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Professional Version

# Multiple Sclerosis (MS)

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**Multiple sclerosis (MS) is characterized by disseminated patches of demyelination in the brain and spinal cord. Common symptoms include visual and oculomotor abnormalities, paresthesias, weakness, spasticity, urinary dysfunction, and mild cognitive symptoms. Typically, neurologic deficits are multiple, with remissions and exacerbations gradually producing disability. Diagnosis requires clinical or MRI evidence of ≥ 2 characteristic neurologic lesions that are separated in both time and space (location in the central nervous system). Treatment includes corticosteroids for acute exacerbations, immunomodulatory drugs to prevent exacerbations, and supportive measures.**

(See also Overview of Demyelinating Disorders.)

Multiple sclerosis is believed to involve an immunologic mechanism. One postulated cause is infection by a latent virus (possibly a human herpesvirus such as Epstein-Barr virus), which, when activated, triggers a secondary autoimmune response.

An increased incidence among certain families and presence of human leukocyte antigen (HLA) allotypes (HLA-DR2) suggests genetic susceptibility.

MS is more common among people who spend their first 15 years of life in temperate climates (1/2000) than in those who spend them in the tropics (1/10,000). One explanation is that lower levels of vitamin D are associated with an increased risk of MS, and vitamin D levels correlate with the degree of sun exposure, which is lower in temperate climates. Cigarette smoking also appears to increase risk.

Age at onset ranges from 15 to 60 years, typically 20 to 40 years; women are affected somewhat more often.

Neuromyelitis optica spectrum disorder (Devic disease), previously considered a variant of MS, is now recognized as a separate disorder.

# Pathophysiology of MS

Localized areas of demyelination (plaques) occur, with destruction of oligodendroglia, perivascular inflammation, and chemical changes in lipid and protein constituents of myelin in and around the plaques. Axonal damage is common, and neuronal cell bodies may also die or be damaged.

Fibrous gliosis develops in plaques that are disseminated throughout the central nervous system (CNS), primarily in white matter, particularly in the lateral and posterior columns (especially in the cervical regions), optic nerves, and periventricular areas. Tracts in the midbrain, pons, and cerebellum are also affected. Gray matter in the cerebrum and spinal cord can be affected but to a much lesser degree.

# Symptoms and Signs of MS

Multiple sclerosis is characterized by varied CNS deficits, with remissions and recurring exacerbations. When MS is not treated with immunomodulating drugs, exacerbations average about 1 every 2 years, but frequency varies greatly. Although MS may progress and regress unpredictably, there are typical patterns of progression:

- **Relapsing-remitting pattern:** Exacerbations alternate with remissions, when partial or full recovery occurs or symptoms are stable. Remissions may last months or years. Exacerbations can occur spontaneously or can be triggered by an infection such as influenza. Relapsing forms of MS include active secondary MS (defined as a clinical relapse or new lesion seen on an MRI scan of the brain or spinal cord).
- **Primary progressive pattern:** The disease progresses gradually with no remissions, although there may be temporary plateaus during which the disease does not progress. Unlike in the relapsing-remitting pattern, there are no clear exacerbations.
- **Secondary progressive pattern:** This pattern begins with relapses alternating with remissions (relapsing-remitting pattern), followed by gradual progression of the disease.
- **Progressive relapsing pattern:** The disease progresses gradually, but progression is interrupted by sudden, clear relapses. This pattern is rare.

The **most common initial symptoms** of multiple sclerosis are the following:

- Paresthesias in one or more extremities, in the trunk, or on one side of the face
- Weakness or clumsiness of a leg or hand

- Visual disturbances (eg, partial loss of vision and pain in one eye due to retrobulbar optic neuritis, diplopia due to internuclear ophthalmoplegia, scotomas)

Other common early symptoms of MS include slight stiffness or unusual fatigability of a limb, minor gait disturbances, vertigo, and mild affective disturbances; all usually indicate scattered CNS involvement and may be subtle. Most patients with MS have difficulty with bladder control (eg, frequency, urgency, hesitancy, incontinence, retention).
Fatigue is common. Excess heat (eg, warm weather, a hot bath, fever) may temporarily exacerbate symptoms and signs (Uhthoff phenomenon).
Mild cognitive symptoms are common. Apathy, poor judgment, or inattention may occur. Affective disturbances, including emotional lability, euphoria, or, most commonly, depression, are common. Depression may be reactive or partly due to cerebral lesions of MS. A few patients have seizures.

