Demylinating diseases

Demyelinating disorders

are immune-mediated conditions characterized by preferential destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared, and most patients have no evidence of an associated systemic illness.

Multiple sclerosis (MS), the most common disease in this category, is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood.

Multiple Sclerosis

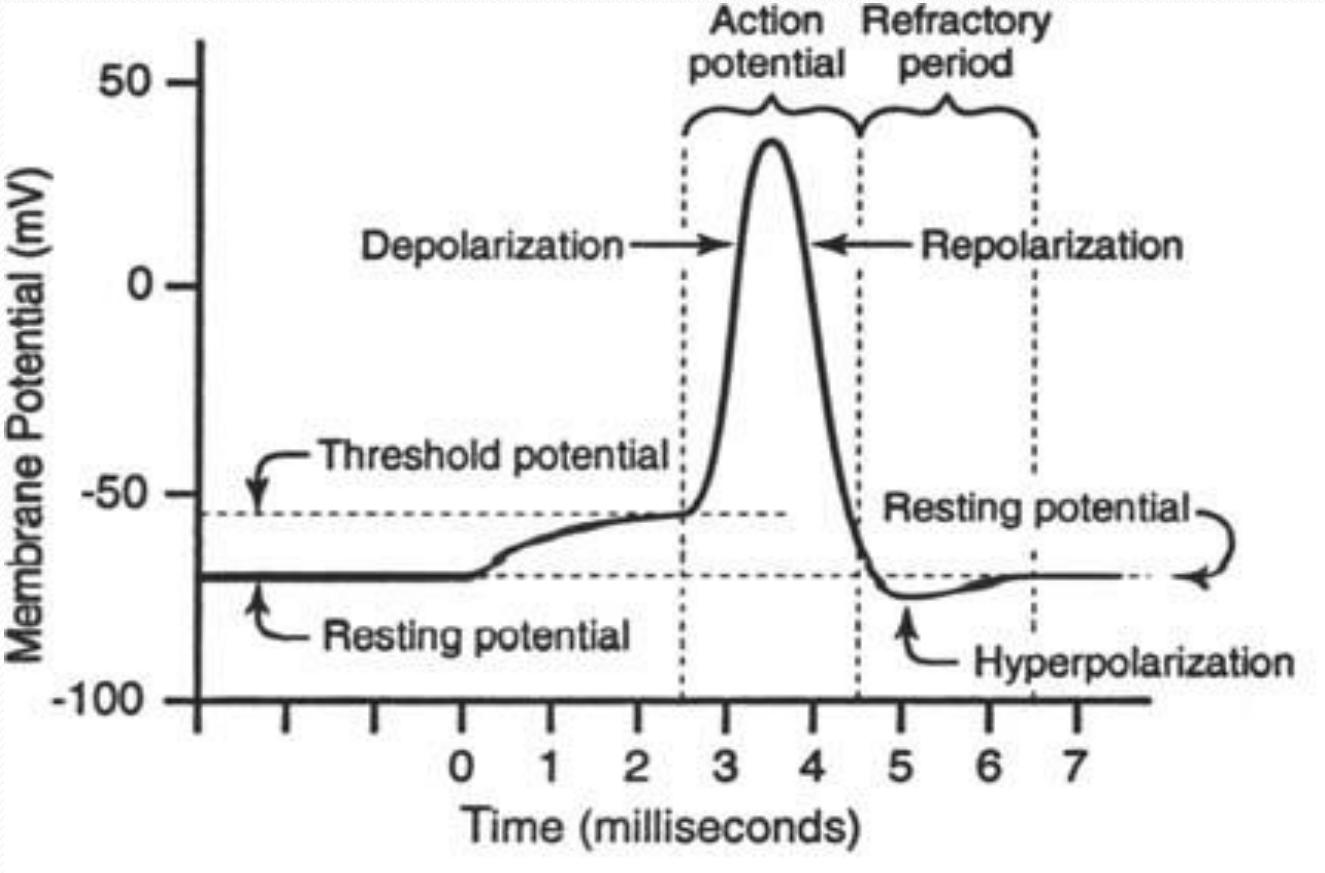
Multiple sclerosis (MS) is a chronic disease characterized by inflammation, demyelination, gliosis (scarring), and neuronal loss

