Multiple Sclerosis

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March 9, 2025

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1 Introduction

Multiple sclerosis is a chronic autoimmune disease affecting the central nervous system (CNS) and is characterized by inflammation, **demyelination**, gliosis, and neuronal loss. This condition manifests with a wide range of neurological symptoms, such as vision impairment, numbness and tingling, focal weakness, bladder and bowel dysfunction, and cognitive impairment.

Pathologically, perivascular lymphocytic infiltrate and macrophages lead to the degradation of myelin sheaths surrounding neurons, causing symptoms that vary depending on lesion location. Clinical symptoms characterized by acute relapses typically appear first in young adults, followed by a gradually progressive course leading to permanent disability within 10 to 15 years.

Multiple sclerosis presents various disease courses and is classified into several categories, as outlined below.

Relapsing-remitting (RR) This initial onset is observed in 70% to 80% of multiple sclerosis patients and is characterized by the below-mentioned neurological presentation.

- New or recurrent neurological symptoms that are consistent with multiple sclerosis
- Symptoms lasting 24 to 48 hours
- Symptoms developing over days to weeks

Primary progressive (PP) This course presents in 15% to 20% of patients and shows a gradual deterioration from onset without relapses.

Secondary progressive (SP) Following an initial relapsing-remitting course, this course is marked by a more gradual neurological decline.

Progressive-relapsing (PR) This course involves gradual deterioration with superimposed relapses and is seen in 5% of patients.

When discussing multiple sclerosis, clinicians commonly focus on the relapsing-remitting course due to its high prevalence among affected patients. Relapses in relapsing-remitting multiple sclerosis often show partial or complete recovery over weeks or months, sometimes without treatment. However, residual symptoms from these relapses, without complete recovery, can accumulate over time and contribute to overall disability. Diagnosis of relapsing-remitting multiple sclerosis typically requires evidence of at least 2 CNS inflammatory events. Although various diagnostic criteria exist for multiple sclerosis, the general principle for diagnosing the relapsing-remitting course involves establishing episodes separated in time and space.

This entails that episodes must be temporally separated and involve distinct locations within the CNS. A prompt diagnosis of multiple sclerosis enables the timely initiation of disease-modifying therapy, leading to effective management. Treatment goals include decreasing relapses and magnetic resonance imaging (MRI) activity while minimizing permanent disability and addressing various patient concerns such as bladder and bowel dysfunction, depression, cognitive impairment, fatigue, sexual dysfunction, sleep disturbances, and vertigo.

2 Etiology

Although the exact etiology of multiple sclerosis is unknown, factors involved in pathogenesis are broadly grouped into 3 categories— immune factors, environmental factors, and genetic associations.

Dysimmunity with an autoimmune attack on the CNS is the leading hypothesized etiology of multiple sclerosis. Researchers hypothesize that an unknown antigen triggers and activates Th1 and Th17 cells, leading to their attachment to CNS endothelium, crossing the blood-brain barrier, and subsequently causing an immune attack through cross-reactivity. This triggers an inflammatory-mediated tissue damage.

Environmental factors, such as latitudinal gradients observed in various countries, have been extensively studied. Vitamin D deficiency has been considered a possible etiology for the noted predisposition of populations in higher latitudes to multiple sclerosis. Certain viral infections may also contribute to the disease. Complex interactions between various environmental factors and patient genetics are apparent, and ongoing research aims to understand these pathways more comprehensively.

Patients with biological relatives with multiple sclerosis have a heightened risk of developing the condition. Having a first-degree relative with multiple sclerosis is associated with a 2% to 4% risk of developing multiple sclerosis as compared to 0.1% in the general population.

Some human leukocyte antigen (HLA) types strongly correlates with multiple sclerosis.

3 Epidemiology

Multiple sclerosis is the most common immune-mediated inflammatory demyelinating disease of the CNS. This condition affects approximately 400,000 individuals in the United States and 2.5 million individuals worldwide. The disease is 3-fold more common in females than in males. Although onset typically occurs in individuals between the ages of 20 and 40, multiple sclerosis can present at any age, with the mean age of onset being 25 to 29 for relapsing-remitting multiple sclerosis and 39 to 41 for primary progressive multiple sclerosis. Almost 10% of the cases are present before the age of 18. The overall prevalence is cited as 1 in 1000 for populations of European ancestry.

Less is known about the prevalence of multiple sclerosis in non-European populations, with most data indicating lower prevalence in individuals of East Asian and African descent. However, recent studies have observed a higher prevalence in African-American populations, similar to those with European ancestry. Multiple sclerosis demonstrates a prevalence gradient based on latitude, with higher prevalence in northern latitudes of Europe and North America. Additionally, observations have noted variable genetic susceptibility factors among different human subpopulations, apart from latitude, suggesting poorly understood genetic factors interacting with environmental influences.

3.1 Pathophysiology

The pathophysiology of multiple sclerosis primarily affects the CNS and involves various areas such as the cortical gray matter, periventricular and juxtacortical white matter, optic nerves, spinal cord, cerebellum, and meninges.

