

Multiple Sclerosis: The Basics and Beyond

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Multiple sclerosis (MS) is the most common acquired inflammatory demyelinating disease of the central nervous system. Over the past decade, there have been remarkable advances both in understanding the pathogenesis of MS and treating the disease. Immunomodulatory and immunosuppressive therapies have been developed that decrease relapse rate, slow progression of disability, and stabilize magnetic resonance imaging (MRI) changes.



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Demographics. Multiple sclerosis (MS) is a relatively common neurological disease, especially among younger people. In the United States, there are 350,000 to 400,000 people who have been diagnosed with MS. Worldwide, there are about 2.5 million cases of MS. The annual cost of the disease is estimated to be \$2.5 billion per year in the United States. Typically, those who are diagnosed with MS are young (20 to 40 years old), Caucasian (especially Northern European descent), and female (female:male ratio of 2-3:1). There are, however, many exceptions to this typical presentation.¹

Clinical Features and Diagnosis. Four major clinical subtypes of MS exist. Most people with MS (about 85 percent) have a relapsing-remitting MS (RRMS), which is characterized by discrete relapses with neurologic deficits such as visual difficulties, weakness, numbness, gait dysfunction, or incoordination. Generally, there is total or partial recovery from these relapses. Over time (usually 10 to 25 years), the relapsing-remitting course converts to a progressive course, known as secondary progressive MS (SPMS), in which there is slow neurological worsening, especially with gait instability and lower extremity dysfunction. Primary progressive MS (PPMS) is characterized by

slow worsening from the onset — people with this form of MS do not experience attacks. The least common form of MS (about 5 percent) is progressive-relapsing MS, in which there is a progressive course initially. Subsequently, attacks are superimposed on the progressive course.²

In addition to the neurological exam, 2 important elements for diagnosing MS are the history and the diagnostic test results. With the history, there should typically be 2 or more different types of neurologic events (“attacks”) that are separated by a month or more *and* cannot be explained by any other diagnosis. In addition, MRI of the head (and possibly spine) should show typical lesions and other MS “mimic” processes, such as lupus and vitamin B12 deficiency, should be ruled out with blood tests. If indicated, the diagnosis may be further clarified with CSF studies and evoked potentials.

Recent revisions in the diagnostic criteria now extend the use of MRI in making a diagnosis. Specifically, MS can now be diagnosed if a patient experiences a single clinical event and subsequently develops a new lesion on MRI. In other words, a new MRI lesion may substitute for a clinical event.^{3,4}

Clinically Isolated Syndrome. An important and increasingly recognized entity

is “clinically isolated syndrome” (CIS). This refers to the situation in which a patient has one clinical event (as opposed to 2 events) that is typical for an MS attack. When this clinical history is combined with an MRI that shows multiple lesions, the risk for having a second clinical event or developing a new MRI lesion in the future is high. In fact, even though patients with this syndrome do not meet the criteria for an MS diagnosis, the risk for developing MS is high enough that these patients are usually treated with MS disease-modifying medications.⁵

Differential Diagnosis. When MS presents in a typical fashion, such as optic neuritis and an MRI with characteristic demyelinating lesions, the diagnosis is usually straightforward. However, the diagnosis may be challenging with atypical presentations of MS and MS variants, which include neuromyelitis optica (Devic syndrome) and acute disseminated encephalomyelitis (ADEM).

The diagnosis may also be challenging with “MS mimic” diseases.⁶ Categories of MS mimic diseases, with representative examples, include:

- Inflammatory/rheumatologic-Sjogren’s syndrome, lupus, sarcoidosis
- Vascular-vasculitis
- Infectious-Lyme disease
- Metabolic-vitamin B12 deficiency
- Degenerative-genetic-primary lateral sclerosis, cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy (“CADASIL”)
- Oncologic-primary CNS lymphoma
- Spinal cord disease-spinal stenosis, spinal cord tumors

Evolving Pathology and Treatment: “Old school” vs “New school.” In MS, as in other diseases, there is a close interplay

between our understanding of the pathology and our development of therapies. In the case of MS, we currently have a *partial* understanding of the underlying pathology and we have *partially* effective disease-modifying therapies.