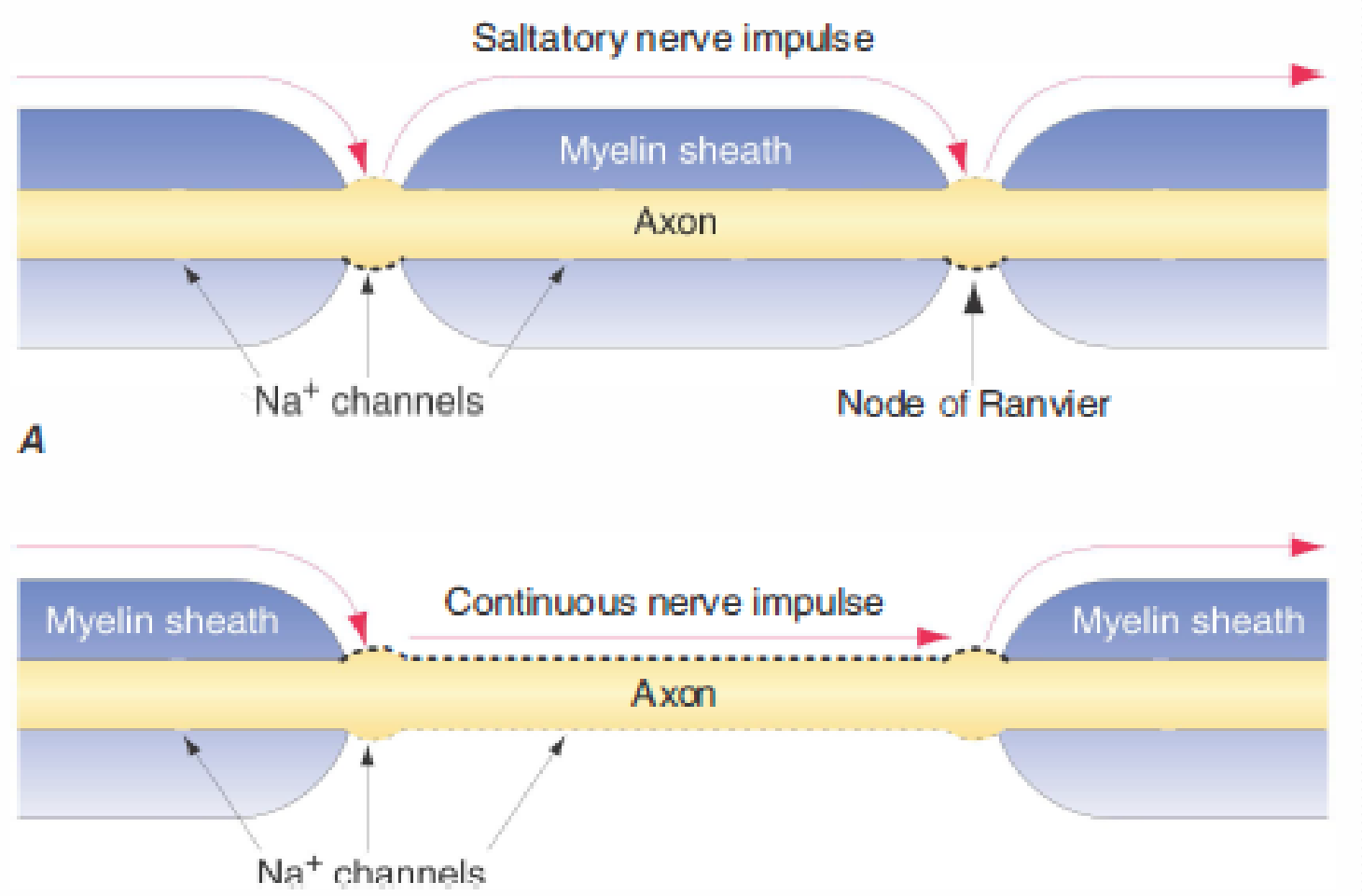
the course can be relapsing-remitting or progressive.

Lesions typically occur at different times and in different CNS locations (disseminated in time and space).

It affects 2.5 million individuals worldwide.

It threefold more common in women than men. The age of onset is typically between 20 and 40 years.


Action potential
Refractory period
50
0
-50
-100
Membrane Potential (mV)
Depolarization
Repolarization
Threshold potential
Resting potential
Resting potential
Hyperpolarization
0 1 2 3 4 5 6 7
Time (milliseconds)


Saltatory nerve impulse
Myelin sheath
Axon
Na+ channels
Node of Ranvier
A
Myelin sheath
Continuous nerve impulse
Myelin sheath
Axon
Na+ channels

Clinical Manifestations

The onset of MS may be abrupt or insidious. Symptoms may be severe or so trivial that a patient may not seek medical attention for months or years.

Symptoms are extremely varied and depend on the location and severity of lesions within the CNS .

