are rarely the solution for chronic pain in MS. For refractory TN, IV phenytoin may provide rapid relief. Baclofen, mexiletine, misoprostol, valproic acid, topiramate, and lidocaine have also been suggested but have shown variable success. Surgical procedures to relieve medically intractable pain include rhizotomy, injection of anesthetics, and gamma knife. Paroxysmal dystonic spasms can be seen in MS and respond well in most instances to low doses of some antiepileptic drugs.

Bladder, Bowel, and Sexual Dysfunction The first step in managing a neurogenic bladder is to determine whether the problem is one of failure to

empty, failure to store, or a combination of both called detrusor external sphincter dyssynergia. A thorough history and urinalysis to rule out infection is appropriate. Immediate treatment of bacteriuria with antibiotics, even in the absence of typical dysuria, is necessary in MS because of the known propensity for infection to cause disease exacerbation. A postvoid residual urinary volume is the best means to determine if there is retention. Anticholinergic drugs are the initial drugs of choice for irritative bladder symptoms in the absence of infection. Oxybutynin, 5 mg, is increased gradually until symptom relief or distressing side effects, such as dry mouth, blurred vision, or worsening constipation, occur. Oxybutynin is also available in a long-acting formulation with reduced peak side effects and enhanced efficacy compared with other agents. Tolterodine, 1 to 2 mg twice a day, is a useful alternative with fewer anticholinergic side effects. Solifenacin, 5 to 10 mg daily, and Trospium, 20 mg two times a day, are newer overactive bladder agents. Propantheline bromide and hyoscyamine sulfate are older alternative anticholinergic agents. Anticholinergic drugs can be used intermittently if bladder symptoms are distressing at particular times, such as at bedtime or before a long automobile ride. The patient should be made aware of possible urinary retention with anticholinergics. Urinary residual volume should be checked after initiating therapy or should concerns arise about retention. In cases of concomitant retention and urgency, anticholinergics can be used in combination with intermittent bladder self-catheterization. Patients failing to achieve urinary continence with anticholinergic pharmacotherapy, with or without self-catheterization, need formal urologic evaluation for consideration of diversion procedures.

Drug treatment of urinary retention is usually ineffective, but some patients may benefit from attempts at decreasing bladder neck tone using α_1-adrenergic receptor antagonists such as terazosin, doxazosin, prazosin, and tamsulosin. Desmopressin, a vasopressin analogue, can be used at a dose of 20 mg by intranasal administration nightly to treat nocturnal incontinence by temporarily suppressing urine production. This approach should be used with caution in patients with hypertension or hyponatremia.

Constipation is very common in MS and should be managed aggressively to avoid long-term complications. Eating foods rich in fiber may help with mild constipation. Stool softeners and/or laxatives can be used for moderate constipation. For fecal incontinence, the addition of fiber in the form of a bulk fiber laxative (e.g., Metamucil) twice a day can provide enough bulk to the stool to allow a partially incompetent sphincter to hold in the bowel movement long enough to allow the patient to reach a bathroom. The use of anticholinergics or antidiarrheal agents may be effective for short periods to combat incontinence associated with diarrhea.

A careful sexual history to determine the problem(s) is a good first step in treating sexual dysfunction. Counseling the patient regarding avoiding the ill effects of elevated body temperature can be critical in managing problems that worsen with sexual intimacy. Erectile dysfunction (ED) in MS can be managed with sildenafil effectively initiated at 50 mg 60 minutes before intercourse (higher doses may be necessary). Sildenafil should be used with caution in older patients or in those with a history of heart disease. This agent is contraindicated in patients taking medications with nitrates in them and in patients with macular degeneration. Newer agents including vardenafil and tadalafil can also help with ED. Discontinuation of medications known to decrease libido (selective serotonin reuptake inhibitors [SSRIs]) or impotence (β-blockers) should be considered if possible.

