# Epidemiology of Multiple Sclerosis

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**KEYWORDS**

• Multiple sclerosis • Neuroepidemiology • Public health

**KEY POINTS**

- Multiple sclerosis (MS) which includes a clinically isolated syndrome, neuromyelitis optica or Devic disease, and acute disseminated encephalomyelitis are common complex neurodegenerative disease of the central nervous system. It manifests as a progressive disease through dissemination in time and space in the brain and spinal cord, due mainly to autoimmune inflammation.
- The disorder engenders an enormous burden of disease and comorbidity, varying with world regions and population ethnicity.
- Genome-wide association studies serve as powerful tools for investigating the genetic substrate of MS.
- There are novel biologic treatments, including fingolimod and natalizumab.
- Supportive treatment includes management of disability, support of generalized symptoms, and psychiatric care.

## EPIDEMIOLOGY

### *Prevalence and Incidence*

#### *The Americas*

In 2007, Poser and Brinar[1] noted that published prevalence rates of multiple sclerosis (MS) could be misleading with the reliance on clinical information and brain MRI interpretation leading to one-third of incorrect MS diagnoses. This opinion was epitomized by the findings of a clinical questionnaire survey of 30 complete MS clinical histories and examinations, including cerebrospinal fluid (CSF), sent to prominent clinical neurologists around the world.[2] All of the cases were autopsied, 25 patients had clinical MS, 1 had MS plus brain tumor, 1 had MS and stroke, and 3 did not have MS at all. When asked to indicate if the diagnosis was probable, possible, or unlikely MS

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according to their own diagnostic criteria, 108 neurologists responded, correctly identifying only two-thirds of the cases but not the same ones. Experience, country of training, and practice and specialization in MS were inconsequential. Poser and Brinar[1] noted that common errors in global prevalence studies might be the failure to distinguish between the clinical and MRI characteristics of MS and disseminated encephalomyelitis (DEM) in both their acute and chronic forms, cases with onset before entering the study group or moving to the geographic area, and counting cases of the variant neuromyelitis optica (NMO) as an oriental form of MS, falsely inflating prevalence rates of MS in Far Eastern countries and failing to recognize some cases of NMO as instances of DEM.

Evans and colleagues[3] reviewed the incidence and prevalence of MS in the Americas, noting high heterogeneity among all studies even when stratified by country, making comparisons difficult, and noting variation in the quality of the studies. Among 9 epidemiologic studies that estimated MS prevalence and incidence in the United States reported between 1989 and 2007,[4–12] prevalence was highest in Olmstead County, Minnesota,[7] with age-standardized rate (ASR) of 191.2 per 100,000, and lowest in Lubbock, Texas, and the 19 surrounding counties, with an ASR of 39.9 per 100,000. Incidence of MS was reported in Olmstead County, MN[7] with an ASR of 7.3 per 100,000.

Among 12 epidemiologic studies estimating prevalence and incidence in Canada from 1986 to 2010,[13–24] 1 nationwide study used self-reporting information from a national population-based health survey conducted in 2000 to 2001 from a stratified random sample that estimated the crude prevalence of MS to be 240 per 100,000[19] Crude prevalence in individual regions of Canada ranged from 56.4 per 100,000 in Newfoundland in 1985[13] to 298 per 100,000 in Saskatoon in 2005.[22] The highest reported incidence of MS was in Alberta, with an ASR of 20.6 per 100,000 in 2002[25] and 23.9 per 100,000 for 2004.[23] However, the latter was based on invalidated administrative health claims.

A total of 6 studies from 4 countries in Central and South America examined the prevalence and incidence of MS from 1992 to 2009[26–31] but only 1[31] produced estimates for the entire country, noting a crude prevalence for Panama during 2000 to 2005 of 5.24 per 100,000 and annual incidence from 1990 to 2005 of 0.15 per 100,000.[31] Both prevalence and incidence were highest in the Argentine Patagonia region with a 2002 crude prevalence of 17.2 per 100,000 and annual incidence of 1.4 per 100,000.[29]

A meta-analysis evaluating prevalence estimates from 59 countries found a statistically significant latitudinal gradient for prevalence even after age-standardization and adjustment for prevalence year,[32] whereas a previous review of MS prevalence in Canada found no striking latitudinal or longitudinal gradient[33] similar to another study[29] that found and no south-north gradient in prevalence within the Argentine Patagonia. Prevalence estimates of MS were much lower in South America compared with North America, according to Evans and colleagues,[3] despite the studied regions being similar distances from the equator. This was possibly due to variations in the methodologies used, the quality of medical care, and the differential population susceptibility to MS.[34] Such conflicting findings suggest that geography alone may not predict the prevalence or risk of MS. Although it has been suggested that the prevalence of MS has increased in recent years,[35] it may partly be explained by a longer life expectancy in those with MS, and not necessarily an indicator of an increased risk of the disease, as well as advances in the identification of affected cases as a consequence of increased access to neurologists and improved methods of case ascertainment. Although most studies examine prevalence, incidence may be a better measure of increased disease risk.[34]

### *Europe*

Kingwell and colleagues[36] did a comprehensive literature search of population-based studies of MS prevalence and incidence in European populations published between 1985 and 2011, noting that study estimates were highly heterogeneous also within regions or countries. Together with the Italian peninsula, the British Isles was the most studied. Prevalence estimates in the British Isles ranged from 96 per 100,000 in Guernsey[37] to more than 200 per 100,000, with the highest estimates originating from Scotland and Northern Ireland.[38,39] These 2 countries had the highest annual incidence rates, ranging from 7.2 to 12.2 per 100,000. With rare exceptions, prevalence and incidence estimates were higher in women with ratios of 3 to 1. Epidemiologic data at the national level were uncommon and there were marked geographic disparities in available data, with large areas of Europe unrepresented and other regions well-represented in the literature. Only 37% of the studies provided standardized estimates.