Examination often reveals evidence of neurologic dysfunction, often in asymptomatic locations (patient may present with symptoms in one leg but signs in both).

TABLE 458-2 INITIAL SYMPTOMS OF MS

Symptom	Percentage of Cases	Symptom	Percentage of Cases
Sensory loss	37	Lhermitte	3
Optic neuritis	36	Pain	3
Weakness	35	Dementia	2
Paresthesias	24	Visual loss	2
Diplopia	15	Facial palsy	1
Ataxia	11	Impotence	1
Vertigo	6	Myokymia	1
Paroxysmal attacks	4	Epilepsy	1
Bladder	4	Falling	1

Weakness of the limbs may manifest as loss of strength, speed, or dexterity, as fatigue, or a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the (UMN) type and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and Babinski's signs.

Spasticity is commonly associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms interfering with ambulation, work, or self-care.

Optic neuritis

- presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision.
- These symptoms can be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception.
- Visual symptoms are generally monocular but may be bilateral.
- Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss.
- An afferent pupillary defect is usually present.
- Funduscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON.

Visual blurring in MS may result from ON or diplopia (double vision); if the symptom resolves when either eye is covered, the cause is diplopia.

Diplopia

may result from internuclear ophthalmoplegia (INO) or from palsy of the sixth cranial nerve (rarely the third or fourth).

A bilateral INO is particularly suggestive of MS.

common gaze disturbances in MS include

(1) a horizontal gaze palsy,

(2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and

(3) acquired pendular nystagmus.

Sensory symptoms

are varied and include both:

- paresthesias (e.g., tingling, prickling sensations, formications, "pins and needles," or painful burning)

- hypesthesia (e.g., reduced sensation, numbness, or a "dead" feeling).

Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common.

sensory level indicates that the spinal cord is the origin of the sensory disturbance. It is often accompanied by a bandlike sensation of tightness around the torso.

Ataxia usually manifests as cerebellar tremors . Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech).

Bladder dysfunction is present in >90% of MS patients, and in a third of patients, dysfunction results in weekly or more frequent episodes of incontinence.

During normal reflex voiding, relaxation of the bladder sphincter (alpha-adrenergic innervation) is coordinated with contraction of the detrusor muscle (muscarinic cholinergic innervation).

- *Detrusor hyperreflexia*, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, and nocturia.

- *Detrusor sphincter dyssynergia*, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

Constipation occurs in >30% of patients. Fecal urgency or *bowel incontinence* is less common (15%).

Cognitive dysfunction can include memory loss, impaired attention, difficulties in problem solving, slowed information processing, and problems shifting between cognitive tasks.

Euphoria (elevated mood) occurring in <20% of patients.

Cognitive dysfunction sufficient to impair activities of daily living is rare.

Depression, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself, and can contribute to fatigue.

Fatigue is experienced by 90% of patients; and is the most common reason for work-related disability.It can be exacerbated by elevated temperatures, depression, or by sleep disturbances.

Sexual dysfunction may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

Facial weakness due to a lesion in the pons may resemble idiopathic Bell's palsy. Unlike Bell's palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis.

Hearing loss may also occur in MS but is uncommon.

Ancillary Symptoms

Heat sensitivity refers to neurologic symptoms produced by an elevation of the body's core temperature. Such as (*Uhthoff's symptom*). or worsening of MS symptoms during febrile illnesses.

Lhermitte's symptom is an electric shock–like sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. It can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis).

Paroxysmal symptoms are distinguished by:

- their brief duration (10 s to 2 min),
- high frequency (5–40 episodes per day),
- lack of any alteration of consciousness or change in background electroencephalogram during episodes,
- and a self-limited course (generally lasting weeks to months).
- They may be precipitated by hyperventilation or movement.

These syndromes may include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other syndromes.

They probably result from spontaneous discharges, arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts.

Trigeminal neuralgia, hemifacial spasm, and *glossopharyngeal neuranlgia* can occur.

atypical features of trigeminal neuralgia that should raise concerns that MS could be responsible include:

- onset before age 50 years,
- bilateral symptoms,
- objective sensory loss,
- or nonparoxysmal pain.

Disease Course

Four clinical types of MS have been described:

1. *Relapsing/remitting MS* (RRMS) accounts for 85% of MS cases at onset and is characterized by discrete attacks that generally evolve over days to weeks . There is often complete recovery over the ensuing weeks to months. Between attacks, patients are neurologically stable.

