Multiple sclerosis (MS) is an idiopathic inflammatory disease of the central nervous system that is characterized by demyelination and subsequent axonal degeneration. It is the most common nontraumatic cause of disability in young adults, generally striking between the ages of 15 and 50 years. Women are twice as likely as men to develop MS. Estimates place the prevalence at 250,000 to 350,000 people in the United States alone, but the true prevalence is believed to be higher. Epidemiologic data also point to people of Northern European ancestry as being particularly vulnerable, although recent trends suggest that racial blending and other factors have resulted in more diffuse manifestations across populations.

**Epidemiology:** MS is the most common nontraumatic cause of disability in young adults, generally striking between the ages of 15 and 50 years. Women are twice as likely as men to develop MS. Estimates place the prevalence at 250,000 to 350,000 people in the United States alone, but the true prevalence is believed to be higher. Epidemiologic data also point to people of Northern European ancestry as being particularly vulnerable, although recent trends suggest that racial blending and other factors have resulted in more diffuse manifestations across populations.

**Review Summary:** This review summarizes the clinical signs and symptoms of MS as well as new diagnostic criteria. Current treatments and areas fertile for future research also are discussed.

**Type of Available Evidence:** Nationally recognized guidelines for disease diagnosis, review articles, randomized clinical control trials, expert opinion.

**Grade of Available Evidence:** Good.

**Conclusion:** Primary care physicians play a particularly important role in the early recognition of clinical signs of MS and are uniquely positioned to ensure early treatment.

**Abstract**

Multiple sclerosis (MS) is an idiopathic inflammatory disease of the central nervous system that is characterized by demyelination and subsequent axonal degeneration. It is the most common nontraumatic cause of disability in young adults, generally striking between the ages of 15 and 50 years. Estimates place the prevalence at 250,000 to 350,000 people in the United States alone, but the true prevalence is believed to be higher as MS can remain undiagnosed for years, even decades. A recent estimate put the annual cost of MS in the United States at $6.8 to $11.9 billion including the cost of lost productivity, pointing to the harsh economic impact of this disease and the need for treatment.

Women are twice as likely as men to develop MS, and epidemiologic data also point to people of Northern European ancestry as being particularly vulnerable. However, the ethnic profile of the MS population seen, for instance, in Baltimore shows a much broader-based ethnicity; 11% of our patients are African American. Because the symptoms of MS spontaneously remit, the disease frequently goes undiagnosed for many years. An alert primary care clinician can make a crucial difference by recognizing the symptoms of MS and facilitating prompt diagnosis and treatment.

**Symptoms**

Fatigue and depression are common symptoms in clinical practice and may be related to...
any number of illnesses. Before ascribing such symptoms to psychiatric illness the primary care clinician should consider the possibility of MS. Fatigue and depression frequently precede other neurologic symptoms in MS. Sensory symptoms also are common and may consist of hand numbness that is misdiagnosed as carpal tunnel syndrome, or a burning sensation in the extremities that resembles peripheral neuropathy. Acute onset of motor symptoms is rare but can occur and may be confused for stroke. Patients with this presentation should be referred for imaging and neurologic evaluation. Urinary retention and urgency as well as sexual dysfunction are common subacute and chronic symptoms in patients with MS and should be assessed in the clinical history. The most common symptoms of MS are shown in Table 1.

All of the primary symptoms associated with MS are a result of the inflammatory, demyelination process in the central nervous system (CNS). Demyelination and axonal damage impair transmission of nerve impulses to muscles and other organs, resulting in impaired function. Symptoms can vary widely and may be mistaken for other disease states (Tables 2 and 3), frequently confounding an early diagnosis. Some patients may only experience 1 or 2 symptoms over the course of the disease, whereas other patients may experience multiple symptoms that occur and remit spontaneously. Many symptoms can be managed effectively with medication, rehabilitation, and other strategies.

