MULTIPLE SCLEROSIS: A PRIMER AND UPDATE*

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ABSTRACT

Multiple sclerosis (MS) is a chronic neurologic disorder that is characterized by central nervous system inflammation, loss of myelin, and eventual progressive neurodegeneration and neurologic impairment. Most patients are initially diagnosed with relapsing-remitting MS. This form of MS is characterized by attacks—new symptoms lasting at least 24 hours and separated from other new symptoms by at least 30 days—followed by remissions, during which symptoms resolve or partially resolve. Over time, a majority of patients develop secondary-progressive MS, which is characterized by an irreversible progression of symptoms without improvement. MS is probably caused by the interaction of genetic susceptibility, altered function of the immune system, and exposure to certain viruses or other environmental risk factors. A number of clinical, radiologic, and laboratory methods are used to diagnose MS, to track the progression of the disease over time, and to monitor the effects of therapy. MS therapy typically requires long-term parenteral treatment, and treatment adherence is often a significant challenge. Medication adherence may be improved by patient education about MS and the positive effects of therapy on the course of the disease, in addition to techniques to reduce the pain or discomfort of regular injections.


MULTIPLE SCLEROSIS: IMPACT AND CLINICAL COURSE

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by myelin destruction and axonal damage. The term “multiple sclerosis” refers to the 2 defining characteristics of the disease—the numerous affected areas of the brain and the spinal cord, which produce multiple neurological symptoms that accrue over time, and the characteristic plaques or sclerosed regions that are visible with radiographic assessment of the central nervous system (CNS), especially of the optic nerves and white matter. MS affects approximately 250,000 to 350,000 people in the United States. It is the second most common cause of neurologic disability in the United States, following only traumatic accidents, and is the leading cause of non-traumatic disability in young adults. The treatment of MS is associated with healthcare costs that total more than $10 billion each year in the United States. Known risk factors for MS include age, sex, race, geographic location, and genetic factors. MS most often occurs for the first time between the ages of 20 and 45 years. It is more common among females than males, by a ratio of approximately 2:1 to 3:1, and is more common among whites than among individuals of other racial or ethnic groups. In general, the prevalence of MS increases with increasing distance from the equator. Genetic studies suggest that MS is at least partly heritable, although MS also occurs in the absence of a family history of the disorder.

The structure of a healthy nerve fiber and the effects of MS on nerve function are shown in Figure 1. Nerve impulses are carried along the axon, a long fiber that is surrounded by a fatty substance known as myelin. Myelin is produced by a specialized type of CNS cell, the oligodendrocyte. The myelin sheath is divided into segments, with a myelin-free region known as the node of Ranvier between each myelinated portion. Myelin supports and insulates the axon,
and contributes to the rapid transmission of nerve impulses. As shown in Figure 1, MS is characterized by the destruction of myelin, which results in the loss of normal nerve conduction. This myelin destruction is caused by the infiltration of immune cells—in particular, CD4+ and CD8+ T lymphocytes—into the CNS. Although these cells are normally prevented from entering the CNS by the blood-brain barrier, they are able to penetrate CNS tissues in individuals with MS. For many years, it was generally believed that the long-term progression of MS was caused by the gradually increasing loss of myelin. More recently, it has become clear that the long-term progression of MS is more closely related to the destruction of axons and subsequent neurodegeneration, rather than to accumulating inflammation and demyelination.

As shown in Figure 2, there are several different types of MS, which vary in their initial presentation and long-term clinical course. The most common form of MS upon diagnosis is relapsing-remitting MS (RRMS), which accounts for approximately 85% of patients who are initially diagnosed with MS. RRMS is characterized by a pattern of clearly defined acute MS attacks, with full recovery of function between attacks. Over time, some residual impairment may persist between episodes. Approximately 50% of patients who initially have RRMS develop secondary progressive MS (SPMS) within 10 years of the initial diagnosis. SPMS is characterized by the gradual, irreversible loss of neurological function. Some patients may also have periods of acute exacerbation in association with the gradual decline of SPMS. Primary progressive MS (PPMS), which affects approximately 10% of patients with MS, is characterized by a progressive and nearly continuous decline in function from the onset of the disease, without an initial period of relapses and remissions. Finally, approximately 5% to 10% of patients have benign MS, which is characterized by an abrupt onset, few exacerbations, and little or no permanent disability. Benign MS can really only be diagnosed in hindsight, after a period of 20 to 30 years with no significant progression of the disease. No consistent early markers of benign MS have been identified.