2. *Secondary progressive MS* (SPMS) always begins as RRMS. At some point, however, the clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase). SPMS produces a greater amount of fixed neurologic disability than RRMS.

For a patient with RRMS, the risk of developing SPMS is 2% each year, meaning that the great majority of RRMS ultimately evolves into SPMS.

3. *Primary progressive MS* (PPMS) accounts for 15% of cases. These patients do not experience attacks but only a steady functional decline from disease onset .

4. *Progressive/relapsing MS* (PRMS) overlaps PPMS and SPMS and accounts for 5% of MS patients. Like patients with PPMS, these patients experience a steady deterioration in their condition from disease onset. However, like SPMS patients, they experience occasional attacks superimposed upon their progressive course .

Diagnosis

Diagnostic criteria for clinically definite MS require:

- documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS.
- Symptoms must last for >24 h and occur as distinct episodes that are separated by a month or more.
- At least one of the two required signs must be present on neurologic examination. The second may be documented by abnormal paraclinical tests such as MRI or evoked potentials (EPs).
- In patients who experience gradual progression of disability for 6 months without superimposed relapses, documentation of intrathecal IgG synthesis may be used to support the diagnosis.

TABLE 458-3 DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS (MS)

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For dissemination in space • ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a second clinical attack implicating a different CNS site AND For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack
Insidious neurologic progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) PLUS 2 out of the 3 following criteria Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Diagnostic Tests

