Multiple sclerosis: clinical aspects
By Anthony T Reder MD (Dr. Reder of the University of Chicago served on advisory boards and as a consultant for Bayer, Biogen, Caremark Rx, Genzyme, Novartis, Questcor, Serono, and Teva-Marion.)
Originally released October 23, 2014; expires October 23, 2017

Introduction

This article includes discussion of disseminated sclerosis, primary progressive multiple sclerosis, relapsing-remitting multiple sclerosis, remitting-relapsing multiple sclerosis, and secondary progressive multiple sclerosis. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Multiple sclerosis affects every part of the neuraxis and has replaced syphilis as the great mimicker in neurology. In this article, the author describes the entire spectrum of multiple sclerosis signs and symptoms, focal and diffuse brain lesions, look-alike diseases, the overactive immune response, the complex pathology of demyelination, death and dysfunction of oligodendroglia and neurons, MRI and CSF abnormalities, and the treatment of symptoms and course of multiple sclerosis. This revision includes new comments on vitamin D and the immunology, pathology, and benefits and dangers of treatment of multiple sclerosis.

Key points

- The incidence of multiple sclerosis is increasing around the world.
- Multiple sclerosis lesions cause focal neurologic deficits. Problems with fatigue, cognition, and bladder control are common but often overlooked.
- Diagnosis is complex and requires neurologic history, clinical and MRI examination, and sometimes spinal fluid and evoked potential analysis.
- Demyelinating diseases that mimic multiple sclerosis include neuromyelitis optica and CNS Sjögren's syndrome as well as many other toxic, inflammatory, and metabolic disorders.

Historical note and terminology

Greek and Roman physicians did not document multiple sclerosis, but it may have been mentioned in 13th century Icelandic sagas. Saint Lidwina of Holland appears to have developed multiple sclerosis in 1396 (Medaer 1979). The court physician was not optimistic after examining Lidwina, stating, "Believe me, there is no cure for this illness; it comes directly from God. Even Hippocrates and Gallenus would not be of any help here." The clinical description and prognosis of multiple sclerosis have improved in the intervening 500 years, but progress in understanding its etiology is debatable.

Elizabeth Foster of Coldingham, north of the Scottish/English/North Sea border, developed intermittent paralysis, sensory symptoms, and possible optic neuritis starting in 1742 at age 18 (Lincoln and Ebers 2012). Multiple sclerosis was clearly depicted in 1822 in the diary of Sir Augustus D' Este, grandson of King George III of England (Firth 1948). One of his relapses is portrayed here:

At Florence, I began to suffer from a confusion of sight. About the 6th of November, the malady increased to the extent of my seeing all objects double. Each eye had its separate visions. Dr. Kissock supposed bile to be the cause. I was twice blooded from the temple by leeches. Purges were administered. One Vomit and twice I lost blood from the arm. The Malady in my eyes abated, again I saw all object naturally in their single state. I was able to go out and walk" (Murray 2005).

Cruveilhier in Paris and Carswell in London clearly illustrated central nervous system plaques and sclerosis in the 1840s. Charcot published detailed clinical descriptions and characterized the demyelination in plaques, and Rindfleisch...
described the perivascular inflammatory CNS lesions in the 1860s (Cook 1998). These observers documented the intermittent and seemingly random neurologic symptoms of multiple sclerosis and the variable evolution of the disease. The history of multiple sclerosis is extensively reviewed by Murray (Murray 2005).

**Clinical manifestations**

**Presentation and course**

Multiple sclerosis lesions in the brain and spinal cord damage every function of the central nervous system. Clinical symptoms vary from mild to aggressive; the course can be relapsing-remitting or progressive, and the symptoms and course evolve over time. Protean symptoms include fatigue and disturbed sensory, motor, bladder, bowel, sexual, cerebellar, brainstem, optic nerve, and cognitive realms. Symptoms, especially fatigue, limit activity in three fourths of patients.

In most patients, symptoms of an exacerbation arise over hours to days, typically last 2 to 6 weeks, and then remit, sometimes completely. Forty percent of these attacks cause long-lasting deficits, but 20% of patients will improve after attacks (Lublin et al 2003). Resolved symptoms can reappear transiently during infections, exercise, stress, menses, afternoon circadian temperature rise, or heat (“ghost symptoms,” Uhthoff phenomenon, pseudo-exacerbation) in up to 80% of multiple sclerosis patients (Guthrie and Nelson 1995).

The neuroanatomical location of plaques is not completely random. Lesions have a predilection for the periventricular white matter, so certain symptoms and signs are common. For instance, periaqueductal damage to the medial longitudinal fasciculus causes internuclear ophthalmoplegia, a frequent sign of multiple sclerosis. The following section describes focal symptoms and then generalized phenomena.

**Optic neuritis.** The optic nerves are frequently involved (approximately two thirds clinically), especially in younger patients. Thirty-one percent of army recruits with multiple sclerosis have optic signs. “Asymptomatic” patients, free of optic neuritis, frequently have abnormal visual evoked potentials or perimetry.

Optic neuritis typically begins with subacute loss of vision in one eye. The central scotoma is described as blurring or a dark patch. Color perception and contrast sensitivity are disturbed. Subjective reduction of light intensity is often associated with an ipsilateral Marcus Gunn hypoactive pupillary response. Ninety-two percent have retro-orbital pain with eye movement.

With acute lesions, there is occasional blurring of the disc margin or florid papillitis, but this is not typical. With papillitis (in 5%), inflammation near the nerve head causes disc swelling, cells in the vitreous, and deep retinal exudates. With retrobulbar inflammation, the fundus is initially normal. After the neuritis resolves, the disc is usually pale (“optic pallor”), commonly in its temporal aspect. Using an ophthalmoscope, slit-like defects in the peripapillary nerve fiber layer appear with red-free (green) light. This axonal damage in the retina, an area free of central nervous system myelin, suggests that optic nerve pathology extends beyond central nervous system plaques. Retinal nerve fiber layer atrophy and thinning is obvious on optical coherence tomography. The fellow eye is often abnormal on OCT, though not as severely.

Bilateral simultaneous optic neuritis led to multiple sclerosis in 1 of 11 adults after an interval of up to 30 years. Sequential optic neuritis led to multiple sclerosis in 8 of 20 (Parkin et al 1984). In children, 1 of 17 developed multiple sclerosis after bilateral onset.

Visual function usually begins to improve several weeks after the onset of optic neuritis, and resolution continues over several months. Complete recovery of visual acuity is the rule, even after near blindness. However, other disturbances of vision often persist, such as visual “blurring,” poor low-contrast visual acuity, and red or blue desaturation that causes colors to appear drab (“not as vivid”). There is progressive loss of color discrimination with longer duration multiple sclerosis. Bright lights cause a prolonged afterimage, a “flight of colors.” Depth perception is impaired and is worse with moving objects (“Pulfrich phenomenon,” where laterally moving object seems to trace an ellipse, due to light attenuation in one eye). Eye movements sometimes cause fleeting flashes of light (“movement phosphenes”). The mechanism corresponds to the fleeting cervical sensory changes of Lhermitte sign (Lhermitte of the eye). Increased body temperature can amplify all of these symptoms and diminish visual acuity (“Uhthoff phenomenon”).

Uveitis and pars planitis (intermediate uveitis; near where the iris contacts the vascular choroid and the sclera) are
present in 1% of multiple sclerosis patients. Conversely, 20% of patients with pars planitis develop multiple sclerosis or optic neuritis. Some of these patients will develop macular edema, vitreous opacities, papillitis, *vasculitis* and vitreous hemorrhage, and cataracts. Perivenous sheathing is an inflammatory change of the retinal veins seen in one fourth of multiple sclerosis patients. Occipital cortex lesions can distort vision, eg, visual inversion. Retinal periphlebitis (see Eales disease) affects the peripheral retina in occasional multiple sclerosis patients and correlates with more severe multiple sclerosis, retinal nerve fiber atrophy, and microcystic macular edema.

**Brainstem abnormalities, including diplopia.** Lesions in the brainstem disrupt intra-axial nerves, nerve nuclei, and internuclear connections as well as autonomic, motor, and sensory long tracts. Proton density MRI is best for imaging brainstem abnormalities, including plaques in the median longitudinal fasciculus.