### Cranial nerves

Unilateral or asymmetric optic neuritis and bilateral internuclear ophthalmoplegia are typical.
Central vision is affected more than peripheral vision.
Optic neuritis causes loss of vision (ranging from scotomas to blindness), eye pain during eye movement, and sometimes abnormal visual fields, a swollen optic disk, or a partial or complete afferent pupillary defect.
Internuclear ophthalmoplegia results if there is a lesion in the medial longitudinal fasciculus connecting the 3rd, 4th, and 6th nerve nuclei. During horizontal gaze, adduction of one eye is decreased, with nystagmus of the other (abducting) eye; convergence is intact. In MS, internuclear ophthalmoplegia is typically bilateral; unilateral internuclear ophthalmoplegia is often caused by ischemic stroke.
Rapid, small-amplitude eye oscillations in straight-ahead (primary) gaze (pendular nystagmus) are uncommon but characteristic of MS. Vertigo is common. Intermittent unilateral facial numbness or pain (resembling trigeminal neuralgia), palsy, or spasm may occur. Mild dysarthria may occur, caused by bulbar weakness, cerebellar damage, or disturbance of cortical control. Other cranial nerve deficits are unusual but may occur secondary to brain stem injury.

### Motor

Weakness is common. It usually reflects corticospinal tract damage in the spinal cord, affects the lower extremities preferentially, and is bilateral and spastic.
Deep tendon reflexes (eg, knee and ankle jerks) are usually increased, and an extensor plantar response (Babinski sign) and clonus are often present. Spastic paraparesis produces a stiff, imbalanced gait; in advanced cases, it may confine patients to a wheelchair. Painful flexor spasms in response to sensory stimuli (eg, bedclothes) may occur late. Cerebral or cervical spinal cord lesions may result in hemiparesis, which sometimes is the presenting symptom.
Reduced mobility increases the risk of osteoporosis.

### Cerebellar

In advanced MS, cerebellar ataxia plus spasticity may be severely disabling; other cerebellar manifestations include slurred speech, scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable), and Charcot triad (intention tremor, scanning speech, and nystagmus).

### Sensory

Paresthesias and partial loss of any type of sensation are common and often localized (eg, to one or both hands or legs).
Various painful sensory disturbances (eg, burning or electric shocklike pains) can occur spontaneously or in response to touch, especially if the spinal cord is affected. An example is Lhermitte sign, an electric shocklike pain that radiates down the spine or into the legs when the neck is flexed.
Objective sensory changes tend to be transient and difficult to demonstrate early in the disease.

### Spinal cord

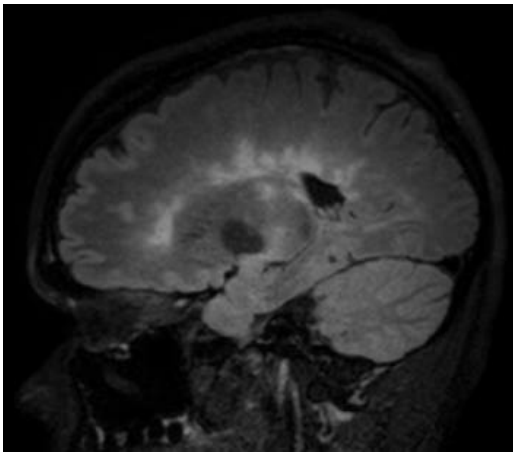
Involvement commonly causes bladder dysfunction (eg, urinary urgency or hesitancy, partial retention of urine, mild urinary incontinence). Constipation, erectile dysfunction in men, and genital anesthesia in women may occur. Frank urinary and fecal incontinence may occur in advanced MS.
Spinal cord lesions (plaques) are a common source of neuropathic pain.
**Progressive myelopathy**, a variant of MS, causes spinal cord motor weakness but no other deficits.