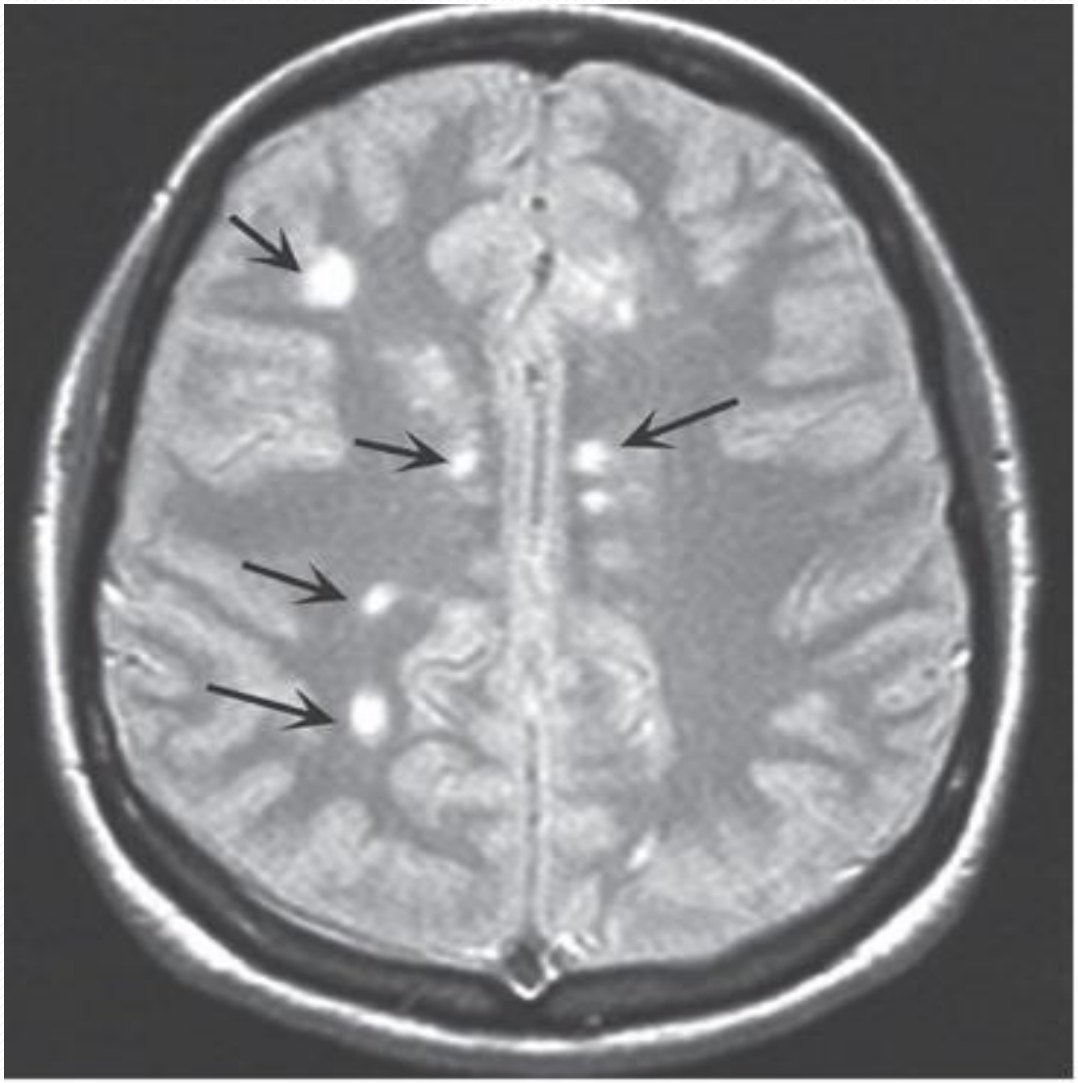
Magnetic Resonance Imaging

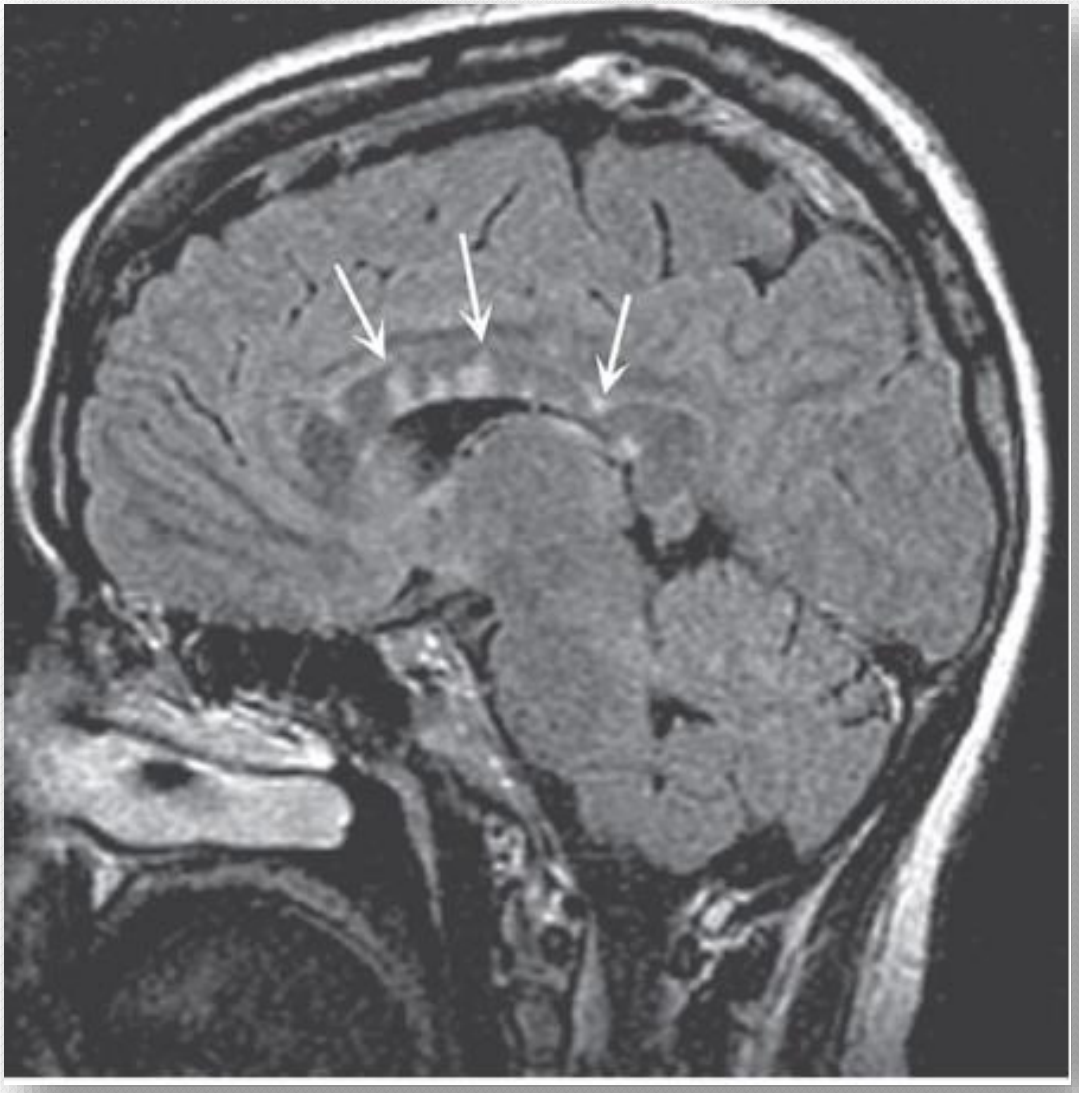
characteristic abnormalities are found in >95% of patients.