The two fundamental processes that constitute general pathological processes observed in multiple sclerosis patients include:

1. Focal inflammation results in macroscopic plaques and injury to the blood-brain barrier.

2. Neurodegeneration involves microscopic damage to various components of the CNS, such as axons, neurons, and synapses.

Together, these 2 primary processes result in macroscopic and microscopic injury. Lesions, called plaques, occur in waves throughout the disease course and result from focal inflammation. Multiple sclerosis plaques predominantly center around small veins and venules, displaying sharp margins. The chief components of plaque pathology include myelin loss, edema, and axonal injury. During active plaque inflammation, disruption of the blood-brain barrier corresponds to enhancement observed on MRI scans. As the inflammatory process subsides over time, it leads to the formation of an astrocytic scar (see Image. Perivascular Plaques in Multiple Sclerosis as seen in MRI).

Microscopically, multiple sclerosis lesions show mononuclear infiltrates with perivenular cuffing and infiltration surrounding the white matter. Innate immune cells such as monocytes and macrophages stimulate T-cell migration across the blood-brain barrier, resulting in blood-brain barrier injury and systemic immune cell infiltration. Microglia, the primary antigen-presenting cells of the primary CNS, often precede cell entry. This CNS injury triggers cytotoxic activities in microglia, leading to the release of nitric oxide and other superoxide radicals. Inflamed areas with blood-brain barrier breakdown are visible on MRI as gadolinium-enhancing lesions.

Recently, a greater understanding of the critical role of B cells and antibody production has been recognized in the pathogenesis of multiple sclerosis. B-cell follicles in the

meninges of multiple sclerosis patients have been noted, and they are associated with early-onset multiple sclerosis. The pathological events ultimately lead to demyelination, neuroaxonal degeneration, loss of synapses, dying-back oligodendrogliopathy, tissue injury, and astrogliosis. Go to:

3.2 Histopathology

Histologically, multiple sclerosis plaques are primarily characterized by inflammation and myelin breakdown. Additional features include neurodegeneration and oligodendrocyte injury. The common histopathological stains used to detect multiple sclerosis, with adjunct immunohistochemistry assisting in diagnosis, include hematoxylin and eosin staining, myelin stains such as Luxol fast blue, monocyte and macrophage markers such as CD68, and axonal and astrocyte stains.

Active plaques exhibit varying degrees of the following features:

- Extensive macrophage infiltration
- Myelin debris often found within macrophages
- Presence of major myelin protein, notably in late active plaques
- Perivascular inflammatory infiltrates
- Presence of lymphocytes, particularly CD8-positive cytotoxic T cells
- Plump-shaped and mitotic astrocytes
- Variable degrees of oligodendrocyte injury
- Activated microglia, particularly evident in the peri-plaque white matter zone

Chronic plaques are known for their circumscribed demyelinated lesions, and they occur more frequently and exhibit the following features:

- Hypocellularity and demyelination
- Macrophages laden with myelin
- Relatively decreased perivascular inflammation compared to active plaques
- Resolving edema
- In remyelinated plaques, thinly myelinated axons and axons with newly formed myelin sheaths are apparent.
- Presence of oligodendrocyte precursor cells, typically seen in remyelinated plaques

4 History and Physical Examination

Multiple sclerosis presents with a broad range of symptoms reflective of the multifocal lesions of the CNS. The severity and diversity of symptoms are influenced by the burden, location, and extent of tissue injury. Interestingly, symptoms may not always align with MRI evidence of active plaques due to the involvement of repair mechanisms and neural plasticity in tissue injury and recovery processes.

Typical clinical manifestations noted in patient history include:

- Vision symptoms such as vision loss (either monocular or homonymous), double vision, symptoms relating to optic neuritis, and pain with eye movement
- Vestibular symptoms such as vertigo and gait imbalance
- Bulbar dysfunction, which manifests as dysarthria and dysphagia
- Motor symptoms such as weakness (hemiparesis, monoparesis, or paraparesis), tremors, spasticity, and fatigue
- Sensory symptoms such as loss of sensation, paresthesias, dysesthesias, and a band-like sensation around the chest or abdomen
- Urinary and bowel symptoms ranging from incontinence, retention, urgency, constipation, diarrhea, and reflux
- Cognitive symptoms such as memory impairment, executive function impairment, and difficulty concentrating
- Psychiatric symptoms such as depression and anxiety
- Brainstem symptoms such as facial muscle weakness and/or reduced facial sensations, diplopia, oscillopsia (jerking sensation in the visual field)

Features considered atypical for multiple sclerosis include seizures, steady progression of symptoms, deficits developing rapidly within minutes, onset before age 10 or after 50, rigidity or sustained dystonia, cortical deficits such as apraxia, alexia, aphasia, or neglect, and early onset of dementia.

