Overview and Diagnosis of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS), a chronic inflammatory disease of unknown etiology, involves an immune-mediated attack of the central nervous system (CNS) that produces demyelination and axonal/neuronal damage, resulting in characteristic multifocal lesions apparent on magnetic resonance imaging and a variety of neurologic manifestations. The disease pathology is characterized by multifocal lesions within the CNS, in both the white matter and gray matter, with perivenular inflammatory cell infiltrates, demyelination, axonal transection, neuronal degeneration, and gliosis. MS pathogenesis is complex, as it involves both T- and B-cell mechanisms and is heterogeneous in presentation. Relatively recently, the historical 4 core clinical categories of MS were revised in an effort to improve characterization of the clinical course, better identify where a given patient is positioned in the disease spectrum, and to guide clinical studies. In young and middle-aged adults, MS is one of the most common contributors to neurologic disability, and it exerts detrimental effects on a patient's productivity and health-related quality of life. Typically, patients with MS have a long life span, although healthcare utilization increases over time. As a consequence, the disease places a substantial burden on patients and their caregivers/families, as well as employers, the healthcare system, and society.

Am J Manag Care. 2016;22:S141-S150

For author information and disclosures, see end of text.

Epidemiology

In the United States, multiple sclerosis (MS) affects approximately 400,000 individuals; worldwide, the disease affects 2.5 million individuals, and varies greatly by geographic region.[1] The disease is predominant in women, being more than 3 times more likely in women than men. Results from a systematic review by Alonso and Hernán showed that the female-to-male ratio in MS incidence has increased with time, from an estimated 1.4 in 1955 to 2.3 in 2000. These researchers reported an overall incidence rate of MS of 3.6 cases per 100,000 person-years (95% CI, 3.0-4.2) in women and 2.0 (95% CI, 1.5-2.4) in men.[2] The age of onset of MS is between 20 and 40 years, and it is slightly later in men than in women; however, MS can present across the lifespan. Approximately 10% of MS cases begin before age 18.[3] The incidence of MS peaks at age 30, and the prevalence peaks at age 50.[4]

Risk Factors

The pathogenesis of MS is complex, as both genetic factors and environmental exposures are contributors (Table 1[4,5]).[4,5] Both ethnicity and geography influence the prevalence of MS, suggesting that heritable factors contribute to MS pathogenesis, as well.[6] The relatives of patients with MS are at greater risk for the disease; however, the genetic basis of MS is complex and heterogeneous. Multiple genes contribute cumulatively to disease risk and disease behavior, and the genes and alleles involved vary from patient to patient. Genes encoded in the class II region of the major histocompatibility complex (MHC) on chromosome 6, specifically the *HLA-DR2* haplotype DRB1*1501-DQB1*0602 have been implicated. It is believed that the MHC-disease association results from effects on antigen-presenting cells, which alter immune reactivity to auto-antigens, possibly myelin-related auto-antigens.[7]

A number of epidemiologic studies have reported unequal geographic distribution of MS; the disease is

Table 1. Putative Risk Factors for MS[4,5]

Genetic	Environmental
• HLA-DRB1 on chromosome 6 • First-degree relative • Maternal > paternal effect	• Europe, Russia, southern Canada, northern United States, New Zealand, Southeast Australia descent • Latitude >40 degrees north • Migration before adolescence to high-risk area or migration after adolescence from a high-risk area • Birth in May • Low vitamin D levels • Smoking • Epstein-Barr virus • Obesity

HLA-DR indicates human leukocyte antigen-antigen D related beta 1; MS, multiple sclerosis.

relatively rare in the tropics and increases in prevalence with increasing latitude in both the northern and southern hemispheres.[2,8-10] Compared with other ethnic groups residing at the same latitudes, those with northern European ancestry are at higher risk for MS; however, more recently, an increasing incidence of MS has been reported in southern Europe.[2,6,8-11]

There is also evidence of tempering of the latitude gradient in MS incidence during the past 2 decades.[2] This may be due, in part, to the increased incidence of MS in geographic regions closer to the equator and to an increase in the female-to-male ratio of MS with time. Migration data suggest that the risk of developing MS is determined at the time of puberty or before. Other putative risk factors include infectious agents, a diet high in salt and low in long-chain fatty acids, environmental toxins, and low exposure to sunlight—although none have been definitively associated.[3,7]