In addition to the primary symptoms caused by demyelination, other problems or complications can occur as indirect results of the primary symptoms or the experience of having a chronic illness. For example, inactivity can result in loss of muscle tone and disuse weakness (not related to demyelination), decreased bone density (and resultant increased risk of fracture), and shallow, inefficient breathing. Immobility can lead to pressure sores. Though secondary symptoms can be treated, the optimal goal is to avoid their occurrence by treating the primary symptoms.4

Tertiary symptoms of MS are the social, vocational, and emotional complications associated with the primary and secondary symptoms. For example, MS can prevent a person from working or engaging in satisfying personal relationships. Whereas depression can be a primary symptom, it also can be a tertiary symptom resulting from the patient’s altered life situation. Professional assistance from psychologists, social workers, physical and occupational therapists, and public health agencies is indicated for managing many of these psychosocial and vocational issues.4

**PATHOGENESIS**

The pathogenesis of MS is not clearly understood. Researchers believe that it is caused by a variety of factors and affected by a number of physiologic and biochemical mechanisms. The immune reaction in MS is characterized by inflammation at certain points along neurons, destruction of the myelin (leading to demyelination of the axon), and damage to the axon itself. Trapp and colleagues have reported that this process begins at the earliest stages of the disease.3 However, the patient does not become symptomatic from the axonal damage until the CNS is no longer capable of compensating. Thus, it is not uncommon for a patient to remain asymptomatic prior to diagnosis, even in the presence of as many as 20 or 30 lesions.

The major cause of the paralysis, blindness, and numbness that are reported by patients is conduction block, which is caused largely by demyelination and inflammation, and possibly by defects in synaptic transmission. Demyelination of axons interferes with the normal smooth conduction of nerve impulses, resulting in weakness and sensory difficulties. As axonal function is restored with resolution of the inflammation (edema), partial remyelination, or restoration of conduction to axons through redistribution of sodium channels, symptoms frequently resolve and patients experience a state of remission.6 However, with each repeated bout of inflammation the damage

<table>
<thead>
<tr>
<th>Table 1. Most Common Signs and Symptoms of Multiple Sclerosis*</th>
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<tbody>
<tr>
<td>• Depression</td>
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<tr>
<td>• Dizziness or vertigo</td>
</tr>
<tr>
<td>• Fatigue</td>
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<tr>
<td>• Heat sensitivity</td>
</tr>
<tr>
<td>• Lhermitte’s sign (electrical sensation down the spine upon neck flexion)</td>
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<tr>
<td>• Numbness, tingling pain</td>
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<tr>
<td>• Urinary bladder and/or bowel dysfunction</td>
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<tr>
<td>• Visual impairment (monocular or diplopia)</td>
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<tr>
<td>• Weakness</td>
</tr>
<tr>
<td>• Action tremor</td>
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<tr>
<td>• Decreased perception of pain, vibration, or position</td>
</tr>
<tr>
<td>• Decreased strength</td>
</tr>
<tr>
<td>• Hyperreflexia, spasticity, Babinski’s sign</td>
</tr>
<tr>
<td>• Impaired coordination and balance</td>
</tr>
<tr>
<td>• Impaired visual acuity or red color perception with optic disc pallor and afferent papillary defect, dysconjugate eye movements</td>
</tr>
<tr>
<td>• Nystagmus</td>
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accumulates and many patients evolve into a downward progressive stage of the illness.

There is no apparent single factor that elicits the immune response resulting in the damage that characterizes MS. The disease is thought to be an autoimmune process that is precipitated by any number of common microbial infections, such as Epstein-Barr virus or human herpesvirus 6. It is believed that through a process of molecular mimicry, the immune system mistakes fragments of myelin for viral infection, then vigorously attacks them. However, possibilities are also actively being considered that there is either a primary CNS infection of the oligodendrocyte or a permanent reservoir of virus in B cells or other antigen-presenting cells that then mediates bystander activation.

**TYPES OF DISEASE**

Because the etiology of this disease involves the interaction of genetic, environmental, and immune factors, it manifests in varied patterns (Figure 1).

Relapsing-Remitting MS (RRMS) is the most common type of MS, affecting 80% to 85% of patients at onset and 55% of the general MS population at any given time. RRMS is characterized by frequent inflammation, demyelination, axonal transection, and remyelination. Full recovery from an attack may occur early on, but with subsequent attacks recovery is incomplete. In RRMS the MRI is less likely to show new lesions, but evidence of tissue loss may be observed as enlarged ventricles, thinning of the corpus callosum, and diffuse atrophy of the whole brain and spinal cord. At any given time about 30% of the general MS population is in the SPMS stage.

