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OVERVIEW OF MULTIPLE SCLEROSIS

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National
Multiple Sclerosis
Society

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Table of Contents

Introduction

Multiple sclerosis (MS) is a chronic, often disabling disease of the central nervous system (CNS)—the brain, spinal cord, and optic nerves. It is thought to be an immune-mediated disease in which the immune system recognizes self cells and tissues within the CNS and orchestrates an inflammatory response that damages and/or destroys:

- Myelin – the insulating substance wrapped around the nerve fibers (axons) in the white matter of the CNS
- Axons
- Oligodendrocytes - the CNS myelin-making cells (Karussis 2014).

Damaged myelin (demyelination) forms scar tissue (sclerosis), giving the disease its name. When the myelin sheath and/or nerve fiber is damaged or destroyed, nerve impulses transmitted to and from the brain and spinal cord are distorted or interrupted, producing a variety of symptoms. Inflammation, demyelination and degeneration occur in both the white and gray matter of the CNS beginning early in the disease course (Charil & Filippi, 2007; Frischer et al., 2009; Klaver et al., 2013).

It is estimated that there are approximately 2.3 million worldwide (Multiple Sclerosis International Federation, 2013) Most people are diagnosed between the ages of 20 and 50, but MS can also occur in the pediatric and geriatric populations. MS is at least 2-3 times more common in women than men.

Etiology

The etiology of MS is unknown, but decades of research indicate that MS may be the result of an abnormal immune response to some infectious or environmental trigger in a genetically susceptible individual. Each of these factors—immunologic, environmental, infectious, and genetic—is the subject of intensive ongoing research.

- Since viruses are well recognized as causes of demyelination and inflammation, it is possible that a virus or other infectious agent is the trigger in MS. More than a dozen viruses and bacteria – including measles, canine distemper, human herpes virus-6, Chlamydia pneumonia and Epstein-Barr – have been or are being investigated but none have been positively identified as the trigger in MS. Currently, attention is focused on the Epstein-Barr virus (Ascherio & Munger, 2016; Simon et al., 2015).
- Other risk factors have been identified, including smoking, low levels of vitamin D (Munger et al., 2017) and adolescent obesity (Hedstrom et al., 2016).
- MS is not directly inherited, but genetics play an important role in a person's risk of developing MS. While the risk in the general population is 1/750, the risk rises to 1/40 in anyone who has a close relative (parent, sibling, child) with the disease. Even though identical twins share the same genetic makeup, the risk for an identical twin is only 1/4—which means that some factor(s) including genetics are involved (Ebers, 2013),

(Patsopoulos et al., 2011).

- Scientists also study MS clusters—defined as higher-than-expected numbers of cases of MS that have occurred over a specific time period and/or in a certain area. Clusters may provide clues to environmental (such as industrial toxins, diet, or trace metal exposures) factors that might cause or trigger the disease. To date, cluster studies have not produced clear evidence for the existence of any triggering factor or factors in MS.

Epidemiology

- Historically, it has been observed that the risk of MS is greater farther from the equator (with reduced vitamin D exposure from the sun). However, some recent studies have not indicated the same geographic gradient, which could suggest either a change in regional risk determinants for MS or a broadening recognition of MS around the world (Koch-Henriksen et al. 2011 Ha-Vinh et al., 2016).
- Migration data suggest that exposure to an environmental agent or agents occurring before puberty may predispose a person to develop MS. Studies of migration patterns have shown that people born in areas with a high risk of MS who move to an area with a lower risk before the age of 15, acquire the risk of their new area (Kurtzke, 2000).
- MS occurs in most ethnic groups, including African-Americans, Asians and Hispanics/Latinos, but is more common in Caucasians of northern European ancestry. Some ethnic groups, such as the Inuit, Aborigines and Maoris, have few documented cases of MS. A study by Langer-Gould and colleagues (Langer-Gould et al., 2013) reported that African-American women have a higher than previously reported risk of developing MS and several studies have suggested that African-Americans may have a more active, rapidly progressive disease course (Cree et al., 2004; Weinstock-Guttman, 2010). These variations in prevalence and disease progression suggest that geography, ethnicity, and other factors interact in some complex way (Rosati, 2001), (Pearson et al., 2014) to impact a person's risk of developing MS and of disease progression.

Disease courses

Four clinical courses (phenotypes) have been identified in MS (Lublin et al., 2014).

- **Clinically isolated syndrome** (CIS) is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS.

