Multiple Sclerosis and Allied Demyelinating Diseases 69

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INTRODUCTION

Among demyelinating diseases, multiple sclerosis (MS) is the most common and widely recognized. It is the leading cause of nontraumatic neurologic disability in young people. The identification of a pathologic autoantibody has definitively separated neuromyelitis optica (NMO) from MS, where it was previously considered an MS subtype. Marchiafava–Bignami disease, a rare demyelinating condition often associated with alcoholism, is discussed here as well, although the mechanism is thought to be toxic rather than inflammatory. The discussion that follows considers each disease state separately with the unifying pathophysiology of demyelination.

MULTIPLE SCLEROSIS

MS is a chronic inflammatory demyelinating disease of the central nervous system (CNS) of unknown cause. The course is extremely variable, but most patients initially experience relapses with complete or near-complete recovery interspersed with periods of clinical remission. Although a minority of patients has only minimal symptoms, many become disabled in time as a result of incomplete recovery from relapses or conversion to a progressive form of the disease.

EPIDEMIOLOGY

MS affects approximately 400,000 people in the United States and 2.5 million worldwide. It is a leading cause of nontraumatic disability in young adults. The disease typically begins between the ages of 20 and 40 years. The first symptoms rarely occur before age 10 years or after age 60 years. Women are affected approximately twice as often as men except in individuals with the primary progressive form of the disease where there is no gender preponderance.

PATHOBIOLOGY

The etiology of MS is unknown. It probably results from complex interactions between environmental factors and susceptibility genes, which lead to an aberrant immune response and damage to the myelin sheath, oligodendrocytes, axons, and neurons.

Studies in a mouse model of MS, experimental autoimmune encephalomyelitis (EAE), histopathologic studies of MS lesions, and immunologic markers in serum and cerebrospinal fluid (CSF) of MS patients suggest that MS is an immune-mediated disease. A virus, bacterium, or other environmental toxin might induce an immune response in genetically susceptible persons. Antigen-presenting cells (APCs) provide relevant antigens to CD4+ T-helper cells in the periphery, which lead to their activation and the subsequent generation of autoreactive proinflammatory T-helper (Th) 1 and

17 subsets. B cells and monocytes are also activated. These autoreactive T cells interact with adhesion molecules on the endothelial surface of CNS venules and, with antibodies and monocytes, cross the disrupted blood–brain barrier with the aid of proteases (e.g., matrix metalloproteinases) and chemokines. Within the CNS, target antigens are recognized (putative antigens include myelin basic protein, myelin-associated glycoprotein, myelin-oligodendrocyte glycoprotein, proteolipid protein [PLP], αB-crystallin, phosphodiesterases, and S-100 protein), T cells are reactivated, and the immune response is amplified. Proinflammatory T-helper cells proliferate and B cells continue their maturation to antibody-secreting plasma cells, whereas monocytes become activated macrophages. Together, these immune cells produce inflammatory cytokines (e.g., interleukin [IL]-12, IL-23, interferon γ, tumor necrosis factor [TNF]-α), proteases, free radicals, antibodies, nitric oxide, glutamate, and other stressors that collectively lead to damage of myelin and oligodendrocytes. In the appropriate cytokine milieu, CD4+ Th2 cells proliferate and secrete anti-inflammatory cytokines (e.g., IL-4, Il-5, IL-13, and transforming growth factor-β) that suppress the immune response. Depending on the location and extent of damage, demyelination may impair or block nerve conduction and result in neurologic symptoms. With a loss of trophic support from oligodendrocytes, axons may degenerate to cause irreversible neurologic deficits. Spontaneous improvement of symptoms is attributed to resolution of inflammation, adaptive mechanisms (e.g., reorganization of sodium channels), or remyelination.

It had long been thought that Th1 and Th2 subsets arose from the terminal differentiation of the CD4+ T cells. However, a third pathway has been identified, induced by IL-1, IL-6, and transforming growth factor-β, and then expanded and maintained by IL-23, which is secreted by APCs. This third subset, a proinflammatory T-helper cell, is known as *Th17* because it produces IL-17. Th17 cells secrete a number of cytokines, including TNF-α and granulocyte macrophage colony stimulating factor (GM-CSF), which are critical for the development of EAE. MS patients have monocyte-derived dendritic cells that secrete higher levels of IL-23 than healthy controls. Higher levels of IL-17 mRNA-bearing mononuclear cells are found in the serum of MS patients having relapses than in patients in remission.

Although MS is typically considered a T-cell–mediated disease, a growing body of evidence supports a pathogenic role of B cells, including the frequent observation of intrathecal production of immunoglobulin in MS patients, identification of antibodies that react to specific myelin antigens within MS lesions, a pathologic pattern of MS characterized by antibody-associated demyelination (see the following text), and the discovery of B-cell follicles in the meninges of patients with secondary progressive MS. Pathologic studies have shown that B-cell clones are shared between the meninges and parenchyma of individual MS patients. Furthermore, B cells

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are efficient APCs and B-cell depletion is a promising therapeutic approach in MS.

Chronic demyelinating plaques appear translucent, sharply demarcated, and are most frequently found in the periventricular white matter, brain stem, cerebellum, and spinal cord. Lesions are characterized by extensive demyelination, gliosis, variable axonal loss, and a minimal inflammatory infiltrate consisting of T lymphocytes and macrophages. Demyelination accompanied by a perivascular infiltrate consisting predominantly of T cells, lipid-laden macrophages, and prominent reactive astrocytes are typical features of actively demyelinating lesions. Although demyelination with relative preservation of axons is often considered the pathologic hallmark of MS, axonal transection is common, especially in areas of active inflammation and demyelination. In autopsies of 52 MS cases, prominent cortical demyelination was seen with a mild but diffuse inflammatory infiltrate with microglial activation in normal-appearing white matter of patients with secondary or primary progressive MS. Cortical demyelination was rare in patients with relapsing–remitting MS.

Lucchinetti and colleagues identified four distinct pathologic patterns in an immunohistopathologic study of actively demyelinating MS lesions in 83 cases (51 biopsies and 32 autopsies). All four patterns contained an inflammatory infiltrate consisting of T lymphocytes and macrophages. The most common type, pattern II, was characterized by the deposition of immunoglobulin and complement. Pattern I was characterized by macrophage-associated demyelination. In patterns III and IV, demyelination was due to an oligodendrogliopathy. Pattern III was differentiated from pattern IV by a preferential loss of myelin-associated glycoprotein. Multiple active lesions were discovered in 27 autopsy cases. The same lesion pattern was observed within each patient, but there was marked heterogeneity between patients, suggesting that MS might have multiple pathogenic mechanisms. However, the results of this study were challenged by another autopsy series of 12 relapsing–remitting MS patients who died in the setting of an acute relapse. Most cases, including one who died 17 hours after an exacerbation, included lesions characterized by extensive oligodendrocyte apoptosis with intact myelin sheaths and slight or no inflammatory infiltrate. More than one of the aforementioned patterns were observed in some patients. The investigators concluded that pattern III lesions represent an early stage of lesion formation that precedes inflammation and demyelination. However, biopsy and some autopsy studies are susceptible to inherent selection bias and the findings may not be representative of typical MS.

Genetic Risk Factors

The strongest known genetic factor influencing MS susceptibility is the human leukocyte antigen (HLA)-DRB1*1501 haplotype. However, it is not essential for the development of MS, increases the risk two- to fourfold, and is present in 20% to 30% of normal individuals. Linkage and association analysis of 931 family trios (individuals with MS and their parents) screened 300,000 single-nucleotide polymorphisms and identified two genes outside of the HLA region, interleukin-2 receptor alpha gene (IL2RA) and interleukin-7 receptor alpha gene (IL7RA), which also increase the risk of MS. IL2RA encodes the alpha chain of the IL-2 receptor, which is essential for regulation of T-cell responses and has been implicated in the pathogenesis of other autoimmune diseases, including Graves disease and type 1 diabetes mellitus. IL7RA encodes the alpha chain of the IL-7 receptor. IL-7 functions in the homeostasis of memory T cells and may play a role in the generation of autoreactive T cells in MS patients. The effect of these allelic variants on overall MS risk is

small but statistically significant. Additional genome-wide association studies have identified 110 MS risk variants in 103 loci, which are not within the major histocompatibility complex.

Additional evidence for a genetic predisposition includes increased risk in some ethnic groups (e.g., Caucasians of northern European ancestry) and decreased risk in others (e.g., Native Americans), varying prevalence rates among different racial groups in the same geographic location, a 20% to 40% increased risk of MS in first-degree relatives, whereas adopted children of MS patients have a risk similar to the general population, and 25% to 30% concordance in monozygotic twins compared to 5% in dizygotic twins. However, 70% of identical twins are discordant for MS, so environmental factors and other unknown influences must contribute to susceptibility.

Environmental Influences

In general, there is a latitudinal gradient with an increased prevalence of MS further from the equator in both hemispheres. Large differences in the frequency of MS are observed in some homogenous populations living at different latitudes. Several regions with similar latitude have vastly different MS prevalence rates, which in some instances can be accounted for by differences in ethnic susceptibility (e.g., Great Britain and Japan lie at the same latitude, but the prevalence in Britain is approximately 60 times more than in Japan).

Further evidence of an environmental effect comes from migration studies and apparent epidemics and disease clusters. In general, immigrants who move from one area to another before the age of 15 years acquire the MS prevalence rate of the new region. The altered risk develops gradually and may be imperceptible in the immigrants themselves but is obtained by their children. Notable exceptions include Israeli-born children of European and American immigrants who have a frequency of MS similar to that of their parents. Therefore, genetics may sometimes be more important than the environment. Migrating after age 15 years does not affect the risk of MS.

Apparent MS epidemics occurred in Iceland and the Faroe Islands after World War II, suggesting an infectious or other environmental cause. The arrival of British troops to the Faroe Islands in 1940 also brought the first neurologist to the islands, so that increased awareness of the disease and better case ascertainment may have led to the apparent "epidemic." However, the onset of the disease occurred after 1942 in all of the identified cases except for a few who had spent time away from the islands.