The classic, “old-school” understanding of MS is that it is an immune disease characterized by recurrent inflammation and loss of myelin (the “insulation” on nerve fibers) in the central nervous system. These recurrent inflammatory events cause MS attacks (as seen in relapsing-remitting MS) and the characteristic demyelinating lesions seen on MRI. In this model, inflammation is the central pathologic process. Consequently, the current disease-modifying MS drugs are designed to act primarily as anti-inflammatory agents through immunosuppression or immunomodulation.

There are currently 6 FDA-approved drugs in the anti-inflammatory category. These drugs have been shown to decrease the frequency and severity of attacks, decrease MRI lesion activity, and slow disability progression. The most commonly used drugs are the injectable (subcutaneous or intramuscular) immunomodulatory agents: glatiramer acetate, also known as Copaxone, and beta-interferons, which include Avonex, Betaseron, and Rebif. These drugs should be strongly considered in patients with relapsing forms of MS and also, as noted above, in patients with clinically isolated syndrome.

There are 2 other FDA-approved MS drugs, which are usually used when the injectable immunomodulatory agents (glatiramer acetate, interferon) are not effective. Mitoxantrone (Novantrone) is an immunosuppressive chemotherapy compound that is typically given intravenously every three months. The newest FDA-approved medication is natalizumab (Tysabri), a monoclonal antibody which, by binding to



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alpha-4-integrin, inhibits the migration of immune cells across the blood-brain barrier. With natalizumab, which is given intravenously every 28 days and was approved by the FDA in 2006, there is a very small but real risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral brain infection that is usually fatal. Consequently, this drug needs to be used with close monitoring.⁷

The “new school” approach to MS pathology is actually a resurrection of an old observation. Specifically, in the mid-1800’s, Charcot, the famous French neurologist, noted that there was a loss of axons (the nerve fibers), not just demyelination, in MS. This finding was rediscovered about 10 years ago and has led to important new insights into MS pathology and treatment.⁸

Axonal loss is a neurodegenerative process which is distinct from inflammation. It is believed that this slow degeneration accounts for slowly progressive clinical courses (as seen in primary progressive and secondary progressive MS) and atrophy of the brain and spinal cord on MRI. The exact relationship between inflammation and degeneration has not been elucidated and continues to raise questions: Does inflammation lead to degeneration? Or, does degeneration cause inflammation? Alternatively, are there multiple subtypes of MS in which either inflammation or degeneration are more important?

The fact that degeneration occurs in MS raises important treatment issues. The treatment strategy for degeneration is known as *neuroprotection*. At this point, these strategies have undergone more investigation in aging-related neurodegenerative diseases, such as Alzheimer’s and Parkinson’s disease, than in MS. Current MS therapies, such as glatiramer acetate and interferons, may have

indirect effects on degeneration — these drugs may help prevent degeneration by decreasing inflammation. In addition, these drugs may increase levels of growth factors which may have neuroprotective (as well as anti-inflammatory and neuroregenerative) effects.

An exciting area of neurodegeneration research involves exercise and growth factors.⁹ In animal studies, exercise leads to increased brain levels of various growth factors. A forced exercise program has therapeutic effects in animal models of other neurodegenerative diseases, including Parkinson’s disease and amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease). Also, in humans, exercise may decrease the risk of developing Parkinson’s disease. This area of research is relatively unexplored in MS — these findings in other diseases raise the question as to whether exercise could have a disease-modifying effect in MS.

In the past, MS was not typically thought of as a neurodegenerative disease. In the future, however, MS could actually become a model for clinical trials of neuroprotective agents. The clinical attacks, due to inflammation, that typically occur early in MS could serve as an indicator of an underlying, subclinical, neurodegenerative process — thus, neuroprotective agents could be administered at a very early time point in this process. This is in contrast to other diseases that are more purely degenerative, such as Alzheimer’s and Parkinson’s disease. When these diseases become symptomatic, a significant amount of degeneration has already occurred and it may be too late to obtain significant therapeutic effects from neuroprotective therapies.

Conclusion. The Future of MS Research. This is a hopeful time for MS

research. Our improved understanding of the underlying pathology of the disease has led to the development of many promising new therapies. Several oral disease-modifying drugs have produced therapeutic effects in smaller studies and are now being tested in large clinical trials. There are 10 to 20 different monoclonal antibodies in development. Also, in the area of degeneration, many different strategies are being developed for neuroprotection, neuroregeneration, and remyelination.

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