Multiple sclerosis

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system, destroying the myelin and the axon in variable degrees and producing significant physical disability within 20–25 years in more than 30% of patients. The hallmark of multiple sclerosis is symptomatic episodes that occur months or years apart and affect different anatomic locations.

The term "multiple sclerosis" refers to two characteristics of the disease:

- numerous affected areas of the brain and spinal cord (CNS) producing multiple neurologic symptoms that accrue over time
- the characteristic plaques or sclerosed areas that are the hallmark of the disease.

Pathophysiology

The basic physiologic derangement in multiple sclerosis is stripping of the myelin sheath surrounding CNS axons. This activity is associated with an inflammatory, perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement.

Demyelination renders axons susceptible to damage, which becomes irreversible when they are severed. Irreversible axonal damage correlates with disability and can be visualized as hypointense lesions, or "black holes," on T1-weighted MRI.

Classification

Multiple sclerosis is divided into the following categories, principally on the basis of clinical criteria, including the frequency of clinical relapses, time to disease progression, and lesion development on MRI:

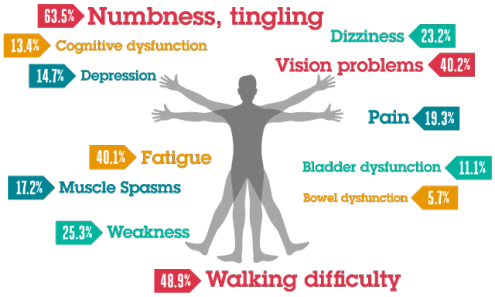
- Relapsing-remitting multiple sclerosis (RRMS): Approximately 85% of cases
- Secondary progressive multiple sclerosis (SPMS)
- Primary progressive multiple sclerosis (PPMS)
- Progressive-relapsing multiple sclerosis (PRMS)

The following 2 subgroups are sometimes included in RRMS:

- *Clinically isolated syndrome* (CIS): A single episode of neurologic symptoms.
- *Benign multiple sclerosis*: multiple sclerosis with almost complete remission between relapses and little if any accumulation of physical disability over time.

Clinical presentation

Most patients with multiple sclerosis present with nonspecific complaints. Many have problems with their vision or paresthesias.



Primary symptoms & signs

Sensory loss	Paresthesia is usually an early complaint.	
Spinal cord symptoms	Autonomic symptoms	Bladder, bowel, and sexual dysfunction
	Motor symptoms	• Muscle cramping secondary to spasticity • Pain, weakness, ataxia and fatigue • Gait problems and falls
Cerebellar symptoms	Charcot triad of dysarthria (scanning speech), nystagmus, and intention tremor	
Visual complaints	optic neuritis	
Psychological changes	Depression is a common symptom	
Cognitive changes		

Diagnosis

Multiple sclerosis is a diagnosis of exclusion on the basis of clinical findings and supporting evidence from ancillary tests. Tests include the following:

- Magnetic resonance imaging (MRI).
- Evoked potentials: Used to identify subclinical lesions; results are not specific for multiple sclerosis.
- Lumbar puncture: May be useful if MRI is unavailable or MRI findings are nondiagnostic; CSF is evaluated for oligoclonal bands and intrathecal IgG production.

Treatment

Treatment of MS falls into three broad categories:

- Treatment of exacerbations (Treatment of acute relapses)
- Disease-modifying therapies (DMTs) = disease-modifying agents for MS (DMAMS)
- Symptomatic therapies.

Treatment of ***acute relapses*** is as follows:

IV ***methylprednisolone***	IV methylprednisolone can hasten recovery from an acute exacerbation of MS.
Plasma exchange (***plasmapheresis***)	It can be used short term for severe attacks if steroids are contraindicated or ineffective.
Dexamethasone	It is commonly used for acute transverse myelitis and acute disseminated encephalitis.