- **Relapsing-remitting MS** (RRMS) – the most common disease course (approximately 85 percent at the time of diagnosis) – is characterized by clearly defined attacks of new or increasing neurologic symptoms. These attacks – also called relapses or exacerbations – are followed by periods of partial or complete recovery (remissions).

During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. At different points in time, RRMS can be further characterized as either **active** (with relapses and/or evidence of new MRI activity) or **not active**, as well as **worsening** (a confirmed increase in disability over a specified period of time following a relapse) or **not worsening**.

- **Secondary progressive MS** (SPMS) follows an initial relapsing-remitting course. Most people who are diagnosed with RRMS will eventually transition to a secondary progressive course in which there are fewer inflammatory changes (clinical relapses and/or new inflammatory CNS activity seen on the MRI) and a progressive worsening of neurologic function (accumulation of disability) over time. SPMS can be further characterized at different points in time as either **active** (with relapses and/or evidence of new MRI activity) or **not active**, as well as **with progression** (evidence of disease worsening on an objective measure of change over time, with or without relapses) or **without progression**.

- **Primary progressive MS** (PPMS) is characterized by worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions. PPMS can be further characterized at different points in time as either **active** (with an occasional relapse and/or evidence of new MRI activity) or **not active**, as well as **with progression** (evidence of disease worsening on an objective measure of change over time, with or without relapse or new MRI activity) or **without progression**. Approximately 15 percent of people with MS are diagnosed with PPMS.

Diagnostic criteria

The long-standing criteria (McDonald et al., 2010) for diagnosing MS require:

- Evidence of damage in at least two separate areas of the CNS (dissemination in space)
- Evidence that the damage occurred at distinct time points at least one month apart (dissemination in time)
- Ruling out other possible causes

At the present time, there are no symptoms, physical findings or laboratory tests that can, by themselves, determine if a person has MS. The diagnostic process includes a thorough medical history, neurologic exam, and tests including magnetic resonance imaging (MRI), evoked potential (EP) testing and spinal fluid analysis.

Recent proposed revisions to the McDonald diagnostic criteria (Thompson et al., 2018) allow for an earlier diagnosis in many people.

- In a patient with a typical clinically isolated syndrome (CIS) and fulfilment of clinical or MRI criteria for "dissemination in space" and no better explanation for the clinical presentation, demonstration of CSF-specific oligoclonal bands allows an MS diagnosis to be made without the previously required "dissemination in time."
- Both symptomatic and asymptomatic MRI lesions can be used for fulfilling MRI criteria for dissemination in space or dissemination in time. Previously, only asymptomatic MRI lesions could fulfill these criteria.
- In addition to juxtacortical lesions, cortical lesions can also be used to demonstrate dissemination in space requirements.
- The requirements for the diagnosis of primary progressive MS have not changed.

The main aims of these revisions are to clarify components of the 2010 McDonald criteria in order to facilitate earlier diagnosis and reduce misdiagnosis.

Treatment strategies

Comprehensive MS care included the treatment of acute exacerbations (also called relapses or attacks), disease management, symptom management, rehabilitation, psychosocial support and wellness strategies.

- **Treatment of acute exacerbations.** Exacerbations (flares, flare-ups, relapses, attacks) of MS are caused by inflammation in the CNS that damages the myelin and slows or blocks transmission of nerve impulses. An exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. However, most exacerbations last from a few days to several weeks or even months. Exacerbations can be mild or severe enough to interfere with a person's ability to function at home and at work. Symptoms associated with a MS exacerbation are variable, and can include a change in energy level, sensation, motor function, cognitive function and/or mood. Exacerbations that interfere with function are typically treated with intravenous, high-dose corticosteroids to reduce the inflammation, and accelerate recovery. Comparably high doses of oral steroids may be used instead of IV steroids (Berkovich, 2016). Steroids may decrease acute inflammation in the CNS but have no long-term benefits. ACTH (adrenocorticotropic hormone) is also approved to treat MS relapses and can be self-administered by subcutaneous injection. It is used less frequently due to high cost.