Primary-Progressive MS (PPMS) is characterized by insidious worsening from the time of onset, with no detectable relapses. This form of MS usually begins with difficulties walking, steadily worsening motor dysfunction, and increased disability. Disease characteristics notable on the MRI may include fewer and smaller cerebral lesions, but often show extensive spinal cord involvement. PPMS affects about 10% of patients.

Progressive-Relapsing MS (PRMS) is a rare subtype in which patients commence with a progressive course upon which relapses are superimposed. PRMS is the least common form, affecting about 5% of patients.
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DIAGNOSIS

The classical definition of MS requires the demonstration of lesions disseminated in time and space (within the CNS) for which there is no better explanation.13 Because of the growing awareness of the importance of MRI in diagnosing MS, the National Multiple Sclerosis Society and the International Federation of MS Societies convened an International Panel on the Diagnosis of MS in July 2000. The main purpose of this meeting was to clarify and simplify the Poser criteria definitions widely used to diagnose MS by generating an update that would integrate both clinical and MRI diagnostic criteria. One of the major differences between the proposed update and the Poser criteria is the recommendation that MRI findings be used to supplement clinical findings in order to establish dissemination of lesions in space and/or time.14 The panel extended the Poser definition to allow a diagnosis to be made with only 1 clinical episode of demyelination followed by detection of new lesions on MRI 3 months after the initial attack.14

The proposed criteria also defined more precisely the characteristics of MS lesions to allow for more accurate diagnosis (Table 4; Figure 3). In cases in which an MRI scan performed 3 months after an attack of symptoms revealed the formation of new lesions with characteristics suggestive of MS, an early diagnosis could be made. Although these recommendations were designed to transform the diagnosis of MS into a “science” rather than an “art,” there have been concerns that the criteria may be too restrictive and more applicable to clinical trials than to day-to-day practice. Thus, the proposed criteria have not been adopted by the neurology community.

The primary care clinician’s clinical observations usually are what motivate further testing and diagnostic confirmation by a neurologist experienced with MS. Imaging studies, and in some cases cerebrospinal fluid (CSF) analysis and evoked potentials, can provide confirmatory evidence. An MRI scan of the brain is the most useful test for confirming the diagnosis of MS; it is found to be abnormal in almost all patients with MS,14 revealing lesions that appear predominantly in the cerebral white matter or spinal cord. Periventricular, gadolinium (Gd)-enhancing, juxtacortical, and posterior fossa lesions are features suggestive of MS plaques. The plaque burden at the time of clinically isolated demyelinating syndrome is predictive of the likelihood of developing a second clinical attack, and increased T2-weighted MRI lesion load forebodes a worse prognosis. Thus, MRI has played an increasingly important role in the diagnosis, prognosis, and evaluation of patients with MS.


*Adapted with permission from Lublin et al. Neurology. 1996.9
MRI may be used to assess disease activity in patient follow-up and to determine effectiveness of immunotherapies. In addition, MRI assessments have played an important role in clinical trials of therapies for MS, and are used as secondary outcome measures. Much has been learned about the neuropathology of MS via the various types of MRI techniques. However, despite the increasing role of MRI in MS, there is not yet a clear correlation between clinical disability and MRI findings. The clinical effect of MS lesions visualized by MRI is dependent on lesion location, extent and duration of inflammation, and the underlying response of the nerve tissue to inflammatory injury and demyelination. T2-weighted MRI lesions are pathologically nonspecific and may represent demyelination, tissue matrix destruction, edema, gliosis, and lesions in the process of remyelinating. Gd-enhanced lesions are thought to represent areas of blood-brain barrier permeability and have been associated with inflammatory cell influx pathologically; thus this measure may be useful to determine lesion activity. Combined histopathologic and MRI studies have provided the most compelling evidence that marked hypointense T1-weighted MRI lesions reflect severe tissue damage. These studies have demonstrated a strong correlation between lesion hypointensity on T1-weighted images and the percentage of residual axons.