In the Italian peninsula, Sardinia had a higher incidence and prevalence of MS compared with the rest of Italy.[40] Of 6 studies of the Sardinian population,[41–45] 5 found an estimated prevalence of MS greater than 100 per 100,000. The only study with a lower estimate noted 69 per 100,000 in 1985.[46] When considering the incidence of MS, the Sardinian estimates of 3.4 to 6.8 per 100,000 were not unlike those seen across the entire Italian peninsula.

Although prevalence and incidence estimates tended to be higher in the northern regions of the British Isles and in the Nordic countries, implicating the role of latitude, this pattern was not uniform, with higher estimates originating as far south as Greece. There, the crude prevalence rate of definite MS cases increased between 1984 and 2006 from 10.1 per 100,000 recorded in northeastern Greece to 119.61 per 100,000; and mean annual incidence rates that increased between 1984 and 1989 from 2.71 per 100,000 to 10.73 per 100,000.[47]

### *Asia*

Makhani and colleagues[48] examined published studies between 1985 and 2011 of MS incidence and prevalence from Kuwait, Israel, Turkey, Jordan, Iran, India, China, Japan, and Taiwan,[49–69] noting MS incidence and prevalence lowest in Africa and highest in Australia. Prevalence of MS increased over time in many countries, ranging from 0.67 per 100,000 per year in Taiwan to 3.67 per 100,000 in Australia; with the lowest prevalence in South African blacks of 0.22 per 100,000 and highest among Australian-born of 125 per 100,000.

## *Genetic Aspects*

Genes involved in MS have long been sought and several approaches to this problem have been applied with varied success. A candidate gene approach was used for many decades wherein genes potentially associated with MS were chosen based on family aggregation and twin studies but, more recently, on the presumed autoimmune MS etiopathogenesis invoking human leukocyte antigen (HLA) class I and II, particularly the latter, which control immune response genes.[70]

### *Family aggregation studies*

Familial aggregation in MS has not been compelling. Monozygotic twins of afflicted individuals had a 30% risk of the disease, with a similar rate in dizygotic twins to other siblings, demonstrating a significant genetic component to the illness without likely contribution of intrauterine factors.[71,72] Siblings were conferred a 2% to 5% lifetime risk, and parents and children of MS patients had a 1% lifetime risk.[73] The Multiple Sclerosis Genetics Group[74] reported demographic and clinical characteristics of 89

multiplex families, noting a mean difference in age of onset between probands and affected siblings of 8.87 years and a higher concordance rate among sister pairs than among brother pairs but without differences in affection rate among sons or daughters of either affected mothers or affected fathers. In a cohort of 807 MS families with 938 affected aunt or uncle and niece or nephew pairs ascertained from a longitudinal, population-based Canadian database, Herrera and colleagues[75] observed an increased number of avuncular pairs connected through unaffected mothers compared with unaffected fathers ($P = .008$) noting a maternal parent-of-origin effect in susceptibility to MS. Ebers and colleagues[72] (1986) studied familial aggregation of MS in a sample of 5,463 MS cases in Canada, noting an excess of monozygotic twins and a marked excess of concordance among monozygotic twin pairs. They quoted previous studies that indicated a 300-fold increase of risk for monozygotic twins of index cases and 20-fold to 40-fold increase for biological first-degree relatives.[76] Together, these studies suggested that familial aggregation in MS was genetic. However, because most monozygotic twins remained discordant, nongenetic risk factors are clearly important. Baranzini and colleagues[77] reported the genome sequences of 1 MS-discordant monozygotic twin pair, and mRNA transcriptome and epigenome sequences of CD4+ lymphocytes from 3 MS-discordant, monozygotic twin pairs, noting no reproducible differences between cotwins among approximately 3.6 million single nucleotide polymorphisms (SNPs) or in approximately 0.2 million insertion-deletion polymorphisms; nor was there evidence for genetic, epigenetic, or transcriptome differences that explained disease discordance.

### *Genome-wide association studies*

Bashinskaya and colleagues[78] provided an excellent review of genome-wide association studies (GWAS) in MS. Powerful tools for investigating the genetic architecture of MS, GWAS have the potential to identify the genetic factors of disease susceptibility, clinical phenotypes, and treatment response. The GWAS data for MS can be found in the regularly updated National Human Genome Research Institute-European Bioinformatics Institute website: www.ebi.ac.uk/gwas.[79] Established in 2008, it includes data of all published GWAS assaying at least 100,000 SNP.