- **Disease management.** At the present time, there are more than a dozen disease-modifying therapies have been approved by the U.S. Food and Drug Administration (FDA) to treat relapsing forms of MS (including RRMS and SPMS and PPMS in those individuals who continue to have relapses). One of these medications is also approved to treat PPMS. These medications have different mechanisms of action and modes of delivery (injectable, oral, infused). It is the consensus of the Multiple Sclerosis Coalition that:
    - Initiation of treatment with an FDA-approved disease-modifying therapy is recommended:

        - As soon as possible following a diagnosis of relapsing or primary progressive multiple sclerosis, regardless of the person's age
        - For individuals with a first clinical event and MRI features consistent with MS in whom other possible causes have been excluded
        - For individuals with progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory activity
    - Treatment with a given disease-modifying medication should be continued indefinitely unless any of the following occur (in which case an alternative disease-modifying therapy should be considered):
        - Sub-optimal treatment response as determined by the individual and his or her treating clinician
        - Intolerable side effects
        - Inadequate adherence to the treatment regimen
        - Availability of a more appropriate treatment option
    - Movement from one disease-modifying therapy to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
    - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.
    - The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed collaboratively by the individual and his or her treating clinician.

Early, adequate control of disease activity – including the reduction of clinical and sub-clinical attacks and the delay of the progressive phase of the disease—appears to play a key role in preventing accumulation of disability, prolonging the ability of people with MS to remain active and enhancing quality of life (Gold et al., 2010). In considering disease activity and progression in MS, it is important to remember that cognitive as well as physical impairments are common in all disease courses (Dackovic et al., 2016) and throughout the disease course, beginning prior to initial clinical symptoms (Cortese et al., 2016; Ruano et al., 2016).

- **Symptom Management:** The inflammation, demyelination and neurodegeneration that comprise the MS disease process result in a number of possible symptoms that vary from one individual to another and over time for any given individual (see Publications for Clinicians for detailed discussions of individual symptoms; download the free Mult Scler Dx & Mngmt App for iPhone and Droid to see management strategies and psychosocial implications). Primary symptoms, which are the direct result of damage to the myelin and nerve fibers in the CNS, include the following:
    - **Fatigue:** One of the most common symptoms, occurring in about 80% of people (Induruwa et al., 2012), (Managing MS Fatigue). People living with MS can experience fatigue from many sources such as sleep disturbance, overactivity, or metabolic disorders. A type of fatigue that is unique to MS – often described as lassitude – is characterized by abrupt exhaustion occurring at a similar time each day. It is unrelated to sleep, activity or MS disease course and is worsened by

heat. MS fatigue interferes with usual daily activities.

- **Vision problems:** A common first symptom of MS. Symptoms may include optic neuritis, typically unilateral, which causes temporary blurring or loss of vision, often accompanied by pain on eye movement. It may also cause a "blind spot" [scotoma] in the center of vision). Other common visual symptoms include diplopia (double vision)and nystagmus, a rhythmic jerkiness or bounce in one or both eyes) (Managing MS Visual Impairment).
- **Ambulation problems:** Impaired walking, balance, coordination (Managing MS Ambulation Problems)
- **Spasticity:** Feelings of stiffness and a wide range of involuntary muscle spasms. Spasticity can range from relatively mild to quite severe, and treatment is approached in a step-wise fashion. *Note: Some degree of spasticity may be required to support weakened limbs.* (Patejdl & Zettl 2017)
- **Bladder dysfunction:** Occurs in at least 80% of people with MS. Most commonly a neurogenic overactive bladder characterized by urgency, frequency and possibly incontinence. Less frequent may be difficulty emptying the bladder, characterized by urgency, frequency, double voiding, incontinence and infection (Managing MS Bladder Dysfunction).
- **Bowel dysfunction:** Constipation and involuntary loss of bowel control (Managing MS Bowel Dysfunction) (Talking with your MS Patients about Bowel disorders)
- **Sensory problems/pain:** Including numbness, tingling, and neuropathic pain in the face, body, or extremities (Pain in MS)
- **Cognitive dysfunction:** Approximately 65% of people with MS will develop problems with high-level functions including processing speed, new learning and memory, executive functions. (Sumowski & Leavitt, 2013) (Assessment and Management of Cognitive Impairment) (Cognitive Dysfunction in MS) (Talking about Cognitive Dysfunction)
- **Depression:** More than 50% of people with MS will experience a major depressive episode; more common in MS than in the general population or in other equally disabling chronic illnesses. (Feinstein et al., 2014) (Emotional Disorders) (Talking about Emotional Disorders)
- **Sexual dysfunction:** May include impaired arousal, sensory changes, reduced vaginal lubrication, erectile dysfunction. (Lew-Starowicz & Gianotten, 2015) (Assessment and Treatment of Sexual dysfunction) (Talking about Sexual dysfunction)
- **Dizziness and Vertigo:** A sensation that the individual or his/her surroundings are in motion. May be accompanied by nausea. (Burina et al., 2008) (Managing MS Vertigo-Dizziness)
- **Dysarthria**: A speech disorder caused by muscle weakness and characterized by slow, slurred, or low volume speech. (Managing MS Dysarthria-Dysphonia)
- **Tremor:** Uncontrollable shaking of the limbs, trunk, voice, eyes or head with movement and/or against gravity. (Managing MS Tremor) (Oakes et al., 2013)

