

Geography. In general, MS is more prevalent in temperate regions of the world than in the tropics. Multiple sclerosis affects about one in every 1000 people in Western nations. Specifically, prevalence is highest in northern Europe, southern Australia, and the middle regions of North America. The incidence has been increasing in southern Europe. It is unclear whether this pattern is attributable to environmental factors or to genetics.

From this site:

<http://www.reutershealth.com/wellconnected/doc17.html>

http://www.emedicine.com/emerg/topic321.htm#section%7Fauthor_information

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INTRODUCTION

Section 2 of 11 [Back](#) [Top](#) [Next](#)

[Author Information](#) [Introduction](#) [Clinical Differentials](#) [Workup](#) [Treatment](#) [Medication](#) [Follow-up](#) [Miscellaneous](#) [Pictures](#)
[Bibliography](#)

Background: Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disease of the CNS. Patients with MS commonly present with an individual mix of neuropsychological dysfunction, which tends to progress over years to decades.

The diagnosis of MS is based on a classic presentation (ie, optic neuritis, transverse myelitis, internuclear ophthalmoplegia, paresthesias) and on the identification of other neurologic abnormalities, which may be indicated by the patient history and exam. Typical findings on an MRI also help establish a diagnosis of MS.

Patients with atypical presentations and/or a normal or atypical MRI may require evoked potential studies, to uncover subclinical neurologic abnormalities, or cerebral spinal fluid

(CSF) analysis, which also serves to exclude treatable disorders and document MS-like immune activity in the CNS.

By convention, the confidence in the diagnosis of MS is described as definite, probable, or possible MS. It includes a classification with respect to clinical presentation, which correlates somewhat with the prognosis and is useful in clinical trials.

About 70% of patients present with the more favorable relapsing-remitting (RR) type, which is characterized by acute exacerbations with full or partial remissions....

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Pathophysiology: MS is regarded as an autoimmune disease. Most of what is known about MS is derived from its model in animal research, which is experimental allergic encephalomyelitis.

The autoantigen in MS most likely is one of several myelin proteins (eg, proteolipid protein [PLP], myelin oligodendrocyte glycoprotein [MOG], MBP). Microglial cells and macrophages perform jointly as antigen-presenting cells, resulting in activation of cytokines, complement, and other modulators of the inflammatory process, targeting specific oligodendroglia cells and their membrane myelin.

The pathologic hallmark of MS is multicentric, multiphasic CNS inflammation and demyelination. Originally, each MS lesion was thought to evolve through episodes of demyelination and remyelination into a chronic burned-out plaque with relative preservation of axons and gliosis. Thus, the neuropsychological dysfunction occurred, despite an essentially intact neural network, until late in the disease course. However, recent studies have demonstrated that axonal transections do occur during acute exacerbations; furthermore, axonal damage, as measured by magnetic resonance spectroscopy, was found to correlate with clinical disability. Clearly, more work is needed to understand the associations among inflammation-mediated demyelination, axonal injury, and clinical disability.

For unclear reasons, lesions characteristically involve the optic nerve and periventricular white matter of the cerebellum, brain stem, basal ganglia, and spinal cord. Identifying MS lesions in gross specimens is difficult, as is identifying MS lesions in gray matter on radiographic images; hence, the predilection for white matter may not be disease related. The peripheral nervous system rarely is involved.

Frequency:

- **In the US:** MS is the most common debilitating illness among young adults. The incidence is 0.5-1 per 1000 people, and the general population has a 0.2% lifetime risk of acquiring MS. Approximately 25,000 new cases are diagnosed each year.
- **Internationally:** Approximately 1 per 1,000,000 people acquire MS.

Mortality/Morbidity:

- MS affects quality of life rather than duration of life.
- Worsening disability from any cause is strongly associated with increased mortality rate.
- Deaths attributable to MS are the result of fulminant MS, which is rare; complications from chronic disability (eg, pneumonia, pulmonary embolism, infected decubiti); and suicide.

Race:

- Incidence is higher in Caucasians than in other races for which incidences are known. The incidence may be twice as high in Caucasians as in other races.
- MS essentially is unknown among Eskimos and Bantus, and it is rare among Native Americans and Asians.
- MS is 5 times more prevalent in temperate climates than in the tropics, but the risk seems to be associated entirely with childhood years spent in a temperate climate. The risk of acquiring MS is higher in those who have lived in a temperate climate before age 15, but not in those who move to a temperate climate after age 15.

Sex:

- Throughout adulthood the female-to-male ratio is 2:1.
- The sex ratio is more pronounced in those younger than 16 years (ie, approaches 3:1), but it is less pronounced in those older than the fifth decade.
- On average, men present 1-2 years later than women, and men have a greater tendency for having the progressive disease at onset.