## Diagnosis of MS

- Clinical criteria
- Brain and spinal MRI
- Sometimes cerebrospinal fluid (CSF) IgG levels and evoked potentials

Multiple sclerosis is suspected in patients with optic neuritis, internuclear ophthalmoplegia, or other symptoms that suggest MS, particularly if deficits are multifocal or intermittent. If MS is suspected, brain MRI and spinal MRI are done. **MRI** is the most sensitive imaging test for MS and can exclude other treatable disorders that may mimic MS, such as nondemyelinating lesions at the junction of the spinal cord and medulla (eg, subarachnoid cyst, foramen magnum tumors). Gadolinium-contrast enhancement can distinguish actively inflamed from older plaques. Also, higher-field MRI magnets (3 to 7 Tesla) can distinguish perivenular MS plaques from nonspecific white-matter lesions.

### MRI (FLAIR) Multiple Sclerosis





MS must be distinguished from the following:

- Clinically isolated syndromes (consisting of only a single clinical manifestation typical of MS)
- Radiologically isolated syndrome (MRI findings typical of MS that are incidentally noted in patients with no clinical manifestations)

MS can be distinguished because diagnosis of MS requires evidence of CNS lesions that are separated in both time and space (location in the CNS). For example, any of the following can indicate separation in time:

- A history of exacerbations and remissions
- MRI that shows simultaneous enhancing and nonenhancing lesions, even if patients are asymptomatic
- A new lesion on a subsequent MRI in patients with a previous lesion

Separation (dissemination) in space can be established by finding lesions in ≥ 2 of the 5 following CNS areas typically affected by MS (1):

- Periventricular: ≥ 3 lesions
- Cortical/juxtacortical (white matter next to cortex and/or cortex): ≥ 1 lesions
- Infratentorial: ≥ 1 lesions
- Spinal cord: ≥ 1 lesions
- Optic nerve: ≥ 1 lesions (either by MRI or clinical evaluation)

## Additional testing

If MRI plus clinical findings are not diagnostic, additional testing may be necessary to objectively demonstrate separate

neurologic abnormalities. Such testing may include evoked potentials and, occasionally, CSF examination or blood tests.

**Evoked potentials** (delays in electrical responses to sensory stimulation) are often more sensitive for MS than symptoms or signs. Visual evoked responses are sensitive and particularly helpful in patients with no confirmed cranial lesions (eg, those with lesions only in the spinal cord). Somatosensory evoked potentials and brain stem auditory evoked potentials are sometimes also measured.

**CSF examination** is being done less frequently (because the diagnosis can usually be based on MRI) but can be helpful if MRI plus clinical findings are inconclusive or if infection (eg, CNS Lyme disease) must be ruled out. CSF tests include opening pressure, cell count and differential, protein, glucose, IgG, oligoclonal bands, and usually myelin basic protein and albumin. IgG is usually increased as a percentage of CSF components, such as protein (normally < 11%) or CSF albumin (normally < 27%). IgG levels correlate with disease severity. Oligoclonal IgG bands can usually be detected by electrophoresis of CSF. Myelin basic protein may be elevated during active demyelination. CSF lymphocyte count and protein content may be slightly increased.

**Blood tests** may be necessary. Sometimes systemic disorders (eg, SLE) and infections (eg, Lyme disease) can mimic MS and should be excluded with specific blood tests. Blood tests to measure an IgG antibody specific for neuromyelitis optica spectrum disorder (aquaporin-4 antibody [also known as NMO-IgG]) may be done to differentiate that disorder from MS.

### Diagnosis reference

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## Prognosis for MS

The course of multiple sclerosis is highly varied and unpredictable. In most patients, especially when MS begins with optic neuritis, remissions can last months to > 10 years.

Most patients who have a clinically isolated syndrome eventually develop MS, with a second lesion becoming evident or MRI detecting a lesion, usually within 5 years after the initial symptoms begin. Treatment with disease-modifying therapies can delay this progression. If patients have a radiologically isolated syndrome, progression to MS is a risk, but further study of this risk is needed.