Smell is reduced in 40% of multiple sclerosis patients (*Dahlslett et al 2012*). Loss correlates with more MRI plaques and olfactory bulb or tract demyelination at autopsy. Olfactory dysfunction is worse in *neuromyelitis optica* than in multiple sclerosis. Taste is reduced in 20%. It is lost or altered (dysgeusia) from lesions in the brainstem and sometimes in the medial ventralis posterior thalamic nucleus and recovers within 3 months. Clinically, the third nerve is the most frequent target for brainstem lesions. Cerebellar and brainstem lesions disrupt eye movements, usually coinciding with more severe disability. Third, sixth, and rarely fourth nerve lesions cause diplopia.

Medial rectus weakness is usually part of an “internuclear ophthalmoplegia.” In a young patient, internuclear ophthalmoplegia is nearly pathognomonic of multiple sclerosis. In older patients, infarcts, trauma, and disparate other causes are possible (*Keane 2005*). Internuclear ophthalmoplegia is paresis or weakness of addition ipsilateral to a medial longitudinal fasciculus lesion, along with dissociated *nystagmus* of the abducting eye. Lesions, usually in the pons or midbrain, cause internuclear ophthalmoplegia when they interrupt connections between the pontine paramedian reticular formation that innervates the ipsilateral abducens nucleus and the contralateral third nerve nucleus. This illustrates an important principle: plaques predominate in periventricular regions and cause characteristic signs.

Convergence may be normal despite an affected medial rectus. Medial longitudinal fasciculus lesions are seen best with proton density MRI but are even more apparent with the clinical examination. Internuclear ophthalmoplegia is often worse with heat and better with cooling (*Frohman et al 2008*). The medial longitudinal fasciculus is near the locus ceruleus in the rostral pons, and both are near the ventricular system. An internuclear ophthalmoplegia could, thus, correlate with sympathetic abnormalities and possibly depression (*Arnason personal communication 2014*).

Internuclear ophthalmoplegia is subclinical or “latent” in 80% of patients (in this case, it would be termed “internuclear ophthalmoparesis”). Rapid eye movements can bring out this hidden, minimal oculomotor weakness, causing slowing of the early adducting saccades—an adduction lag. A medium rate of finger motion will detect loss of smooth pursuit and demonstrate ataxic eye movements from cerebellar lesions.

Nystagmus is common in multiple sclerosis. It is usually inconsequential, but nystagmus and *oscillopsia* can be severe enough to prevent reading or driving a car.

There are reports of high T2 signal MRI lesions in peripheral fifth (in 2% of patients, with two thirds bilateral), seventh, sixth, third, and eighth nerves. Seventh nerve lesions can mimic *Bell palsy*. Facial myokymia is from lesions of the facial nerve in the pontine tegmentum, and can be reversed with *carbamazepine* and possibly botulinum toxin.

Hearing loss is relatively rare, but auditory processing could be slowed by brainstem and deep white matter lesions. Central hearing defects with abnormal brainstem auditory evoked potentials can help differentiate multiple sclerosis from benign *positional vertigo*, which has no central defect. Vertigo is common and sometimes so incapacitating that patients are bed-bound. Isolated autoimmune disease of the auditory nerve can also cause hearing loss and vertigo. The relation to multiple sclerosis is unclear.

Up to one fourth of patients have problems swallowing. Attacks can cause an oculo-palatal tremor. *Horner syndrome* is occasionally present.

**Transverse myelitis.** The cord symptoms in idiopathic transverse *myelitis* are generally more severe than in multiple
sclerosis. In multiple sclerosis, a complete transverse lesion is less common than a partial cord lesion (ie, a Brown-Séquard syndrome). Progressive myelopathy can arise from solitary lesions of the cervicomedullary junction, often associated with positive CSF oligoclonal bands.

**Cerebellar dysfunction and tremor.** The cerebellum or its pathways are damaged in 50% of patients. “Charcot’s triad” of cerebellar signs is nystagmus, intention tremor, and “scanning” speech (in the sense of examining words carefully, “scandés” from Charcot). In 3% of patients, intention tremor of the limbs, ataxia, head or trunk titubation, and dysarthria can be totally disabling. Surprisingly, patients with severe ataxia are often strong and thin and would otherwise be fully functional. The Stewart-Holmes rebound maneuver to detect cerebellar dyssynergia does not correlate well with kinetic tremor (flex or extend at elbow) and intention tremor (finger-to-nose). This suggests damage to different anatomic pathways (Waubant et al 2003). Poor cerebellar function correlates with loss of cerebellar MRI volume. Ataxia and poor ambulation correlate with lesions of the dentate nucleus. Severe cerebellar signs correlate with poor pulmonary function.

Dystonia and parkinsonian symptoms are occasionally caused by a multiple sclerosis plaque. Extrapyramidal symptoms disappear as the plaque resolves (Maimone et al 1991).

**Weakness.** The long course of axons traveling through the cord from the motor cortex to lumbar motor neurons increases the likelihood that a random plaque will interrupt motor neuron conduction. Legs are usually affected more than arms, causing foot-drop, tripping, or poor stair climbing. The hip flexors are frequently weak, likely from multiple cervical cord lesions that destroy input to the iliopsoas; this weakness is out of proportion to other leg muscles. Patients can walk backwards more easily than they walk forward because gluteal muscles are stronger than the iliopsoas. Hyperreflexia, spasticity, and a Babinski sign are common. Rarely, plaques interrupt intra-axial nerve roots, the deep tendon reflexes disappear, and muscles atrophy. Some muscle weakness and fatigue can be explained by a shift in myosin heavy chain isoforms and less contractile force, a result of muscle inactivity and deconditioning (Garner and Widrick 2003). Walking ability can be measured with a timed 25-foot walk, the 6-spot step test, and the timed 10-foot tandem walk (TTW10), which incorporate coordination and balance. Motor function can be longitudinally monitored in a patient diary with a weekly 5-minute walking test (Scott personal communication 2014).

Falls and fractures are increased in multiple sclerosis. Osteoporotic fractures double, a consequence of weakness (Bazelier et al 2012). Osteoporosis is from low vitamin D levels, less weight-bearing exercise, a consequence of fatigue, some medications (antidepressants, anticonvulsants), and perhaps genetic links as discussed below in “Environmental Influences.”

**Spasticity.** Spasticity increases with a full bladder or bowels, pain, exposure to cold, and sometimes on the day after IFN-beta injections (an effect of cytokines or direct modification of neuronal excitability). On arising, the first few steps are difficult from transient stiffness after physical inactivity. Similarly, internuclear ophthalmoplegia is most obvious with the first eye movements of the examination. Painful tonic spasms are common in patients with severe spasticity and can be provoked by exertion or hyperventilation.

**Bladder and sexual dysfunction.** Bladder dysfunction is common and markedly reduces quality of life. It is the initial symptom in 5% of patients and eventually develops in 90%. Two thirds of symptomatic patients have bladder hyperreflexia with urgency and frequency. This is complicated by sphincter dyssynergia in 50% of the patients (Schoenberg 1983; Andrews and Husmann 1997; Betts 1999). Some of these patients are initially areflexic. The other third have hyporeflexic bladders. Patients’ sensation of residual volume is often unreliable, so volume should be measured with office sonography or catheterization. Detrusor hypreflexia is linked to pontine lesions; detrusor-sphincter dyssynergia is linked to cervical spinal cord lesions. Both are more common in Japanese populations than in Western populations.

Glomerular filtration rate is reduced by 20% (Calabresi et al 2002). This could be from chronic neurogenic bladder, urinary tract infections, antibiotics, ionic contrast agents, long-term use of non-steroidal anti-inflammatory drugs, and chronic dehydration.

