

Overview of the Epidemiology, Diagnosis, and Disease Progression Associated With Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The cause of MS is unknown. Most patients with MS initially experience relapses with complete or near-complete recovery interspersed with periods of clinical remission. Although some patients have only minimal symptoms, the majority ultimately develop disability over time as a result of incomplete recovery from relapses and/or conversion to a progressive phase of the disease. However, MS is an extremely variable illness and the course of the disease is essentially impossible to predict in an individual patient. Consequently, counseling patients early in the course of the disease about the variable nature of MS and determining the most appropriate treatment options among the increasing number of available agents are often challenging for clinicians.^{1,2} This article addresses the current understanding of the epidemiology, pathophysiology, and diagnosis of MS, and discusses treatment and managed care implications.

Epidemiology

MS affects approximately 400,000 people in the United States and 2.5 million worldwide. More than 200 people are diagnosed with MS each week in the United States.¹ MS typically begins between the ages of 20 and 40 years and it is the leading cause of non-traumatic disability in young adults. Initial 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.¹

The etiology of MS is unknown. It likely results from complex interactions between environmental and genetic factors, which lead to an aberrant immune response and damage to the myelin sheath, oligodendrocytes, axons, and neurons. A number of factors appear to influence the risk of MS. The strongest known genetic factor affecting MS susceptibility is the HLA-DRB1*1501 haplotype. However, it is not essential for the development of MS, as it only increases the risk by 2- to 4-fold and is present in approximately 20% to 30% of healthy individuals. Additional evidence for a genetic predisposition includes a 20- to 40-fold increased risk of MS in first-degree relatives of patients with MS and a 25%

Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that affects approximately 400,000 people in the United States. The etiology of MS is unknown, but it is likely the result of a complex interaction between genetic and environmental factors and the immune system. The clinical manifestations of MS are highly variable, but most patients initially experience a relapsing-remitting course. Patients accumulate disability as a result of incomplete recovery from acute exacerbations and/or gradual disease progression. This article briefly reviews the immunopathology of MS, the symptoms and natural course of the disease, and the recently revised MS diagnostic criteria.

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to 30% concordance in monozygotic twins, compared with only 5% in dizygotic twins. However, approximately 70% of identical twins are discordant for MS, so environmental factors and other unknown influences most likely contribute to disease susceptibility.^{1,3}

The prevalence rates of MS have been reported to vary by continent and geographical latitude. The condition is of high prevalence (>30 per 100,000) in northern parts of Europe and North America; medium prevalence (5-30 per 100,000) in southern Europe and southern United States; and Central and South America (10-20 per 100,000); and low prevalence (<5 per 100,000) in Asia and South America.³

Koch-Henriksen and Sørensen conducted an extensive literature search and meta-regression analysis to evaluate the changes in MS incidence and prevalence worldwide.³ Their analysis indicated that the prevalence and incidence of MS are increasing over time. The increase in prevalence was presumed to be due to prolonged survival of patients with MS, while the increase in incidence was thought to be due to a number of factors. In particular, the ratio of disease in women to men has increased over time from less than 1.5 to greater than 2. This increase in MS among females appears to be driving the increase in incidence, and may be due to changes over time in occupation, cigarette smoking, obesity, birth control, and later childbirth. Furthermore, the previously proposed latitude-related differences in prevalence were dispelled in the northern hemisphere but supported in the southern hemisphere. MS is fairly common in Caucasians of northern European ancestry, but less common where non-Caucasians live, in low-income countries, and in tropical zones. Thus, factors which influence MS incidence include population genetics, the interplay between genes and a geographically determined physical environment, and socioeconomic structure, including availability of medical facilities.^{1,3}

Other environmental factors which may relate to MS are sunlight and ultraviolet radiation exposure, vitamin D, Epstein-Barr virus (EBV) and other viruses, and other infective agents.⁴ The hypothesis that higher exposure to sunlight, and consequently ultraviolet radiation, is associated with a lower incidence of MS tends to conveniently fit with the latitude-based observations; however, exceptions exist. Israeli-born individuals of African descent have higher MS rates than their immigrant predecessors, although it is unlikely that their exposure to sunlight was different. For the same reasons, the relationship between vitamin D and MS is unclear. Although epidemiologic studies correlated increased vitamin D intake with decreased MS incidence, exceptions among Israeli-born individuals do not support the association. Exposure to EBV at an early age in children

has been linked to reduced incidence of MS, while exposure in the form of infectious mononucleosis later in life (late adolescence) is linked to an increased risk. EBV prevalence also appears to correlate with the observed differences in MS based on latitude and socioeconomic structure. It has also been postulated that the lower rate of herpes simplex virus (HSV) in patients with MS may suggest a protective effect of HSV, or an immunomodulatory effect on the outcome of EBV. Exposure to certain bacteria (ie, *Acinetobacter* species, *Chlamydia pneumoniae*, *Pseudomonas aeruginosa*), mycobacteria, or helminthes has also been linked to MS, although the data are not strongly associated.