Age: MS rarely occurs in those younger than 20 years or those older than 50 years. The occurrence of MS is even more rare in those younger than 15 years and in those older than 60 years

History: The review of systems should concentrate on the evidence of bladder, kidney, lung, or skin infection and irritative or obstructive bladder symptoms.

- Classic MS symptoms
 - Sensory loss (ie, paresthesias) usually is an early complaint.
 - Motor (eg, muscle cramping secondary to spasticity) and autonomic (eg, bladder, bowel, sexual dysfunction) spinal cord symptoms may be present.
 - Cerebellar symptoms (eg, Charcot triad of dysarthria, ataxia, tremor) may occur.
 - Constitutional symptoms, especially fatigue (which occurs in 70% of cases) and dizziness, may be present.
 - Subjective difficulties with attention span, concentration, memory, and judgment may be noted any time during the disease course.
 - About 50% of patients with MS have impairment, usually mild, in information processing on neuropsychological testing.
 - Depression is common, but euphoria is less common.
 - Over the course of the disease, 5-10% of patients develop an overt psychiatric disorder (eg, manic depression, paranoia, major depression) or dementia.
 - Eye symptoms, including diplopia on lateral gaze, occur in 33% of patients.
 - Trigeminal neuralgia may occur.
- Optic neuritis (ON) (ie, inflammation or demyelination of optic nerve) is the initial presentation of 15% of patients with MS. Fifty percent of all patients who present with ON have MS. Isolated episodes of ON, even if they are recurrent, do not represent MS.
 - Acute onset (ie, occurring over minutes or hours, rarely days) of single eye visual blurring, decreased acuity (ie, usually scotoma), decreased color perception, and/or discomfort of the moving eye(s) are symptoms that are indicative of ON.
 - The 3 phenomena associated with ON or compressive/ischemic neuritis are as follows:

- Phosphenes, or flashes of light, usually are precipitated by eye movements.
 - Uhthoff phenomenon or deterioration of vision is induced by exercise, a hot meal, or a hot bath.
 - The Pulfrich effect occurs when latencies between the eyes are unequal, resulting in a sense of disorientation in moving traffic.
- Acute transverse myelitis
 - Partial acute transverse myelitis, rather than total, usually is a manifestation of MS. Strongly consider mechanical compression in the differential diagnosis.
 - Acute partial loss of motor, sensory, autonomic, reflex, and sphincter function below the level of the lesion indicates acute transverse myelitis.
- Devic syndrome is acute transverse myelitis accompanied by bilateral ON.
- Acute disseminated encephalitis is pathophysiologically and radiographically identical to MS. It is characterized by acute onset of motor, sensory, cerebellar, and cranial nerve dysfunction with encephalopathy, progressing to coma and eventual death in 30% of such cases.
- MS as a sole symptom is unusual, but MS may present with many other typical MS presentations, including the following:
 - Aphasia or dysphasia
 - Hemianopsia
 - Seizures (5% of patients with MS)
 - Significant motor complaints without sensory deficits or dysautonomia (eg, bladder)

Physical: Classic MS findings on neurologic examination include the following:

- Eye
 - Optic neuritis
 - Acutely, 50% of patients present with retrobulbar involvement; hence, funduscopy results are normal. "The patient sees nothing and the doctor sees nothing."
 - Anterior involvement causes papillitis, and differentiating this from papilledema is important. When inflammation involving the retina is extensive, look for presence of a macular star.
 - After several weeks, optic atrophy may be seen.
 - An afferent pupillary defect may be seen in the affected eye.
 - Visual acuity usually is impaired (ie, subtle to total blindness).

- The classic finding is bilateral (unilateral much less common) internuclear ophthalmoplegia (INO), a lesion in the median longitudinal fasciculus (MLF) resulting in a weakness in adduction of the ipsilateral eye with nystagmus on abduction of the contralateral eye, an incomplete or slow abduction of the ipsilateral eye upon lateral gaze, with complete preservation of convergence.
- Other eye findings include abnormal pupillary responses, acquired pendular nystagmus or sinusoidal involuntary oscillations of one or both eyes, and/or loss of smooth eye pursuit.
- Regardless of the stage or classification, most authorities question the diagnosis of MS in a patient without at least one of these findings.
- Spinal cord involvement
 - Acute transverse myelitis
 - Sphincter paralysis and unchanging level
 - Distinguish from Guillain-Barré syndrome
 - Paralysis, spasticity, and hyperreflexia are indicative of upper motor neuron dysfunction (ie, lateral corticospinal tracts). Decreased joint position and vibration sense (ie, dorsal columns) are common findings.
 - Decreased pain and temperature (ie, lateral spinothalamic tracts) are less common. The sparing of these symptoms may be diagnostically helpful.
 - The degree of corticospinal tract findings tends to correlate with bladder, bowel, and sexual dysautonomias.
- Cerebellar findings: Disequilibrium, truncal or limb ataxia, scanning (ie, monotonous) speech, intention tremor, and saccadic dysmetria are common cerebellar findings.
- Lhermitte sign: Neck flexion results in an electric shocklike feeling in the torso or extremities
- Acute disseminated encephalitis
 - Most commonly, altered mental status and/or personality changes
 - Focal findings (eg, cranial nerve defects, hemiparesis, focal seizures, autonomic dysfunction)
 - Cranial nerve defects

- Ataxia
 - Dysphasia
 - Meningismus, usually less common and pronounced than in meningitis
- Unusual findings in MS include the absence of eye findings and isolated motor, sensory, cerebellar, and cranial nerve lesions.