Neurobehavioral Manifestations The most common neurobehavioral manifestation amenable to drug therapy is depression, which occurs in more than 50% of patients with MS. Moderate or severe depression should be treated with one of the SSRIs. For patients with psychomotor retardation and depression, fluoxetine, 20 to 80 mg daily, or sertraline, 50 to 200 mg daily, may be particularly effective. Paroxetine, 100 to

200 mg daily, is often useful for patients who are anxious and depressed. These drugs increase the levels of tricyclic antidepressants (TCAs), so care should be exercised in combining SSRIs with TCAs. Amitriptyline, 50 to 200 mg at bedtime, can be useful in depressed patients who are also having difficulty sleeping, headaches, or other pain. Treatment should be instituted gradually to minimize anticholinergic or CNS side effects. The patient and family should be warned of the delay between initiating therapy and observing a benefit. The pseudobulbar syndrome of pathologic laughing or weeping may respond to amitriptyline in low doses. Several newer antidepressants may be useful when the anticholinergic side effects of TCAs or the sexual side effects of SSRIs (decreased libido and orgasm) become intolerable. Bupropion, citalopram, escitalopram, and venlafaxine all may be better tolerated. Bipolar disorder is also increased in MS and commonly treated with valproic acid or lithium. SSRIs can aggravate mania complicating treatment of bipolar disorder, which may warrant psychiatric consultation.

Alprazolam, a benzodiazepine analogue, has been useful for anxiety in some patients. A dose of 0.25 to 0.50 mg two or three times a day is usually sufficient. Diazepam can be used as an alternative drug. Infrequently, antipsychotic medications are needed in MS. Atypical antipsychotic agents (risperidone, olanzapine, quetiapine) are preferred over typical agents (Haldol, Thorazine) to minimize the potential for extrapyramidal and anticholinergic side effects. As with other symptomatic therapies, the need for pharmacotherapy over time should be assessed intermittently, and the drug should be tapered if appropriate.

Fatigue Some types of MS fatigue may respond to short periods of rest, but if this is not possible, or in cases of severe fatigue, medication should be considered. Amantadine, 100 mg twice a day, may be effective in treating about one third of the cases of fatigue. Modafinil, a newer narcolepsy drug that acts as a CNS stimulant, was found to be effective in patients with MS at a dose of 200 mg in the morning. Occasionally, treatment with an SSRI (fluoxetine and sertraline) can have a positive effect on fatigue even in the absence of overt depression. 4-Aminopyridine (Fampridine or 4-AP) is an investigational voltage-gated potassium channel (Kv1.4) blocker, that may help with fatigue, endurance, and ambulation in MS by prolonging action potentials. In higher doses, this agent has been associated with seizures and confusion limiting its use. A newer sustained-release formulation of 4-AP is under intense investigation. A recent dose comparison study suggested that walking speed in some patients may improve with the sustained-release form; however, two people experienced de novo seizures at the higher dose. Future studies are planned to further assess the risk–benefit profile of this newer formulation.

Special Challenges for Hospitalized Patients
Patients with MS may be hospitalized either during severe exacerbations or for other medical problems. In the case of an MS exacerbation, the patient should be screened for sources of infection and treated with antibiotics as appropriate. Rapid control of fever is also important to prevent worsening of symptoms. Exacerbations that warrant hospitalization are usually related to acute inability to ambulate or loss of self-care in the more advanced patient, and IV corticosteroids are usually instituted. Plasma exchange may be useful in steroid-unresponsive cases and requires hospitalization. Physical and occupational therapy should be initiated immediately, and a rehabilitation plan should be put in place with attention to adaptive devices for the home and orthotics or ambulation aids. For non–MS-related hospitalization, it is equally important to be vigilant about infections to prevent exacerbation. MS rarely causes respiratory compromise, and there are no absolute contraindications to anesthesia. Cosmetic surgery is discouraged, but necessary operations are usually well tolerated. Patients with MS do not have any impairment in wound healing. Postpartum exacerbations usually do not occur for several weeks after delivery and thus are not

a major obstetric complication. Counseling, social work, and attention to severe depression should be considered during periods of stress such as may occur during hospitalization.

