National Multiple Sclerosis Society
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Information for Health Professionals

Overview of Multiple Sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a disease that affects the central nervous system, which includes the brain, spinal cord, and optic nerves. MS is believed to affect approximately 400,000 Americans, typically striking between the ages of 20 and 50. While some persons will have a limited number of "attacks" or "relapses" and remain fairly healthy for decades, others may deteriorate rapidly from the time of diagnosis. MS is, therefore, a variable and unpredictable disease, and poses a complex and unique clinical challenge for healthcare professionals.

PATHOPHYSIOLOGY OF MS

Immune Dysfunction and Damage to CNS

MS is characterized by the formation of multiple lesions along the nerve fibers in the brain and spinal cord. The key players include:

- Axons, the nerve fibers that transmit information via electrical signals
- Myelin, the fatty substance that wraps around the axons like an insulating sheath
- Oligodendrocytes, the cells that make up the myelin
- Blood vessels that supply oxygen and nutrients
- Inflammatory factors, such as cytokines
- T-cells, a form of white blood cell
- Antigen-presenting cells, which introduce the myelin antigen to the T cell

MS is thought to be an autoimmune disease, but what triggers the immune system to attack the body is still unclear (Murray, 2000). During this immune response, cells that identify antigens are somehow triggered to interpret one of the components of myelin as foreign. When antigen-presenting cells introduce the myelin antigen to the T cells, the T cells pass through the

blood–brain barrier and mount an attack on the myelin, activating more T cells and other immune cells in the process. Other inflammatory factors, such as cytokines, are released, and the end result is an immunologic cascade that produces tissue damage, not only to the myelin sheath, but to the underlying axons as well.

This "demyelination" makes the transmission of information via axons more difficult. Ultimately, there is interference with the conduction of nerve impulses from the sensory organs to the CNS and from the CNS to the muscles. Injury to the axons themselves, called "axonal damage," can be part of this destructive process even early in the disease and may result in permanent loss of neuronal transmission.

At least initially, however, the process of MS is typically a waxing and waning one. Inflammatory episodes occur in the form of periodic acute attacks, and once the inflammation subsides, impaired function is usually recovered either completely or partially. Reversal of inflammation or the process of "remyelination" can occur over and over, or, permanent damage may occur at any time (Herndon, 2000).

Possible Triggers

While MS is almost certainly an autoimmune disease, the factor or factors that trigger an attack on the spinal cord and brain's white matter remain unknown. A number of hypotheses are being explored, one being the role of **viruses**. Peripheral blood antibody titers to many viruses are elevated in people with MS. These include varicella zoster, vaccinia, rubella, Epstein–Barr, human herpes virus 6 (HHV-6), and others. In some cases, virus-specific antibody is also detected in the cerebrospinal fluid, and recently some viruses, especially HHV-6, have been detected near the characteristic brain lesions of some persons with MS. The relevance of these findings to the pathophysiology of the disease remains to be determined (Olek, 2005).

Environmental factors may also be involved. MS occurs more often in countries with a moderate, cool climate than in warmer countries. In both the northern and southern hemispheres, MS is more frequent at greater distances from the equator. This applies to regions within a country itself—in the U.S., the incidence of MS is greatest in the northern states (Halper & Holland, 2002).

More certain is the **genetic link** seen in MS. MS prevalence rates are quite variable between different ethnic and racial groups, being highest in northern European Caucasians, and lowest in Asians. While no causative gene has been identified, the risk for MS is 10 to 50 times higher for persons with an affected relative than for persons with no family history; the risk, however, remains low. The concordance in identical twins is approximately 30%, as compared to 3–5% in fraternal twins. It is likely that multiple genes are involved, and an interaction with an external trigger, such as a virus or environmental factor, may be necessary to initiate disease (Miller, Lublin & Coyle, 2003).

CLINICAL PATTERNS

MS is essentially divided into four main courses (Lublin & Reingold, 1996):

- **Relapsing-remitting**—Episodes of acute worsening of neurologic function, with some amount of recovery (the most common form) and no progression in between.
- **Primary-progressive**—Continuing worsening of disease without distinct relapses.
- **Secondary-progressive**—Relapsing-remitting disease initially, eventually converting to a progressive form with a gradual loss of function.
- **Progressive-relapsing**—Progressive disease from onset, with acute relapses and continuing disease progression.

DIAGNOSIS

MS is often suspected on the basis of symptoms. Events that are highly suggestive of MS include gait disturbances, optic neuritis, persistent binocular double vision or numbness. Such symptoms may occur periodically, then disappear for months or years.

Several tests are used in the diagnostic work-up:

- **Magnetic resonance imaging (MRI) scans**, which may reveal the characteristic lesions or plaques in the white matter that depict areas of inflammation or demyelination. MRI also helps track the progression of MS over time. The characteristic lesions include:
  - **Enhancing lesions**—These lesions are seen with gadolinium enhancement, which reflects leaks in the blood/brain barrier, the site of immune attack. Gadolinium-enhanced lesions are considered new or active; enhancement of these lesions comes and goes.
  - **Non-enhancing lesions**—These lesions are detected without gadolinium. Hypointense lesions are thought to represent areas of axonal loss and therefore more permanent damage.
- **Lumbar puncture**, which may reveal an excess of inflammatory proteins and oligoclonal bands, the specific antibodies produced by plasma B-cells, in the cerebrospinal fluid (CSF).
- **Visual evoked potentials (VEP)**, which may demonstrate reduced transmission of impulses across nerve fibers, due to demyelination. Visual evoked potentials are the most sensitive of the evoked potential tests to MS-related damage.