If the initial brain or spinal MRI shows more extensive disease, patients may be at risk of earlier disability, as may patients who have motor, bowel, and/or bladder symptoms when they present or who have incomplete recovery during relapses. Some patients, such as men with onset in middle age and with frequent exacerbations, can become rapidly incapacitated. Cigarette smoking may accelerate disease progression.

Life span is shortened only in very severe cases.

## Treatment of MS

- Corticosteroids
- Immunomodulators to prevent exacerbations and delay eventual disability
- Baclofen or tizanidine for spasticity
- Gabapentin or tricyclic antidepressants for pain
- Supportive care

Goals for treatment of multiple sclerosis include the following:

- Shortening acute exacerbations
- Decreasing frequency of exacerbations
- Relieving symptoms
- Delaying disability, particularly maintaining the patient's ability to walk (which is important)

### Treatment of exacerbations and relapses

**Corticosteroids**, given in brief courses, are used to treat acute onset of symptoms or exacerbations that cause

objective deficits sufficient to impair function (eg, loss of vision, strength, or coordination); regimens include

- Methylprednisolone 500 to 1000 mg IV once a day for 3 to 5 days
- Less commonly, prednisone 1250 mg orally per day (eg, 625 mg orally twice a day or 1250 mg orally once a day) for 3 to 5 days

Recent data show that high-dose methylprednisolone (1000 mg/day for 3 consecutive days) orally or IV may have similar efficacy (1, 2). Some evidence indicates that IV corticosteroids shorten acute exacerbations, slow progression, and improve MRI measures of disease.

If corticosteroids are ineffective in reducing the severity of an exacerbation, plasma exchange may be used. Plasma exchange can be used for any relapsing form of MS (relapsing-remitting, progressive relapsing, secondary progressive). It is not used for primary progressive MS.

Plasma exchange and hematopoietic stem cell transplantation may be somewhat useful for severe, intractable disease.

## Disease-modifying therapies

For additional information, see Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis.

Immunomodulatory therapy, such as interferons or glatiramer, decreases the frequency of acute exacerbations and delays eventual disability. Typical regimens include the following:

- Interferon beta-1b 250 mcg subcutaneously every other day
- Interferon beta-1a (Avonex®) 30 mcg IM once a week
- Interferon beta-1a (Rebif®) 22 mcg or 44 mcg subcutaneously 3 times a week
- Interferon beta-1a (Pledgridy®) 125 mcg subcutaneously once every 2 weeks

Common adverse effects of interferons include flu-like symptoms and depression (which tend to decrease over time), development of neutralizing antibodies after months of therapy, and cytopenias.

Glatiramer acetate 20 mg subcutaneously once a day or 40 mg subcutaneously 3 times a week (given ≥ 48 hours apart) may be used.

The following oral immunomodulatory drugs can be used to treat relapsing forms of MS, including active secondary MS.

- Fingolimod 0.5 mg orally once a day
- Siponimod 1 or 2 mg orally once a day (maintenance dose), depending on CYP2C9 genotype (initial dose is 0.25 mg once a day)
- Ozanimod 0.92 mg orally once a day (maintenance dose; initial dose is 0.23 mg once a day)
- Teriflunomide 14 mg orally once a day
- Dimethyl fumarate 240 mg orally twice a day

These oral immunomodulatory drugs are probably more effective in some patients than glatiramer and the interferons (3, 4, 5).

Because most people are averse to self-injection, oral immunomodulatory drugs are being increasingly used as first-line treatments for relapsing forms of MS.

Disease-modifying therapies can be used to treat relapsing forms of MS. There is no consensus regarding choice of disease-modifying immunomodulatory therapy. Many experts recommend patient education and shared decision-making, including when disease-modifying therapies are offered to patients who have > 1 lesion (seen on imaging) and a clinically isolated syndrome. If one drug is ineffective, a different one can be tried.

The immunosuppressant mitoxantrone, 12 mg/m2 IV every 3 months for 24 months, may be helpful, particularly for progressive MS that is refractory to other treatments. However, mitoxantrone has been used less since the advent of monoclonal antibodies to treat MS.