Overall, 3 major epidemiologic shifts in MS have been observed in recent years: (1) an increased prevalence of MS, mostly because of longer survival; (2) a possible true increase in the incidence of MS in many regions, particularly in women, leading to higher female-to-male sex ratios; and (3) a lessening of the idea of a latitudinal gradient in Europe and North America. The increase in the female-to-male sex ratio suggests an environmental influence to the risk of MS; however, environmental factors may be acting at the population level rather than at the individual level.[4]

Clinical Manifestations

The broad range of signs and symptoms of MS reflect multifocal lesions in the central nervous system (CNS), including the afferent visual pathways, cerebrum, brainstem, cerebellum, and spinal cord (Table 2[12,13]).[12,13] In general, the range and severity of manifestations in an individual at a particular time reflects the extent of lesions, their location, the severity of tissue damage, and the rate of accumulation. However, the correlation between lesions (as seen on standard magnetic resonance imaging [MRI]) and clinical manifestations is only approximate. This may be because repair and neural plasticity compensate for damage, and residual function may not parallel changes in MRI. In addition, recent work has demonstrated that there are pathological features in both white and gray matter not visible on standard MRI.[12]

MS symptoms result from interruption of myelinated tracts in the CNS.[3] The initial symptoms often include 1 or more of the following: weakness or diminished dexterity in 1 or more limbs, a sensory disturbance, monocular visual loss (optic neuritis), double vision (diplopia), gait instability, and ataxia. As MS ensues, bladder dysfunction, fatigue, and heat sensitivity occur in many patients. Additional symptoms, which are listed in Table 2[12,13], include Lhermitte's sign, facial weakness or pain, vertigo, brief tonic spasms, and other paroxysmal symptoms, which are believed to represent discharges along demyelinated axons.[12,13] Cognitive deficits are common, particularly in advanced cases, and include memory loss, impaired attention, problem-solving difficulties, slowed information processing, and difficulties in shifting between cognitive tasks.[12,13]

Prognostic Factors

Several prognostic factors have been reported to predict a poor prognosis, more rapid disease progression, or conversion from clinically isolated syndrome (CIS), which is the first clinical episode typical of MS.[14] These include being older than 40 years at disease onset; male sex; ethnic origin (non-Caucasian); initial presentation with motor, cerebellar, sphincter, or polyregional symptoms; incomplete recovery from initial attacks; frequent attacks during the first years of the disease; a short interval between the first 2 attacks; rapid disability progression during the first years; progressive disease from onset; cognitive impairment at disease onset; the presence of oligoclonal immunoglobulins in the cerebrospinal fluid (CSF); and high burden of disease or gadolinium (Gd) enhancement on initial MRI.[12,14]

Diagnosis

Clinically, MS is characterized by discrete episodes ("attacks" or "exacerbations" or "relapses") of neurologic dysfunction. The type and severity of symptoms

Table 2. Clinical Manifestations of MS[12,13]

Vision	Visual loss, double vision
Vestibular	Vertigo, imbalance
Bulbar	Dysarthria, swallowing dysfunction
Motor	Weakness, spasticity, incoordination, tremor
Sensory abnormalities	Sensory loss, paresthesia, dysesthesia, neuropathic pain
Gait	Varies based on visual impairment, vestibular symptoms, weakness, spasticity, ataxia, imbalance, sensory loss, pain, fatigue
Urinary	Urgency, frequency, hesitancy, retention, incontinence, frequent urinary tract infections
Bowel	Constipation, urgency, incontinence
Sexual	Decreased libido, erectile dysfunction, anorgasmia
Cognitive	Poor concentration or attention, slowed thinking, poor memory, particularly short term, impaired executive function
Mood	Depression, anxiety, affective release
Fatigue	Handicap fatigue: increased effort to perform routine tasks Motor fatigue: decreased performance or endurance with sustained effort Heat intolerance: worsening sensory or motor symptoms/signs with increased body temperature Systemic fatigue: persistent lassitude
Pain	Chronic neuropathic pain, paresthesias, dysesthesias, paroxysmal sensory symptoms (eg, Lhermitte's phenomenon), spasticity, paroxysmal motor phenomenon (eg, tonic spasms), pain associated with acute inflammatory lesions and irritation of adjacent meninges (eg, optic neuritis), mechanical back or joint pain from immobility, compression fractures
Paroxysmal phenomena	Epileptic seizures, nonepileptic paroxysmal motor or sensory phenomena