More than the expected number of MS cases has been reported in several areas, including Key West, Florida; Orange County, California; Los Alamos County, New Mexico; Hordaland, Norway; and Colchester County, Nova Scotia, raising the possibility of a shared environmental exposure causing the disease. Mercury toxicity, zinc, viruses, and other toxins have been suggested but no credible evidence has explained these clusters, which may have occurred by chance.

Multiple environmental factors may influence the risk of MS, including vitamin D, which has emerged as one compelling possibility. The active form of vitamin D, 1,25-dihydroxyvitamin D_3, has immunomodulatory properties and can prevent or ameliorate experimental allergic encephalomyelitis (EAE), a mouse model of MS. Numerous studies have found an inverse correlation between sunlight exposure (the most common source of vitamin D) and dietary intake of vitamin D and the risk of MS. The relationship to sunlight exposure may help explain the latitudinal variation of MS prevalence. Furthermore, a study of U.S. military personnel found that higher serum levels of 25-hydroxyvitamin D_3 (25[OH]D_3) were associated with a lower risk of MS. Similar findings in the

Netherlands were reported, but only in women, as well as a negative correlation between 25(OH)D$_3$ levels and disability. However, it is not known whether vitamin D supplementation modifies the disease in people already diagnosed with MS.

High-salt diet has been shown to increase severity of EAE and induce pathogenic TH17 cells in humans and mice *in vitro*. This has been hypothesized to explain in part the increasing incidence of MS and other autoimmune diseases in countries with "Western diet."

Among the possible infectious causes, the case for EBV is of interest. The frequency of MS is low in people who are seronegative for EBV, but the risk is increased in those who have had infectious mononucleosis. The evidence for other microbial agents is less compelling, but it is possible that a number of viruses or bacteria might act as a nonspecific trigger of MS in genetically susceptible individuals.

Physical trauma or psychological stress might precede the onset of either MS or MS exacerbations. Although temporal associations are common, a clear causal relationship is lacking. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology concluded that there is no significant association between trauma and MS onset or exacerbation. The committee also concluded that, although possible, there is no clear relationship between antecedent psychological stress and the onset of MS or exacerbations. However, a study in Israel concluded that stress associated with the 2006 war between Israel and Lebanon increased exacerbations in civilians with MS.

CLINICAL MANIFESTATIONS

A clinically isolated syndrome (e.g., optic neuritis, transverse myelitis, or a brain stem or cerebellar syndrome) heralds the onset of the disease in approximately 85% to 90% of all cases. A relapsing–remitting course ensues and is often followed by a progressive phase of the disease. Symptoms, which depend on lesion location and extent of tissue destruction, range from mild and intermittent to severe and persistent or progressive (Table 69.1). The disease begins insidiously and gradually worsens in the remaining 10% to 15% of patients, termed *primary progressive multiple sclerosis*.

Acute optic neuritis is one of the most common manifestations. Patients typically note unilateral visual loss that evolves over a few days and is preceded or accompanied by orbital pain that occurs with or is exacerbated by eye movement. Progressive visual failure over many years is uncommon. On examination, visual loss varies from mild to severe. Visual acuity of 20/200 or worse is found in about 33% of patients, but complete loss of vision is rare. Dyschromatopsia and a central scotoma or other visual field defects are common. A relative afferent pupillary defect (RAPD), which may be the only clinical evidence of optic neuritis, is invariably present unless there is a prior history of or current optic neuritis in the opposite eye. The absence of a RAPD in a person with acute visual loss raises the possibility of uveitis, which occurs with increased frequency in MS. Funduscopy in optic neuritis is often normal, but swelling of the optic disc is observed in 35% of patients. Retinal hemorrhages and exudates are uncommon.

Spontaneous recovery of vision usually occurs within the first month, even when visual loss is severe. Lack of improvement suggests an alternative diagnosis because 98% of patients with visual acuity 20/50 or worse improve at least three lines on a Snellen letter chart within 6 months after the onset of symptoms. Optic atrophy is frequently found after the acute episode resolves.

Temporary worsening of vision with physical activity was originally described by Uhthoff in 1890. Uhthoff phenomenon now refers to new or worsening neurologic symptoms that occur in some patients with elevations in temperature (often during exercise or a hot shower). Symptoms are transient and attributed to reversible conduction block along demyelinated nerve fibers.

Oculomotor abnormalities are common. Diplopia usually results from a sixth nerve palsy or internuclear ophthalmoplegia. Other forms of nystagmus (e.g., gaze-evoked or pendular) are also common. Smooth pursuit and saccadic eye movement abnormalities may be observed. Third or fourth nerve palsies, the one-and-a-half syndrome (reflecting damage to the parapontine reticular formation or the sixth nerve nucleus causing ipsilateral gaze palsy as well as impaired adduction in contralateral gaze due to damage to the medial longitudinal fasciculus), opsoclonus, and symptomatic homonymous field defects are rare.

TABLE 69.1   Classic Signs and Symptoms of Relapsing Multiple Sclerosis

Symptom	Sign	Localization
Blurred vision	Relative afferent pupillary defect	Optic nerve
	Disc pallor	
	Papillitis	
	Red desaturation	
Diplopia	Nystagmus	III, IV, and VI nerve nuclei and outflow tracts
	Internuclear ophthalmoplegia	MLF
	One-and-a-half syndrome	PPRF
Vibratory or electrical sensation with neck flexion	None—"Lhermitte sign" is a symptom	Cervical spine
Paroxysmal dystonia	Brief, often painful, usually unilateral muscle spasms	Corticospinal tracts
	May manifest as paroxysmal dysarthria or facial spasms	
Pseudobulbar affect	Laughing or crying uncontrollably without emotional congruence with the displayed affect	Brain stem, also frontal and parietal subcortical white matter

MLF, medial longitudinal fasciculus; PPRF, paramedian pontine reticular formation.

Facial numbness and vertigo can be difficult to distinguish from peripheral vestibular dysfunction, or facial weakness that is usually of the upper motor neuron type, but may mimic an idiopathic Bell palsy. Sudden hearing loss is uncommon and should raise the possibility of Susac syndrome. Intractable hiccups are rare but may result from lesions in the medulla or upper cervical spine. Intractable hiccups or vomiting should raise the possibility of NMO. Dysphagia is uncommon except in advanced MS. Limb weakness is common in MS and may occur during an acute exacerbation or incomplete recovery from an acute attack. The legs are more often affected than the arms and hands.

Approximately 70% of patients have some spasticity, which most commonly involves the legs. Spasticity is often accompanied by painful spasms and upper motor neuron signs. Spasticity often impairs mobility and activities of daily living and disrupts sleep. Gait abnormalities are common and usually a result of ataxia, weakness, or spasticity. However, in some instances, spasticity of the leg extensors permits weight bearing and improves gait. In nonambulatory patients, spasticity may interfere with transfers and personal hygiene.

An extensor plantar response is seldom the only evidence of corticospinal tract dysfunction. Demyelinating lesions in the anterior horn cells and dorsal root entry zones occasionally result in atrophy and hyporeflexia.

Paresthesias, dysesthesias, hypesthesia, or the Lhermitte sign (whereby neck flexion generates an electric sensation that usually radiates from the back of the neck to the lower back and possibly into one or more limbs) are common initial manifestations of MS and occur in most patients at some time.

An action tremor of the arms is common in MS patients. It is often accompanied by other signs of cerebellar disease, including gait ataxia, dysmetria, dysdiadochokinesia, and dysarthria. Tremor of the head, trunk, and legs is much less frequent. Incapacitating tremor, scanning speech, and truncal ataxia are seen in advanced disease.

Paroxysmal symptoms in MS are brief, repetitive, stereotyped attacks of neurologic dysfunction that are thought to result from ephaptic spread of abnormal electrical discharges from partially demyelinated nerve fibers ("cross-talk"). These discharges can arise from areas with acute inflammation and demyelination or chronic tissue damage. The symptoms usually last a few seconds to a few minutes and may occur anywhere from a few to 200 times per day. Attacks may occur spontaneously or be provoked by sudden noises, emotion, movement, hyperventilation, or tactile stimulation. The most common symptoms are trigeminal neuralgia and tonic spasms. Paroxysmal dysarthria, ataxia, diplopia, itching, paresthesias, pain, hemifacial spasm, and glossopharyngeal neuralgia are less frequent.

Trigeminal neuralgia occurs in about 2% of MS patients. The character and quality of the pain is usually indistinguishable from idiopathic trigeminal neuralgia. However, trigeminal neuralgia in MS is more likely to involve both sides of the face and is often accompanied by trigeminal neuropathy or other signs of brain stem dysfunction.

Paroxysmal dystonia, or tonic spasms, the second most common movement disorder in MS (only tremor occurs more frequently), are stereotyped, sometimes painful attacks of unilateral dystonic posturing of the limbs. They are occasionally bilateral and rarely involve the face. The attacks last between 30 seconds and 2 minutes and can occur up to 60 times a day. Tonic spasms are probably caused by demyelinating lesions involving the corticospinal tract. However, they are not pathognomonic for MS and are occasionally seen in patients with cerebral ischemia or spinal cord trauma.

Pseudobulbar affect is characterized by episodes of laughing or crying that do not coincide with the individual's emotional state.

This can cause significant emotional distress to both patients and caregivers.

Fatigue is one of the most common and disabling MS symptoms. It is out of proportion to physical activities and is typically worse in the afternoon. Fatigue may precede the first clinical demyelinating event by months or years in one-third of patients. The etiology of MS-related fatigue is poorly understood. No association exists between fatigue and disease course; disability; brain volume; or MRI lesion load, location, or activity.

Bladder dysfunction, which can result in failure to store or empty urine, or a combination of the two, affects approximately 75% of patients. In 15%, symptoms are severe enough to prevent the patients from leaving home or attending social activities. Demyelinating lesions above the level of the pons may result in detrusor hyperreflexia with uninhibited bladder contractions, which causes urinary urgency that is often accompanied by frequency, nocturia, and urge incontinence. Lesions involving the reticulospinal pathways above S2 and below the pons may also lead to involuntary bladder contractions or cause simultaneous contraction of the bladder wall and urethra, a condition known as *detrusor-sphincter dyssynergia*. Patients with detrusor-sphincter dyssynergia have storage and emptying dysfunction and a combination of urgency, frequency, difficulty initiating voiding, incomplete emptying, and incontinence. Damage to the upper urinary tract and kidneys as a result of increased intravesicular pressure is rare. Hypocontractility and failure of the bladder to empty properly occurs with demyelination of the lower sacral anterior horn cells. Complete inability to void is uncommon.