Most of ***disease-modifying therapies (DMTs)*** have been approved for use only in ***relapsing forms of MS***. They include the following:

Interferons (INF)	INF beta-1a, INF beta-1b, peginterferon beta-1a
Sphingosine 1-phosphate (S1P) receptor modulators	• Siponimod, fingolimod, ozanimod • Laquinimod (*available in Russia*)
Monoclonal antibodies	Alemtuzumab, natalizumab, ocrelizumab, ofatumumab
Immunomodulators	Glatiramer acetate, mitoxantrone, teriflunomide, cladribine, dimethyl fumarate (DMF), monomethyl fumarate (MMF),
Off-labeled agents	Rituximab, methotrexate, azathioprine

*In 2016, **daclizumab** was approved for the treatment of relapsing multiple sclerosis in adults. In 2018, it was voluntarily withdrawn from the market after reports of autoimmune encephalitis.*

The following agents are disease-modifying therapies for **aggressive MS**.

Cyclophosphamide	High-dose cyclophosphamide has been used for induction therapy of aggressive MS. (*off-label*)
Mitoxantrone	Mitoxantrone is approved for reducing neurologic disability and/or the frequency of clinical relapses in patients with SPMS, PRMS, or worsening RRMS.

Vitamin D supplementation may reduce the risk of developing MS and of conversion from a first clinical event suggestive of MS to clinically definite MS. Vitamin D may also reduce the relapse rate among patients with relapsing-remitting MS.

Immunomodulatory Therapy for Progressive MS

Few treatments are available for PPMS, SPMS and PRMS.

Ocrelizumab	It is approved for primary progressive MS (PPMS).
Siponimod	It is approved for active secondary progressive MS (SPMS).
Cladribine	Because of its safety profile, it is generally recommended for patients with inadequate response to, or unable to tolerate, an alternate MS drug therapy.
Methotrexate	It has shown some effectiveness in delaying progression of impairment of the upper extremities in patients with SPMS.
Mitoxantrone	It is approved for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (long-term) progressive, progressive relapsing, or worsening relapsing remitting MS, but not for primary progressive MS.
IFN beta-1b	It showed a highly significant delay in time to disease progression in SPMS.
Rituximab	Off-label use.

Symptomatic therapies:

Fatigue	amantadine, fluoxetine (*Off-label*) Modafinil, armodafinil, dextroamphetamine, and methylphenidate
Cognitive dysfunction	Modafinil and methylphenidate
Depression	SSRIs are preferred
Spasticity	• Baclofen, dantrolene and tizanidine are effective in most cases. • Benzodiazepines (Diazepam and Clonazepam) are used as second-line agents • Botulinum toxin
Pain	• TCAs are first-line drugs for primary pain • Anticonvulsants can also be used for the treatment of secondary pain in MS. (carbamazepine, phenytoin, pregabalin, topiramate, gabapentin) • Duloxetine (SNRI) is used as an antidepressant and for relief of neuropathic pain • NSAIDs

Optic neuritis	Intravenous methylprednisolone may speed recovery
Urinary urgency or incontinence	• Scheduled voiding • Limiting fluid intake in the evening • Eliminating diuretics (eg, caffeine) • Using anticholinergic medications (eg, oxybutynin and tolterodine) • Injecting Botulinum toxin (Botox) into the bladder

Botulinum toxin (Botox) or ***OnabotulinumtoxinA toxin*** is approved for the treatment of upper limb spasticity in MS. Also, it is approved for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., MS) in adults who have an inadequate response to, or are intolerant of, an anticholinergic medication.

Dalfampridine, a broad-spectrum potassium blocker is approved as a treatment to improve walking in patients with MS. The improvement in walking was demonstrated by an increase in walking speed.

Stem Cell Transplantation

Autologous hematopoietic stem cell transplantation (AHSCT) may be effective for slowing the course of MS and for repairing damage to the nervous system.

Mesenchymal stem cells provide support for developing immune cells while also having immunomodulatory properties. While a small trial showed safety of ***mesenchymal stem cell transplantation***, larger blinded studies are needed to verify its efficacy.