MS indicates multiple sclerosis.

produced by these episodes vary considerably between patients and depend upon the site of neurologic involvement. Commonly, patients may experience numbness, tingling, weakness, vision loss, gait impairment, incoordination, imbalance, and bladder dysfunction. In between these attacks, at least during the remitting periods of the illness, patients have fairly stable neurologic function. Nevertheless, residual symptoms may persist and many patients experience fatigue or heat sensitivity in the interval between attacks. Over several years to decades, many patients who begin with relapsing-remitting MS (RRMS) evolve to the secondary progressive features of illness, in which they experience an insidious worsening of function and the accumulation of neurologic disability unrelated to any acute attacks that may or may not occur. This is especially true in untreated patients.[15]

MS diagnosis is greatly influenced by clinical judgement.[16] The diagnosis of MS is primarily clinical and relies on the demonstration of symptoms and signs attributable to white matter lesions on MRI that are disseminated in time (ie, the disease course) and space (ie, the affected areas in the CNS), along with the exclusion of other conditions that may resemble MS.[17,18] There is no single laboratory test diagnostic for MS.[19] In addition to a thorough history and physical examination, diagnostic tools required to diagnose MS and exclude other diagnoses include MRI, CSF analysis, and evoked potential testing. CSF analysis shows increased immunoglobulin concentrations and 2 or more oligoclonal bands (OCBs) in more than 90% of patients. Delayed latencies of the visual, somatosensory, and auditory evoked potentials on electrophysiological studies, as well as prolonged central motor conduction times, are characteristic of demyelination; this may indicate clinically silent lesions. Blood tests are typically used to rule out other diseases that resemble MS.[17]

MRI

MRI is an indispensable test for the diagnosis and monitoring of patients with MS.[17] MRI criteria and techniques have constantly evolved, and MRI remains the most sensitive method to detect and demonstrate MS lesions. MRI is used to support the diagnosis of MS, estimate lesion load and disease activity, measure brain atrophy (a correlate of axonal loss), follow disease progression, provide prognosis, serve as a surrogate outcome, and provide outcome measures in clinical trials. MS lesions are hyperintense on T2-weighted, proton density, or fluid-attenuated inversion recovery imaging, and hypointense

Table 3. Paraclinical Evidence in MS Diagnosis[23-25]

Evidence for DIS	Evidence for DIT	Evidence for Positive CSF
≥1 T2 lesion in at least 2 of 4 areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord • Gd enhancement of lesions is not required for DIS • If a patient has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count	A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan—irrespective of the timing of the baseline MRI—or simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions any time	Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index

CNS indicates central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; Gd, gadolinium; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS; multiple sclerosis.

or isointense on T1-weighted imaging. Lesions are typically ovoid in shape, small in size (although giant plaques may occur), and located mainly in the periventricular white matter. They are also common in the posterior fossa, spinal cord, and in subcortical locations. Lesions tend to be perpendicular to the ventricles, involve the corpus callosum and U-fibers, and may enhance with Gd, particularly during active inflammation due to disruption of the blood-brain barrier. Newer MRI techniques facilitate the detection of both gray matter and white matter microstructural damage, and combined histopathologic-MRI correlation help to clarify the pathologic specificity and sensitivity of these techniques.[12,20] Due to the asymptomatic nature of many cerebral lesions and relative difficulty detecting significant brainstem and spinal cord lesions, MRI burden can be very discordant with clinical disability and disease activity.