The role of the GWAS has been led by 3 international consortia possessing individual DNA samples from various clinics worldwide, including the International Multiple Sclerosis Genetic Consortium (IMSGC), Welcome Trust Case Control Consortium 2 (WTCCC2), and Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene). Affymetrix and Illumina genome-wide platforms are used by most GWAS for targeting SNPs regularly distributed throughout the genome, covering arrays with a range of 262 to 600 K. Formed in 2 phases, the first or discovery phase of a GWAS includes detection of associations followed by a second or replication phase.

Of 13 GWAS described by Bashinskaya and colleagues,[78] the most significant signals mapped to HLA-*DRB1* class II gene.[80–83] Their review of GWAS in MS summarized more than a dozen studies, several of which met significance levels of association of $P<4 \times 10^{-225}$.[80–82] Two chromosomal loci mapping to 6p21.32 in HLA-*DRB1* and *DQB1* gene loci (Online Mendelian Genetics in Man [MIM] 142857 and 604305) and another at 2q37.3 in the *PDCD1* gene (MIM 604305) locus share phenotypic-genetic relationships with either susceptibility (MIM 142857, 604305) or disease progression of MS (MIM 600244).[84] SNPs identified and replicated in GWAS of MS have been located mainly in or near protein-coding genes directly involved in immune-related functions. Because it is well known that the HLA locus is an essential

component directing the immune response and immune developments, it is not surprising that the major histocompatibility complex (MHC) region still represents about one-half of the MS genetic risk.

Non-HLA genes associated with MS are associated with T-cell function and may indicate the leading role of T-cell immunity in MS development. Many aspects of the immune system have demonstrated involvement in MS. Circulating T cells bind to blood brain barrier endothelium and then pass into the parenchyma. Microglia stimulate proliferation, leading to the release of a broad range of cytokines; further recruitment of T cells; activation of B cells; and, collectively, the destruction of myelin. Th1-like cytokines levels and other T-cell–related cytokines in the CSF have been correlated with disease progression.[85] Reciprocal upregulation of T-cell migration mediated by T-cell–released cytokines via interaction with MCH class II molecules provides an important avenue for neuroinflammation. A variety of inflammatory mediators are involved, including tumor necrosis factor (TNF), oxygen free radicals, and nitric oxide. The effects of these on neuronal function may contribute to myelin breakdown.[86] Pathogenic B-cell activation is suggested by elevated CSF oligoclonal bands (OCBs), increased levels of CSF immunoglobulin-G (IgG), and anti–myelin-associated glycoprotein (MAG) antibody in affected patients.[87] Viral and other infectious exposures may predispose a host to an autoimmune attack. An association with latent Epstein-Barr virus (EBV) has been implicated; activation of latent EBV has been found in some active MS lesions,[88] although this has been inconsistently replicated.[89,90] Whatever the associating factors, critical exposure seems to occur before the age of 15 years, based on migration studies.[91,92] In keeping with most autoimmune illnesses, female patients are affected 2 to 3 time more frequently than male patients. Individuals of white ancestry have the highest incidence of the disease. Although the disease is less common in African Americans, it tends to have a more severe course in this population. Overall, MS is the third most common cause of disability in United States in individuals 15 to 50 years of age, following only trauma and musculoskeletal disease.[93] The calculation of disability-adjusted life years, a measure of premature morbidity and disability, equivalent to years of healthy life lost due to MS, occurs in the adult population between 25 and 54 years of age, which results in major financial burdens of the patient, family, health system, and society.[94]

## PATHOLOGIC FINDINGS

The primary trigger of immune response in MS is unknown. Early in the inflammatory cascade, a response is triggered against myelin antigens, such as myelin basic protein (MBP), proteolipid protein (PLP), myelin/oligodendrocyte glycoprotein, MAG, and gangliosides. Although plaques may occur throughout the CNS, they are most common in the optic nerves, cerebral periventricular white matter, brainstem, and spinal cord white-matter tracts. MS lesions are classified histologically as acute, chronically active, and inactive. Acute lesions have marked perivascular inflammatory cell infiltrates, composed predominantly of mononuclear cells, T cells, and macrophages, with occasional B cells and plasma cells. Over time, demyelination ensues, with phagocytosis of myelin debris by macrophages and microglial cells. Oligodendrocytes, the myelin-producing cells, proliferate but are destroyed by inflammatory infiltration and gliosis. The resulting demyelination leads to slowed conduction or even conduction block, as well as ectopic signal transmission, which leads to symptomatology.[95] Remyelination is activated by oligodendrocyte progenitor cells, not the surviving oligodendrocytes. With severe and longstanding demyelination, axonal

loss is often found on histologic examination. This process is likely responsible for the nonremitting, chronic, and progressive symptoms in MS patients. The extent of axonal injury is associated with the inflammation in active MS lesions, although later in the course even clinically silent acute lesions may contribute to axonal injury. Subpial gray matter lesions may contribute to permanent disability even early in the disease.[96]