Bowel dysfunction often coexists with bladder dysfunction and is present in up to 70% of patients. Constipation, which may be caused by immobility, decreased fluid intake, or medication side effects (especially those used to treat bladder dysfunction), is common.

Sexual dysfunction is present in up to 90% of patients. It is most likely to occur in progressive MS but affects up to two-thirds of patients with relapsing–remitting disease. The most common symptoms among men are erectile and ejaculatory dysfunction. Women have difficulties achieving orgasm, decreased vaginal lubrication, and reduced vaginal sensation. Both men and women may have reduced libido. Physiologic (e.g., fatigue, weakness, spasticity, pain, hypesthesia) and psychological factors (e.g., depression, anxiety about bladder and bowel dysfunction) may interfere with sexual activity. Many of the medications commonly used to treat other MS symptoms, including anticholinergics, antidepressants, and baclofen, can adversely affect sexual function.

Depression is clearly the most common affective disorder in MS with a lifetime prevalence of 50% before age 60 years. Some patients experience depressive symptoms but do not meet diagnostic criteria for major depression. The etiology of depression is likely multifactorial with psychosocial and biologic factors contributing to such a high frequency. There is concern that the β-interferons may cause or exacerbate depression. Episodes of major depression may occur during periods of exacerbations, remission, or disease progression. Although much less common than depression, bipolar disorder, anxiety, pseudobulbar affect, and euphoria are also prevalent in patients with MS.

Cognitive impairment occurs in up to 65% of patients with MS. Short-term memory, attention, concentration, verbal intelligence, visuospatial skills, and information processing are the domains most commonly affected. Disturbances of language and immediate and long-term memory occur less frequently. Disability and disease duration are generally poor predictors of cognitive dysfunction, which can occur early in the course of MS. However, cognitively impaired patients have more lesions, more severe tissue

damage, and smaller brain volumes than unimpaired patients as measured by conventional and nonconventional MRI techniques. Changes detected by magnetization transfer imaging in normal-appearing brain tissue may have a stronger correlation with cognitive dysfunction than T1 or T2 lesion load.

In most patients, cognitive dysfunction is subtle and goes undetected in the neurologist's office. The Mini-Mental State Examination is not useful because it may fail to identify nearly 75% of MS patients deemed to be cognitively impaired by detailed neuropsychological testing.

Approximately 70% of patients experience pain at some time. Pain can occur during an acute exacerbation (e.g., ocular pain with optic neuritis or dysesthesias with demyelinating plaques involving spinal cord), but almost half of MS patients have chronic pain. It is not a major problem for most, but 20% have severe pain. In addition to painful muscle spasms, paroxysmal phenomena, and the sensory symptoms discussed earlier, MS patients are more likely to have joint, muscular, and extremity pain than age- and sex-matched controls. Many patients also complain of neck and back pain, which may be due to posture or gait abnormalities.

Disease Course

No biologic markers or MRI features distinguish the several forms of MS. The current classification system is based on consensus and relies on the clinical course (Fig. 69.1). Appropriate classification

FIGURE 69.1 The course of MS has been divided into four subtypes based on consensus of specialists. Most patients begin with a relapsing–remitting course (RRMS). Many of these eventually follow a secondary progressive pattern (SPMS). Approximately 10% to 15% of patients have primary progressive disease (PPMS), whereas the progressive relapsing form (PRMS) is very uncommon. The *top two lines* show that disease is labeled as RRMS irrespective of whether recovery from relapses is complete (*first line*) or incomplete (*second line*), as long as a stable baseline is reestablished. The *next two lines* demonstrate that disease is called *secondary progressive multiple sclerosis* irrespective of whether relapses continue, as long as the disease is gradually worsening either between attacks or in the absence of attacks. The *next two lines* show that disease may steadily worsen (*first line*) or there may be periodic plateaus (*second line*). The *bottom line* shows progression from onset followed by the development of relapses. (Reprinted with permission from Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology*. 1996;46:907–911.)

of patients is imperative for appropriate treatment with the disease-modifying drugs (see the following text).

Relapsing–remitting MS is the initial form of the disease in 85% to 90% of patients. It is characterized by acute relapses interspersed with clinical remissions. Symptoms from a relapse typically evolve over several days to a week before reaching a nadir. Recovery is variable, but approximately 40% of relapses result in persistent neurologic deficit and patients may accumulate disability in a stepwise fashion. When left untreated, most patients with relapsing–remitting MS ultimately enter the secondary progressive phase of MS, which is characterized by gradual deterioration with or without occasional superimposed relapses.

Ten percent to 15% of patients have primary progressive MS, which is characterized by continuous and usually gradual deterioration of neurologic function (e.g., a slowly progressive monoparesis). There may be plateaus and slight fluctuations, but relapses do not occur. Fifteen percent to 40% of patients who start with the primary progressive form later have an acute relapse, which may not occur for many years after the original symptoms. This type of MS is referred to as *progressive relapsing multiple sclerosis* and is the least common form.

Different mechanisms may be responsible for symptomatic worsening. An inflammatory component may result in relapses, whereas neurodegeneration may be responsible for progressive disease.

Pregnancy

Pregnancy is protective in MS, particularly during the third trimester when there is a 70% reduction in the annualized relapse rate compared with the year prior to pregnancy. However, when MS is left untreated, about 30% of women have a relapse in the first 3 months postpartum before the risk returns to the prepregnancy rate 4 to 6 months after delivery. These effects may be the result of changes in Th1 and Th2 immune responses mediated by estriol or vitamin D, both of which are markedly elevated during the final trimester of pregnancy and fall abruptly after delivery; other hormonal changes that occur during pregnancy may also play a role.

Women with relapses during pregnancy or in the year prior to pregnancy are more likely to have a relapse in the first 3 months postpartum than women without relapses during these periods, but it is impossible to accurately predict who will have a relapse. In an uncontrolled study, intravenous immunoglobulin (IVIG) ameliorated the increased risk of postpartum exacerbations. However, the results of a subsequent randomized, double-blind trial were not as encouraging. Furthermore, there is now good evidence from well-designed, large, placebo-controlled trials that IVIG is an ineffective therapy for relapsing–remitting and secondary progressive MS. Breastfeeding does not affect the postpartum course of MS.

Vaccination

Infections, including minor upper respiratory infections, increase the risk of MS exacerbations. Strategies that minimize the risk of infection should be incorporated. Concerns that vaccinations may trigger MS exacerbations are based on anecdotes. However, a prospective, randomized, double-blind, placebo-controlled trial, showed that influenza immunization does not increase the risk of relapse or disease progression and patients should be routinely vaccinated. Hepatitis B, tetanus, and varicella vaccines appear to be safe in MS patients. There are few data regarding the safety of other vaccines in MS, but patients who meet the CDC guidelines should be advised to have them. Patients treated with fingolimod or mitoxantrone should not receive live attenuated vaccines, as there is some risk of developing the infection the vaccine is meant to prevent, or they may have an

attenuated response to the vaccination. It is probably best to delay immunizations for 4 to 6 weeks in the setting of an MS relapse because the goal of relapse management is to diminish the immune system's reactivity, and vaccination has the opposite effect.

DIAGNOSIS

The diagnosis of MS is established based on clinical criteria usually in combination with MRI. Examination of the CSF may be helpful. However, no single test result is pathognomonic of MS.

Imaging

Brain MRI abnormalities are present in more than 95% of recently diagnosed MS patients. Five to 10 new or enlarging gadolinium-enhancing or T2 brain lesions are identified for every one clinical exacerbation in patients with relapsing MS. Spinal cord lesions are detected by MRI in 75% to 90% of those with established MS.

Fifty percent to 70% of clinically isolated syndrome patients have asymptomatic T2 brain lesions, and 27% to 42% have clini-

cally silent spinal cord lesions. However, conventional MRI lacks pathologic specificity, and areas of edema, demyelination, axonal damage, gliosis, and remyelination all appear as T2 hyperintensities. Furthermore, there is poor correlation between disability and T2-weighted abnormalities. Nonconventional MRI techniques, including diffusion tensor imaging, magnetic transfer imaging, and proton magnetic resonance spectroscopy (MRS), have more pathologic specificity than conventional MRI and can detect and quantify tissue damage within visible T2 lesions and normal-appearing brain tissue. These techniques may enhance the ability to monitor disease evolution and understanding of the mechanisms that lead to irreversible disability.