Natalizumab, an anti–alpha-4 integrin antibody, inhibits passage of leukocytes across the blood-brain barrier; given as a monthly infusion, it reduces number of exacerbations and new brain lesions but may increase the risk of progressive multifocal leukoencephalopathy (PML).

Drugs that increase the risk of PML include the following (in descending order of risk):

- Natalizumab
- Rituximab
- Fingolimod

- Rarely, dimethyl fumarate

If any of these drugs are used, consultation with a neurologist with training in MS is highly recommended. Before these drugs are started, blood tests should be done to check for antibodies to JC virus (JCV), which causes PML. Based on the results, the following is done:

- If results are positive, patients should be counseled about the risk of PML.
- If results are negative, antibody tests should be done every 6 months as long as any of these drugs is used because seroconversion is common.
- If test results become positive, patients should be counseled again about the risk, and clinicians should consider switching to a drug without this risk.

If the high-risk drug is continued, MRI of the brain should be done about every 6 months.
Development of PML symptoms (eg, aphasia, change in mental status, hemianopia, ataxia) requires immediate brain MRI, with and without gadolinium. MRI can often distinguish PML from MS. After MRI, a lumbar puncture should be done, and cerebrospinal fluid should be tested for JCV DNA by polymerase chain reaction (PCR). A positive result indicates PML, and emergency consultation with a neurologist and an infectious disease specialist is needed. Also, if patients with a positive result have taken natalizumab, plasma exchange can be done to remove the drug quickly, and if immune reconstitution inflammatory syndrome (IRIS) develops, corticosteroids are given.

### Pearls & Pitfalls

If altered consciousness, aphasia, hemianopia, or ataxia develops in a patient taking natalizumab or fingolimod, do immediate brain MRI, followed by lumbar puncture, to check for PML.

Alemtuzumab, an anti-CD52 humanized monoclonal antibody given IV, has been shown to be effective in the treatment of MS. However, because it increases risk of autoimmune disorders, serious infusion reactions, and certain cancers, alemtuzumab is usually used only when treatment with ≥ 2 other drugs has been ineffective. Alemtuzumab 12 mg IV once a day is given for 5 days, followed in 12 months by 12 mg IV once a day for 3 days and repeated every 12 months as needed.
Cladribine is effective in relapsing forms of MS and may be an appropriate treatment for relapsing MS that is highly active. Cladribine is given orally in two yearly treatment courses (1.75 mg/kg per course). Each treatment course is divided into two cycles of 4 or 5 days, separated by about 4 weeks. Lymphocyte counts should be monitored before, during, and after treatment, and patients should be closely monitored for adverse effects related to immunosupression.
Ocrelizumab, an anti-CD20 (B-cell) humanized monoclonal antibody, given as an infusion every 6 months, is also effective in the treatment of relapsing MS (6). Dosage is 300 mg given by IV infusion, followed 2 weeks later by another 300-mg IV infusion, then 6 months later, by 600-mg IV infusions every 6 months. Ocrelizumab can also be used to treat primary progressive MS, typically in ambulatory patients.
Rituximab (off label for MS in the US) is also more effective than glatiramer and the interferons (7); it is commonly used throughout Europe and Canada because it is much less expensive than ocrelizumab. Usual dosage of rituximab is two doses of 1000 mg IV, separated by 15 days; they are followed by 1000-mg doses given every 6 months or when the CD19 B-cell count is> 2%.
There is no consensus concerning the comparative efficacy of the various disease-modifying drugs that are currently available. Treatments should be tailored to the patient and managed by MS specialists with expertise in their use.
If immunomodulatory drugs are ineffective, monthly IV immune globulin may help.
Immunosuppressants other than mitoxantrone (eg, methotrexate, azathioprine, mycophenolate, cyclophosphamide, cladribine) have been used for more severe, progressive MS but are controversial.

## Symptom control

Other treatments can be used to control specific symptoms:

- **Spasticity** is treated with escalating doses of baclofen 10 to 20 mg orally 3 to 4 times a day or tizanidine 4 to 8 mg orally 3 times a day. Gait training and range-of-motion exercises can help weak, spastic limbs.