The causes of MS are not completely understood. MS is probably caused by a combination of factors, which may include genetic susceptibility, altered func-
tion of the immune system, and exposure to certain environmental factors (including measles, mumps, rubella, and Epstein-Barr virus). A number of factors have been associated with a relatively favorable or unfavorable prognosis. Predictors of more favorable outcome include female sex, onset of MS before age 35 years, attacks that are restricted to only one region of the brain, complete recovery between exacerbations, no evidence of brain stem involvement, infrequent attacks, and sensory involvement (eg, sensations of tingling or numbness). Conversely, indicators of a relatively poor prognosis include male sex, onset after age 35 years, involvement of multiple brain regions, poor recovery after attacks, brain stem involvement, and frequent attacks.

DIAGNOSING MS AND ASSESSING TREATMENT OUTCOMES

Several tests are used to diagnose MS and to monitor its progression over time. No single test or procedure is sufficient for a diagnosis of MS. Tests include magnetic resonance imaging (MRI) to identify CNS lesions, measures of nerve function (eg, visual evoked potentials), and lumbar puncture for the evaluation of cerebrospinal fluid (CSF). Traditionally, a diagnosis of MS required evidence of lesions or plaques in at least 2 distinct areas of the CNS, with lesions occurring at 2 or more points in time. More recently, a modified set of diagnostic criteria for MS (the McDonald Criteria) were introduced by the International Panel on MS Diagnosis. These revised diagnostic criteria require the presence of multiple lesions that are separated in time and space, and they permit the use of MRI, CSF, or evoked potential findings to identify second MS attacks. The progression of MS may be assessed using MRI, or using a clinical rating scale. The most widely used clinical scale is the Kurtzke Expanded Disability Status Scale (EDSS; Table). This scale is easy to use in clinical practice because it is based on a numerical score from 1 to 10, divided in increments of 0.5. However, the EDSS is not a strictly linear scale—progressing from a score of 1 to 2 represents a modest change in function, whereas progressing from a score of 8 to 9 represents more serious disability. In addition, the EDSS primarily considers the patient’s ability to walk, and does not include an assessment of cognitive function. An alternative approach is the use of the MS Functional Composite (MSFC) scoring system, which combines results from 3 individual measures into a single score—ambulation, arm and hand function, and cognition. It is expected that the MSFC will eventually replace the EDSS for the evaluation of the clinical progression of MS. Progression of MS may also be evaluated using MRI scans, which are helpful for confirming disease progression in patients for whom clinical evidence of disease activity is unclear. It should be noted that approximately 5% of people with MS do not exhibit evidence of the disease on MRI scans. In general, 3 types of lesions may be identified using MRI methods. Lesions (T1) are generally a marker of tissue destruction. Extensive T1 lesions are sometimes referred to as “black holes.” Lesions detected with T2-weighted MRI commonly represent either edema in an active lesion, or a chronic inactive lesion with variable degree of axon loss. Finally, gadolinium (Gd) contrast-enhancing lesions reflect the breakdown of the blood-brain barrier and indicate sites of active inflammation. A number of new techniques are being developed to improve the ability of MRI to assess tissue injury and the response to treatment, but these methods are not yet widely used in clinical practice.

IMPROVING TREATMENT ADHERENCE

All of the treatments for MS are parenteral agents that are administered by repeated self-injection over a long-term period. Many patients find it difficult to adhere to long-term treatment. A number of techniques may help to improve treatment adherence. Patient education is essential so that patients understand

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EDSS = Expanded Disability Status Scale.
Data from Kurtzke.
stand that the treatments primarily work over time to prevent disease, rather than producing an immediate benefit. Patients may be counseled about ways to reduce the pain or discomfort associated with some MS medications, including:

- Using antipyretic medications to relieve flu-like symptoms
- Receiving injection training with a nurse
- Using autoinjectors
- Injecting medications at room temperature or body temperature
- Icing or using warm compresses on the site before and after injection
- Rotating injection sites to minimize discomfort

Patients should also be counseled that adverse effects of treatment (eg, flu-like symptoms with interferons and postinjection reaction with glatiramer acetate) are usually transitory.

**CONCLUSIONS**

Multiple sclerosis is a chronic, disabling neurologic condition that generally follows a pattern of relapses and remissions during the early stages, with eventual progression to irreversible disability. The causes of MS are not completely understood, but probably include interactions between genetic, immunologic, and environmental factors. Adherence to long-term treatment is often difficult for patients, and may be improved by patient education or by measures to reduce treatment-associated pain and discomfort.