On T2-weighted imaging, brain lesions are typically 3 to 15 mm in diameter, round or ovoid, and located in the periventricular white matter, corpus callosum, centrum semiovale, juxtacortical regions, pons, floor of the fourth ventricle, cerebellar peduncles, or cerebellar hemispheres (Figs. 69.2 and 69.3). Larger lesions in the cerebral hemispheres associated with mass effect, edema, or ring enhancement, which resemble tumors and are known as
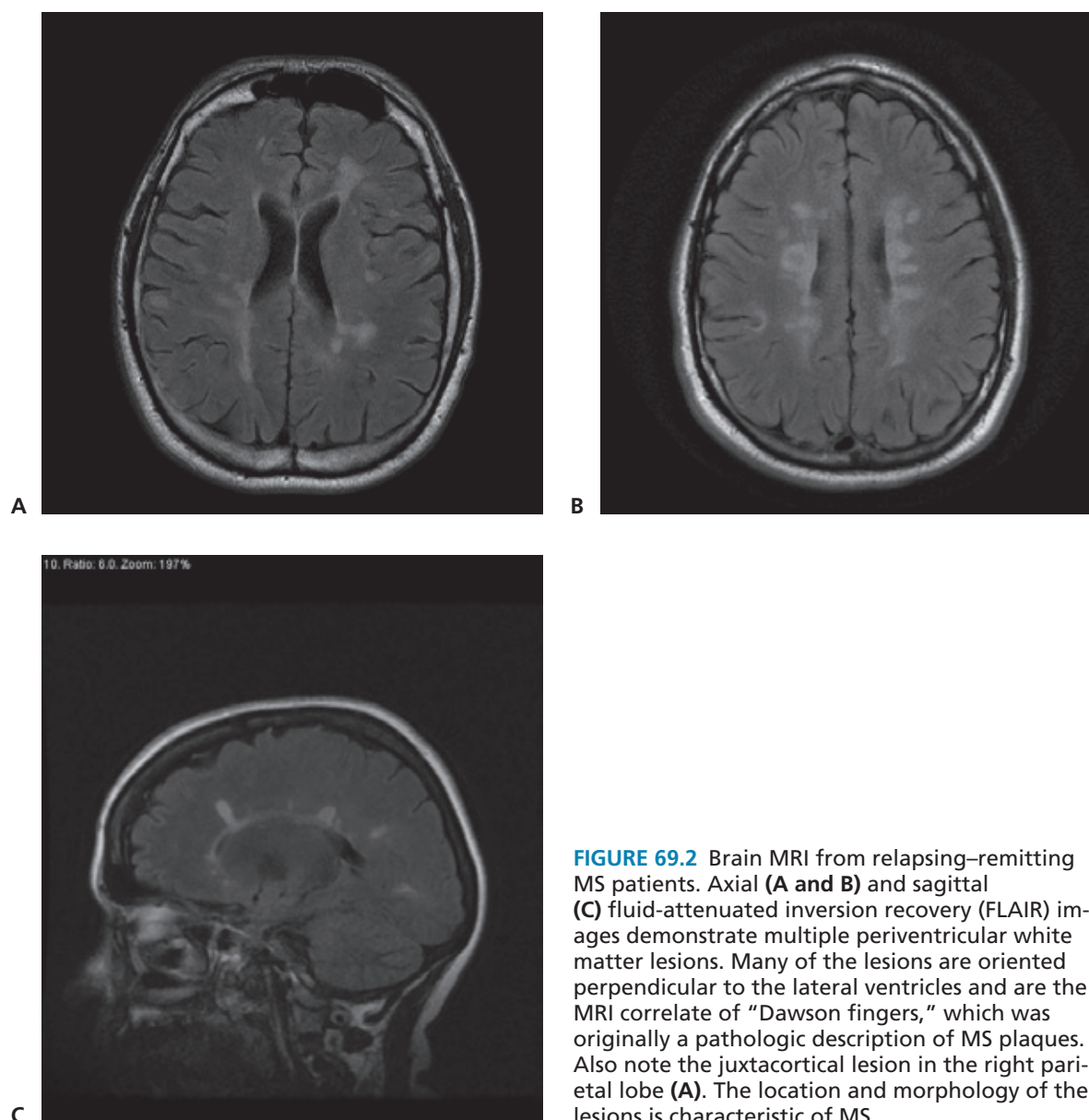

FIGURE 69.2 Brain MRI from relapsing–remitting MS patients. Axial **(A and B)** and sagittal **(C)** fluid-attenuated inversion recovery (FLAIR) images demonstrate multiple periventricular white matter lesions. Many of the lesions are oriented perpendicular to the lateral ventricles and are the MRI correlate of "Dawson fingers," which was originally a pathologic description of MS plaques. Also note the juxtacortical lesion in the right parietal lobe **(A)**. The location and morphology of the lesions is characteristic of MS.
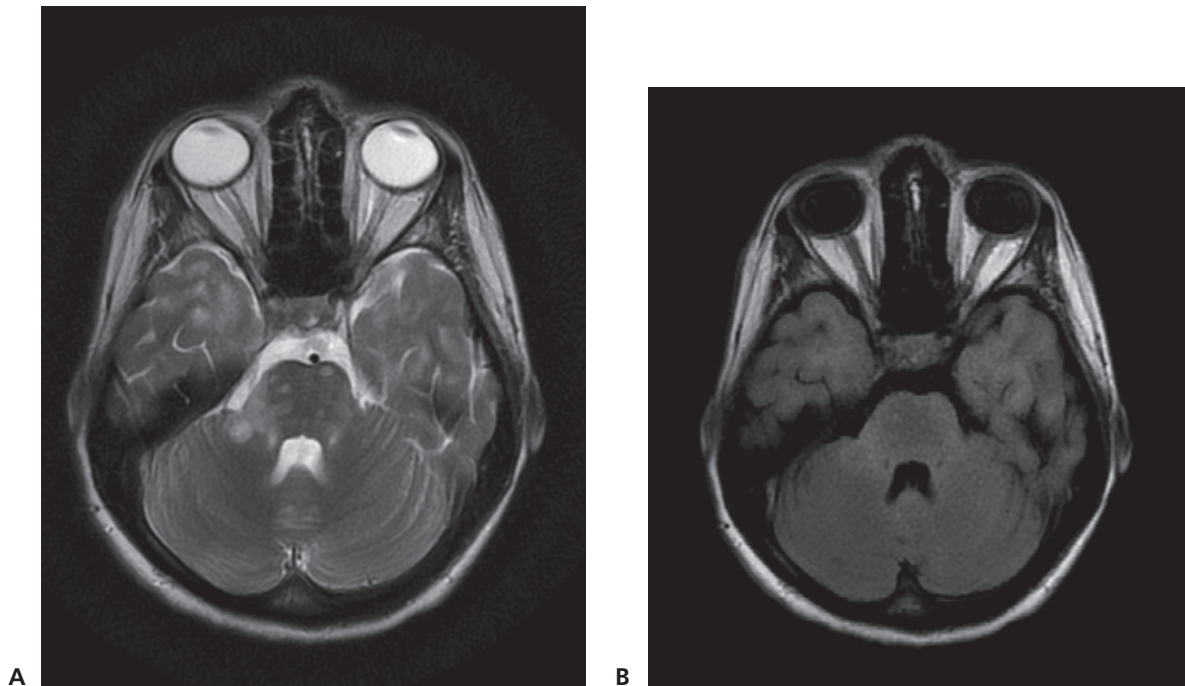
FIGURE 69.3 Brain MRI of the posterior fossa in an MS patient. An axial T2-weighted image **(A)** reveals multiple infratentorial lesions consistent with MS. The lesions are not well visualized on the FLAIR image **(B)**. Although FLAIR is a more sensitive sequence than T2 for demonstrating supratentorial lesions, it is suboptimal for detecting infratentorial lesions.

tumefactive lesions, are occasionally observed (Fig. 69.4). Cortical lesions are not well visualized by standard MRI techniques.

In patients with relapsing MS, gadolinium enhancement, which represents active inflammation and disruption of the blood–brain barrier, is the earliest phase of lesion development seen on conventional MRI (Fig. 69.5). Almost all new brain T2 lesions demonstrate enhancement on postgadolinium T1-weighted imaging, and 65% to 80% are hypointense on the corresponding pregadolinium T1-weighted sequence. Gadolinium enhancement typically resolves after 2 to 4 weeks. Persistent enhancement raises
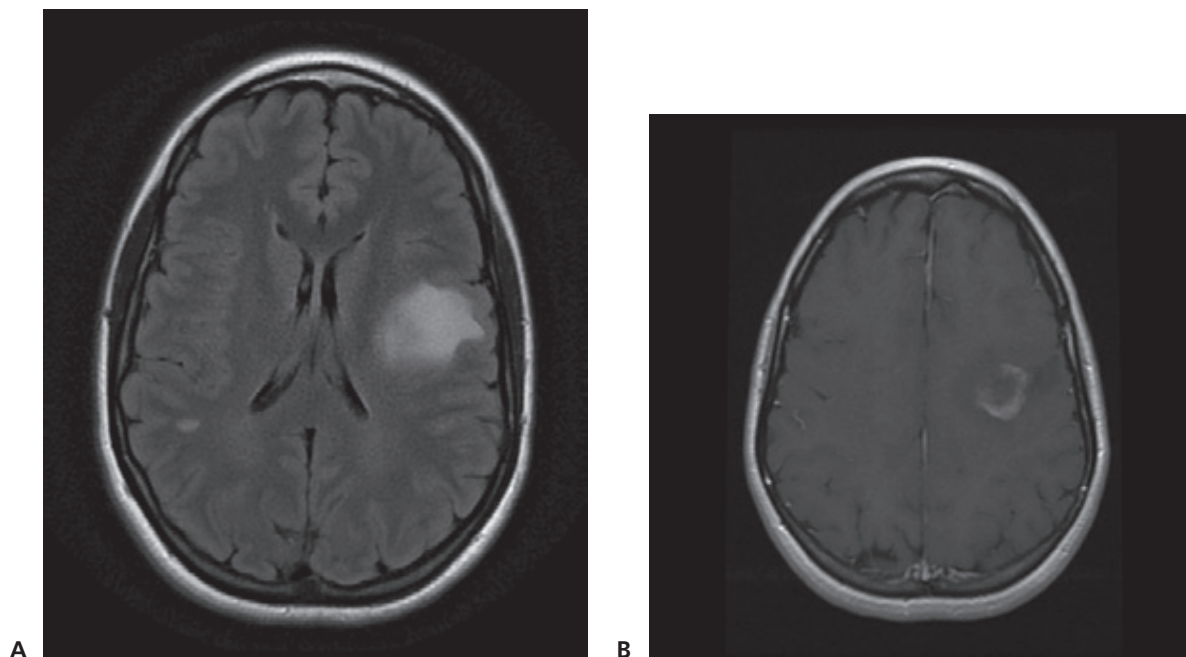