The relapsing-remitting course of multiple sclerosis, observed in a majority of patients, is characterized by exacerbation and relapses of neurological symptoms, with stability between episodes. The following features generally characterize the relapsing-remitting course of multiple sclerosis:

- New or recurrent neurological symptoms
- Symptoms developing over days and weeks
- Symptoms lasting between 24 and 48 hours

Symptoms from relapses frequently resolve. However, over time, residual symptoms relating to episodes of exacerbation accrue. This accrual of symptoms, generally after 10 to 15 years, results in long-term disability over time. Neurological manifestations are heterogeneous in severity and degree of recovery. The secondary progressive course is often noted in patients with relapsing-remitting after 10 to 15 years of onset and is characterized by a more gradual worsening of symptoms with continued progression with or without superimposed relapses.

A small subset of patients experience a progressive worsening of disability from the disease's onset, known as the primary progressive course of multiple sclerosis. Clinical manifestations in this course commonly include myelopathy, cognitive symptoms, and visual impairments. Diffuse and chronic symptoms may arise from global brain atrophy and widespread cortical demyelination.

4.1 Evaluation

Pathognomonic tests do not exist to diagnose multiple sclerosis. Diagnosis is established by considering the patient's history and physical examination, along with MRI findings, evoked potentials, and cerebrospinal fluid (CSF) or blood studies, while also excluding other causes of the patient's symptoms. Clinically, a diagnosis of multiple sclerosis is supported by evidence of one or more relapses, which can be confirmed through objective clinical evidence of one or more lesions or objective clinical evidence of one lesion with reliable historical evidence of a prior relapse.

Dissemination in space (DIS) and dissemination in time (DIT) are 2 key criteria for accurately diagnosing multiple sclerosis. DIS is assessed by integrating information from the patient's history and physical examination to determine the location of CNS involvement. MRI and evoked potentials also have vital roles in establishing DIS. DIT is established by charting the disease course with a thorough history and documenting the presence of multiple exacerbations over time. The 2010 McDonald criteria determined that new lesions can demonstrate DIT on a follow-up MRI compared to a baseline scan.

DIS is established by observing at least a T2 lesion in 2 of the 4 following CNS sites—spinal cord, infratentorial, juxtacortical, and periventricular regions. Revisions in the 2017 McDonald criteria increased the sensitivity of diagnosis by introducing oligoclonal bands in the CSF analysis as a marker for establishing DIT. Symptomatic lesions were also included to establish DIT and DIS, and cortical lesions were used to demonstrate DIS.

Evoked potentials help demonstrate slowed conduction indicative of subclinical involvement. These findings are often asymmetric. MRI, CSF, and blood studies are essential in ruling out other etiologies. When possible, all patients should undergo an MRI. Additionally, specific blood studies such as complete blood count (CBC), thyroid-stimulating hormone (TSH), vitamin B12 levels, erythrocyte sedimentation rate (ESR), and antinuclear antibody (ANA) testing should be performed as part of the diagnostic workup.

The main characteristics of multiple sclerosis lesions on brain MRI can be outlined as follows:

- Lesions are T2 hyperintense and T1 isointense or hypointense, also known as black holes (see Image. Sagittal FLAIR MRI Brain Image Demonstrating Linear Hyperintense Lesions).
- Lesions are typically oval or patchy.
- A high predilection for periventricular white matter.
- Active lesions often exhibit gadolinium enhancement, presenting as diffuse or rim enhancement.
- Thinning of the corpus callosum and parenchymal atrophy

5 Treatment / Management

Glatiramer acetate, dimethyl fumarate, fingolimod, interferon-beta preparations, natalizumab, and mitoxantrone are some of the primary disease-modifying therapies. Immediate treatment initiation upon diagnosis is key for multiple sclerosis. Short-term goals focus on decreasing MRI lesion activity, while long-term goals aim to prevent secondary progressive multiple sclerosis. Post-treatment challenges include ensuring patient compliance and monitoring for drug toxicity.

In the realm of treatment and management for multiple sclerosis, several disease-modifying therapies, as mentioned below, offer various mechanisms to address the underlying pathology.

- Glatiramer acetate.
- Interferon-beta preparations.
- Natalizumab.
- Mitoxantrone.
- Fingolimod.

Patients with secondary progressive, progressive-relapsing, and primary progressive multiple sclerosis primarily experience neurodegenerative processes. Due to this, disease-modifying therapies show varying effectiveness, ranging from possible benefits to limited impact on disease progression. Typically, younger patients with a shorter duration of progression tend to benefit more from these therapies.

5.1 Treatment of Acute Exacerbation of Multiple Sclerosis

Neurological symptoms may include increased disability, impairments in strength, cerebellar function, vision, or significant sensory disturbances.

IV or oral steroids may be prescribed by a physician, as described below, depending on a patient's conditions and symptoms.

- IV methylprednisolone: This can be administered as a 3- to 7-day course at 500 to 1000 mg daily, optionally followed by a short prednisone taper.
- Oral prednisone: This can be administered at a dosage of 1250 mg/d of prednisone, with/without a short taper, and is an alternative to 3 to 7 days of oral methylprednisolone administered at 1000 mg/d.