## PATHOPHYSIOLOGY

A variety of motor deficits can result from MS lesions, including spasticity, weakness, tremor, and ataxia. Spasticity, an upper motor neuron (UMN) sign, results from the loss of inhibitory inputs from the corticospinal tracts to $\gamma$-motor neurons and interneuron networks. Weakness and impairment of fine motor control are due to interruption of input to $\alpha$-motor neurons. Although the primary pathologic finding is UMN in nature, chronic disuse will rarely lead to muscle weakness, wasting, and atrophy, resembling lower motor neuron disease. Tremor and ataxia are related to lesions of the cerebellum and related pathways through the brainstem, red nucleus, thalamus, and basal ganglia. Ganglia in the Mollaret triangle, comprising the dentate nucleus of the cerebellum, inferior olive, and red nucleus, are specifically implicated in the development of tremor. In some patients, proprioceptive loss may be the primary cause of tremor, though a wide variety of injuries and circuit involvements may lead to this symptom. Fatigue, defined as a loss of force-generating capacity during sustained motor activity, contributes to disability in patients without other objective signs of motor dysfunction on examination.[97]

## CLINICAL AND LABORATORY DIAGNOSIS

MS is typically divided into relapsing-remitting MS (RRMS) noted in about 85% of cases; and a chronic progressive pattern known as primary progressive MS (PPMS) in about 10% of cases. One-half of those with RRMS may evolve into secondary progressive MS.[98] Discrete episodes of neurologic dysfunction develop over hours to days and are called relapses, flares, attacks, or exacerbations. Attacks may be quite devastating, though most patients recover well. Occasionally, however, attacks can be debilitating if left untreated, especially if the brainstem or spinal cord is involved. During a severe exacerbation, inflammatory damage to myelin affects underlying axons, which can lead to poor recovery and permanent disability. Although patients may have residual disability from MS attacks, there is no progression of disability independent of attacks. Some inference on course can be made based on early prognostic features with initial sensory symptoms generally prognostically positive,[99] whereas motor and cerebellar signs, early relapse, and onset after age 40, are typically prognostically negative and associated with a more aggressive and rapid debilitating course.[100–102] Unlike RRMS, PPMS presents equally in men and women, and tends to occur at an older age. Certain presentations, such as optic neuritis, are common in RRMS but rare in PPMS compared with RRMS. The classic presentation is a male patient presenting after age 40 with progressive myelopathy that steadily worsens with eventual paraparesis, variable upper limb involvement and few other deficits, or symptomatic lesions in cerebral subcortical white matter.

The diagnosis of MS is based on 2 discrete episodes of neurologic dysfunction at least 30 days apart in different locations of the CNS, alternatively, in those with 1 relapse who show evidence of dissemination in time (DIT) and dissemination in space (DIS) on MRI. Patients with a single attack that does not meet formal criteria for MS are considered to have a clinically isolated syndrome (CIS), whereas those with imaging consistent with MS but discovered incidentally are considered to have a radiographically isolated syndrome. The diagnosis of MS is, therefore, based on the

demonstration of multiple lesion DIT and DIS, while excluding alternative diagnoses through clinical, radiographic, and laboratory methods.

DIS is recognized by the following:

- One or more $T_2$ lesions in at least 2 out of 4 areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord
- Gadolinium enhancement of lesions is not required for DIS.

DIT is recognized by either of the following:

- A new $T_2$ and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
- Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.

Diagnostic criteria for MS suggested by Poser and colleagues[103] were initially defined for the purposes of epidemiologic studies and clinical trials, whereas later criteria by McDonald,[104] and Polman and colleagues,[105] were clinically relevant and applicable to practice. They included the caveat that MRI could aid in diagnosis and even mitigate it as in CIS,[106,107] early conversion to clinically definite MS,[108] as well as in predicting responsiveness to immunotherapy with interferon beta-1a[109] and in documenting the first demyelinating episode.[110] The revised McDonald criteria[111] incorporated MRI criteria for the demonstration of DIS,[112,113] whereas those of Montalban and colleagues[111] demonstrated DIT.[107] Recognizing the special diagnostic needs of spinal PPMS, the 2010 McDonald criteria[104,106] maintained that 2 of 3 MRI or CSF findings for PPMS replaced previous brain imaging criteria for DIS.[112] The final criteria for PPMS included 1 year of retrospective or prospective disease progression, plus 2 of the 3 following: (1) 1 or more $T_2$ lesions in at least 1 area characteristics for MS, such as periventricular, juxtacortical, or infratentorial; (2) 2 or more $T_2$ lesions in the cord; or (3) positive CSF by isoelectric focusing evidence of OCB and/or elevated IgG index. Gadolinium enhancement on MRI was not required.

The MRI appearance of MS lesions in the brain and spinal cord is shown in **Figs. 1–9**. Typical MS brain lesions are ovoid foci of $T_2$/fluid-attenuated inversion

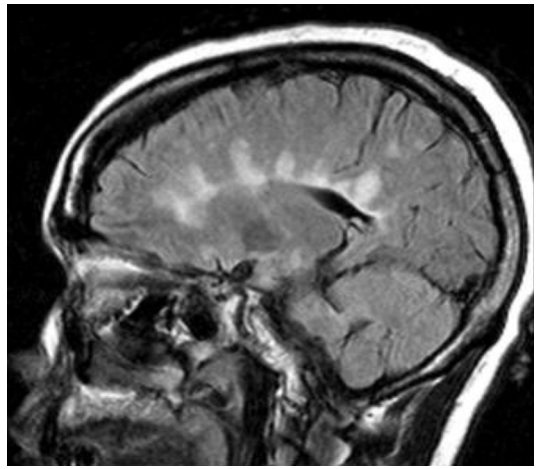

**Fig. 1.** Sagittal fluid-attenuated inversion recovery (FLAIR) image demonstrates typical periventricular lesions so called, Dawson fingers.