FIGURE 69.4 Brain MRI from a patient with relapsing–remitting MS. Axial FLAIR **(A)** and postgadolinium T1-weighted **(B)** images reveal a large ring-enhancing mass-like lesion with surrounding vasogenic edema in the left hemisphere. There is also a much smaller nonenhancing lesion in the right hemisphere. The findings are consistent with tumefactive MS.
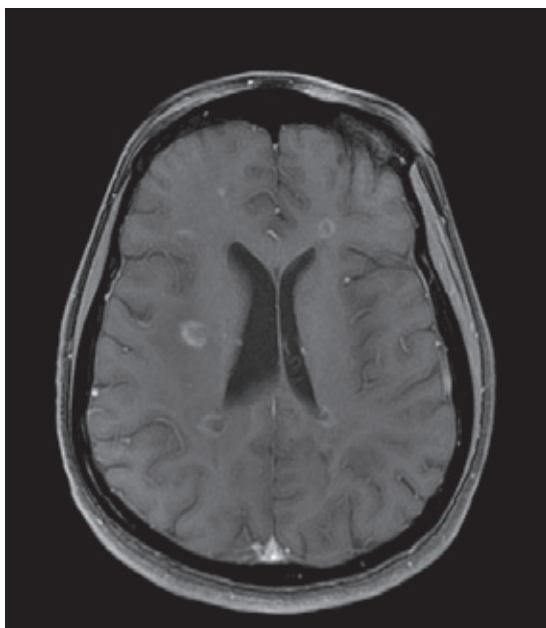
FIGURE 69.5 Brain MRI from a relapsing–remitting MS patient. A postcontrast T1-weighted image reveals multiple gadolinium-enhancing lesions. Gadolinium enhancement, which represents disruption of the blood–brain barrier and active inflammation, is the earliest phase of lesion development that can be detected on conventional MRI.

the possibility of neurosarcoidosis or neoplasm because only 3% to 5% of MS lesions enhance for more than 8 weeks. T2 lesions may become smaller, but they rarely disappear, whereas the majority of T1-hypointense lesions become isointense in 6 to 12 months, presumably as a result of resolution of edema and remyelination. However, 30% to 45% of hypointense lesions remain hypointense

and are called *chronic black holes* (Fig. 69.6). Chronic black holes represent areas of extensive demyelination and axonal damage and have a much better correlation with disability than T2 lesions, especially in patients with secondary progressive MS.

Spinal cord lesions are more common in the cervical than thoracic spine, appear hyperintense on T2-weighted imaging, and have a predilection for the white matter in the lateral and posterior columns. Adjacent gray matter is commonly involved. Lesions typically occupy less than half of the cross-sectional area of the cord and extend fewer than two vertebral segments (Fig. 69.7). Hypointense lesions on T1-weighted spinal cord MRI are uncommon in MS patients. Unlike gadolinium-enhancing brain lesions, active spinal cord lesions are frequently accompanied by clinical symptoms. However, asymptomatic spinal cord lesions are also common. Clinically silent spinal cord lesions are particularly useful for diagnosing MS in patients with vague neurologic symptoms and nonspecific findings on brain MRI because intramedullary cord lesions are rare in healthy people.

In general, relapsing–remitting MS patients have more gadolinium-enhancing lesions than those with progressive disease. Patients with secondary progressive MS tend to have more chronic black holes than those with the relapsing–remitting or primary progressive disease. Primary progressive MS patients are more likely to have few T2 brain lesions and diffuse spinal cord abnormalities. However, MRI characteristics are not diagnostic of the subtypes of MS—these remain clinically based.

Biomarkers

Examination of the CSF can aid in the diagnosis of MS and helps to exclude alternative diagnoses. CSF contains fewer than six white blood cells (WBCs) per cubic millimeter and normal protein content in most patients with a clinically isolated syndrome or established MS. A mild lymphocytic pleocytosis or elevated protein level is seen in about 35%. More than 50 WBCs per cubic millimeter or a protein content over 100 mg/dL are rarely observed and raise the possibility of an alternative diagnosis.
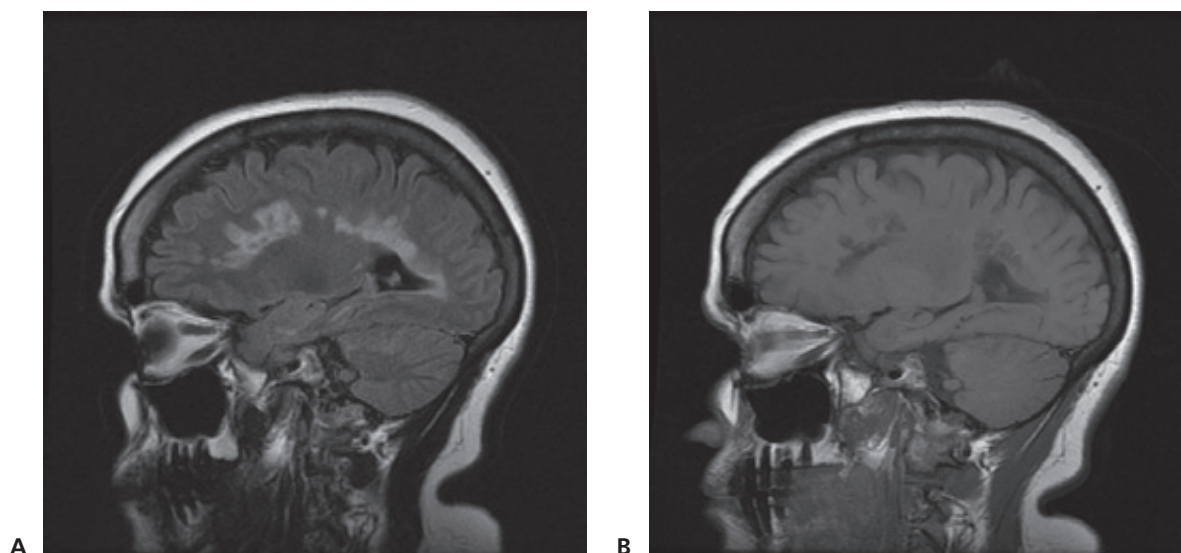

FIGURE 69.6 Brain MRI from a patient with secondary progressive MS. A sagittal FLAIR image **(A)** reveals multiple periventricular white matter lesions consistent with MS. Note that many of the lesions are hypointense on the pregadolinium T1-weighted image **(B)**. Persistent T1-hypointense lesions ("black holes") represent areas of significant demyelination and axonal damage and have a stronger correlation with disability than T2-hyperintense lesions, especially in patients with secondary progressive MS.
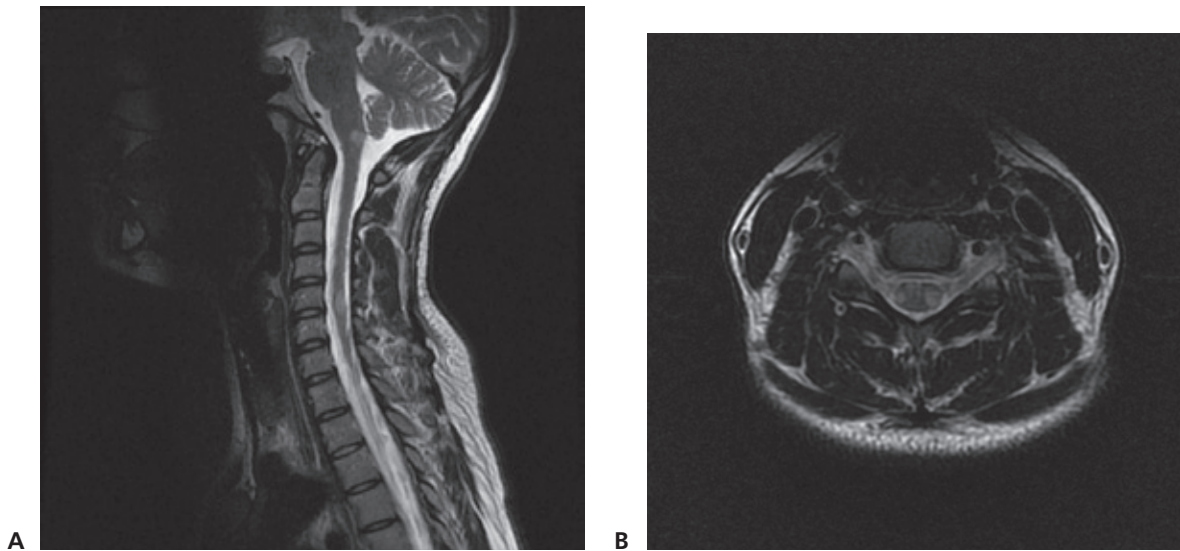
FIGURE 69.7 Cervical spine MRI from a relapsing–remitting MS patient. Axial **(A)** and sagittal **(B)** T2-weighted images reveal intramedullary lesions at C5–C6 consistent with demyelination. Also note the lesion at the cervicomedullary junction.

CSF immunoglobulin abnormalities are common. The immunoglobulin (Ig) G index, which measures intrathecal production of IgG, is elevated in 70% to 85% of MS patients. Isoelectric focusing followed by immunoblotting detects oligoclonal bands (OCBs) in more than 95% of patients (two or more bands detected in the CSF that are not present in the serum are considered abnormal). Unfortunately, many U.S. clinical laboratories use older and less sensitive methods to identify OCBs. Treatment with corticosteroids lowers the IgG index but has no effect on OCBs. An elevated IgG index and the presence of OCBs are not restricted to MS and are observed in 20% to 40% of patients with other inflammatory, demyelinating, or infectious diseases and occasionally other neurologic disorders, including the Guillain–Barré syndrome and other peripheral neuropathies. Therefore, CSF abnormalities should always be considered in conjunction with the clinical and MRI findings.

A single immunoglobulin band restricted to the CSF is of unclear significance and may be found in healthy individuals, as well as a variety of illnesses, including clinically isolated syndromes, MS, infectious and inflammatory diseases, CNS lymphoma, peripheral neuropathy, or migraine headaches. However, when the CSF is reexamined after an average of 6 months, one-third of patients, the majority of whom have demyelinating disease, show a change from a monoclonal to oligoclonal pattern.

A high CSF level of myelin basic protein indicates damage to myelin and is not useful in differentiating MS from other illnesses, including cerebrovascular disease, infections, neoplasms, or inflammatory diseases.

Visual-evoked potentials (VEPs) are sensitive for detecting clinically silent lesions in the anterior visual pathways although they are no longer included in the MS diagnostic criteria. VEPs are abnormal (prolonged P100 latency or greater than 6 milliseconds interocular difference if the latencies are normal) in approximately 30% of patients with clinically isolated syndromes other than optic neuritis and more than 50% of MS patients without a history of visual symptoms or clinical evidence of optic nerve dysfunction. However, abnormal VEPs may be observed in patients with other disorders, including compressive lesions of the optic nerve or chiasm, glaucoma, retinal disease, vitamin B_{12} deficiency, infectious

diseases (e.g., neuroborreliosis, neurosyphilis), systemic lupus erythematosus (SLE), and neurosarcoidosis.