Secondary symptoms are the complications that can arise as a result of the primary symptoms. Secondary symptoms such as infection from bladder symptoms, pressure sores caused by immobility or decreased bone density due to inactivity can be addressed and treated, but the goal is to prevent them from happening in the first place.

- **Rehabilitation:** Although we now have disease-modifying therapies available to help slow the progression of multiple sclerosis, most people with MS will continue to have limitations. Rehabilitation in MS involves the intermittent or ongoing use of multidisciplinary strategies to promote functional independence, prevent complications, and enhance overall quality of life. It is an active process directed toward helping the person recover and/or maintain the highest possible level of functioning and realize his or her optimal physical, mental, and social potential given any limitations that exist.

  Rehabilitation specialists (including physiatrists, physical therapists, occupational therapists, and speech/language pathologists) target the following impairments in their work with individuals with MS: fatigue, weakness, spasticity, cognitive impairments, imbalance, sensory loss, ataxia/tremor, pain, paraparesis, speech and swallowing problems, visual disturbances, and bowel and bladder problems. The goal of these rehabilitation interventions is to reduce "disablement," as defined by the World Health Organization (WHO) in the International Classification of Impairments, Activities, and Participation: A Manual of Dimensions of Disablement and Health (ICIDH-2). Although rehabilitation interventions cannot reverse the neurologic damage caused by MS, they can reduce disablement by:

    - Minimizing the impact of existing impairment(s) on day-to-day functioning
    - Enhancing the person's ability to carry out daily activities and participate to the fullest extent possible in all of his or her life roles

  Initiating rehabilitation early in the disease course is essential for education, fatigue management, exercise recommendations and prevention of unnecessary complications.

- **Psychosocial support:** Psychosocial support is the fifth major category of treatment in MS, encompassing:
    - Disease-related education (more recently termed psychoeducation – a supportive educational process designed to enhance people's understanding of the disease, adaptive coping strategies and available resources)
    - Diagnosis/treatment of emotional and/or cognitive problems
    - Family interventions designed to support family members' efforts to cope with the intrusion of MS into the household
    - Support for people's efforts to remain productively employed as long as they are able and interested, and to transition out of the workforce when, and if, it is necessary to do so
    - Helping individuals with MS and their families to access available resources

- **Health and wellness:** In addition, wellness – and the strategies needed to achieve it – is a high priority for people living with MS. Wellness encompasses many dimensions: physical well-being (diet, exercise and healthy behaviors); emotional well-being; spiritual well-being; cognitive health; participation in work, home and leisure activities; and healthy relationships. The National MS Society's Wellness Discussion Guide for People with MS and Their Healthcare Providers summarizes key findings in the areas of physical well-being (health maintenance strategies, diet, exercise, smoking cessation, sleep), emotional well-being and the role of complementary therapies in MS management and links to more comprehensive information about each topic. Each section of the Guide highlights important points for patient-provider discussion and provides opportunities for the person with MS to record questions for their providers, list personal goals and track progress toward achieving those goals.

Summary

MS is a complex disease that impacts each individual and family in varied and unpredictable ways. People affected by MS benefit from ongoing partnerships with caring, knowledgeable clinicians in a wide range of disciplines to enhance health and wellbeing, mobility, safety, independence, participation in meaningful activities and quality of life.

Patient resources

What is MS (video): nationalmssociety.org/videos
Diagnosis: The Basic Facts: nationalmssociety.org/brochures
Living with MS: nationalmssociety.org/brochures
Multiple Sclerosis: Just the Facts: nationalmssociety.org/brochures

Other resources for
Talking with Your MS Patients include:

Cognitive Dysfunction
Diagnosis of Multiple Sclerosis
Progressive Disease
Elimination Problems
Sexual Dysfunction
Depression and Other Emotional Changes
Initiating and Adhering to Treatment with Injectable Disease Modifying Agents
Family Issues
Reproductive Issues
The Role of Rehabilitation
Life Planning
Primary Progressive MS (PPMS)
Palliative Care, Hospice and Dying
Wheeled Mobility

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