Immunopathophysiology

Studies in experimental allergic encephalomyelitis (EAE), histopathological studies of MS lesions, and immunologic markers in serum and cerebrospinal fluid 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.^{5,6}

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 pro-inflammatory T helper (Th) 1 and 17 subsets.⁵ 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 (eg, 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, α B-crystallin, phosphodiesterases, and S-100 protein), T cells are reactivated, and the immune response is amplified. Pro-inflammatory Th cells proliferate and B cells continue their maturation to antibody-secreting plasma cells, while monocytes become activated macrophages.⁷ Together, these immune cells produce inflammatory cytokines (eg, IL-12, IL-23, interferon γ , tumor necrosis factor 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 (eg, 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.⁸⁻¹⁰ With a loss of trophic support from oligodendrocytes, axons may degenerate to cause irreversible neurological deficits. Spontaneous

improvement of symptoms is attributed to resolution of inflammation, adaptive mechanisms (eg, 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 pro-inflammatory T helper cell, is known as Th17 because it produces IL-17. Th17 cells secrete a number of cytokines, including tumor necrosis factor α and GM-CSF, which are critical for the development of EAE. Patients with MS have monocyte-derived dendritic cells that secrete higher levels of IL-23 than healthy people.^{5,11,12} Higher levels of IL-17 mRNA-bearing mononuclear cells are found in the serum of patients with MS experiencing relapses than in those with MS 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 patients with MS, identification of antibodies that react to specific myelin antigens within MS lesions, a pathological pattern of MS characterized by antibody-associated demyelination (see below), and the discovery of B cell follicles in the meninges of patients with secondary-progressive MS.¹³ Furthermore, B cells are efficient antigen-presenting cells, and B cell depletion is a promising therapeutic approach in MS.

Acute MS lesions have indistinct margins, hypercellularity, intense perivascular infiltration by lymphocytes, parenchymal edema, loss of myelin and oligodendrocytes, widespread axonal damage, plasma cells, myelin-laden macrophages, hypertrophic astrocytes, and little astroglial scarring.⁴ Chronic MS lesions have sharp edges, with a perivascular cuff of infiltrating cells, lipid-laden and myelin-laden macrophages, hypertrophic astrocytes, some degenerating axons, dissolution of myelin into droplets which are phagocytized by macrophages, and demyelination associated with immunoglobulin deposition. Chronic lesions may also exhibit an increase in oligodendrocytes and remyelination.⁵

Lucchinetti and colleagues identified 4 distinct pathological patterns in an immunohistopathological study of actively demyelinating MS lesions from 83 cases, which included 51 biopsies and 32 autopsies.¹⁴ All 4 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 oligodendroglialopathy. Pattern III was differentiated from pattern IV by a preferential loss of myelin-associated glycoprotein. 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 patients with relapsing-remitting MS (RRMS) who died in the setting of an acute relapse. Most cases, including 1 patient 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 1 of the aforementioned patterns were observed in some patients.¹⁴ The investigators concluded that pattern III lesions represent an early stage of lesion formation that precedes inflammation and demyelination. Recent evidence from another biopsy study indicates that the cortical demyelinating lesions are present in 81% of patients with early MS, and are associated with meningeal inflammation.¹³ These data suggest that the cortical lesions may be associated with acute MS, and not just progressive forms, and may contribute to cognitive impairment and irreversible disability.¹⁴ However, biopsy and some autopsy studies are susceptible to inherent selection bias and the findings may not be representative of typical MS.

Symptoms

The clinical manifestations of MS are highly variable, but an attack of neurologic dysfunction (eg, optic neuritis, incomplete transverse myelitis, brain stem or cerebellar syndrome), referred to as a clinically isolated syndrome (CIS), heralds the onset of the disease in approximately 90% of patients.^{1,15} A relapsing-remitting course ensues and may be followed by a progressive phase of the disease. MS begins insidiously and gradually worsens in about 10% of patients. Symptoms, which depend on lesion location and extent of tissue destruction, range from mild to severe.¹⁵ Common symptoms of an MS exacerbation (relapse or attack) include numbness, tingling, weakness, impaired balance, blurred vision, double vision, vertigo, and bladder or bowel dysfunction.^{2,16,17} Facial weakness, trigeminal neuralgia, hearing loss, and slurred speech are less common.