VEPs are prolonged in almost all patients with a recent episode of optic neuritis, and routine testing for diagnostic purposes is not indicated. However, latencies shorten (presumably as a result of remyelination or ion channel reorganization) between 3 months and 2 to 3 years after acute optic neuritis and return to normal in about 25% of patients, so normal responses do not exclude the possibility of prior optic neuritis. Multifocal VEPs, which simultaneously record responses from multiple regions of the visual field are more sensitive than conventional VEPs but are not currently widely available.

MRI has largely supplanted the use of somatosensory and brain stem auditory-evoked potentials, which are rarely useful for identifying patients at increased risk for developing MS and are not included in the MS diagnostic criteria.

Optical coherence tomography (OCT) is a noninvasive technique that uses low-frequency infrared light to measure retinal nerve fiber layer thickness (RNFL) and macular volume. OCT, which has been used by ophthalmologists since 1990 to monitor glaucoma, is now used in MS. Thinning of the RNFL occurs after optic neuritis as a result of loss of retinal axons. The eyes of MS patients without a history of optic neuritis also undergo thinning of the RNFL. OCT is used as a secondary and tertiary outcome measure in clinical trials and by some neurologists and ophthalmologists to follow patients with or without a history of optic neuritis.

Diagnostic Criteria

New MS diagnostic criteria, referred to as the *McDonald criteria* (after the late Ian McDonald), were established in 2001 and revised in 2005 and 2010 (Table 69.2). MRI abnormalities may be used to demonstrate dissemination in space and time, provided an individual has had one episode of neurologic dysfunction consistent with demyelinating disease (see the following text). This has allowed for an earlier diagnosis. Eighty percent of patients diagnosed with MS based on MRI criteria will develop *clinically definite multiple sclerosis* (CDMS), a term formerly used to indicate two clinical demyelinating attacks separated in time and space, within 3 years if they

TABLE 69.2   Multiple Sclerosis Diagnostic Criteria

Clinical Presentation	Additional Data Required for MS Diagnosis
Two or more attacks with objective evidence of two or more lesion on clinical examination or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	None
Two or more attacks with objective evidence of one lesion on clinical examination	Dissemination in space demonstrated by one of the following: a. DIS on MRI[a] b. Second clinical attack
One attack with objective evidence of two or more lesions on clinical examination	Dissemination in time demonstrated by one of the following: a. MRI[b] b. Second clinical attack
One attack with objective evidence of one lesion on clinical examination	Dissemination in space demonstrated by one of the following: a. MRI[a] b. Second clinical attack *and* Dissemination in time demonstrated by one of the following: a. DIT criteria for MRI[b] b. Second clinical attack
Insidious neurologic progression suggestive of MS (i.e., a clinical presentation consistent with primary progressive MS)	One year of disease progression *and* two of the following: a. Dissemination in space in brain according to 2010 McDonald criteria b. Spinal cord MRI with two T2 lesions c. Positive CSF[c]

If all criteria are fulfilled and alternative diagnoses have been excluded, the diagnosis is MS. If there is a suspicion of MS but only some of the criteria are met, the diagnosis is "possible MS."

[a]See Table 69.3 for MRI criteria for dissemination in space.

[b]See Table 69.4 for MRI criteria for dissemination in time.

[c]Positive CSF: two or more oligoclonal bands detected in the CSF that are not present in the serum or an elevated IgG index.

MS, multiple sclerosis; DIS, dissemination in space; MRI, magnetic resonance imaging; DIT, dissemination in time, CSF, cerebrospinal fluid.

Adapted from Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria." *Ann Neurol*. 2011;69:292–302.

are left untreated. Early diagnosis is of great importance because MS disease-modifying drugs seem to be most effective when given early in the disease and a delay in treatment can result in irreversible neurologic damage.

The diagnosis of relapsing–remitting MS requires at least one episode of neurologic dysfunction consistent with inflammation and demyelination occurring in the absence of fever or infection and lasting at least 24 hours along with objective evidence of lesions disseminated in space and time. Dissemination in space may be demonstrated by two anatomically distinct lesions on examination that are consistent with CNS demyelination (e.g., an extensor plantar response and optic atrophy) or a focal lesion on examination along with MRI evidence of dissemination in space (Tables 69.2 and 69.3). In the absence of two clinical attacks, dissemination in time may be demonstrated by subclinical disease evolution on MRI (Table 69.4). The diagnosis of primary progressive MS requires at

TABLE 69.3   Magnetic Resonance Imaging Criteria for Dissemination in Space

T2 lesion in at least two of the four following areas:

- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord

If brain stem or spinal cord lesion is symptomatic, it is excluded from lesion count for DIS.

Adapted from Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria." *Ann Neurol*. 2011;69:292–302.

TABLE 69.4   Magnetic Resonance Imaging Criteria for Dissemination in Time

One of the following:

- One new T2 and/or contrast-enhancing lesion on any follow-up MRI
- Presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any one time

MRI, magnetic resonance imaging

Adapted from Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria." *Ann Neurol*. 2011;69:292–302.

TABLE 69.5   Radiologically Isolated Syndrome

CNS white matter abnormalities meet the following criteria:

- Ovoid well circumscribed and homogeneous foci with or without involvement of corpus callosum
- T2 hyperintensities >3 mm^2 and meeting three of four Barkhof criteria for dissemination in space
- CNS anomalies to not fit vascular pattern

No history of remitting clinical symptoms consistent with neurologic dysfunction

MRI anomalies do not account for clinically apparent impairments

MRI anomalies not related to toxic substances or medical condition

MRI anomalies not better accounted for by another disease

Exclusion of MRI phenotypes of leukoaraiosis or extensive white matter involvement without involvement of corpus callosum

CNS, central nervous system; MRI, magnetic resonance imaging.

Adapted from Okuda D, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology*. 2009;72(9):800–805.

least 1 year of insidious neurologic progression combined with variety of MRI and CSF abnormalities (see Table 69.2).

Characteristic MS lesions are occasionally discovered on MRI in individuals with no history of neurologic symptom and a normal examination. In the absence of clinical evidence of demyelination, even if MRI abnormalities are accompanied by the presence of CSF OCBs, an elevated IgG index, and delayed VEPs, a diagnosis of MS cannot be established. Formal criteria for this, termed *radiologically isolated syndrome*, were established in 2009 (Table 69.5).

DIFFERENTIAL DIAGNOSIS

In the absence of a definite diagnostic test, MS remains a diagnosis of exclusion. Most of the disorders that may mimic MS can be excluded by a detailed history, thorough examination, and appropriate laboratory tests and diagnostic studies.

Infections that may mimic MS include neuroborreliosis, neurosyphilis, and rarely progressive multifocal leukoencephalopathy. Human T-lymphotropic virus type-1 (HTLV-1) and HIV should be considered in patients with a progressive myelopathy. Acute disseminated encephalomyelitis may be impossible to distinguish from a first attack of MS. However, it is more likely to follow an infection or vaccination; more common in children; and generally includes encephalopathy, which is a rare manifestation of MS. Although patients with sarcoidosis may initially present with neurologic symptoms, evaluation usually reveals evidence of systemic sarcoidosis. Other autoimmune diseases that should be considered include Behçet syndrome, Sjögren syndrome, SLE, vasculitis, and the antiphospholipid antibody syndrome. Susac syndrome is an autoimmune microangiopathic endotheliopathy that affects brain, retina, and cochlea and results in encephalopathy, hearing loss, and branch retinal artery occlusions. It may be mistaken for MS because of prominent white matter lesions that are observed on brain MRI. Drug-induced demyelination is a strong possibility in patients with Crohn disease or rheumatoid or psoriatic arthritis treated with antitumor necrosis factor therapies. NMO and the NMO spectrum of disorders may be difficult to distinguish from MS, particularly early in the disease, in patients with recurrent optic neuritis and minimally abnormal brain MRI, or in patients with brain MRI findings more characteristic of MS. NMO-IgG seropositivity may help differentiate the diseases. Neoplasms (especially primary CNS lymphoma and gliomas) occasionally enter the differential diagnosis. Hyperacute onset of symptoms suggests stroke. Primary lateral sclerosis may simulate primary progressive MS but does not relapse and is monosymptomatic. MRI and CSF analysis usually help differentiate the two diseases. Hereditary spastic paraparesis should be considered in patients with a progressive spastic paraparesis, especially if there is a family history of similar illness. Other causes of a progressive myelopathy that should be considered in patients suspected of having progressive MS include adrenomyeloneuropathy, vitamin B_{12} deficiency, copper deficiency, spondylotic myelopathy, spinal cord tumors, and a spinal dural arteriovenous fistula.

TREATMENT

Therapy for MS consists of treatment of acute exacerbations, disease-modifying drugs, and symptomatic therapies. Optimal management often requires a multidisciplinary approach with pharmacologic and nonpharmacologic measures.

Treatment of Acute Exacerbations

High-dose intravenous (IV) corticosteroids hasten recovery from acute exacerbations but do not seem to affect the degree of recovery. A typical regimen consists of a 3- to 5-day course of 1,000 mg of IV methylprednisolone with or without an oral prednisone taper. Some patients with severe attacks seem to respond better to an additional 2 to 5 days of treatment. Because treatment does not seem to affect long-term outcome, not every MS exacerbation (e.g., mild sensory symptoms) requires treatment. In the Optic Neuritis Treatment Trial, patients who received oral prednisone 1 mg/kg/day did not improve any faster than the placebo-treated group. Furthermore, treatment with oral prednisone was associated with an increased risk of subsequent optic neuritis. Therefore, there does not appear to be a role for low-dose oral corticosteroids in the treatment of MS acute exacerbations [**Level 1**].[1]

Fever and infections, including asymptomatic urinary tract infections, can cause transient worsening of MS symptoms without a corresponding worsening of the underlying disease. This is known as a *pseudoexacerbation*. Infections should be excluded in the setting of new or worsening symptoms before treatment with corticosteroids is initiated and fevers should be treated aggressively.