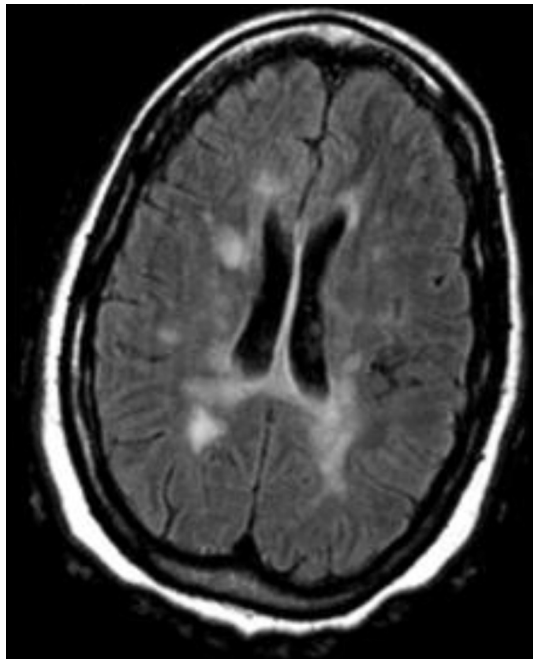

**Fig. 2.** Axial FLAIR image demonstrates typical periventricular lesions so called, Dawson fingers.

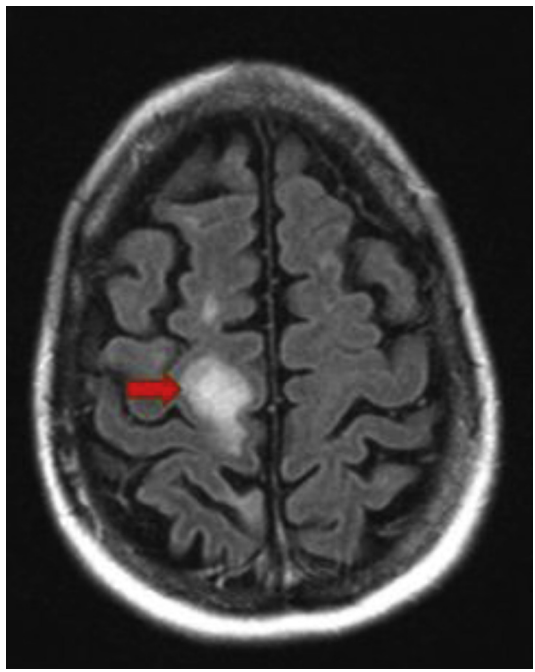

**Fig. 3.** Axial FLAIR image demonstrates a large juxtacortical lesion (*arrow*).

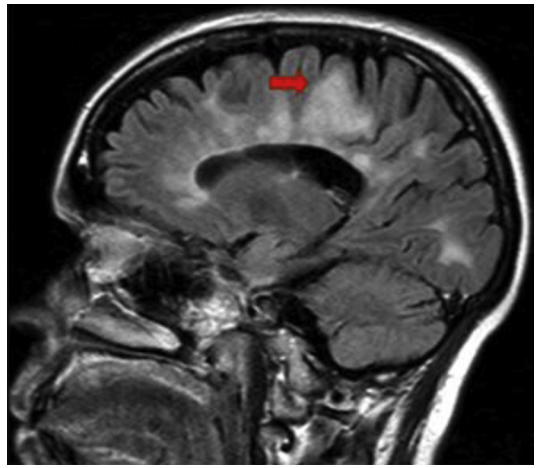

**Fig. 4.** Sagittal FLAIR image demonstrates a large juxtacortical lesion (*arrow*).

recovery (FLAIR) hyperintensity that radiate away from the ventricles best appreciated on sagittal FLAIR images. For every clinical relapse the patient experiences, the MRI shows 5 to 10 times as many lesions. Actively inflamed lesions demonstrate enhancement after the administration of gadolinium secondary to breakdown of the blood-brain barrier. There is characteristic complete or incomplete ring enhancement, often with the opening of the ring pointing to the cortex. Other times, lesions may enhance homogenously.

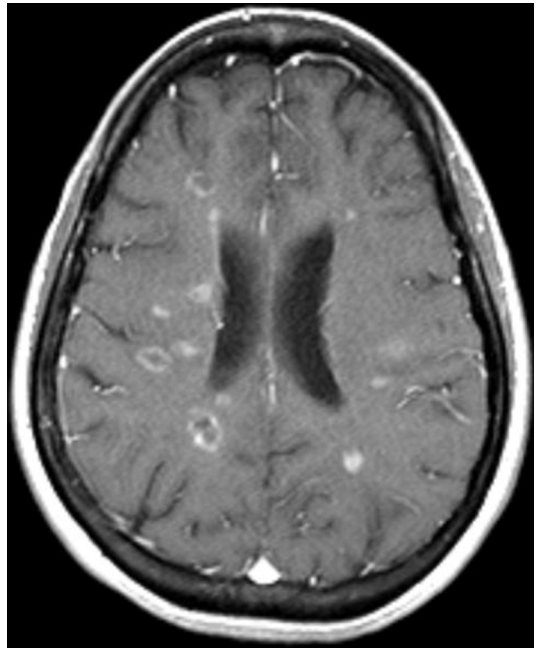

**Fig. 5.** Postcontrast axial $T_1$-weighted image demonstrates numerous enhancing lesions. Incomplete ring-enhancing lesions are highly suggestive of MS.