Disease Course

The current MS classification system is based on consensus and relies on the clinical course of the disease. RRMS is the initial form of the disease in approximately 90% of patients.¹ It is characterized by acute relapses interspersed

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with periods of clinical remission that are characterized by a lack of disease progression. When MS is left untreated, the majority of patients with RRMS enter a progressive phase known as secondary-progressive MS, which is characterized by the gradual accumulation of disability with or without occasional superimposed relapses.¹⁸ Approximately 10% of patients have primary-progressive MS. In this form of the disease, there is continuous and usually gradual deterioration of neurologic function. There may be occasional plateaus and slight fluctuations, but relapses do not occur.¹⁸ Approximately 15% to 40% of patients with an initial primary-progressive course experience at least 1 subsequent relapse, which may not occur until many years after the onset of their original symptoms.¹⁸ This type of MS is referred to as progressive-relapsing MS and is the least common form of the disease.

Diagnosis

The diagnostic criteria for MS have evolved over time.^{16,19-21} New MS diagnostic criteria, which are often referred to as the McDonald criteria, were established in 2001 and revised in 2005 and 2010 (Table).¹⁶ A diagnosis of RRMS requires at least 1 episode of neurologic dysfunction consistent with inflammation and demyelination that occurs in the absence of fever or infection and lasts for at least 24 hours along with objective evidence of lesions disseminated in space and time.¹⁶ Dissemination in space and time may be demonstrated clinically or by magnetic resonance imaging (MRI) (see Table). The new diagnostic criteria allow for an earlier MS diagnosis, which is of considerable importance as disease-modifying drugs appear to be most effective when initiated early in the course of the disease. Furthermore, a delay in treatment may result in irreversible neurologic deficit.

Prognosis

MS is an extremely variable illness. Therefore, counseling patients with CIS 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. Approximately 50% of patients who initially have optic neuritis and at least 3 T2 hyperintense lesions experience a second clinical attack disseminated in space and time within 5 years, compared with only 16% who have normal brain MRI.²² A second exacerbation separated in space and time occurs within 20 years in 82% of patients with CIS with at least 1 T2 lesion, compared with just 21% with a normal baseline brain MRI.²² Interestingly, individuals with only 1 to 3 lesions have a risk of MS similar to those with at least 10 lesions. In recent CIS studies which required patients to have

at least 2 or 3 asymptomatic brain lesions for entry, 41% to 50% of patients given placebo developed a second exacerbation disseminated in space and time within 2 to 3 years. In those studies, the risk of MS at 18 to 24 months was greatest in patients with more than 8 T2 hyperintense lesions or at least 1 or 2 gadolinium-enhancing lesions on a baseline brain MRI. In general, the higher the number of baseline brain MRI lesions at the time of a CIS, 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.²²

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 2 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 outcomes. 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 Caucasians, but tend to accumulate disability more rapidly.²²

In 1 natural history study, 24% of patients with a CIS who were followed for an average of 4 years reached an Expanded Disability Status Scale (EDSS) score of at least 6 (a score of 6 is defined as unable to walk 100 meters without unilateral assistance) and 40% of those followed for 6 to 15 years entered the secondary-progressive phase of the disease.²³ In another study, the natural course of the disease was less aggressive, with only 24% of patients reaching an EDSS score of at least 6 and 39% developing secondary-progressive MS 20 years after the onset of their first clinical demyelinating event.²³

Some patients have a very mild form of RRMS, with minimal or no disability at least 10 years after disease onset, which is often referred to as benign MS. 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.

■ **Table.** The 2010 McDonald Criteria for Diagnosis of MS¹⁶

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

CNS indicates central nervous system; CSF, cerebrospinal fluid; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary-progressive multiple sclerosis.

If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is “MS”; if suspicious, but the criteria are not completely met, the diagnosis is “possible MS”; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is “not MS.”

^aAn attack (relapse, exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic of MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

^bClinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

^cNo additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

^dGadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

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Conclusion

The etiology of MS is unknown, but it is likely due to complex interactions between environmental and genetic factors and the immune system. The clinical manifesta-

tions and the course of MS are extremely variable, but most patients accumulate disability over time. To optimize treatment outcomes, clinicians need to be familiar with the immunopathogenesis, symptoms, and natural

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course of the disease, and the recently revised MS diagnostic criteria.

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