It the van Waesberghe study, postmortem tissue samples from 17 MS patients were evaluated on the basis of T2-weighted imaging, including normal-appearing white matter and T1-weighted hypointense lesions, and magnetization transfer ratios (MTR, which is another MRI-based method of assessing tissue changes in the brain). Postmortem tissue sampling by MRI revealed a range of pathology, illustrating the high sensitivity and low specificity of T2-weighted imaging. T1-weighted hypointensity and MTRs were strongly associated with axonal density, emphasizing their role in monitoring disease progression in MS. Beyond the MRI, additional tests are also sometimes useful for identifying subclinical lesions in sensory pathways or lesions that are clinically suspected based on patient symptoms. The visual evoked potential test is the most useful test in this regard as it can provide evidence of optic nerve demyelination that may not be visible on MRI scan. Lumbar puncture can be useful in situations in which MRI or evoked potential tests are inconclusive. CSF analysis is neither specific nor sensitive for MS. In established disease approximately 90% of patients with MS will have increased CSF immunoglobulin G (IgG) concentrations or oligoclonal bands (OCB), but early-on the sensitivity may be significantly lower. In addition, elevated IgG and OCB may be seen in other immune-related conditions, thus, this test is not 100% specific for MS. Finally, it is important to obtain blood work to rule out systemic conditions that sometimes mimic MS.

Table 4. Magnetic Resonance Imaging Criteria for Brain Abnormality

Must show 3 out of 4 of the following:

- 1 Gd-enhancing lesion or 9 T2-hyperintense lesions if there is no Gd-enhancing lesion
- At least 1 infratentorial lesion
- At least 1 juxtacortical lesion
- At least 3 periventricular lesions

Note: 1 spinal cord lesion can be substituted for 1 brain lesion. Gd = gadolinium.

Figure 3. Applying New Diagnostic Criteria for Multiple Sclerosis

Paired transverse MRI slices from a patient with MS at baseline (left) and 3 months later (right). The follow-up scan shows development of a new T2 bright MS plaque (top right), which also is shown to enhance with contrast (bottom right). Development of a new enhancing lesion 3 months after an initial demyelinating episode provides evidence for dissemination in time and allows one to make a diagnosis of MS. Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis.
TREATMENT

Three formulations of interferon β (IFNβ) and glatiramer acetate are currently Food and Drug Administration (FDA) approved for the treatment of RRMS.

INTERFERON BETA AND GLATIRAMER ACETATE

The disease-modifying agents IFNβ-1a and -1b and glatiramer acetate have been shown to reduce brain lesion development, and also to reduce the frequency and severity of relapses (Figure 4).\textsuperscript{19,26} It is widely believed but not universally accepted that these agents reduce future disability and improve the quality of life for many individuals with RRMS.\textsuperscript{27} Data from studies of IFNβs in secondary-progressive disease also support a beneficial effect on relapses and MRI-defined disease activity in these patients, but not a consistent effect on slowing progression at this stage of the disease.\textsuperscript{27,28} The IFNβs or glatiramer acetate may be used as first-line treatments in patients with RRMS. The decision of which drug to use should be made by an experienced neurologist in conjunction with the patient and should be based on efficacy, disease activity, and the patient’s preferences.

The interferons currently available in the US market are intramuscular IFNβ-1a, subcutaneous IFNβ-1a, and IFNβ-1b. The major difference among these drugs is their dosing: intramuscular IFNβ-1a is given once a week and subcutaneous IFNβ-1a and IFNβ-1b are given every other day or 3 times per week. Influenzalike symptoms occur in approximately 60% of patients treated with these agents, but these typically dissipate with continuing therapy and can be managed with prophylactic nonsteroidal anti-inflammatory agents. Liver function tests must be monitored in all patients receiving IFNβ therapy.