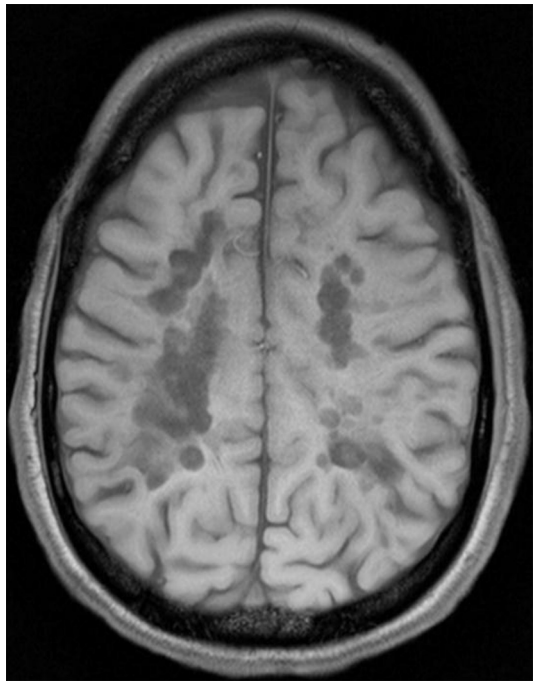

**Fig. 6.** Axial $T_1$-weighted image demonstrates hypointense lesions in the white matter. Older lesions appear hypointense on $T_1$-weighted images. They are called black holes and are evidence of irreversible axonal damage.

Magnetic resonance spectroscopy (MRS) is based on organic molecules in tissue as opposed to water. MRS has been studied with creatine (Cr), N-acetyl aspartate (NAA), choline, and myoinositol. NAA, which localizes to neurons, and Cr, which localizes to neurons and glial cells, relate to neuronal integrity, with deviations from normal levels indicating loss and injury; while correlating with neurologic disability.[114] Lymphocytic CSF pleocytosis of 5 to 50 cells/mm3 present in up to two-thirds of patients with MS; and OCB are found in greater than 90% of cases[115]; however it may not be recognized for several years. The latter is a nonspecific marker for CNS and may be found in encephalitis, meningitis, Guillain-Barré syndrome, and cerebral infarction.[116] Trimodal visual evoked responses, brainstem auditory evoked responses, and somatosensory evoked responses are potentially useful adjunctive studies in selected patients. Transcranial magnetic stimulation can demonstrate significant intraspinal delays in motor conduction.[117]

## MULTIPLE SCLEROSIS VARIANTS AND DIFFERENTIAL DIAGNOSIS

### *Neuromyelitis Optica*

Neuromyelitis optica has phenotypic similarities to MS although the underlying pathophysiology is quite different.[118] This disorder presents with inflammation and demyelination, which may relapse similarly to MS but, unlike MS, there is little to no progression independent of relapses. It is an uncommon disease that affects 0.5 to 5 per 100,000 persons. It is 10 times more common in women than in men, compared with MS, which is only 2 to 3 times more common in women. Unlike MS, it is more

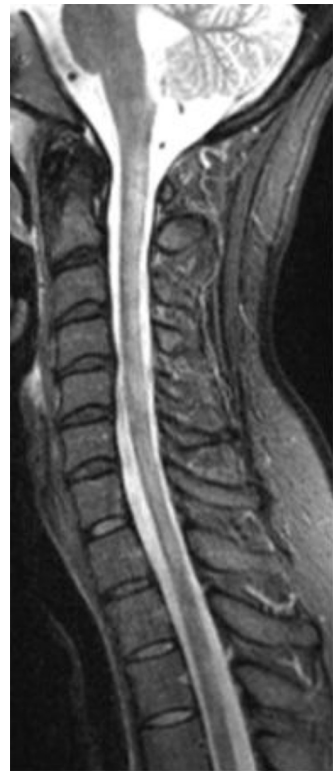

**Fig. 7.** Sagittal $T_2$-weighed image demonstrates hyperintense spinal cord lesions typical for MS. These lesions appear as discrete plaques within spinal cord white matter becoming more confluent over time. On axial imaging, the lesions are typically eccentric within the cord and do not occupy the entire cord.

common in African Americans, Asians, and Hispanics than in white persons. It typically presents between the ages of 30 and 40 years, although it may present at any age. It results in optic neuritis and transverse myelitis, both of which are longitudinally extensive. Patients can present with brainstem syndromes manifesting nausea, vomiting, and intractable hiccups, as well as hypothalamic lesions leading to narcolepsy, excessive sleepiness, obesity, and autonomic dysfunction.