With regard to MRI diagnostic criteria for MS, dissemination in time (DIT) means that there must have been at least 2 discrete episodes of inflammatory disease activity separated by at least 1 month.[21,22] The purpose of this requirement is to ensure that monophasic illnesses do not get classified as MS, which, by definition, is a recurrent, inflammatory process. In the pre-MRI era, these episodes needed to be identified clinically. However, the most recent international diagnostic criteria allow the use of purely imaging events to establish such time dissemination.[21] Dissemination in space (DIS) requires demonstration that the disease process involves at least 2 discrete neuroanatomic areas within the CNS. In the pre-MRI era, this demonstration required the elicitation of neurologic signs, which could be unequivocally attributed to 2 or more locations within the CNS.[13] In contrast, in the modern era, DIS can be established using paraclinical evidence, primarily MRI, and clinical findings.[19,21,22]

Paraclinical Investigations

Paraclinical investigations, which include the examination of the CSF, the recording of evoked potentials, urodynamic studies of bladder function, and ocular coherence tomography, may be helpful in establishing the diagnosis of MS for individual patients (Table 3[23-25]).[13,15,17,23-25] The detection of a CSF oligoclonal immunoglobulin G (IgG) response by isoelectric focusing (IEF) is a nonspecific, yet sensitive, aid to diagnosis. It should be used in parallel with evoked potentials and MRI to help the clinical diagnosis of MS, as each set of investigations provides different information about the pathogenesis of the condition. Importantly, the CSF oligoclonal IgG response is not only a diagnostic, it may be a predictive test, as well. It may help to assess the risk of conversion from CIS to MS. The standard CSF profile is also useful in identifying potential conditions that resemble MS. Although there are several candidate molecular, predictive, diagnostic, disease activity, and treatment-response biomarkers under investigation (eg, cytokines, chemokines and receptors, and tau proteins), none has been sufficiently validated for widespread clinical use.[12,26,27]

In a systematic review (N = 71) of articles published post-1980 of OCB detected by IEF with immunofixation in MS and CIS, OCB positivity strongly predicted conversion from CIS to MS, and latitude predicted OCB status in patients with MS (P = .009).[28] Of the 12,253 patients with MS, 87.7% were OCB-positive, and of the 2685 patients with CIS, 68.6% were OCB-positive. In patients with CIS, the presence of OCBs was associated with a markedly increased risk of conversion to MS. The magnitude of this risk equated to an odds ratio of 9.9, irrespective of the anatomical location of the CIS.[29] However, another study that evaluated a cohort of patients with MS (N = 407; disease duration ≥5 years) in eastern France showed that routine CSF biologic markers at diagnosis did not predict MS progression.[28] The median time from disease onset to CSF testing was 4.6 years (range, 1.0-7.0 years). Researchers did not demonstrate the value of the CSF IgG index and presence of OCB at a mean of 8.9 ± 3.8 years of follow-up for prognosis of disability in MS.[28]

Table 4. 2010 McDonald MS Diagnostic Criteria[21]

Clinical (Attacks)	Lesions	Additional Criteria to Make a Diagnosis
2 or more	Objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of prior attack	None. Clinical evidence alone will suffice; additional evidence desirable, but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	DIS, or await further clinical attack implicating a different site in the CNS
1	Objective clinical evidence of ≥2 lesions	DIT, or await a second clinical attack
1	Objective clinical evidence of 1 lesion	DIS, or await further clinical attack implicating a different site in the CNS and DIT, or await a second clinical attack
0 (progression from onset)		1 year of disease progression (retrospective or prospective) AND at least 2 of the following: • DIS in the brain based on ≥1 T2 lesion in periventricular, juxtacortical, or infratentorial regions • DIS in the spinal cord based on ≥2 T2 lesions • Positive CSF

CNS indicates central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; MS, multiple sclerosis.
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Evoked potentials are used to demonstrate subclinical involvement (slowed conduction) in CNS sensory pathways when the neurologic examination and MRI are insufficient to provide objective evidence of a multifocal disease process.[12] Evoked potentials can be used to evaluate the afferent visual pathways (visual-evoked potentials), auditory pathways (brainstem auditory-evoked potentials), and dorsal column sensory pathways (somatosensory-evoked potentials) with median nerve (upper extremity) or posterior tibial nerve (lower extremity) stimulation. Slowing of central conduction times, particularly if asymmetric, suggests MS in the appropriate clinical setting.[12]