Seventy percent of patients complain of sexual problems—orgasmic difficulty, poor erections or lubrication, low pleasure, low libido, poor physical movement, and genital numbness. Impotence develops in 40% to 70% of male patients. Fifty percent of women with multiple sclerosis have significant sexual problems and complain of loss of libido,
organs, and genital sensation. Orgasmic dysfunction correlates with loss of clitoral vibratory sensation and cerebellar deficits (Gruenwald et al 2007). Difficult or no orgasm is associated with abnormal or absent (26/28) pudendal somatosensory evoked potential, although desire is normal (Yang et al 2000). Occasional women feel diffuse orgasmic spasms, not in skeletal muscle, that last for up to 5 minutes. Others mention increased vaginal sensation and orgasmic intensity.

Sexual problems often follow or coincide with bladder dysfunction. Both are associated with loss of sweating below the waist from lesions of sympathetic pathways and disruption of genital somatosensory pathways. MRI T1 lesions in the pons correlate with sexual dysfunction, far better than other MRI measures, urodynamics, and pudendal or tibial evoked potentials. Other literature varies on the anatomical links to plaque location. Neurons in the medial preoptic areas are stimulatory; those from the ponto-medullary paragigantocellular nucleus release serotonin to inhibit erections. Antidepressants that raise serotonin levels can cause impotence.

**Constipation.** Fifty percent of clinic patients experience constipation. It is more prevalent in progressive than in relapsing forms of multiple sclerosis. Poor voluntary squeeze pressure on anal manometry, combined with little sensation of “fullness” is typical. Occasionally, insensitivity to rectal filling causes incontinence. Gastroparesis has occurred with acute medullary lesions, and half of multiple sclerosis patients have slow gastric emptying. Disruption of autonomic pathways in the medulla and cord may underlie the gastrointestinal dysfunction. Gut neurons have not been studied as direct targets of the immune system in multiple sclerosis, but the readily accessible enteric nervous system has been analyzed in Parkinson disease and diabetes. Enteric glia have more antigenic resemblance to central nervous system glia than to peripheral nervous system glia (Gershon et al 1994) and may be immune targets in multiple sclerosis.

**Autonomic problems.** Cortical, hypothalamic, brainstem, and spinal cord plaques often interrupt the sympathetic nervous system. The hypothalamus controls temperature, sleep, sexual activity, and autonomic functions. Damage causes slow colonic transit, bladder hyperreflexia, and sexual dysfunction. Less-recognized phenomena from sympathetic nervous system disruption are vasomotor dysregulation (cold, purple feet); cardiovascular changes (orthostatic changes in blood pressure and dizziness, blood pressure response to straining, and poor variation of the EKG R-R interval on Valsalva maneuver, possibly increasing risk of surgery); poor pilocarpine-induced sweating, poor sympathetic skin responses—especially in progressive multiple sclerosis (Karaszewski et al 1990; Acevedo et al 2000), subnormal rise in serum catecholamines on standing, pupillary abnormalities, and possibly fatigue. Rarely, plaques in brainstem autonomic pathways cause atrial fibrillation or neurogenic pulmonary edema, sometimes preceded by multiple sclerosis lesion-induced cardiomyopathy. Cold hands and feet often precede the diagnosis of multiple sclerosis, raising the possibility that undetected spinal cord lesions have already affected the autonomic nervous system.

Sixty percent of patients have pupillary reactions that are abnormal in rate and degree of constriction (de Seze et al 2001). Some pupillary defects caused by sympathetic disruption may correlate with visual-evoked potentials or history of optic neuritis. An afferent pupillary defect can follow optic neuritis.

Autonomic dysfunction correlates with axonal loss and spinal cord atrophy yet not often with cord MRI lesions. It is possible that plaques in the insular cortex, hypothalamus, periaqueductal gray of the brainstem, and cord all disrupt sympathetic pathways. The periaqueductal gray (because it abuts the ventricular system) and the insular cortex (deep in the Sylvian fissure near germinal center-like areas) are likely to be seriously damaged in multiple sclerosis. Parasympathetic and sympathetic dysfunction correlates with duration of multiple sclerosis but not with disability (Gunal et al 2002). Parasympathetic dysfunction (eg, heart rate variation with respiration, abnormal pupillary reactions) is most pronounced in primary progressive disease. Sympathetic dysfunction can worsen during exacerbations. It is tied to dysregulated immunity (Flachenecker et al 2001); worse autoimmune disease in animal models and worse multiple sclerosis (Karaszewski et al 1991); less response to the beta-adrenergic agonist, isoproterenol (Giorelli et al 2004); and the progressive form of multiple sclerosis.

Periodic hyperthermia is rare, but chronic hyperthermia is occasionally seen and can worsen during an attack with profound decreases to 28°C/79°F (author’s observation). Cognition is surprisingly preserved with hyperthermia in multiple sclerosis. Hypothalamic or thalamic plaques presumably cause the abnormal temperature regulation. Hypothermic patients are at high risk for infection because immunity is compromised at low temperature. Worsening hypothermia also can forecast an infection. Interferon-beta elicits fever by direct effects on thermosensitive neurons in the preoptic or anterior hypothalamus, without elevation of other pyrogenic cytokines.
**Sensory symptoms.** Sensory symptoms are common in multiple sclerosis. Patients often have difficulty describing these sensations because they are spontaneous or distorted perceptions of everyday stimuli modified by areas of demyelination and ephaptic connections unique to each patient.

Positive sensory symptoms are common. They are described as tingling, numbness, a tight band (usually at T6-T10, the "multiple sclerosis hug"), pins and needles, a dead feeling, "ice" inside the leg, standing on broken glass, and something "not right." Paresthesias typically begin in a band (a "multiple sclerosis hug") around the trunk at T6-T9 (often from a cervical plaque). They sometimes start in a hand or foot and progress over several days to involve the entire limb. The sensations then resolve over several weeks.

Sensory loss ranges from decreased olfaction to marked loss of pain perception in small spots or over the entire body. Poor perception of vibration in the feet, but spared position sense, is present in more than 90% of multiple sclerosis patients. Vibratory loss can be quantified with a tuning fork and sometimes improves with drug therapy. Sensory paths are unable to transmit impulses from the rapidly oscillating tuning fork, from a combination of demyelination and cytokines that interfere with axonal conduction (Smith et al 2001).

**Lhermitte sign.** In 1924, Lhermitte described an electric discharge following flexion of the neck in multiple sclerosis. Forty percent of multiple sclerosis patients have Lhermitte sign (symptom, phenomenon), and 95% of these have cervical cord MRI lesions. This rapid and brief "electric shock," "zapping," or "vibration" runs from the neck down the spine. Intensity of the pain is directly related to the amplitude and rapidity of neck flexion. In an instinctive protective reflex, the patient may straighten her neck. This sign is from mechanical stimulation of irritable demyelinated axons. It is similar to ulnar nerve trauma triggering the “funny bone” at the elbow. Cord compression can also generate the sign.

**Trigeminal neuralgia.** Trigeminal neuralgia is relatively rare in multiple sclerosis (occurring in 0.5% to 1% of patients), but incidence is higher than in the normal population (Rushton and Olafson 1965). Bilateral trigeminal neuralgia may be pathognomonic of multiple sclerosis (Jensen et al 1982).

In the elderly, trigeminal neuralgia can be caused by arteries compressing the trigeminal nerve at the junction of the central and peripheral nervous system (root entry zone) (Meaney et al 1995). Vascular compression causes demyelination and remyelination, sometimes aberrant, allowing ephaptic conduction between active and silent nerve fibers and between light touch and pain fibers (Love and Coakham 2001).

Trigeminal neuralgia of multiple sclerosis, however, is from a plaque in the fifth nerve nucleus (Olafson et al 1966) or the brainstem entry zone of nerve fibers (Gass et al 1997), suggesting that therapies will differ between the elderly and multiple sclerosis forms of trigeminal neuralgia. The brainstem or cisternal (peripheral) fifth nerve enhances on MRI in 3% to 7% of multiple sclerosis patients, but this is usually clinically silent (Nakashima et al 2001). Herpes infections, which are latent in the majority of trigeminal ganglia, potentially enhance inflammation. Ganglia in the majority of autopsies contain T cell and macrophage markers, interferon-gamma, and interferon-induced markers (Theil et al 2003); these are likely to suppress virus replication, but could enhance inflammation in multiple sclerosis. Secondly, after facial nerve injury, IFN-gamma increases, but pituitary adenylyl cyclase-activating polypeptide (PACAP) recruits anti-inflammatory and neuroprotective Th2 cells.