The formal criteria for NMO are divided into those with and without NMO-IgG antibodies directed against the aquaporin-4 (AQP4) water channel present on astrocyte foot processes of the blood-brain-barrier. Seropositivity is reported in about 75% of patients with a clinical symptom consistent with NMO, whereas nearly 100% are specific for NMO.[119,120] Guidelines have been developed for the diagnosis and management of NMO.[121]

There are no randomized clinical trials of disease-modifying treatments in NMO, but small case series support the use of immunosuppressive agents, such as mycophenolate mofetil and azathioprine. The monoclonal antibody rituximab, which eliminates circulating B cells, has shown the greatest efficacy. The anti–interleukin-6 receptor antibody, tocilizumab, has shown promise in a small series of patients. Patients are often maintained on oral glucocorticoids as well. The disease-modifying agents in MS do not play a role in NMO, and they may worsen

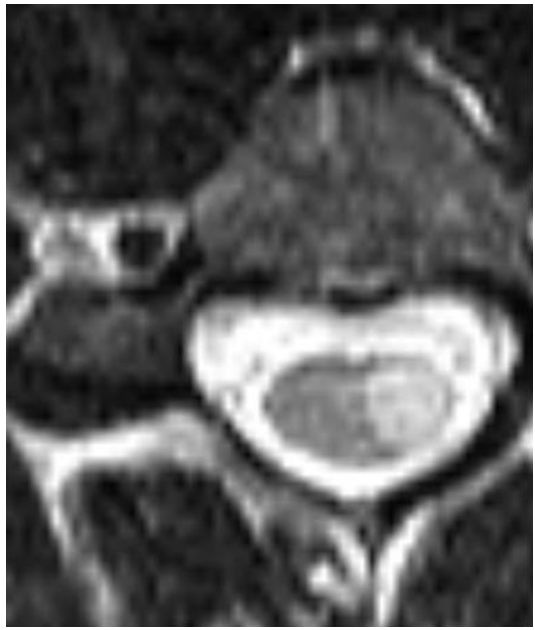

**Fig. 8.** Axial $T_2$-weighed image demonstrates hyperintense spinal cord lesions typical for MS. These lesions appear as discrete plaques within spinal cord white matter becoming more confluent over time. On axial imaging, the lesions are typically eccentric within the cord and do not occupy the entire cord.

the disease. However, other agents currently under study include aquaporumab, which is a nonpathogenic antibody-blocking AQP4-IgG–binding agent; sivelestat, which inhibits neutrophil elastase; and eculizumab, which inhibits the complement cascade.[122]

### *Acute Disseminated Encephalomyelitis*

This monophasic immune-mediated CNS-demyelinating disorder can initially mimic MS; however, it is a predominantly a disorder of childhood and often postviral due to preceding measles, rubella, and mumps infection or vaccination, especially during the spring and winter months. Onset is characterized by fever, vomiting, headache, gait disturbance, and generalized seizures with signs of altered sensorium, nystagmus, diplopia, isolated or multiple cranial nerve palsies; as well as speech disturbance, dystonia, chorea, bladder disturbances, paraparesis, and quadriparesis.[123] Up to one-third of affected patients experience optic neuritis and CSF pleocytosis can be identified in up to two-thirds of patients. MRI shows multifocal demyelinating lesions through the subcortical white matter, midbrain, pons, corpus callosum, basal ganglia, medulla, and cerebellum. Only about one-third of patients have spinal cord lesion on neuroimaging. About 70% of patients will have remission within a week of commencing treatment with high-dose corticosteroids, although the remainder may experience residual symptoms.

Many other illnesses may initially mimic MS, most frequently other autoimmune, infectious or postinfectious, or genetic diseases. Autoimmune differential diagnosis may include systemic lupus erythematosus, Sjögren syndrome, Behçet syndrome, sarcoidosis, and CNS vasculitis.[124] Commonly considered infectious disorders

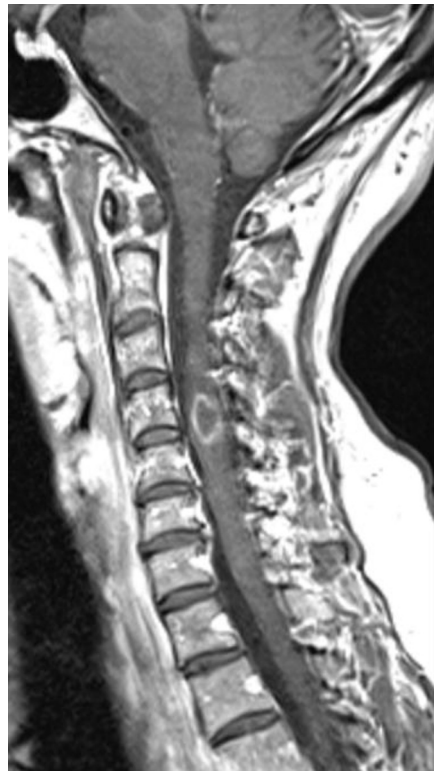

**Fig. 9.** Postcontrast sagittal $T_1$-weighted image demonstrates an enhancing lesion in the cervical spinal cord in patients with MS. Such lesions can have a ring-like appearance or a more punctate pattern of enhancement. Active lesions in the spinal cord, like active lesions in the brain, enhance with the administration of gadolinium.

include syphilis, tuberculosis, Lyme borreliosis, human T-lymphotropic virus type I, cytomegalovirus, herpes simplex virus, and varicella zoster virus. Hereditary disorders that may mimic MS include adrenoleukodystrophy, Refsum disease, spinocerebellar degeneration, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Specific differentiation and diagnosis of MS versus these alternates requires specific evaluation and often relies on detailed laboratory testing.[124,125]