Newer techniques being used in the research setting are yielding a closer look at the pathophysiology of the brain. With magnetization transfer ratio (MTR), tissue damage is more accurately quantified. MTR involves delivering energy to protons in the brain and then measuring how much is transferred or absorbed. This technique can reveal damage in brain tissue that appears normal on MRI (Filippi & Rovaris, 2000). Another approach, magnetic resonance spectroscopy, enables investigators to analyze MRI for signals from certain chemicals, such as N-acetyl-aspartate

(NAA). NAA is found largely in axons; low levels are felt to signify axonal injury (Viala et al., 2000).

CONFIRMING THE DIAGNOSIS

In 2001, the International Panel on the Diagnosis of Multiple Sclerosis, under the leadership of W. I. McDonald, FRCP, issued criteria (referred to in the MS world as the McDonald criteria) that outlined specific guidelines for using certain kinds of laboratory tests to provide evidence of attacks separated in time and space. In 2005, the International Panel met again to review data collected since 2001 and make revisions to the McDonald criteria. These revisions, conveniently called the "2005 Revisions to the McDonald Diagnostic Criteria for MS," are helping to enhance the speed and accuracy of an MS diagnosis.

Once a diagnosis of relapsing MS has been confirmed, treatment with injectable immunomodulating agents is generally recommended. These agents have been shown to reduce the frequency of relapses by about one third and are believed to slow the progression to disability.

Disease-modifying agents offer hope to MS patients; however, studies are still lacking that will validate their sustained ability to prevent disability over time. Other forms of treatment include symptom management and treatment of acute relapses.

CLINICAL SIGNS AND SYMPTOMS

The clinical symptoms and deficits are quite varied among persons with MS, and they typically change (and worsen) as the disease evolves. The most frequent include (Van den Noort & Holland, 1999):

- **Fatigue**—Reported in up to 90% of patients.
- **Motor involvement**—May occur quite early in the disease course of MS, especially in patients who present with multiple symptoms. Symptoms can include weakness in an affected limb, progressing to spasticity, hyper-reflexia, clonus, extensor plantar responses, and muscle contractures.
- **Visual involvement**—A common problem, especially blurring or haziness, which can progress to vision loss. Periorbital pain often occurs, and optic neuritis is a common presenting symptom.
- **Sensory symptoms**—Vague and poorly characterized, including squeezing and burning sensations, or numbness and paresthesias. Such symptoms are often transient, but some can progress to loss of dexterity.
- **Tonic spasms**—Brief increases in flexor tone in one or more limbs, often associated with pain.
- **Brainstem symptoms**—Most commonly, ophthalmoplegia and nystagmus. Vertigo occurs as an initial symptom in about 5% of patients but becomes more common during the

The 2005 Revisions to the McDonald Diagnostic Criteria for MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions	◆ **None**
2 or more attacks; objective clinical evidence of 1 lesion	◆ **Dissemination in space**, demonstrated by: ◆ MRI ***or*** ◆ 2 or more MRI-detected lesions consistent with MS plus positive CSF ***or*** ◆ Await further clinical attack implicating a different site
1 attack; objective clinical evidence of 2 or more lesions	◆ **Dissemination in time**, demonstrated by: ◆ MRI ***or*** ◆ Second clinical attack
1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	◆ **Dissemination in space**, demonstrated by: ◆ MRI ***or*** ◆ 2 or more MRI-detected lesions consistent with MS plus positive CSF **AND** ◆ **Dissemination in time**, demonstrated by: ◆ MRI ***or*** ◆ Second clinical attack
Insidious neurological progression suggestive of MS	◆ **One year of disease progression** (retrospectively or prospectively determined) **AND** ◆ **Two out of three of the following:** ◆ Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potentials; ◆ Positive spinal cord MRI (two or more focal T2 lesions); ◆ Positive CSF

Polman CH, et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald" criteria. *Ann Neurol* 58: 840–846.

disease course. Facial numbness, weakness and pain are less common but do occur, especially trigeminal neuralgia.

- **Cerebellar involvement**—Frequently intention tremor, which can be disabling. Other symptoms are truncal ataxia and ataxia of gait, dysarthria and "scanning speech."
- **Genitourinary symptoms**—Can occur at any time during the course of MS, including urinary urgency, frequency, incontinence, hesitancy and retention, and urinary tract infections. Bowel dysfunction, especially constipation, is also common.
- **Cognitive deficits**—Seen to some degree in about 50–60% of patients, especially short-term memory dysfunction, difficulty managing complex tasks, and confusion.
- **Depression**—The second most common symptom in MS, seen in as many as 70% of patients. Like fatigue, depression does not correlate with disease severity. The incidence of suicide in MS patients is 7.5 times higher than in the general population.

MODELS OF CARE IN MS

The spectrum of MS requires a wide array of professional services throughout the person's lifetime. Many types of healthcare professionals are involved, ranging from neurologists to nurses to neuropsychologists and social workers. The challenge is to sustain a level of support to meet individual and family needs throughout a lifetime, keeping in mind the goals of MS care: disease stabilization, wellness, maximal function and independence, and maintenance of productivity and a meaningful place in society.

SUMMARY

MS is a chronic, progressive and essentially incurable disease that most often affects young adults. It is thought to be an autoimmune diseases that affects the central nervous system. The course of MS is unpredictable and variable on a day-to-day and an individual patient basis. As chronic problems accumulate, the disease may become more steadily progressive, with fewer or no acute relapses. A diagnosis of MS is a clinical one based on a thorough history and neurologic examination, and supported by MRI and other diagnostic tests. Management strategies fall into three general categories: acute treatment of relapses, prevention of progression or reduction in the frequency of relapses, and control of specific symptoms.

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