Causes: MS commonly is believed to result from an autoimmune process. What triggers the autoimmune process is not clear, but the nonrandom nature of its geographic distribution suggests an isolated or additive environmental effect and/or inadvertent activation and dysregulation of CNS immune processes by a retroviral infection that was perhaps acquired in childhood. On the basis of bench research findings, some authorities implicate human herpesvirus-6 (HHV-6) variant B group 2, while others implicate *Chlamydia pneumoniae*.

Polygene inheritance accounts for a familial rate of 10-20%; yet, most studies confirm that a monozygotic twin has only a 30% risk of acquiring MS, suggesting a genetic predisposition to an environmental viral agent.

As in systemic lupus erythematosus (SLE), human leukocyte antigen (HLA) patterns of patients with MS tend to differ from those of the general population.

Although no present studies support a connection between hepatitis B vaccination and MS, worldwide anecdotal reports prompted the Centers for Disease Control and Prevention (CDC) to investigate this possibility (see CDC web site <http://www.cdc.gov/nip/vaesaft/concerns/MS/default.htm>).

- Optic neuritis is attributable to MS in 50% of cases; the remaining 50% of cases are probably postinfectious. Ischemic optic neuropathy, arteriovenous malformations, tumors, and other compressive lesions usually present more gradually with additional symptoms or atypical features, but these complications should be pursued aggressively in any patient presenting with ON.
- Acute transverse myelitis, when not attributable to MS, most likely is infectious (eg, Epstein-Barr virus [EBV], Lyme [rare]) or postinfectious. An important ED exclusion in these patients is mechanical compression by tumor, abscess, or aneurysm.

Acute disseminated encephalitis involves a poorly defined immune-mediated demyelinating process.

Amyotrophic Lateral Sclerosis

Bell Palsy

Brain Abscess

Guillain-Barré Syndrome
HIV Infection and AIDS
Lumbar (Intervertebral) Disk Disorders
Neck Trauma
Sarcoidosis
Spinal Cord Infections
Spinal Cord Injuries
Stroke, Hemorrhagic
Stroke, Ischemic
Subdural Hematoma
Syphilis
Systemic Lupus Erythematosus
Tick-Borne Diseases, Lyme
Transient Ischemic Attack
Trigeminal Neuralgia

Other Problems to be Considered:

Behçet disease
Brainstem tumors
Central nervous system infections
Cerebellar tumors
Friedreich ataxia
Hereditary ataxias
Leukodystrophies
Neurofibromatosis
Pernicious anemia
Progressive multifocal leukoencephalopathy
Ruptured intervertebral disk
Small cerebral infarcts
Spinal cord tumors
Syringomyelia
Vasculitides

Lab Studies:

- CBC with differential
- Serum glucose
 - To rule out hypoglycemia and chronic hyperglycemia as causes of neurological findings
 - Helps in CSF glucose interpretation

- Serum electrolytes: Determine abnormalities associated with neurologic, muscle, or systemic dysfunction (K^+ , Ca^{2+} , P^- , and Na^+).
- Coagulation studies prior to lumbar puncture: These are indicated in patients with history of easy bleeding, liver disease, malnutrition, or alcoholism.
- Urinalysis and microscopy

Imaging Studies:

- CT scan of head with contrast
 - This imaging study is indicated in the ED to assess focal neurological examination or acute changes in mental status prior to lumbar puncture.
 - For all other investigations, MRI is unarguably more sensitive and specific in diagnosing MS and related disorders. In selected patients, MRI will be the preferred imaging study in the ED.
- MRI of head with gadolinium
 - Typical MRI findings support the diagnosis (ie, 50% progress to clinically definite MS within 2 years), but 5% of suspected patients with normal MRI findings similarly progress to MS.
 - T1 shows active lesions (2-6 weeks) reflecting perivascular inflammation and breakdown of blood-brain barrier (BBB). T2 most commonly shows old lesions in periventricular supratentorial white matter, but old lesions occasionally are seen in the cerebellum and brain stem.
 - To visualize the optic nerve, a special MRI technique is required to suppress the fat signal.
 - Acute disseminated encephalitis may be radiographically indistinguishable from MS.