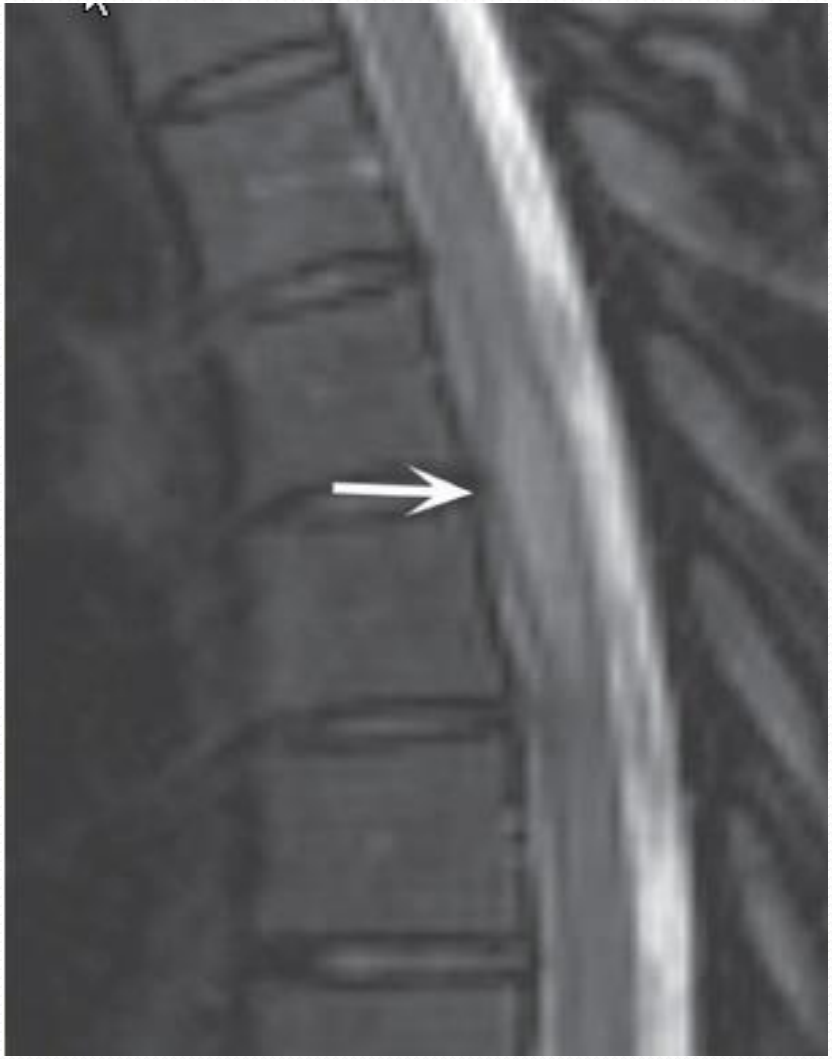
- increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage persists for approximately 1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity on (T2-weighted) images.