Diagnostic Criteria

The current diagnostic criteria (2010 revised McDonald criteria), aimed to retain the useful features of prior criteria, but incorporated imaging more effectively into the diagnostic process, clarified definitions, simplified categories, and created a diagnostic scheme that is useful in both research studies and clinical practice.[21] The conceptual requirement for objective evidence of lesion DIT and DIS was maintained, but formal criteria were introduced to use MRI for this purpose. The diagnostic criteria incorporated recommendations on the use and interpretation of imaging criteria for DIT and DIS (Table 4[21]).[19,21] These indicate that DIT can be demonstrated by a new T2 or Gd-enhancing lesion on a follow-up MRI, with reference to a baseline scan, regardless of when the baseline MRI was obtained. Previous iterations of the diagnostic criteria specified that the reference scan be performed at least 30 days after the initial clinical event; however, this is no longer a requirement. The criteria also indicate that DIS can be demonstrated with at least 1 T2 lesion in at least 2 out of 4 areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord. These lesions do not have to be Gd-enhanced. These revised DIT and DIS criteria allow for a simplified diagnostic process for MS, with equivalent or improved specificity and/or sensitivity compared with past criteria and potentially fewer required MRI examinations in many cases.[21]

In addition to the assessment of DIT and DIS, the 2010 revisions emphasized that the criteria should only be applied to patients who have experienced a typical CIS suggestive of MS.[21] One important area of controversy related to the original McDonald criteria was their applicability to specific populations, such as pediatric, Asian, and Latin American populations. The international panel concluded that the 2010 revised criteria were applicable to the majority of these populations once careful evaluation for other potential explanations for the clinical presentation was made. As with the original criteria, the 2010 revisions continue to be tested with prospective and retrospective datasets to further assess their validity and to provide suggestions for further refinements.[19,21]

Classification of MS

Approximately 85% of patients experience an abrupt onset of MS.[3] Early symptoms may be severe in some cases, while others may seem so insignificant that a patient may not seek medical attention for months or even years. Thereafter, the clinical course may be characterized by acute episodes of worsening (exacerbations or relapses), gradual progression of disability, or a combina-

tion of both.[3] The 4 historical MS phenotypes, and their characteristics, are[30,31]:

- RRMS: clearly defined attacks of new or recurrent neurologic symptoms and signs with full or partial recovery and lack of disease progression between disease relapses. This type accounts for approximately 70% to 80% of initial diagnoses of MS.
- Primary-progressive MS (PPMS): disease progression from onset, with occasional plateaus and temporary minor improvements allowed. Approximately 15% to 20% of patients with MS have PPMS.
- Secondary-progressive MS (SPMS): initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus. Approximately 90% of patients with RRMS convert to SPMS after 25 years.[32]
- Progressive-relapsing MS (PRMS): progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses are characterized by continuing progression. PRMS may present a subtype of PPMS, as they share a similar natural history. Approximately 5% of patients have PRMS. This clinical phenotype appears to be in the process of being consolidated into the other phenotypes because it is so infrequent.[12,33]

Patients with RRMS experience relapses with or without complete recovery and are clinically stable between episodes.[3] Approximately 50% of patients with RRMS convert to SPMS within 15 years of disease onset. The secondary progressive phase is characterized by gradual progression of disability with or without superimposed relapses. Conversely, patients with PPMS experience gradual progression of disability from onset without superimposed relapses. Approximately 15% of patients with MS experience this clinical pattern. Additionally, approximately 1% to 2% of patients experience gradual progression of disability from disease onset, which is later accompanied by 1 or more relapses; this clinical pattern is designated PRMS. Most patients with MS ultimately experience progressive disability. Fifteen years after diagnosis, fewer than 20% of patients with MS have no functional limitation, 50% to 60% require assistance when moving, 70% are limited or unable to perform major activities of daily living, and up to 75% are not employed.[3]

Evolution of MS Phenotypes

More recently, the historical phenotypes have been re-examined and revised, and their descriptions continue to evolve. This is attributed to increased understanding of MS and its pathology, and general concern among experts that the historical phenotypes may no longer sufficiently reflect recently identified clinical aspects of the disease.[30] There is a drive to eliminate uncommon classification categories, such as PRMS; however, an ongoing dilemma with redefining MS phenotypes is the lack of validation of the proposed categories. The clinical phenotypes of CIS, RRMS, and SPMS have been collapsed to "relapsing MS" for regulatory purposes in North America. Furthermore, the evolving criteria for clinically definite MS have led to the use of "early MS" or "first symptom MS" for what is formerly referred to as CIS, due to the substantial minority meeting radiological definitions of MS (ie, both DIS and DIT criteria at first symptom). Revisions to the phenotypic classifications have several practical and clinical advantages, such as improving the characterization of the clinical course to identify where a patient is positioned in the disease spectrum, guiding study inclusion criteria for a better-defined and more homogenous population, evaluating the adequacy of treatment, and guiding design of new studies and use of biomarkers.[30,34]