Brainstem plaques can cause glossopharyngeal neuralgia. Radicular pains in multiple sclerosis, especially if lancinating, may have a similar mechanism.

**Pain.** Pain can be focal or generalized. Up to two thirds of patients with multiple sclerosis have pain at some time during the course of their disease (Clifford and Trotter 1984; Moulin et al 1988; Stenager et al 1991), although pain was regarded as rare in much of the older literature. The pain is chronic most of the time; acute or intermittent pain also occurs. Legs are affected in 90%, and arms in 31%. Radicular symptoms arising from a posterior cord lesion are often painful, but anterior plaques are not. Pain is more common in older women with spasticity or myelopathy and in multiple sclerosis of long duration (Moulin et al 1988; Stenager et al 1991). It is often worse at night and when the ambient temperature changes suddenly.

The spectrum of pain includes central neuropathic pain from focal demyelination (eg, trigeminal neuralgia, dysesthesias—can be associated with paresthesias, and nonspecific pain), dysesthesias from ephaptic transmission...
(Lhermitte symptom, radicular pain, tonic seizures), inflammation or swelling (optic neuritis, headaches), visceral pain from chronic constipation or painful bladder spasms, abnormal motor activity (tonic seizures, spasms, clonus), or simple orthopedic musculoskeletal pain.

Lesions causing disinhibition of central pain pathways, abnormal sodium channel redistribution, perhaps with fewer NaV1.7 and NaV1.8 channels, or maladaptive neural plasticity during plaque repair may cause the central pain. The periaqueductal gray surrounds the aqueduct of Sylvius. Because it abuts the ventricular system, it is likely to be seriously damaged in multiple sclerosis. The periaqueductal gray controls pain, and it is possible that periaqueductal gray lesions cause pain and headaches. Chronic back pain can arise as a secondary consequence of multiple sclerosis, causing unilateral weakness or spasticity and, in turn, poor posture and accelerated degenerative disc disease.

In optic neuritis, a swollen, inflamed optic nerve puts pressure on the dural sheath. Pain in or behind the eye sometimes precedes the visual loss. The frequently-seen pain in optic neuritis and can be present at rest, on voluntary eye movement, and with pressure on the globe. Vasoactive amines, prostaglandins, and kinins released by inflammatory cells may magnify the pain in optic neuritis and in trigeminal neuralgia. Half of non-multiple sclerosis patients with autoantibodies to voltage-gated potassium channels have pain, and most respond to immunotherapy (Klein et al 2012). Because antibodies to voltage-gated potassium channels appear in 5% of children with demyelinating disease, a search for these antibodies in serum could be considered in multiple sclerosis and neuromyelitis optica pain syndromes.

**Headaches.** Headaches are more common in multiple sclerosis (27%) than in matched controls (12%) (Watkins and Espir 1969). They can herald exacerbations. Headaches may reflect cortical inflammation near the meninges.

**Seizures and paroxysmal symptoms.** Epileptic seizures double in incidence in multiple sclerosis and are more common in later stages. They may arise from new or enhancing lesions in the cortex or subcortical areas. They also can be triggered by 4-amino pyridine therapy or rapid reductions in baclofen.

Paroxysmal symptoms last seconds to minutes. Paroxysms include visual complaints, diplopia, convergence spasm, vertigo, dysarthria, facial and limb myokymia, tonic motor seizures, tonic spasms, dystonia, restless legs, akinesia, spontaneous or kinesigenic choreoathetosis, hyperekplexia, rapid eye movement sleep disorders, ataxia, itching, altered taste, and pain and paresthesias (eg, trigeminal neuralgia, Lhermitte sign). They are triggered by hyperventilation (eg, 20 deep breaths), stress, cold, touch, metabolic abnormalities, exercise, or acute exacerbations. Transverse spread between demyelinated axons (ephaptic transmission) is a likely cause. It is probably amplified by cytokines, extracellular potassium, dysfunction of ion channels, and heterogeneity of new sodium channels. Lesions are in internal capsule, cerebral peduncles, and spinal cord.

**Fatigue from central lesions and the role of sleep.** Generalized physical and mental fatigue is the number one problem in two thirds of patients (Reder and Antel 1983; Noseworthy et al 2000). Patients describe fatigue as “profound”; it “disrupts life” and it is “different from any other experiences.” They say that because of the fatigue, “each day of the week at work is cumulatively harder.” It is “worse with heat.”

The normal motor fatigue that follows muscular exertion is magnified after sustained or repetitive muscle contractions and after walking and often develops rapidly after only minimal activity (“fatigability” in 75%). Fatigability is distinct from weakness and may not correlate with strength of individual muscles (Schwid et al 1999). Another type of fatigue is sometimes unprovoked (“lassitude,” “asthenia,” or “overwhelming tiredness,” in 20%). Fatigue limits prolonged neuropsychological testing. Rating scales of multiple sclerosis fatigue are difficult to design and correlate poorly with function because these symptoms are so multidimensional. Self-reports often do not correlate with clinical measurements of muscle and cognitive fatigue.

Fatigue is an essential dimension of the neurologic history. Fatigue can be the only symptom of an exacerbation or one of many. It is least common in primary progressive multiple sclerosis. Thirty percent of multiple sclerosis patients report fatigue before the diagnosis of multiple sclerosis (Berger personal communication 2011). Fatigue does not correlate with MRI plaque load, Gd enhancement, depression, or inflammatory markers. Fatigue seen on the Sickness Impact Profile Sleep and Rest Scale (SIPSR) predicts later brain atrophy (Marrie et al 2005). It is associated with reduced event-related potentials, with low prefrontal activity on PET, with posterior parietal cortical atrophy on MRI, and with low N-acetylaspartate in frontal lobes and basal ganglia on magnetic resonance spectroscopy.
“Primary fatigue” in multiple sclerosis can't be explained by other factors such as depression and apathy, but it is intertwined with lack of sleep. Fatigue usually is worse in heat, in high humidity, and in the afternoon; body temperature is slightly higher in all these situations. This extreme sensitivity to heat is termed “Uhthoff phenomenon,” wherein a minimal elevation of body temperature interferes with impulse conduction by demyelinated axons because of their lower “safety factor.”

CNS fatigue has been attributed to decreased Na+/K+ ATPase in multiple sclerosis plaques, high energy demands of the large number of sodium channels redistributed on axons, disruption of the Kv1.3 potassium channel in mitochondria, inflammatory cytokines (IL-6, prostaglandins, tumor necrosis factor-alpha [TNF-alpha], and interferon-gamma [IFN-gamma]), excess ammonia, serotonin, serum and spinal fluid neuroelectric blocking factors. A report of a specific brain sodium channel blocker (Brinkmeier et al 2000) could not be confirmed (Cummins et al 2003). Other potential causes of primary fatigue in multiple sclerosis are axonal injury and poor axonal conduction, impaired glial function, poor perfusion of deep gray matter area, and neuronal dysfunction and metabolic exhaustion from the need to use wide areas of the cortex. Functional MRI for physical and cognitive tasks shows compensatory (inefficient) reorganization of the damaged CNS, with increased demand on remaining neurons.

In “non-primary fatigue,” contributors to fatigue and central conduction block are acidosis, lactate, and heat after exercise; the circadian rise in body temperature in the afternoon; a half-degree centigrade rise in body temperature during the luteal phase post-ovulation; pain; poor sleep (daytime fatigue with waking at night, “middle insomnia,” often caused by need to urinate, and also spasms, itching, and high incidence of sleep-related movement disorders); depression; low levels of dehydroepiandrosterone (DHEA) and its sulphated conjugate (DHEAS); and low levels of vitamin D. Insula lesions in stroke cause underactivity and tiredness; the insular cortex atrophies in secondary progressive multiple sclerosis. Spasticity amplifies fatigue by creating resistance to movement, complicating routine actions. Fatigue is associated with restless leg syndrome, circadian rhythm disruption, periodic limb movements, and hypersomnolence on sleep studies. Medications, hypothyroidism, anemia, and muscle deconditioning can contribute to fatigue. Other diseases can cause fatigue, including Parkinson disease, amyotrophic lateral sclerosis, post-polio syndrome, myasthenia gravis, stroke, and traumatic brain injury.