**DISCUSSION HIGHLIGHTS**

**Dr Bainbridge:** Is there a difference in the pathophysiology between PPMS and the other presentations? And, does that affect how we diagnose patients using the McDonald Criteria?

**Dr Bennett:** Primary progressive disease is by far the most vexing problem for the treatment of MS. It has failed to respond to anything that we have. That's not terribly surprising because all of our therapies are based on an anti-inflammatory approach. Primary progressive disease causes much less inflammation, and the lesion pathology is slightly different. We shouldn't rush to think that that means that there is a different cause to primary progressive MS. A single cause might cause several different clinical presentations in the CNS due to different immunologic or neurologic responses to injury. Such responses may be based on genetics and environmental exposure.

**Mr Watkins:** This illustrates one of the struggles with many of the diseases that we're now learning how to treat. They are chronic diseases with presumptive diagnoses, so we don't know how many diseases are actually included in the category, or how many physiological pathways may be involved. The presence of these different pathways makes it difficult for the payor to decide on what basis a particular treatment should be covered. We're hoping that over the next few years new diagnostic modalities, such as pharmacogenomics, may tell us something about why one patient responds to a treatment when another patient does not. This information would help us improve the cost effectiveness of expensive biologic drugs, such as those used to treat MS.

**Dr Bennett:** I think that we need to look at the McDonald Criteria as a very positive step forward. Part of the design of the criteria was to include the strength of what we learned about MRI to make diagnosis earlier. It may be that treating these patients earlier is going to be very effective since we're limited to an anti-inflammatory therapy and patients who are diagnosed early using these criteria will tend to have highly inflammatory disease. However, because our current therapies are all anti-inflammatory, by increasing the number of patients with active inflammation in our more recent clinical trials, we may be artificially showing that newer drugs look better than old ones. Because we have no gold standard test for MS, we have to try to be as specific as possible, and the MRI criteria were chosen for specificity, not sensitivity, in an effort to try to screen out confounding disorders.

**Dr Rauchway:** An important part of the criteria is that the symptoms are not attributable to a better explanation. Not every patient who has been diagnosed with MS has been evaluated by a neurologist. Although it's sometimes very clear-cut, other times it's not, and there is always a possibility for misdiagnosis.

**Dr Bennett:** We will get more sophisticated in our ability to diagnose MS earlier, but right now there are some patients who clearly have MS before they meet criteria. However, there's a large group for whom there are no data that they would do any better if they started disease-modifying therapy right away or waited 18 months for a new lesion on an MRI scan or a new clinical attack.

**Dr Bainbridge:** It's difficult to try to keep patients adherent to therapy, especially the ones who are doing more poorly. If you start people on therapy early, are
you going to be able to continue them on therapy after a while if they progress?

Dr Bennett: That touches on what Dr Guthrie brought up in her talk regarding the issue of benign MS. If we’re making the diagnosis earlier, we want to screen out those patients who may not need to be treated. Some studies suggest that the percentage of patients with benign MS may be higher than Dr Guthrie presented, possibly 17% to 20%. The biggest problem that we have is being able to diagnose benign MS. Right now we have to treat everyone at risk because our only criteria for identifying benign MS is retrospective, and it’s still being debated whether 10 years into disease or 20 years into disease is enough time to truly identify it. Once we have more prospective diagnostic criteria, I think we’ll be able to better decide who to treat and when to treat.

Dr Ryan: I think it should be noted that our ability to diagnose has improved considerably since 15 years ago. We’ve come a long way from the days in which you put the patient in a hot water bath to see if they got worse. I think that many people believe that the diagnosis of MS is still very uncertain, but we’ve made great strides with MRI and nerve conduction studies and similar measures. We now have the ability to say with pretty good certainty whether someone has MS or not.

My Watkins: Yes. When the MRI methodology first appeared along with the beta-interferons over 10 years ago, I think most health plan pharmacists were dissatisfied with MRI because it was only an intermediate marker for MS progression, and we generally prefer to see trials that use real clinical endpoints. I think this conversation shows that in the intervening decade we’ve become convinced that MRI evidence correlates quite well with disease progression and activity. That’s unusual if you compare it with other diseases for which the intermediate markers are still considered suboptimal. In fact, in some cases, newer evidence suggests that these markers are less reliable than we had previously thought, such as the relationship between blood pressure and major cardiovascular endpoints, for example.

REFERENCES