Alternative Therapies Used by Patients with Multiple Sclerosis Numerous alternative therapies have been advocated for MS but they are rarely tested in a placebo-controlled manner and, therefore, they cannot be recommended. Because MS is an unpredictable disease characterized early by relapses and spontaneous recovery, patients are very susceptible to placebo effects and misguided judgments about the efficacy of alternative therapies. Bee stings have been used for many years, and for those who are not allergic about half of patients report a temporary boost in energy perhaps related to endogenous corticosteroid release in response to cutaneous inflammation. Procarin is a patch used by some patients with MS and contains vitamin B_{12}, histamine, caffeine, and a proprietary substance. Several diets for MS, such as the Swank diet, have been popular. Acupuncture is used to relieve pain and sometimes boost energy. Low-dose naltrexone (LDN) has been used off-label for MS and other diseases. Naltrexone is an opioid receptor antagonist approved for the treatment of alcohol and opioid dependence. Its use in MS is controversial and there have been no randomized, double-blinded, placebo-controlled trials to assess LDN tolerability or efficacy. A small, open-label pilot study was done suggesting improvements in fatigue; however, the NMSS currently does not support the use of this agent until further testing is done. None of the above approaches has been tested adequately. Complementary medicine advocates recommend yoga, meditation, aqua therapy, body-cooling devices, and stress reduction, all of which are reasonable and safe approaches to dealing with MS.

Physical Therapy Physical therapy has an important role in managing MS. Regular exercise and stretching decrease MS symptoms of stiffness, weakness, and pain and improve overall well-being. Physical therapy has been shown to improve disability from MS independent of drug interventions and should be continued on a regular basis as part of a maintenance regimen.

Novel Experimental Immunomodulatory Approaches

Several treatments are being tested in preliminary trials, including antibodies to various critical immune molecules (CD25 IL-2α receptor, CD20 B-cell marker, and the CD52 leukocyte marker), phosphodiesterase inhibitors, novel NSAIDs, β-adrenergic agonists, and immunosuppressive regimens used during organ transplantation and malignancies. Of these therapies, the monoclonal antibodies (alemtuzumab, daclizumab, rituximab) and novel oral agents (fingolimod, cladribine) seem to have the most promise in MS, as shown in recent clinical trials. Despite the encouraging trial data, there have been several serious complications associated with many of these agents, which will potentially limit their future widespread use. Immunoablative protocols using extremely high doses of chemotherapies, followed by autologous stem-cell rescue, have been used in particularly aggressive forms of MS. This approach has afforded disease stabilization, both clinically and by MRI, but has an unacceptably high morbidity and mortality at present.

Remyelination and Neuroprotection

Theoretical approaches to remyelination include enhancing existing oligodendrocyte precursors or neural stem cells by using growth factors or direct transplantation of oligodendrocytes or autologous stem cells. Growth factors such as insulinlike growth factor carry the inherent risk of nonspecifically activating the immune system. Anti-LINGO antibodies appear to be a promising means of inducing endogenous remyelination by enhancing oligodendrocyte progenitor cell differentiation into myelin-forming cells in vitro and in animal models.

Always Remember

- Multiple sclerosis (MS) has features of inflammation, demyelination, axonal injury, and neurodegeneration.
- Visual dysfunction, sensory disturbances, and gait impairment are very common presenting symptoms.
- MS is diagnosed clinically through the demonstration of CNS lesions disseminated in time and space and with no better explanation for the disease process.
- MRI is the single most useful test in confirming the diagnosis of MS.
- Initiating early disease-modifying treatment can influence the clinical course.
- Symptomatic therapy can greatly improve MS patients' quality of life.
- MS is a complicated neurologic disease, and the approaches to diagnosis and treatment are changing rapidly, therefore, it is appropriate to refer any patient suspected of having MS to a neurologist with MS experience.

QUESTIONS AND DISCUSSION

1. A 24-year-old nursing school student presents to her primary care physician (PCP) with complaints of numbness and tingling in her hands for 1 month. On questioning, she responds that she has had recent fatigue and mild depression, which she attributed to stress. She denies any other past medical history and is only taking birth control pills. Her entire physical examination is normal. The next appropriate step is to:
   A. Recommend EMG/NCS to rule out carpal tunnel syndrome.
   B. Reassure her that she has no abnormal signs on examination and therefore cannot be diagnosed with multiple sclerosis at this time.
   C. Order blood tests and a brain MRI.