Sleep disorders in multiple sclerosis are heterogeneous, often profound, and often unexplained. Patients often complain of insomnia yet still have severe daytime fatigue. Pain, depression, and nocturia impair sleep. Hypothalamic plaques in corticotrophin-releasing factor pathways are common and likely to damage orexin-containing neurons. This would reduce input to the suprachiasmatic nucleus and disrupt circadian clock genes, leading to insomnia and disrupted sleep. In small studies, however, CSF hypocretin (orexin) is normal in multiple sclerosis, except for scattered cases of hypothalamic plaques with hypersomnia, unlike the frequent low levels in narcolepsy. Brainstem lesions correlate with more apnea-hypopnea (AHI), and progressive multiple sclerosis correlates with abnormal central sleep indices (Braley et al 2012).

Shift work at a young age increases the risk of developing multiple sclerosis by 2-fold (Hedstrom et al 2011). Shift work may disrupt circadian rhythm, restrict sleep, elevate cortisol, activate viruses, and lead to proinflammatory immunity.

Cognitive function. Higher cortical functions, language skills, and intellectual function usually appear normal to casual observers. However, careful clinical observation and sensitive neuropsychological tests find slight to moderate cognitive slowing, slow information processing, word-finding difficulties, poor recent “explicit” memory, poor clock-drawing, heightened distractibility, and decline in effortful measures of attention in 50% of patients (Rao et al 1991; Beatty 1999; Arnason 2005). Warm outdoor temperatures impair cognition. Up to half of patients with clinically isolated syndromes are significantly abnormal on some cognitive tests. Complaints range from “I always forget where I put my keys” and “the lights are off in the factory” to “I am no longer able to perform cube roots in my head.” Subcortical signs often appear during complex tasks (especially with concurrent use of affected limbs), speeded responses, working memory, and when multiple visual and sensory stimuli confront the patient: “I feel like I live in an IMAX theater.” The simple question, “Do you have trouble walking through a shopping mall?” is often met with an anguished, “Yes, it’s too overwhelming.”

Patients should be screened at the first examination, for cognitive problems and cognitive slowing (information processing speed, multitasking, sustained and complex attention, working memory). Patients with normal cognition tend to maintain their cognitive function, whereas mild cognitive deterioration predicts progressive decline in cognition over 3 years. The symbol digit modalities test is the best single screening measure (Langdon et al 2012). It can be supplemented with the California Verbal Learning Test and the Brief Visuospatial Memory Test. All three can be
performed in a small center by staff members who may not have neuropsychiatric test training.

Mood swings, irritability, and frustration from slow cognition are common in multiple sclerosis. Cognitive decline impairs employment and daily life. Normal language and attention give a false sense of security, while in the same patient, slowed processing speed interferes with job performance. Patients have more difficulty walking while performing cognitive tasks. The family may notice impairment before the patient does. When disputed by the family, patient complaints of cognitive decline may suggest depression. Cognitive deficits are most pronounced in secondary progressive disease but often do not correlate with physical disability. Cognition is least affected in primary progressive multiple sclerosis when EDSS is matched between groups. Patients with more cognitive reserve are protected against decline, especially early in the disease. Neuropsychological evaluation can review residual strengths and weaknesses that impact employment, social function, and driving ability; evaluation detects depression and leads to therapy.

Decision making is compromised from slower learning plus impaired emotional reactivity. Occasionally, patients go through a phase of wildly illogical thinking that later resolves as the disease progresses. “Low anxiety” leads to inconsistent, risky decisions in a Gambling Task and predominates in early multiple sclerosis (Kleeberg et al 2004). Impulsivity correlates with loss of anterior corpus callosum integrity in cocaine-dependent subjects and possibly also in multiple sclerosis. Multiple sclerosis patients may have more health-adverse behaviors before diagnosis.

Some patients have nearly normal neurologic examinations yet are unable to walk from poor patterning of leg movement and gait. Electrophysiological tests confirm this apraxia and show impaired input to the motor cortex and to pathways involved in motor planning. Spinal learning may also be impaired (Arnason 2005).

Patients with mild cognitive impairment have cortical thinning on MRI. Chronic cases have extensive hippocampal demyelination (Geurts et al 2007). Third ventricular width (thalamic volume, perhaps the best measure at this time), corpus callosum atrophy, basal ganglia hypointensity and atrophy (brain parenchymal fraction), T1 and also T2 brain lesion load, and decreased fractional anisotropy on diffusion tensor imaging all correlate modestly with poor cognition. Lesions in the thalamus and frontal lobes impair executive function, and damage to the corpus callosum slows cognitive speed and math performance. Retinal nerve fiber layer thickness correlates quite well with symbol digit modality tests (r = 0.754) (Toledo et al 2008). Global N-acetyl aspartate has a moderate correlation with cognitive loss. Decreased attention correlates with lower N-acetylaspartate in the locus ceruleus in relapsing-remitting patients. Vitamin B12 and methylmalonate should be checked as abnormal serum levels can hurt cognitive function and cause brain atrophy.

On fMRI, decreased activation of the cerebellum correlates with poor motor learning. Conventional MRI and fMRI abnormalities correlate with slow psychomotor speed and more accidents while driving. Excessive activation (poorly focused) in the supramarginal gyrus, insula, and anterior cingulum correlates with poor episodic memory (Rao personal communication 2005). Excess activation also links to poor hand dexterity, suggesting greater and inefficient allocation of cognitive resources. Cognitively normal multiple sclerosis patients have increased activation in the parahippocampus and anterior cingulate, suggesting functional reorganization and adaptation to brain lesions, but some cognitively impaired patients have less activation in these areas (Hulst et al 2012). Resting state functional connectivity for the default mode network is disrupted in multiple sclerosis. Positron emission tomography shows cortical hypometabolism above subcortical plaques. Cognitive impairment in rats with experimental allergic encephalomyelitis lasts long after the inflammatory lesions resolve.

Exacerbations can reduce cognition, sometimes as the sole symptom. Arnason argues that memory problems appear during exacerbations in early multiple sclerosis, coincident with T cell inflammation in the CNS. Later in the disease, cognition is increasingly impaired, coincident with greater monocyte and microglial activation (Arnason 2005). Cognitive decline can be independent of other disease variables (Kujala et al 1997; Duque et al 2008), suggesting that therapies could impact cognition independently of effects on relapses.

Low bone density is associated with cognitive impairment (Weinstock-Guttman personal communication 2011). This may be a consequence of an underlying cytokine or vitamin D-linked abnormality, or possibly from loss of CNS trophic input to bone.

Visual memory declines in multiple sclerosis. Visual pathways course from optic nerves, around the ventricles to the occipital cortex, and back around the ventricles to temporal memory areas. Visual pathways are interrupted by
periventricular plaques and by inflammatory cytokines (Pliskin et al 1997). IFN-beta therapy benefits visual memory (below).

Aphasia is rare in multiple sclerosis but can arise in acute disseminated encephalomyelitis.

**Depression.** The incidence of depression is increased 2- to 3-fold in multiple sclerosis patients (greater than 50%) and their families. Severe, short-duration multiple sclerosis is associated with more depression, but primary progression is associated with less depression (Arnason 2005). Plaques and hypometabolism in the left arcuate fasciculus (supra-insular white matter) (Pujol et al 1997), right temporal (Berg et al 2000), and left temporal and inferior prefrontal areas (Feinstein et al 2004) are associated with depression. However, depression does not correlate with MRI burden of disease or atrophy, disability, or cognitive deficits.

The incidence of depression is increased 2- to 3-fold in multiple sclerosis patients (greater than 50%) and their families. Severe, short-duration multiple sclerosis is associated with more depression, but primary progression is associated with less depression (Arnason 2005). Plaques and hypometabolism in the left arcuate fasciculus (supra-insular white matter) (Pujol et al 1997), right temporal (Berg et al 2000), and left temporal and inferior prefrontal areas (Feinstein et al 2004) are associated with depression. However, depression does not correlate with MRI burden of disease or atrophy, disability, or cognitive deficits.