Although advanced MRI metrics to differentiate among the clinical phenotypes and predict disease course are lacking, the International Advisory Committee on Clinical Trials in Multiple Sclerosis re-evaluated the core MS phenotype descriptions and provided recommendations to standardize the definitions of MS. **Table 5**[34] summarizes these definitions.[34] One pertinent update to the historical phenotypes is an assessment of disease activity (active vs not active), as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging.[34] Appropriate amounts of disease activity may be more important than the historical phenotypic classifications.

Another important change in phenotypes is a determination of whether disability has progressed over a given interval (**Figure 1**[30] and **Figure 2**[30]).[30] The committee recommended that the former category of PRMS be removed because patients who would have been classified as such are now classified as having PPMS with disease activity. In addition, PPMS is now part of the spectrum of progressive disease, and differences from other forms are considered to be relative rather than absolute. The committee recommended that CIS be included in the spectrum of MS phenotypes, and prospective follow-up of patients with CIS should help to determine their subsequent disease phenotype. According to the committee, radiologically isolated syndrome should not be considered a separate MS phenotype. This is because such

Table 5. International Consensus on MS Definitions[34]

Active disease	• Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection; *and/or* • Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions
Progressive disease	• Clinical: steadily increasing objectively documented neurologic dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur) • Imaging (MRI): imaging measures of progression are not established or standardized and not yet useful as phenotype descriptors for individual patients. Under consideration: increasing number and volume of T1-hypointense lesions, brain volume loss, and changes in magnetic transfer imaging and diffusion tensor imaging
Worsening disease	• Documented increase in neurologic dysfunction/disability as a result of relapses or progressive disease, reserving the term "disease progression" for those solely in a progressive phase of the illness
Confirmed progression or worsening	• Increase of neurologic dysfunction confirmed throughout a defined time interval (eg, 3, 6, or 12 months) • As neurologic dysfunction may still improve (especially in relapsing disease), even if progression is confirmed over 6 or 12 months, it is recommended to abandon the term "sustained"

MRI indicates magnetic resonance imaging; MS, multiple sclerosis. Reprinted with permission from Lublin FD, Reingold SC, Cohen JA, et al. *Neurology*. 2014;83(3):278-286.

patients lack clinical signs and symptoms of the disease. Prospective follow-up is recommended in these patients.[34]

Updated Terminology

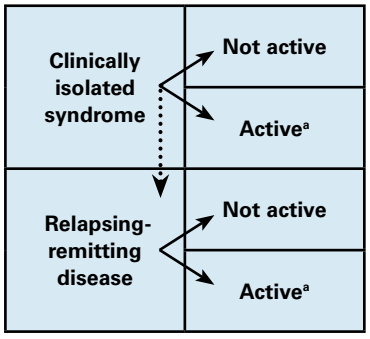
With regard to terminology, the committee noted that the term "worsening" is preferable and less confusing than "progressing" when being used to describe a patient in the relapsing phase of MS whose disease is advancing because of frequent relapses and/or incomplete relapse recovery.[34] With regard to clinical trial or natural history assessment of worsening disease by the Expanded Disability Status Scale or other parameters, the committee recommended the term "confirmed" instead of "sustained" over a defined interval, either within the functional system or without considering the specific functional systems in which worsening is detected. Given that the terms "benign" and "malignant" disease are often misused, the committee recommended that these terms be used with caution. Progress has been made in MS classification; however, further research is warranted to better define the value of imaging and biological markers in assessment, confirmation, and revision of the MS phenotype descriptions.[34]