   D. Treat her for depression and reevaluate in 3 to 6 months for improvement.

The correct answer is C. This woman could have early signs of MS, and because there is strong evidence to support early initiation of therapy, it is important to make a diagnosis. Blood testing is indicated to exclude thyroid disease, vitamin B_{12} deficiency, other inflammatory neurologic disorders, and infections. A brain MRI is the single best screening tool for MS. Depression may be a symptom of MS and should not be considered an adequate explanation for ill-defined somatic symptoms. Carpal tunnel syndrome is a common cause of hand numbness but is usually unilateral and would not explain the other reported symptoms.

2. A 36-year old woman is diagnosed with optic neuritis. Her initial brain MRI reveals several demyelinating lesions. She is referred to a neurologist, but she declines immunomodulating therapy and prefers to "wait and see." Three months later, a repeat MRI is obtained and reveals a new gadolinium-enhancing lesion. At this time:
   A. She has clinically definite MS according to McDonald criteria but treatment is not indicated because this is probably a benign case.
   B. She has clinically definite MS according to McDonald criteria and treatment with either IFNβ or glatiramer acetate would be appropriate.
   C. She has PP-MS for which unfortunately there is no treatment.
   D. In the absence of a second clinical event, she cannot be diagnosed with multiple sclerosis.

The correct answer is B. The demonstration of a new lesion on MRI more than 3 months later provides evidence for dissemination in time and now fulfills criteria for a definite diagnosis of MS. The National Multiple Sclerosis Society and many MS experts now favor early initiation of therapy. Benign MS is defined as no disability after at least 10 years

and can only be diagnosed retrospectively. Progressive MS is defined as 6 months of unabated worsening without exacerbations, and 1 year of disease progression is required to make a diagnosis of PP-MS.

3. A 40-year-old woman with RR-MS presents for routine follow-up. She is being treated with IFNβ injections, and although she has had no exacerbations since being on treatment, she complains of increased stiffness in her legs, and on questioning she also admits to urinary urgency with occasional episodes of incontinence. On examination, she is more spastic and hyperreflexic in her legs than 6 months ago, but there is no clear sensory level over her spine or weakness. At this point:
   A. She should stop taking the medication as she now has secondary progressive disease.
   B. She should switch to another immunomodulating drug as she has failed IFNβ therapy.
   C. A urinalysis should be ordered to rule out a urinary tract infection.
   D. She should stop taking the medication as these are likely side effects of the IFNβ.

   The correct answer is C. Minor changes in neurologic function do not constitute progressive disease, and it is likely that the reduction in relapses suggests that the IFNβ is effective. Although exacerbation of spasticity can be a side effect of IFNβ, bladder frequency is part of underlying MS and is often a sign of urinary tract infection. Antibiotic treatment of bacteriuria often alleviates the bladder symptoms and sometimes other new symptoms as well.

4. A patient with MS presents to the office with several days of dizziness, diplopia, and trouble walking straight. There has been no obvious precipitating factor (infection, heat, stress), and she has been taking her medications on a regular basis. On examination, she is noted to have several new findings including bilateral INO, finger to nose dysmetria, severe gait ataxia, and facial asymmetry. You recommend the following:
   A. Treatment with 2 weeks of prednisone (approximately 1 mg/kg).
   B. Strict bedrest until the symptoms resolve.
   C. A brain MRI as soon as possible to confirm an MS exacerbation.
   D. Treatment with 3 to 5 days of IV methylprednisolone (1 g/day).

   The correct answer is D. The patient is having an acute disabling exacerbation and should be treated with IV methylprednisolone. A brain MRI is a useful means of assessing disease activity (gadolinium-enhancing lesions and new T2 lesions) and determining the extent of breakthrough disease activity but is not obligatory if the clinical picture is clear.

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