Plasma exchange may be warranted for the treatment of acute relapses that result in significant residual disability despite high-dose IV corticosteroid therapy. In a small, but well-designed study, 42% of patients with severe demyelinating events that did not respond to high-dose IV corticosteroids had marked functional improvement after seven plasma exchanges. Patients who responded were treated an average of more than 40 days after the onset of symptoms. The investigators of a larger retrospective study reported similar results and concluded that plasma exchange may be effective when initiated more than 60 days after the onset of an acute demyelinating event.

Disease-modifying Drugs

The β-interferons and glatiramer acetate are commonly used relapsing–remitting MS therapies. They are modestly effective in reducing relapses and have positive effects on a variety of disability and MRI measures [**Level 1**].[2–6] Studies have also shown that these agents are effective (and possibly even more so) when initiated at the time of an initial clinical demyelinating event in patients with

at least two or three asymptomatic brain lesions (i.e., prior to an MS diagnosis), and delaying treatment results in irreversible neurologic deficit [**Level 1**].[7–10] The interferons and glatiramer acetate clearly alter the short-term course of MS. Anecdotes along with retrospective and prospective open-label studies suggest a long-term treatment benefit, but controlled studies are lacking.

In head-to-head studies, the clinical effectiveness of glatiramer acetate was similar to the high-dose interferons (i.e., interferon β-1b 250 μg administered subcutaneously every other day and interferon β-1a 44 μg administered subcutaneously thrice weekly) in patients with relapsing–remitting MS.

The advent of oral therapies for relapsing MS, with the U.S. Food and Drug Administration (FDA) approval of fingolimod in 2010, followed by teriflunomide and dimethyl fumarate in 2012 and 2013, respectively, dramatically increased the options, with 10 therapies approved for the most common form of MS as of 2014. Table 69.6 summarizes available therapies for relapsing forms of MS.

The therapeutic effects of interferon may be due to its antiproliferative action, downregulation of costimulatory molecules, decrease of proinflammatory cytokines, or through effects on matrix metalloproteinases and adhesion molecules, which reduce the permeability of the blood–brain barrier and limit trafficking of T lymphocytes into the CNS. The beneficial effects of glatiramer acetate, a synthetic polypeptide composed of the four amino acids L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, may result

TABLE 69.6	Overview of Disease-Modifying Therapies for Relapsing Forms of Multiple Sclerosis		
Treatment	**Dosage**	**Potential Side Effects**	**Monitoring**
IFNβ-1b	250 μg SC q.o.d.	Flulike symptoms	CBC
IFNβ-1a	30 μg IM q.wk.	LFT abnormalities	LFTs
IFNβ-1a	22 μg or 44 μg SC t.i.w.	Leukopenia	TFTs
		Neutralizing antibodies	
		Depression	
		Injection site necrosis (rare)	
Glatiramer acetate	20 mg SC daily or 40 mg SC t.i.w.	Site reactions Lipoatrophy Immediate postinjection reactions	None
Mitoxantrone	12 mg/m^2 IV q12wk	Heart failure Promyelocytic leukemia Bone marrow suppression Alopecia	MUGA scan annually after completion, assess ejection fraction prior to each dose. CBC Lifetime maximum dose: 140 mg/m^2
Natalizumab	300 mg IV q4wk	Progressive multifocal leukoencephalopathy LFT abnormalities Hypersensitivity reaction	JCV Ab MRI brain LFTs
Fingolimod	0.5 mg PO daily	Bradycardia at first dose LFT abnormalities Lymphopenia Macular edema Reactivation of herpes virus (zoster, oral or genital herpes)	First-dose observation with ECG before and 6 h after dosing and hourly vital signs, VZV immunity, baseline macula exam with follow-up eye exam 3–4 mo after initiation
Teriflunomide	7 mg or 14 mg PO daily	Gastrointestinal side effects Hair thinning LFT abnormalities (black box warning: hepatic failure) Hypertension Tuberculosis reactivation	Monthly LFTs for 6 mo after starting treatment Quantiferon gold or TB skin test
Dimethyl fumarate	240 mg PO b.i.d.	Gastrointestinal upset Flushing LFT abnormalities Lymphopenia	CBC with differential LFT

IFNB, interferon β; SC, subcutaneous; IM, intramuscular; LFT, liver function test; CBC, complete blood count; TFT, thyroid function test; IV, intravenous; MUGA, multigated acquisition; JCV, John Cunningham virus; MRI, magnetic resonance imaging; ECG, electrocardiogram; VZV, varicella-zoster virus; PO, by mouth.

from reactive Th2 cells that cross the blood–brain barrier and increase the secretion of suppressor-type cytokines and downregulate inflammatory activity within the CNS, a process known as *bystander suppression*.

Natalizumab is a humanized monoclonal antibody that is highly effective for reducing relapse rate and new T2 and contrast-enhancing lesions on MRI in relapsing MS [**Level 1**].[11,12] However, because it is associated with a low risk of progressive multifocal leukoencephalopathy (PML), it is used in conjunction with antibody testing for John Cunningham virus to predict risk of PML. Natalizumab likely exerts its therapeutic effects by blocking the binding of the α4-subunit of $\alpha 4\beta 1$ integrin expressed on the surface of activated T cells with its receptor vascular cell receptor molecule-1 (VCAM-1) on the vascular endothelial surface at the blood–brain barrier. The interaction between α4 and VCAM-1 is critical in order for T cells to gain access into the CNS.

Fingolimod is a functional antagonist of the sphingosine 1 phosphate receptor, which prevents egress of lymphocytes from peripheral lymph nodes. Reduction in relapse rate and MRI outcomes was significant compared to placebo and to weekly intramuscular interferon β-1a in two large randomized, double-blind, placebo-controlled trials [**Level 1**].[13,14] Teriflunomide is a pyrimidine synthesis inhibitor, which slows expansion of activated lymphocytes. Modest efficacy in relapse rate reduction as well as reduction in sustained disability production was shown in large double-blind placebo-controlled trials [**Level 1**].[15,16] Dimethyl fumarate is a fumaric acid ester shown to be effective in reducing relapse frequency and MRI activity in relapsing forms of MS [**Level 1**].[17,18] Mechanism of action is hypothesized to be related to scavenging free radicals and acting through modulation of NF-kB and Nrf2 pathways.

Initial treatment decisions should be individualized and based on a combination of efficacy, route of administration, and potential side effects particularly related to concomitant medical issues.

Neutralizing antibodies (NAbs) develop in 15% to 25% of patients treated with interferon β-1a 44 μg subcutaneously three times a week and 25% to 40% treated with interferon β-1b. Interferon β-1a 30 μg administered intramuscularly is clearly less immunogenic with NAbs occurring in only 2% of patients. NAbs typically develop between 6 and 18 months after the initiation of treatment and only rarely after more than 2 years of therapy. Although they may be transient, persistent high-titer NAbs (>100 NU/mL) are associated with a reduced therapeutic effect. Six percent of patients develop persistent anti-natalizumab antibodies, which are associated with a clear loss of efficacy and an increased risk of infusion-related hypersensitivity reactions.

Secondary progressive MS is more difficult to treat than the relapsing–remitting form of the disease. The high-dose interferons and a double dose of once-weekly intramuscular interferon β-1a reduce the number of relapses and MRI activity but do not have a consistent effect on disability progression. Patients with superimposed relapses, gadolinium-enhancing lesions, or rapidly accumulating disability may be most likely to respond to treatment. In a small study, glatiramer did not prevent progression of disability in patients with primary or secondary progressive MS.

Periodic pulses of IV methylprednisolone are not effective in preventing disability in patients with secondary progressive MS. However, in one study of patients with mild relapsing–remitting MS, they had a favorable effect on disability, brain atrophy, and T1-hypointense lesions.

Mitoxantrone is an anthracenedione with immunosuppressive and immunomodulatory properties and the only FDA-approved therapy for secondary progressive MS. However, its effects are modest and safety is a concern, so risks and benefits need to be carefully considered before treatment is initiated. Mitoxantrone is also effective in highly active relapsing MS. Six monthly infusions of 20 mg of mitoxantrone combined with 1 g of IV methylprednisolone dramatically reduce gadolinium-enhancing brain lesions and seem to decrease relapses and disability in patients with rapidly worsening relapsing–remitting and secondary progressive MS and active brain MRI.

There are no proven therapies for primary progressive MS. Mitoxantrone and interferon appear to be ineffective. Glatiramer acetate was evaluated in a large clinical trial, but the study was stopped prematurely because of futility. A trial with rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B cells, also yielded negative results. However, post hoc analyses of the two studies suggest that glatiramer acetate may be beneficial in men and a possible treatment effect with rituximab in several subgroups, including patients younger than age of 51 years and in those with baseline gadolinium-enhancing lesions.

Symptom Management

Therapies to alleviate the daily symptoms of MS are integral part of patient care. Successful treatment often involves a combination of pharmacotherapy with nonpharmacologic measures, such as rehabilitation, exercise, or lifestyle and environmental modifications. See Table 69.7 for an overview of symptomatic management of common MS symptoms.

Management of spasticity includes evaluation and treatment of potentially exacerbating factors. Once exacerbating factors are minimized, a combination of physical therapy interventions and pharmacologic management is optimal. The most commonly used agents are baclofen and tizanidine alone or in combination. Common adverse effects of baclofen include limb weakness, sedation, and confusion. At higher doses, weakness may negate the benefit of spasticity reduction. Abrupt discontinuation of baclofen can result in seizures, confusion, hallucinations, and a marked increase in muscle tone. The use of tizanidine is mainly limited by drowsiness. Increased weakness is usually not a problem. Gabapentin may also be effective. The use of benzodiazepines has largely been supplanted by baclofen and tizanidine, which are better tolerated. Botulinum toxin may be effective for focal spasticity. Intrathecal baclofen may be beneficial for patients with severe leg spasticity that does not respond to oral agents at the highest tolerable dose.