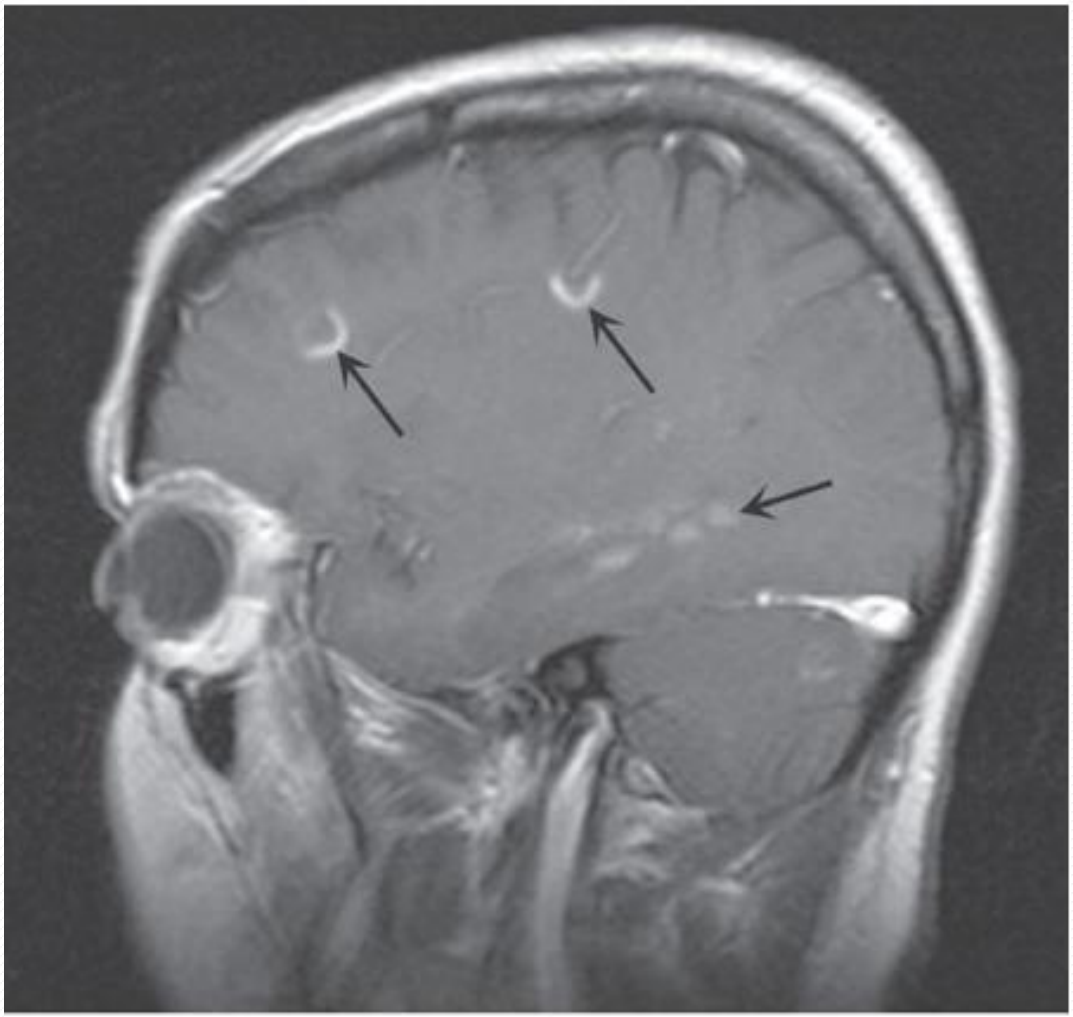
- Lesions are frequently oriented perpendicular to the ventricular surface (Dawson's fingers). Lesions are multifocal within the brain, brainstem, and spinal cord.

- Lesions larger than 6 mm located in the corpus callosum, periventricular white matter, brainstem, cerebellum, or spinal cord are particularly helpful diagnostically.









- The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability, as do measures of brain atrophy.

- Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss.

Evoked Potentials

- EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways.

- These tests provide the most information when the pathways studied are clinically uninvolved.
- Abnormalities on one or more EP modalities occur in 80–90% of MS patients.

- EP abnormalities are not specific to MS, although a marked delay in the latency of a specific EP component (as opposed to a reduced amplitude or distorted wave-shape) is suggestive of demyelination.

Cerebrospinal Fluid

- CSF abnormalities found in MS include a mononuclear cell pleocytosis (>5 cells/L) and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or slightly elevated.

- The measurement of oligoclonal banding (OCB) in the CSF also assesses intrathecal production of IgG. Two or more OCBs are found in 75–90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients the number of bands may increase with time.

- A pleocytosis of >75 cells/L, the presence of polymorphonuclear leukocytes, or a protein concentration >1 g/L (>100 mg/dL), should raise concern that the patient may not have MS.

Differential Diagnosis

The possibility of an alternative diagnosis should always be considered in the following conditions:

- symptoms are localized exclusively to the posterior fossa, craniocervical junction, or spinal cord;
- the patient is aged <15 or >60 years;
- the clinical course is progressive from onset;
- the patient has never experienced visual, sensory, or bladder symptoms.
- laboratory findings (e.g., MRI, CSF, or EPs) are atypical.
- uncommon or rare symptoms in MS: aphasia, parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, or coma)

TABLE 458-4 DISORDERS THAT CAN MIMIC MULTIPLE SCLEROSIS (MS)

Acute disseminated encephalomyelitis (ADEM)
Antiphospholipid antibody syndrome
Behçet's disease
Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
Human immunodeficiency virus (HIV) infection
Ischemic optic neuropathy (arteritic and nonarteritic)
Lyme disease
Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
Neoplasms (e.g., lymphoma, glioma, meningioma)
Sarcoid
Sjögren's syndrome
Stroke and ischemic cerebrovascular disease
Syphilis
Systemic lupus erythematosus and related collagen vascular disorders
Tropical spastic paraparesis (HTLV-1/2 infection)
Vascular malformations (especially spinal dural AV fistulas)
Vasculitis (primary CNS or other)
Vitamin B_{12} deficiency

Prognosis

- Most patients with clinically evident MS ultimately experience progressive neurologic disability.