- **Problems with gait** may be treated with extended-release 4-aminopyridine (dalfampridine) 10 mg every 12 hours.
- **Painful paresthesias** are usually treated with gabapentin 100 to 800 mg orally 3 times a day or pregabalin 25 to 150 mg orally twice a day; alternatives include tricyclic antidepressants (eg, amitriptyline 25 to 75 mg orally at bedtime, desipramine 25 to 100 mg orally at bedtime if amitriptyline has intolerable anticholinergic effects), carbamazepine 200 mg orally 3 times a day, as well as other antiseizure drugs, and opioids.
- **Depression** is treated with counseling and antidepressants.
- **Bladder dysfunction** is treated based on its underlying mechanism.
- **Constipation** may be treated with stool softeners or laxatives, taken regularly.
- **Fatigue** can be treated with amantadine 100 mg orally 3 times a day, modafinil 100 to 300 mg orally once a day, armodafinil 150 to 250 mg orally once a day, or extended-release amphetamine 10 to 30 mg once a day.

## Supportive care

Encouragement and reassurance help patients with multiple sclerosis.
Regular exercise (eg, stationary biking, treadmill, swimming, stretching, balance exercises), with or without physical therapy, is recommended, even for patients with advanced MS, because exercise conditions the heart and muscles, reduces spasticity, prevents contractures and falls, and has psychologic benefits.
Vitamin D supplements (eg, 600 to 4000 IU/day to achieve blood levels of 20 to 50 ng/mL [50 to 125 nmol/L] ) may decrease the risk of disease progression (8). Serum vitamin D levels should be monitored to make sure that dosing is adequate. Vitamin D also reduces the risk of osteoporosis, particularly in patients at increased risk because mobility is decreased or they take corticosteroids.
Patients should maintain as normal and active a life as possible but should avoid overwork, fatigue, and exposure to excess heat. Cigarette smoking should be stopped.
Vaccination does not appear to increase risk of exacerbations.
Debilitated patients require measures to prevent pressure ulcers and urinary tract infections; intermittent urinary self-catheterization may be necessary.

## Treatment references

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## Key Points

## Key Points

- Multiple sclerosis involves demyelination of the CNS; MS may progress unpredictably but has several typical patterns of progression.
- The most common symptoms are paresthesias, weakness or clumsiness, and visual symptoms, but a wide variety of symptoms are possible.
- MS is confirmed if MRI and clinical findings establish characteristic lesions that are separate in time and space; however, progression to MS is likely if patients have even a single characteristic clinical deficit or possibly a single radiologic lesion.
- Treat patients with corticosteroids (for severe exacerbations) and immunomodulatory drugs (to delay or prevent exacerbations).
- Treat patients supportively, using drugs to treat symptoms (eg, spasticity, painful paresthesias, depression, bladder dysfunction, fatigue, gait problems) when warranted.

## Drugs Mentioned In This Article

| Drug Name | Select Trade |
|---|---|
| Baclofen | LIORESAL |
| Tizanidine | ZANAFLEX |
| Gabapentin | NEURONTIN |
| Methylprednisolone | MEDROL |
| Prednisone | RAYOS |
| Interferon Beta-1b | EXTAVIA |
| Interferon Beta-1a | AVONEX |
| Glatiramer Acetate | COPAXONE |
| Mitoxantrone | No US brand name |
| Natalizumab | TYSABRI |
| Rituximab | RITUXAN |
| Alemtuzumab | CAMPATH |
| Cladribine | No US brand name |
| Ocrelizumab | OCREVUS |

| | |
|---|---|
| Immune Globulin | Gammagard S/D |
| Methotrexate | OTREXUP |
| Azathioprine | IMURAN |
| Mycophenolate | CELLCEPT |
| Cyclophosphamide | No US brand name |
| Dalfampridine | AMPYRA |
| Pregabalin | LYRICA |
| Amitriptyline | No US brand name |
| Desipramine | NORPRAMIN |
| Carbamazepine | TEGRETOL |
| Amantadine | No US brand name |
| Modafinil | PROVIGIL |
| Armodafinil | NUVIGIL |
| Amphetamine | ADDERALL XR 10 |