The dexamethasone suppression test reflects neuroendocrine function in depression. It is abnormal during active multiple sclerosis (Reber et al 1987; Fassbender et al 1998), possibly from chronic inflammation, cytokine stress, and induction of CRH/AVP in hypothalamic neurons.

During attacks, depression is strongly correlated with cytokine levels, TNF-alpha, IFN-gamma, and interleukin-10 (Kahl et al 2002), possibly because IFN-gamma increases serotonin transporter and indoleamine dioxygenase levels, lowering serotonin.

Therapy with IFN-beta can occasionally trigger depression. Interferon elevates indoleamine-2,3-dioxygenase, which lowers levels of tryptophan and serotonin. IFN-beta therapy as well as antidepressants could elevate brain serotonin by decreasing IFN-gamma levels. Both agents induce brain-derived neurotrophic factor. Surprisingly, patients taking antidepressants have lower BDNF levels in circulating immune cells (Hamamcioglu and Reeder 2007), possibly because depressed multiple sclerosis patients have low BDNF levels before antidepressant therapy.

Suicide is elevated 7-fold in multiple sclerosis. Suicidal patients are more likely to have a family history of mental illness, to abuse alcohol, to be under social stress or be depressed, and to live alone. Confused thoughts and occasionally psychosis can be seen with multiple sclerosis exacerbations.

Pseudobulbar affect (pathological laughing and crying, involuntary emotional expression disorder) can be disabling. Disinhibition is from multiple supratentorial plaques and is occasionally associated with hiccups and paroxysmal dystonia. Euphoria, despite concurrent neurologic problems, was described by Charcot. It is possible the euphoria is cytokine-mediated, akin to “spes phthisica”—a feeling of hopefulness for recovery seen in patients with tuberculosis.

**Associated diseases.** In multiple sclerosis, there are links between inflammatory bowel disease and thyroiditis. Bone mass is low. Other autoimmune diseases are not associated with multiple sclerosis—and may be less prevalent than in the general population. Many reported associations are likely from the strong autoimmune proclivity in Devic disease or CNS Sjögren disease, variants that comprise 5% of “multiple sclerosis” patients in some series. Cancer and allergy incidence is likely reduced, perhaps from an overactive, Th1-biased immune system.

**Natural history.** The course of multiple sclerosis varies. Heterogeneity over time complicates the use of stage-specific therapies. Classification is important because no therapies are effective in the progressive forms. These categories are not immutable; patients frequently drift from one type of multiple sclerosis to another, become stable, or suddenly develop active disease (Goodkin et al 1989).

At onset, at an average of 28 years old, multiple sclerosis is relapsing-remitting in 85% of patients. This form predominates in young women. Attacks typically occur every 2 years. The mortality rate in multiple sclerosis is 3-fold higher than in age-matched controls. Survival is decreased by 8 to 10 years but can be prolonged by IFN-beta-1b therapy (Goodin et al 2012b).

Fifty percent of relapsing-remitting patients become “secondary progressive” after 10 years, and 89% by 26 years. Relapses in the first 2 years predict earlier onset of progression. However, relapses after the first 2 years predict a lower chance of becoming progressive (Scafa et al 2010), suggesting that immune dysregulation evolves and modifies the course of multiple sclerosis. Progression has features of an age-dependent degenerative process (Kremenchutsky et al 2006). Progression begins, on average, at age 39 in both primary and secondary multiple sclerosis.
The number of neurologic systems affected in the initial attack, and not recovery from the attacks, predicts the chance of developing progressive disease. The onset of progression is a watershed event that strongly determines the outcome of multiple sclerosis. Older age of onset of the first attack leads to an earlier onset of secondary progression by the age of 40 or 50 years (Scalfari et al 2011). Once progression appears, the rate of decline is constant and is unaffected by the prior duration of relapsing multiple sclerosis.

About 10% to 15% are progressive from onset, at an average of 38 years old, with continuing deterioration and without obvious exacerbations or remissions, although the rate of decline fluctuates. Compared to a 10- to 19-year-old patient, the relative risk of primary progression is 2.3 at age 25, 8.1 at 35, 19 at 45, and 47-fold higher at age 50 to 59 years (Stankoff et al 2007). Primary progression is considered a unique form of multiple sclerosis, but 28% of these patients will eventually have exacerbations (Kremenchutzky et al 1999), sometimes after 20 years of pure progression.

The progressive form affects the spinal cord predominantly (in 90%), begins at a later age than the relapsing form, and is approximately as common in men as in women. There is progressive paraparesis and loss of vibration and pinprick sensation in the legs, and typically a small, spastic neurogenic bladder. Brain MRI lesions are 6 times less frequent in primary progressive multiple sclerosis, compared to relapsing-remitting patients who become progressive later on (Thompson et al 1991). White matter that appears normal on conventional MRI, however, has low magnetization transfer ratio and N-acetyl aspartate levels, reflecting widespread neuronal loss or dysfunction (Filippi et al 1999).

Exacerbations contribute to disability by an average of 0.2 to 0.6 EDSS points at more than 30 days after the exacerbation. Forty-two percent to 49% have residual gain of 0.5 EDSS points at 2 to 4 months, and 28% to 33% have a loss of 1 or more EDSS point (Lublin et al 2003; Hirst et al 2008). However, some improve: 19% have a 0.5 point decrease or improvement and 10% have a 1 point decrease in EDSS (Lublin et al 2003). In 700 placebo-treated patients from 11 clinical trials, worsening after exacerbations was nearly equivalent to improvement (Ebers et al 2008). The authors conclude that disability could not be used as an outcome measure in most (short-term) clinical trials.

The clinical course was clarified in 2013 (Lublin et al 2014). Residual symptoms after an attack should be called “worsening.” Progression,” independent of relapses, is not uniform in its rate and is a retrospective clinical term. Progressive disease can have 4 characteristics: (1) plus active relapses, (2) without exacerbations, (3) largely stable for a period with superimposed exacerbation, and (4) largely stable, without exacerbations.

Occasionally, patients have acute fulminant multiple sclerosis (Marburg variant). This malignant form of multiple sclerosis is possibly associated with developmentally immature myelin basic protein (Wood et al 1996). Patients with rapid accumulation of disability at early stages and later, at EDSS of 6, tend do poorly.

Tumefactive multiple sclerosis lesions, larger than 2 cm, can masquerade as tumor or abscess. They are rarely recurrent, and had a surprisingly good prognosis in the first large series (Kepes 1993). After an initial tumefactive lesion, two thirds of patients will develop multiple sclerosis and one third do not (Altintas et al 2012).

Twenty percent of patients have “benign multiple sclerosis,” defined as a Kurtzke disability score of 3/10 or lower. After 20 years, 6% of the overall population is still benign—largely comprised of those with Kurtzke EDSS score of 2 or lower at 10 years (Hawkins and McDonnell 1999). Autopsy studies indicate a large reservoir of undetected and, therefore, benign multiple sclerosis (Reeder and Arnason 1985). Some patients with benign multiple sclerosis have surprisingly large lesion loads on MRI (Strasser-Fuchs et al 2008). Clinical or MRI dissociation is typical when correlating MRI with clinical activity (r is only 0.25). Auspicious predictors include young onset, monosymptomatic, few attacks, no cord symptoms, and few MRI lesions, including few cortical lesions. Cognitive function, fatigue, and pain should be included in assessment of a propitious course as 50% of patients with “benign” multiple sclerosis based on motor disability have cognitive decline.