- 15 years after onset, only 20% of patients had no functional limitation, and between one-third and one-half progressed to SPMS and required assistance with ambulation;

- 25 years after onset, 80% of MS patients reached this level of disability.

Features which suggest a more favorable prognosis include:

- ON or sensory symptoms at onset,
- fewer than two relapses in the first year of illness,
- and minimal impairment after 5 years.

Features which suggest grave prognosis include:

- truncal ataxia,
- action tremor,
- pyramidal symptoms,
- or a progressive disease course.

Treatment

Therapy for MS can be divided into several categories:

(1) treatment of acute attacks,

(2) treatment with disease-modifying agents that reduce the biological activity of MS, and

(3) symptomatic therapy.

Acute Attacks or Initial Demyelinating Episodes

Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated.

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks.

Orally administered methylprednisolone or dexamethasone (in equivalent dosages) can be substituted for the intravenous portion of the therapy, although GI complications are more common by this route.

Outpatient treatment is almost always possible.

Disease-Modifying Therapies for (RRMS and SPMS with Exacerbations)

Seven such agents are approved by the U.S. Food and Drug Administration (FDA):

(1) IFN-ß-1a (Avonex), (2) IFN-ß-1a (Rebif), (3) IFN-ß-1b (Betaseron), (4) glatiramer acetate (Copaxone), (5) natalizumab (Tysabri), (6) fingolimod (Gilenya), and (7) mitoxantrone (Novantrone).

Recipients of IFN-ß-1b, IFN- ß -1a, glatiramer acetate, natalizumab, and fingolimod experienced fewer clinical exacerbations and fewer new MRI lesions compared to placebo recipients.

Mitoxantrone (Novantrone), an immune suppressant, has also been approved in the United States, although because of its potential toxicity it is generally reserved for patients with progressive disability who have failed other treatments.

Interferon- ß

IFN- ß is a class I interferon originally identified by its antiviral properties. It should be considered in patients with either RRMS or SPMS with superimposed relapses. In patients with SPMS but without relapses, efficacy has not been established.

Common side effects of IFN- ß therapy include:

- flulike symptoms (e.g., fevers, chills, and myalgias)
- mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia).
- Subcutaneous IFN- ß also causes reactions at the injection site (e.g., pain, redness, induration, or, rarely, skin necrosis).

Side effects can usually be managed with concomitant nonsteroidal anti-inflammatory medications and with the use of an autoinjector.

Disease-Modifying Therapies for Progressive MS

High-dose IFN- ß probably has a beneficial effect in patients with SPMS who are still experiencing acute relapses.

No therapies have been convincingly shown to modify the course of PPMS or SPMS with no acute relapses.

Symptomatic Therapy

- For all patients, it is useful to encourage attention to a healthy lifestyle, including healthy diet, and regular exercise as tolerated (swimming is often well tolerated because of the cooling effect of cold water).

- It is reasonable also to correct vitamin D deficiency with oral vitamin D, and to recommend dietary supplementation with long-chain (omega-3) unsaturated fatty acids, because of their immunomodulatory properties.

Ataxia/tremor

Clonazepam, Mysoline, propranolol,

Spasticity and *spasms*

- physical therapy,
- regular exercise, and stretching.
- Avoidance of triggers (e.g., infections, fecal impactions, bed sores).
- Effective medications include baclofen (Lioresal), diazepam, tizanidine, and dantrolene.
- For severe spasticity, a baclofen pump (delivering medication directly into the CSF) can provide substantial relief.

Pain

- anticonvulsants (carbamazepine, phenytoin, gabapentin, or pregabalin.
- antidepressants (amitriptyline, nortriptyline)
- antiarrhythmics (mexiletine).

Bladder dysfunction

- Evening fluid restriction or frequent voluntary voiding may help *detrusor hyperreflexia*.
- If these methods fail, propantheline bromide or oxybutynin may be benifecial.

Depression

selective serotonin reuptake inhibitors or tricyclic antidepressants.

Fatigue

Primary MS fatigue may respond to amantadine, methylphenidate, or modafinil.

Cognitive problems

may respond to the cholinesterase inhibitor donepezil hydrochloride.

Paroxysmal symptoms

respond dramatically to low-dose anticonvulsants (acetazolamide, carbamazepine, phenytoin, or gabapentin).