## TREATMENT

Treatment can favorably affect MS by immune modulation, enhancement of myelination, improvement of conduction through demyelinated pathways, and providing symptomatic improvement without directly affecting the underlying disease (**Table 1**). Immune modulatory therapy diminishes the activation and proliferation of immune cells and their migration into the CNS by enhancing intrinsic suppressor activity or limiting the destruction caused by inflammatory processes. Such disease-modifying medications include injectable (interferon-beta and glatiramer acetate) and oral medications (fingolimod, teriflunomide, and dimethyl fumarate), monoclonal antibodies (natalizumab and alemtuzumab), and 1 chemotherapeutic

**Table 1**
**Symptomatic MS treatment**

| Symptom | Treatments |
|---|---|
| Fatigue | Modafinil, amantadine, stimulants, SSRIs |
| Depression | SSRIs, SNRIs, bupropion, psychotherapy |
| Walking difficulty | Dalfampridine (Ampyra) is an oral agent that was approved on 1/22/2010 to help MS patients with walking. It helped about 40% of patients walk 25% faster than baseline, physical therapy, or mobility aids. |
| Nystagmus | Baclofen, clonazepam, gabapentin, memantine |
| Spasticity | Baclofen (either orally or via intrathecal pumps), Zanaflex, benzodiazepines, botulinum toxin. |
| Bladder dysfunction | Oxybutynin, terazosin, desmopressin, intravesicular botulinum toxin type A, self-catheterization |
| Pain or paresthesias | NSAIDs, anticonvulsants, antidepressants, surgery for trigeminal neuralgia |
| Tremor | Anticonvulsants, propranolol, clonazepam, deep brain stimulation |
| Pseudobulbar palsy | Dextromethorphan or quinidine (Nuedexta) |
| Sexual dysfunction | Phosphodiesterase 5 inhibitors (Sildenafil) |

*Abbreviations:* NSAIDs, nonsteroidal antiinflammatory drugs, SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective norepinephrine reuptake inhibitors.

agent (mitoxantrone). They are all indicated for patients with RRMS still in relapse, but, other than mitoxantrone, they do not have a role in the progressive phase of the illness. In patients with newly diagnosed MS and low disease activity, most authorities suggest starting treatment as soon as possible to influence the frequency of relapses, stabilize disease activity, and lessen long-term disability. The nonspecific immunosuppressants azathioprine and cyclophosphamide have been used frequently without clearly established efficacy. Cladribine, mitoxantrone, antilymphocyte globulins, cyclosporine, and tacrolimus are chemotherapeutic agents with use as semispecific suppressors of MS disease activity. In extremely severe cases, total lymphoid irradiation may modulate the immune system, potentially benefiting MS, though controlled trials are lacking. Several peptides are being explored that interfere with binding within the trimolecular complex (T-cell receptor, antigen, and MHC class II molecule),[126] potentially leading to more specific agents decreasing the activity of the disease with minimal systemic immunosuppression.

Acute exacerbations are often initially treated with corticosteroids that enhance the resolution of symptoms and signs, though do not significantly affect the long-term outcome of an exacerbation. There are no certain dosing guidelines, although solumedrol 1g for 5 days is an appropriate course of treatment. Pulse therapy with corticosteroids is associated with many temporary side effects such as insomnia, irritability, fluid retention, increased appetite, weight gain, hyperglycemia, hypertension, dyspepsia, depression, psychosis, bone fractures, and osteoporosis. In patients with poor venous access or otherwise intolerable reactions to corticosteroids, adrenocorticotropic hormone may be used instead. Plasmapheresis is sometimes used in severe relapses that are refractory to corticosteroids.

Therapies focused on improving conduction include 4-aminopyridine (4-AP) and 3, 4-diaminopyridine (3, 4-DAP), both potassium channel blockers that amplify and prolong action potentials. Preliminary studies with 4-AP demonstrated improvement in

may measures of neurologic function. However, when a large, multicenter, double-blind, placebo-controlled, study was performed, it failed to show an effect on the Expanded Disability Status Scale.[127] Unfortunately, higher levels of these medications can result in seizures and encephalopathy, potentially preventing sufficient dosage for demonstrable effect.[128]

Symptomatic therapy for MS is an important aspect of management.[129] Paresthesia may respond to antidepressants and anticonvulsants. Anticholinergic and β-blocker medications can improve bladder function, and fatigue can require amantadine and CNS stimulants. There are no medications currently available to treat muscle weakness, though physical therapy can optimize patient function. Spasticity, muscle cramps, and spasms respond to stretching and antispasticity medications, including baclofen, tizanidine, and benzodiazepines. If necessary, botulinum toxin can be introduced into specific muscles or, if generalized spasticity is refractory to other treatments, intrathecal baclofen administered by an implantable subcutaneous pump or dorsal root rhizotomy may be considered. Adaptive equipment includes ankle-foot orthoses for foot-drop dysfunction and canes, walkers, and wheelchairs for mobility. Tremor may respond to a variety of medications. Propranolol and primidone are often used initially, though isoniazid, buspirone, trazadone, baclofen, carbamazepine, gabapentin, benzodiazepines, and unilateral thalamotomy, can all be effective.[130]

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