Unsuspected and asymptomatic cases. Multiple sclerosis is sometimes unsuspected during life, yet found at autopsy. Twelve unsuspected cases of multiple sclerosis were found in 15,644 autopsies in Switzerland. Only 2 had no reported neurologic signs during life (Georgi 1961). There were 5 diagnosed cases of multiple sclerosis in 2450 autopsies in London and Ontario (Gilbert and Sadler 1983). In autopsy studies, the calculated prevalence of unsuspected multiple sclerosis would be about 31 in 100,000 in Paris (3 in 9300) (Castaing et al 1981); 90 to 128 in 100,000 in Switzerland (Georgi 1961); and 204 in 100,000 in Ontario (Gilbert and Sadler 1983). This suggests that the number of undiagnosed “normal” people with multiple sclerosis approximates the number of patients diagnosed with
Separate axes with little overlap included the following: demonstrated that multiple sclerosis had independent effects on several important factors that impact patients’ lives. Assessment of Multiple Sclerosis (FAMS) quality of life scale (Quality of life and clinical scales.

spinal cord and occurs at an earlier age than the Western form of multiple sclerosis (some groups of Canadian Aboriginals often resembles Devic disease because it typically affects the optic nerves and is rare in Asia (4 per 100,000) (Kurtzke 1975). Multiple sclerosis in Japan, China, Malaysia, in black Africans, and in some groups of Canadian Aboriginals often resembles Devic disease because it typically affects the optic nerves and spinal cord and occurs at an earlier age than the Western form of multiple sclerosis (Cosnett 1981; Phadke 1990).

**Clinically isolated syndromes.** Clinically isolated syndromes include optic neuritis, transverse myelitis, and solitary demyelinating brainstem lesions. Clinically isolated syndrome appears with clinical symptoms when the demyelinating lesions are in optic nerve, spinal cord, or clustered in critical areas of the brain (clinically eloquent or expressive areas). Some cases never evolve to multiple sclerosis (see idiopathic optic neuritis and transverse myelitis). Clinically isolated syndrome evolves into multiple sclerosis most often when the MRI T2 lesion load is high, when the CSF reflects inflammation, when evoked potentials are delayed, and when serum vitamin D is low (Martinelli et al 2014). When clinically isolated symptoms appear in parallel with non-enhancing MRI lesions plus at least 1 enhancing lesion, 70% to 80% of patients will have another gadolinium-positive lesion within 6 months. Partial cervical myelopathy, without brain MRI lesions, often evolves into clinically definite multiple sclerosis if evoked potentials and CSF are abnormal (Bashir and Whitaker 2000).

**Childhood and pediatric multiple sclerosis.** An attack before the age of 16 happens in 4% of all multiple sclerosis patients and in 1% with onset before age 10. The incidence of demyelinating diseases, including multiple sclerosis, optic neuritis, transverse myelitis, and ADEM, is 1.63/100,000 and is higher in blacks than in Asians, Hispanics, and whites in Southern California (Langer-Gould et al 2011). In girls, obesity increases the risk of multiple sclerosis, clinically isolated syndrome, or transverse myelitis by 1.6 and massive obesity by 3.8 (Langer-Gould et al 2013). The combination of obesity, HLA-DRB1*15, and absence of HLA-A*02 increase multiple sclerosis incidence by over 16-fold (Hedstrom et al 2014). Diagnosis is difficult because of the rarity of multiple sclerosis in children and the clinical overlap with childhood infections and other diseases. A family history is more common than in adult forms.

Sensory symptoms and optic neuritis are common (approximately 50%, even though these symptoms may sometimes not be reported by children). Brainstem and cerebellar symptoms, polysymptomatic disease, and seizures are more frequent than in adult onset multiple sclerosis, but recovery from exacerbations is better (Duquette et al 1987; Selcen et al 1996; Ghezzi et al 1999; Ruggieri et al 1999). One third of patients have cognitive problems. As in adult forms of multiple sclerosis, sphincter involvement and a (rare) progressive course have a poor prognosis. Boys predominate over girls between 8 and 10 years of age, but the girl-to-boy ratio is 2:1 after 10 years. Relapses are a bit more frequent in childhood (every 1.6 years versus every 2 years in adults) but are only 4 weeks long versus 7 weeks in adults (Ness et al 2007). The course is slower than in adult-onset multiple sclerosis (Simone et al 2002), and the median time from onset to secondary progression is 28 years. Nonetheless, with continuous exacerbations they become disabled at a younger age than adult-onset patients. Primary progression is exceptionally rare (2% of an already uncommon event).

MRI, EEG, and visual-evoked potentials are each abnormal in 80% of children with multiple sclerosis (Duquette et al 1987; Banwell 2004). Obvious cortical lesions are less common than in adults. However, intracranial volume and head size is reduced. CSF is abnormal in 66% of patients, and CSF IgG levels are lower in children. Bands are positive in only 29% of acute disseminated encephalomyelitis but in 64% of acute multiple sclerosis and in 82% of multiple sclerosis at later times in a medium-sized series (Dale et al 2000). In first demyelination in children, CSF contains molecules that localize to the node of Ranvier but not myelin membrane proteins (Dhaunchak et al 2012). The prolonged relapsing-remitting course suggests multiple sclerosis therapies may be more effective in children than in adults.

**Geographic variation.** The incidence and symptoms of multiple sclerosis are different around the globe. Multiple sclerosis is uncommon at the equator (prevalence 2 to 10 per 100,000) and increases with distance from the equator (up to 200 per 100,000 at latitudinal extremes). This suggests environmental factors influence the incidence. However, emigrating northern Europeans did tend to stay in temperate climates, suggesting genetic influence. Multiple sclerosis is rare in Asia (4 per 100,000) (Kurtzke 1975). Multiple sclerosis in Japan, China, Malaysia, in black Africans, and in some groups of Canadian Aboriginals often resembles Devic disease because it typically affects the optic nerves and spinal cord and occurs at an earlier age than the Western form of multiple sclerosis (Cosnett 1981; Phadke 1990).

**Quality of life and clinical scales.** Responses by 433 patients were used to generate the 59-question Functional Assessment of Multiple Sclerosis (FAMS) quality of life scale (Cella et al 1996; Cella et al 2012). A factor analysis demonstrated that multiple sclerosis had independent effects on several important factors that impact patients’ lives. Separate axes with little overlap included the following:
(1) Mobility. This correlated highly with the neurologic examination (Kurtzke Expanded Disability Status Score, Scripps Numerical Rating Scale, and Ambulation Index) but not with the other subscales.

(2) “Emotional well-being” and “general contentment,” which negatively correlated with psychiatric measures of anxiety and depression.

(3) “Symptoms.”

(4) Family and social well-being.

(5) “Fatigue” plus “thinking,” an indicator of cognitive function. Fatigue is highly prevalent; cognitive loss has the most important impact on quality of life.

Neurologic and social function, fatigue, mood, and cognition are important components of clinical multiple sclerosis that are often more disabling than inability to walk. Because these factors do not correlate, different pathogenic mechanisms are likely. For example, difficulty walking could arise from damage to long tracts or oligodendroglia, and fatigue may be caused by inflammatory cytokines in the CNS. Different pathological causes may also vary in responses to drugs; they should all be evaluated in therapeutic trials. There are trends or significant improvement in quality of life for all approved therapies.

The Kurtzke Extended Disability Status Score is a central clinical measure in most trials. It is based on the neurologic examination and ranges from 0 to 10, where 0 = normal, 4 = walks unaided for greater than 500 meters, 5 = walks unaided for greater than 100 meters, 6 = needs a cane to walk 100 meters, 7 = walks less than 5 meters with aid, 8 = perambulated in wheelchair, and 10 = death. Cognitive problems, fatigue, sexual function, job capabilities, and social factors do not weigh heavily in this scale. This scale is not linear; transition between stages 4 and 6 is fastest.

The Multiple Sclerosis Functional Composite Scale (MSFC) evaluates motor function of legs and arms and cognition. It adds information to the Kurtzke Expanded Disability Status Score and was used in a phase 3 clinical trial of intramuscular IFN-beta-1a (Cohen et al 2001). Correlation between the Kurtzke scale and the multiple sclerosis Functional Composite scale is only $r = -0.15$. One component to the MSFC is the Timed 25-Foot Walk (T25FW). An improvement of 15% to 20% reflects a clinically meaningful change based on patients' self-reports. Slowed walking speed of 6 to 8 seconds over 25 feet is associated with occupational disability and use of a cane. Speed of greater than 8 seconds correlates with collecting disability payments and use of a walker (Goldman et al 2013).