MITOXANTRONE

Mitoxantrone is a chemotherapeutic agent indicated for the reduction of neurologic disability and/or frequency of clinical relapses in patients with SPMS, PRMS, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). It is not indicated in the treatment of patients with PPMS.\textsuperscript{29} A phase III study of mitoxantrone reported that it reduced the number of treated MS relapses by 67% and slowed disease progression significantly.\textsuperscript{30} However, due to its cardiotoxicity, mitoxantrone can be used only for 2 to 3 years, and left ventricular ejection fraction should be measured by echocardiogram before each dose administration. In addition, reports of therapy-related leukemia have raised additional concerns about the use of this agent.

NATALIZUMAB

Natalizumab is a monoclonal antibody that is given via infusion every 4 weeks. It binds to an adhesion molecule called VLA-4 and inhibits migration of T-cells, B-cells, and monocytes from the bloodstream, across the blood-brain barrier, and into the brain and spinal cord.\textsuperscript{31} Two separate 2-year trials were conducted to assess the effect on relapse rates, progression of disability, and MRI measures of disease in patients treated with either natalizumab monotherapy vs placebo (the Antegren Safety and Efficacy in RRMS, or AFFIRM, trial [the original brand name for natalizumab was Antegren]) or natalizumab plus IFNβ-1a vs IFNβ-1a alone (the Safety and Efficacy of Natalizumab in Combination with Avonex\textsuperscript{6}, or SENTINEL, trial [Avonex is the brand name for IFNβ-1a]). Final study data will be published in 2005, but...
preliminary results from the AFFIRM trial have shown that natalizumab reduced relapse rates in study subjects by 68% compared with placebo (P < .0001), prompting the FDA to fast-track the drug’s approval process. Gd-enhancing lesions were reduced by 92% in patients treated with natalizumab compared with placebo. The 2-year data from the AFFIRM trial suggested natalizumab is generally safe and well tolerated; common associated adverse events were headache, fatigue, and arthralgia. Hypersensitivity reactions were observed in 3.8% of patients in AFFIRM, with only 1.4% being classified as serious.

Unfortunately, during the extension phase of the study 2 patients in the combination therapy trial (SENTINEL) developed progressive multifocal leukoencephalopathy, which is caused by JC viral infection of the brain. Natalizumab has been suspended from marketing pending assessment of the ultimate risk of this infection and whether it is related only to the combination of natalizumab and IFNβ-1a or to natalizumab monotherapy itself.

**GENERAL HEALTH MAINTENANCE AND PREGNANCY**

Since many MS patients are young and otherwise healthy they may tend to focus on MS and ignore routine health maintenance. The primary care clinician should remind patients of routine healthcare including physical examinations (eg, PAP smears and breast examinations), blood work (eg, lipid panel, etc), smoking cessation, weight control, and discussion of emotional and social well-being. During pregnancy, the disease often improves, however, there is an increased risk of relapse in the first 3 to 6 months postpartum. It is generally advisable for patients to discontinue their MS medications before becoming pregnant and reinstitute the therapeutic regimen as soon as possible postpartum.

**AREAS FOR FUTURE RESEARCH**

Some types of MS may benefit from therapy that targets B-cells, which have been postulated to play a number of roles in the pathophysiology of autoimmune disease, including autoantibody formation, antigen presentation to T-cells, and cytokine production. One such agent, rituximab, is currently indicated in the United States for relapsed or refractory low-grade or follicular non-Hodgkin’s lymphoma. The drug currently is being tested in MS patients who fail to respond to existing therapies.

Another fertile area for research is neuroprotective approaches to treatment. Selective immunomodulation might be used to inhibit upstream damaging inflammation with specific targeting of proteolytic enzymes. Therapies that specifically target downstream events such as neuronal cell death and axonal degeneration are desperately needed. Candidate drugs are being explored that could interfere with cell death pathways or supply trophic support to dying axons. In addition, reparative strategies such as enhancing remyelination by oligodendrocyte progenitor cells or delivery of neural stem cells will someday change the inexorable course of this devastating disease.

**CONCLUSION**

MS is a common disabling disease of young adults. The primary care clinician who is familiar with the early symptoms and signs of MS can facilitate early diagnosis by obtaining a brain MRI and/or neurologic consultation. Early initiation of immunomodulating therapy can reduce disease relapses and formation of new MRI lesions.

**REFERENCES**

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