Differential Diagnosis

Another critical component of MS diagnosis is the exclusion of alternate explanations. The list of conditions that resemble MS clinically or radiologically is extensive; however, in clinical practice, there are few conditions that truly mimic MS on both fronts. In MS, differential diagnosis must be guided by clinical presentation and neurologic localization.[16,18] Some of the disorders that are often mistaken for MS include nonspecific neurologic symptoms (eg, migraine, functional neurologic disorders, fibromyalgia, and small vessel ischemic disease alone or in combination), other demyelinating disorders (eg, neuromyelitis optica, idiopathic transverse myelitis, and acute disseminated encephalomyelitis), systemic inflammatory diseases with CNS manifestations (eg, sarcoidosis, CNS vasculitis/vasculopathy, HIV infection, toxoplasmosis, and Lyme disease), and neoplasms (eg, primary CNS, lymphoma, glioma).[16]

What constitutes an adequate "rule out" panel of mimics for the patient with a typical presentation of MS will vary somewhat based on local epidemiology and practice patterns.[15] The burden for excluding infection, for example, is necessarily higher in tropical settings where MS incidence is low and CNS infection is relatively high. A "rule out" screening panel for a new diagnosis of MS typically includes a vitamin B12 level (for vitamin B12 deficiency causing the syndrome of subacute combined degeneration), treponemal antibody testing (for syphilis), *Borrelia* serologies (for Lyme disease, depending on geography, local epidemiology, and season), and antiphospholipid antibody syndrome screening. Aquaporin-4 antibody testing for neuromyelitis optica should be performed in any patient with a longitudinally extensive myelitis, and in all patients who experience a first episode of acute optic neuritis. Although erythrocyte sedimentation rate may provide evidence of a systemic inflammatory process, it is extremely nonspecific. Antinuclear antibody testing is an important serologic marker of a number of systemic inflammatory (rheumatologic) syndromes, but false positives occur in otherwise healthy individuals at rates of more than 30% at the 1:40 dilution and 5% at the 1:160 dilution (using human epithelial type 2 cells as the antinuclear antibody test substrate).

■ **Figure 1.** 2013 MS Phenotype Descriptions: Relapsing-Remitting Disease[30]



MS indicates multiple sclerosis; MRI, magnetic resonance imaging.
[a]Activity = clinical relapses and/or MRI (gladolinium-enhancing MRI lesions; new/enlarging T2 lesions).
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A positive test for a putative MS "mimic" does not itself exclude the diagnosis of MS (ie, a patient with MS can be vitamin-B12 deficient and still have MS).[15]

There are also important red flags that clinicians need to consider before making a diagnosis of MS. Among these are nonspecific or nonlocalizing symptoms in a patient with multifocal MRI abnormalities, historical episodes of neurologic dysfunction without objective corroborative findings, new lesions seen on interval MRI examinations using conventional imaging methods, and normal CSF levels.[15,16,18]

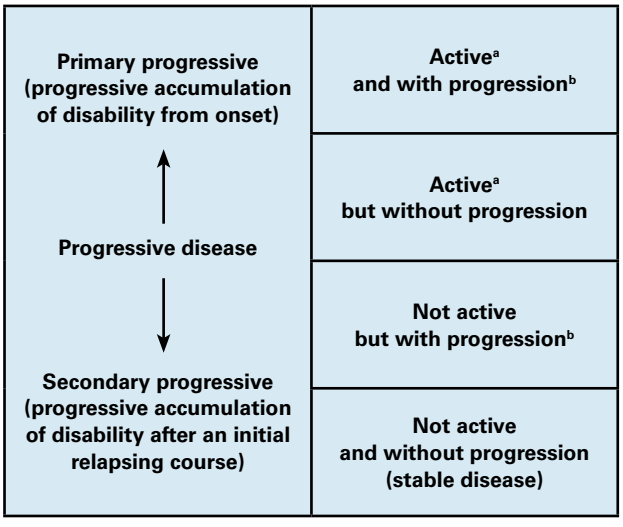
Burden of Disease

Individuals with MS can experience high levels of disability and impaired quality of life (QoL) for many years.[10] The costs of the disease, including healthcare, social care, and productivity losses, are substantial and are associated with disease severity. MS primarily occurs among younger people, and the patients suffer for the remainder of their life.[10] A diagnosis of MS has substantial social and psychological consequences. A number of MS manifestations are frequently underappreciated, including cognitive impairment, psychiatric disorders, pain, and fatigue, but they are often significant contributors to disability.[35,36]