Occupational and physical therapy are the mainstays of treatment for motor impairment. The potassium channel blocker dalfampridine, which is a sustained release formulation of 4-aminopyridine, enhances conduction across demyelinated nerve fibers. It improved leg strength and walking speed in some patients with relapsing and progressive forms of MS in two therapeutic trials. Dalfampridine increases the risk of seizures, especially at higher doses, and is contraindicated in those with history of seizures or impaired kidney function. The risk of seizure appears to be low with the effective dose of dalfampridine, which is 10 mg twice daily [**Level 1**].[19]

Depression responds well to psychotherapy and antidepressants, alone or in combination. Amitriptyline is effective for pseudobulbar affect (pathologic laughing or crying), as is a mixture of dextromethorphan and quinidine [**Level 1**].[20]

To date, there is no clearly effective treatment for MS-related cognitive impairment. Some patients may benefit from cognitive remediation and strategies to compensate for deficits. Donepezil improved memory in one small, controlled trial in MS patients

TABLE 69.7 **Management of Multiple Sclerosis Symptoms**

Symptom	Nonpharmacologic Approaches	Pharmacologic Approaches (Starting Dosage)
Spasticity	Physical and occupational therapy	Baclofen (oral 10 mg t.i.d. or intrathecal)
	Exercise	Tizanidine (4 mg q.h.s.)
	Evaluation of aggravating factors which may include the following:	Benzodiazepines (varies)
		Botulinum toxin
	• Urinary tract infection	Gabapentin (300 mg t.i.d.)
	• Decubitus ulcers	
	• Pain	
	• Constipation	
	• Tight-fitting garments	
	• Interferon β	
Weakness	Physical and occupational therapy	Dalfampridine (10 mg b.i.d.)
Depression	Psychotherapy	Selective serotonin reuptake inhibitors
	Support groups	Serotonin–norepinephrine reuptake inhibitors
Pseudobulbar affect	Psychotherapy to manage triggers	Dextromethorphan/quinidine (20/10 mg b.i.d.)
		Amitriptyline (10 mg q.h.s.)
Fatigue	Improve sleep habits	Amantadine (150 mg b.i.d.)
	Energy conservation techniques	Modafinil (100 mg q.d.)
	Evaluation of other causes of fatigue including the following:	Armodafinil (150 mg q.d.)
	• Anemia	Methylphenidate (10 mg q.d.)
	• Thyroid dysfunction	
	• Sleep apnea	
	• Side effects of other medications	
	• Elevated core body temperature	
Sexual dysfunction	Psychotherapy and relationship counseling to help couples manage sexual difficulties	Selective phosphodiesterase 5 inhibitors for erectile dysfunction
	Mechanical vibrators and vacuum devices to enhance blood flow, increase lubrication, and stimulate orgasm	Estrogen creams for vaginal dryness
Cognitive impairment	Neuropsychological testing to define areas of deficit, identify areas of relative strength for compensatory strategies	No clearly effective pharmacotherapy
	Cognitive remediation	
Urinary dysfunction	Urodynamic studies to define specific type of dysfunction—failure to store or empty	Anticholinergics
	Biofeedback	Mirabegron (25 mg q.d.)
	Evaluate for infection	α-Adrenergic antagonist
	Clean intermittent catheterization	Botulinum toxin
		Desmopressin for nocturia 0.1 mg q.h.s.
Bowel dysfunction	Biofeedback	Stool softener
	Dietary changes to increase fiber	Stimulant laxative
	Increase water intake for constipation	Osmotic laxative
	Scheduled defecation	
Tremor	Deep brain stimulation	Primidone (25 mg q.h.s.)
		Propranolol (20 mg b.i.d.)
		Clonazepam (0.5 b.i.d.)
		Ondansetron (8 mg b.i.d.)

TABLE 69.7   Management of Multiple Sclerosis Symptoms *(continued)*

Symptom	Nonpharmacologic Approaches	Pharmacologic Approaches (Starting Dosage)
Paroxysmal symptoms (trigeminal neuralgia, paroxysmal dystonia)	Avoidance of triggers	Carbamazepine (100 mg b.i.d.)
		Acetazolamide (250 mg b.i.d.)
		Phenytoin (100 mg t.i.d.)
		Lamotrigine (100 mg q.d.)
		Baclofen (10 mg t.i.d.)
Pain	Avoidance of triggers	Gabapentin (300 mg t.i.d.)
		Pregabalin (75 mg b.i.d.)
		Amitriptyline (25 mg q.h.s.)
		Duloxetine (30 mg daily)
		Venlafaxine (37.5 mg b.i.d.)

with mild to moderate cognitive impairment. In an open-label pilot study, donepezil was also effective in improving attention, memory, and executive functioning in severely cognitively impaired patients with MS who were residents of a long-term care facility. In another randomized, double-blind trial, low-dose (4.5 mg daily) naltrexone, an opioid receptor antagonist, improved self-reported cognitive function in MS patients. Disease-modifying drugs that minimize lesion development, tissue destruction, or brain atrophy may limit cognitive decline.

Bladder dysfunction in MS can be well characterized by a urologic evaluation and urodynamic studies. A combination of anticholinergic therapy and an α-adrenergic antagonist (doxazosin, prazosin, tamsulosin, terazosin) may facilitate emptying in individual with sphincter detrusor dyssynergia. Clean intermittent catheterization combined with an anticholinergic agent may be necessary for some patients. Those unable to tolerate medications or perform self-catheterization may require an indwelling catheter. Catheterization is the mainstay of therapy in patients with detrusor hypocontractility and emptying difficulties. Patients with good upper extremity function are usually able to perform clean intermittent catheterization. An indwelling catheter may be necessary for patients who cannot perform self-catheterization because long-term intermittent catheterization by a caregiver is usually not practical. Urologic follow-up is necessary for patients with a chronic indwelling catheter to monitor for the development of urinary tract and genital complications.

Numerous medications have been reported to be successful in treating MS tremor, including carbamazepine, clonazepam, gabapentin, levetiracetam, primidone, ondansetron, propranolol, and tetrahydrocannabinol. However, these agents are rarely effective and tremor can be the most difficult MS symptom to treat. Thalamic deep brain stimulation may result in dramatic improvement. Stable MS patients with disabling tremor for at least 1 year despite medical therapy who have no significant cognitive dysfunction, speech or swallowing problems, or other deficits in the affected limbs may be good candidates.

If treatment is warranted, dysesthesias and pain usually respond to anticonvulsants and antidepressants, either used alone or in combination. Gabapentin, pregabalin, amitriptyline, nortriptyline, and duloxetine commonly provide relief. Myelopathic pain responds to opioids, which may be necessary in some patients. Referral to a pain specialist may be helpful for patients with refractory pain.

OUTCOME

MS is an extremely variable illness. Therefore, counseling patients with clinically isolated syndromes and early MS poses a major challenge for clinicians. However, brain MRI abnormalities after an initial clinical demyelinating event provide important prognostic information regarding the development of MS. Fifty-one percent of patients who initially have optic neuritis and at least three brain MRI T2-hyperintense lesions develop CDMS within 5 years compared to only 16% who have normal brain MRI. CDMS develops within 20 years in 82% of CIS patients with at least one brain MRI T2 lesion compared with 21% with a normal baseline brain MRI. Forty-one percent to 50% of placebo-treated patients in the interferon β or glatiramer acetate clinically isolated syndrome trials, which required at least two or three asymptomatic brain lesions for entry, developed CDMS within 2 to 3 years. In those studies, the risk of MS at 18 to 24 months was greatest in patients with more than eight T2-hyperintense lesions or at least one gadolinium-enhancing lesion on a baseline brain MRI.

In general, the larger the number of baseline brain MRI lesions at the time of a clinically isolated syndrome, the greater the risk of long-term disability. There is also a modest correlation between the change in MRI T2 lesion volume in the first 5 years and long-term disability. However, possible outcomes are wide ranging. In one natural history study, 45% of those with at least 10 lesions on initial brain MRI had reached Expanded Disability Status Scale (EDSS) 6 after 20 years, but 35% had only mild disability.

Although the course of MS is essentially impossible to predict in an individual patient, female sex, younger age at onset, and little disability 5 years after onset are generally favorable prognostic signs. Male sex, older age at onset, frequent attacks early in the course of the disease, a short interval between the first two attacks, incomplete recovery from the first attack, rapidly accumulating disability, cerebellar involvement as a first symptom, and progressive disease from onset are associated with worse outcome. Optic neuritis as a first attack is associated with a favorable short- and

intermediate-term outcome, but 20-year disability is similar among patients who present with optic neuritis, brain stem, or spinal cord syndromes. African-Americans have a lower prevalence of MS than whites but tend to accumulate disability more rapidly.

In one natural history study, 24% of patients with a clinically isolated syndrome who were followed for an average of 4 years reached an EDSS score of 6 or more (EDSS 6 is defined as unable to walk 100 m without unilateral assistance) and 40% of those followed for 6 to 15 years entered the secondary progressive phase of the disease. In another study, the natural course of the disease was less aggressive with only 24% of patients reaching EDSS of 6 or more and 39% developing secondary progressive MS 20 years after the onset of their first clinical demyelinating event.

Some patients have a very mild form of relapsing–remitting MS with minimal or no disability at least 10 years after disease onset, which is often referred to as *benign multiple sclerosis*. Although natural history studies have yielded conflicting results, most suggest that many of these patients will develop significant disability and enter the secondary progressive phase of the disease within 20 years. There are no reliable predictors to identify which patients will continue to have a mild course. Furthermore, neuropsychological testing reveals cognitive impairment in approximately 20% to 45% of patients considered to have benign MS. Therefore, the diagnosis of benign MS should include an assessment of cognitive function and only be considered in retrospect and after prolonged follow-up.

The Marburg variant of MS is a rare, fulminant, and usually monophasic illness that typically results in death within 1 year. It can be difficult to differentiate from severe acute disseminated encephalomyelitis. Pathologically, it is characterized by robust macrophage infiltrate and destruction of axons as well as demyelination and prominent tissue necrosis.

Schilder disease, or myelinoclastic diffuse sclerosis, is a vanishingly rare pediatric form of demyelinating disease characterized by formation of bilateral plaques in the centrum semiovale with pathology consistent with MS without additional lesions in the CNS in the setting of normal peripheral nervous system function, normal adrenal function, and no deficit in very long-chain fatty acids. A handful of cases have been reported since the original description by Schilder in 1912. There is controversy regarding the potential contamination of case series with children eventually found to have adrenoleukodystrophy.

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