The disease most often occurs during a patient's most productive years. Newly diagnosed patients may be shocked by having a disease that is chronic, unpredictable in its course, progressive, incurable, and that impacts functioning. Patients may have to cope with issues regarding reduced physical function, disability, and disruptions in education, employment, sexual and family functioning, friendships, and activities of daily living. Physically, patients may experience fatigue, pain, visual impairments, weakness, bladder and/or bowel dysfunction, and mobility impairment. Psychologically, they may have impaired cognition, depression, reduced social interaction, and increased reliance on others.[12,35] In terms of employment, one study found that rates of unemployment were as high as 75% within 10 years after a diagnosis of MS.[37] The grim prognosis and unpredictability of daily health in RRMS, and the adverse effects of medication, substantially affect QoL.[38]

Moreover, MS can negatively affect a patient's identity. Physical changes and functional limitations may result in a sense of loss of identity or role strain, especially when the individual can no longer perform previously valued activities, or an occupation.[36,38] Each time the individual experiences a new loss of function, this sense of loss may be renewed. One of the major sources of psychological distress related to the physical limitations of MS is sexual dysfunction. Results from a longitudinal study (N = 93) of sexual function among persons with MS showed that the number of patients having sexual intercourse significantly decreased at the 6-year follow-up. In addition, researchers found an increasing risk for the development of sexual

■ **Figure 2.** 2013 MS Phenotype Descriptions: Relapsing-Remitting Disease[30]



MS indicates multiple sclerosis; MRI, magnetic resonance imaging.
[a]Activity = clinical relapses and/or MRI (gladolinium-enhancing MRI lesions; new/enlarging T2 lesions).
[b]Progression measured by clinical evaluation at least once yearly.
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dysfunction in both men and women with MS during the study interval. The percentage of patients with at least 1 symptom of sexual dysfunction increased from 77.8% to 88.9% in men and from 72.7% to 87.9% in women.[39]

Another burden to consider is the profound psychological impact of MS. The lifetime prevalence of depression in patients with MS is as high as 50%, and up to 15% of patients attending MS clinics die due to suicide. The pathophysiology of depression in those with MS is not well understood; however, there is some belief that depressed patients have more lesions at particular regions of the brain. This suggests that depression may be a secondary manifestation of MS, not simply a comorbid condition. Anxiety, bipolar disorder, and psychosis also occur in higher rates among patients with MS than among the general population. This is particularly important to clinicians, because corticosteroid administration may transiently cause depression, mania, or psychosis.[40]

When measuring the burden of MS, it is also important to consider impairment and disability related to symptoms and health-related quality of life (HRQoL), or the degree to which the disease affects a patient's self-reported life perception. Results from a study evaluating HRQoL with the Short Form-36 in patients with MS (N = 57) showed that unemployment, smoking, and night waking were the most significant individual factors that lowered HRQoL in patients with MS. Other factors that were also significant contributors were introversion, physical pain, and difficulty falling asleep.[35]

Conclusion

MS is a chronic, inflammatory disease that profoundly affects patients physically, psychologically, and socially. Its prevalence is increasing, and the disease is more predominant in women. There appears to be a tempering of the latitudinal gradient in MS incidence in Europe and North America. Both environmental and genetic factors are believed to contribute to the development of MS. Although there are certain clinical features that are typical of MS, disease presentation varies widely in symptoms, pace, and progression.

Besides a thorough history and physical examination, diagnostic tools used to diagnose MS and exclude other diagnoses include the gold standard test, which is an MRI, and may include CSF analysis and evoked potential testing. Importantly, phenotype classifications have been modified in an effort to improve the characterization of the clinical course of the disease and to better define study populations. Although MS is not curable, QoL can be substantially improved or at least maintained by early diagnosis and management strategies aimed at reducing relapses, postponing worsening of disease and disability, and addressing psychosocial issues of the patient with MS.

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Funding source: This activity is supported by educational grants from Novartis Pharmaceuticals Corporation and Genzyme, a Sanofi Company.

Author disclosure: Dr Hunter reports serving as a consultant for AbbVie, Bayer, Genentech/Roche, and Sanofi-Genzyme. He also reports multicenter clinical research trial participation for Adamas, Biogen, Genentech/Roche, and Teva. Dr Hunter has received research grant support from Sanofi-Genzyme, and has served on speakers' bureaus for Mallinckrodt, Novartis, Sanofi-Genzyme, and Teva.

Authorship information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and supervision.

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