Patient-rated scales provide important information about independent factors that are missed when examinations are limited to assessment of mobility. Telephone and self-administered scales correlate well ($r = 0.9$) with physician examinations.

The global multiple sclerosis Severity Scale (MSSS) combines disease duration with the Kurtzke score to combine rate and severity (Roxburgh et al 2005). Many of the patients who defined the MSSS were on therapy, so untreated progression rates are probably even higher than the table indicates.

**Prognosis and complications**

The overall life expectancy for multiple sclerosis patients is 7 years less than normal, or 80% of expected survival (Weinshenker and Ebers 1987; Sadovnick et al 1992). Mortality increases with more disability. Case fatality ratios are 1:5 for patients with Kurtzke disability scores of less than or equal to 7 but 1:1 for those with scores greater than 7 (Sadovnick et al 1992).

The cause of death in 50% of a clinic population and in approximately 75% of all multiple sclerosis patients is from complications of multiple sclerosis, usually pneumonia (Sadovnick et al 1991; Reder et al 2012). Patients most commonly die as disability scores approach 8.0. Brainstem lesions occasionally cause loss of inspiratory drive, causing the patient to stop breathing; this is most common at night. Deaths from malignancy are less common than in age-matched controls (Sadovnick et al 1991). The cumulative lifetime dose of disease-modifying therapy improves prognosis. Interferon-beta-1b extends survival by at least 6 years (see below).

The suicide rate is increased 7.5-fold in multiple sclerosis (Sadovnick et al 1991). The lifetime risk of suicide is 2%. Less-disabled young patients within 5 years of diagnosis are the most likely actors (Sadovnick et al 1992; Stenager et
The future course of multiple sclerosis is poor if there are cerebellar or pyramidal symptoms, slow timed-walk test at baseline, early sphincter symptoms, multi-site onset, frequent early attacks, development of progression or a primary progressive course, and age over 40 years at onset. Good prognostic signs include optic neuritis, sensory symptoms, and continuing exacerbations and remissions (Weinshenker and Ebers 1987; Phadke 1990). Attacks after the first 2 years correlate with better prognosis, perhaps indicating that the patient has relapsing and not progressive multiple sclerosis. The course is a more important predictor than age of onset. Development of a progressive course is the strongest predictor of poor outcome. The second strongest predictor is the number of relapses in the first two years. After a first demyelinating episode, a second attack is more likely in younger patients with abnormal CSF, with more than eight T2 MRI lesions (dissemination) or one Gd-enhancing lesion (activity). Complete recovery is more likely with mild severity and mono-lesional exacerbations. Clinic-based cohorts have more severe multiple sclerosis than population-based groups, where many patients remain stable or progress minimally over 10 years (Pittock et al 2004). Multiple sclerosis reduces quality of life throughout its course.

Patients with relapsing-remitting multiple sclerosis take 15 years from onset to reach an Expanded Disability Status Scale score of 6.0 (using a cane to walk 100 meters), based on longitudinal studies in Ontario, Canada (Ebers 2000). Those with primary progressive multiple sclerosis take 8 years to use a cane; early progression and multi-system symptoms hasten the rate of progression. Patients with 1 attack in the first 2 years do not need a cane for 20 years; those with 5 or more attacks need a cane within 7 years. Once a patient becomes unable to walk 500 m (EDSS = 4; typically after 11 years), progression is no longer affected by relapses. Later onset multiple sclerosis is more common in men and is often primary progressive. The transition from relapsing-remitting disease to progressive multiple sclerosis is earlier in men than in women.

The average rate of decline is similar in all groups once multiple sclerosis becomes progressive (including primary progressive at onset, "bout onset progression," or at the transition from relapsing-remitting to secondary progression) (Rice 1997; Ebers 2000; Kremenchutsky et al 2006). This happens on average at the age of 40, preferentially targets the corticospinal tract, and is not obviously influenced by prior relapses. Within the progressive group, however, rates vary ("sooner to cane, sooner to wheelchair"), even though the average rate for progression is the same for secondary and primary progressive multiple sclerosis after progression starts. Long-duration, low-disability multiple sclerosis is likely to remain stable.

On MRI, bad prognostic signs include a large number of T2 lesions or high T2 volume, T1 hypointensities, many enhancing lesions, low magnetization transfer, lesions in juxtacortical, infratentorial, and periventricular sites, and brain atrophy--especially early atrophy. Gray matter damage, loss of volume in the gray matter faction, weakly predicts worse disability (odds ratio = 0.79) (Filippi et al 2013). Good signs are little tissue damage and sparing of important regions. An MRI with a few large lesions gives a better prognosis than one with the same volume of many, smaller lesions (Kepes 1993; Zivadinov personal communication 2005). In a 20-year follow-up of 107 relapse-onset clinically isolated syndrome patients, lesion growth was 0.80 cc/year in those who were relapsing-remitting but was 2.89 cc/year in secondary progression (Fisniku et al 2008). These baseline characteristics will influence prognosis. Baseline lesions and clinical activity must be matched in randomized cohorts to evaluate apparent responses to drugs (Goodin et al 2012a).

In clinically isolated syndromes (lesions in optic nerve, brainstem, or spinal cord), total T2 lesion volume on MRI at onset correlates with disability at 10 years (r = 0.45). All patients with clinically isolated syndrome who have a total lesion volume greater than 3 cc progress to definite multiple sclerosis by 4 years (Sailer et al 1999). Thalamic atrophy and ventricular enlargement or new T2 MRI lesions 3 months after the first symptoms also strongly predict clinically definite multiple sclerosis ~ 88% after a positive MRI versus 19% after a negative MRI (Brex et al 2002). In this patient cohort at 20 years, 79% of patients with clinically isolated syndrome and no MRI lesions had not had a second attack (Fisniku et al 2008). A second attack had occurred in 21 of those with no MRI lesions at baseline, 80% with 1 to 3 lesions, 85% with 4 to 9 lesions, and 81% with more than 10 lesions. The latter were much more likely to need a cane. The McDonald criteria (below) incorporated these findings to allow new T2 lesions to define "multiple sclerosis." In 532 patients with clinically isolated syndromes followed for up to 9 years, definite multiple sclerosis developed in only 35% of those with no asymptomatic baseline lesions but in 74% of those with 3 of 4 of the following lesions: (a) 1 enhancing or 9 T2, (b) 3 periventricular, (c) 1 juxtacortical, or (d) 1 infratentorial (revised McDonald criteria) (Korteweg et al 2006). In the BENEFIT clinically isolated syndrome study, 9 baseline T2 lesions (hazard ratio = 1.6) or 3 periventricular
lesions (hazard ratio = 1.7), or when one lesion changed to more than one, predicted conversion to multiple sclerosis. Multiple sclerosis is most likely to develop when the lesions are in the corpus callosum (hazard ratio of 2.7) or in fibers that control motor function. In patients with clinically isolated syndrome and monofocal non-cord symptoms who do not fulfill the McDonald criteria, a subclinical spinal cord MRI lesion increases the risk of developing definite multiple sclerosis by over 14-fold (Sombekke et al 2013). When clinically isolated symptoms appear in parallel with non-enhancing MRI lesions plus at least 1 enhancing lesion, 70% to 80% of patients will have another gadolinium-positive lesion within 6 months. Partial cervical myelopathy, without brain MRI lesions, often evolves into clinically definite multiple sclerosis if evoked potentials and CSF are abnormal (Bashir and Whitaker 2000).

Children with isolated symptoms at onset, multiple MRI lesions, elevated IgG index, and oligoclonal bands in CSF are more likely to develop multiple sclerosis than those with polyclonal onset and negative CSF tests. Adults develop multiple sclerosis when the MRI is abnormal, the CSF reflects inflammation, evoked potentials are delayed, and serum vitamin D is low (Martinelli et al 2014).

After starting thrice-weekly interferon beta-1a therapy, first-year MRI lesions increase the chance of progression at 2 years by 4%. Clinical relapses after the first year increase the chance of progression by 49% (Sormani et al 2011). New lesions while on therapy may be more ominous than in the therapy-naïve patient, but this has not been adequately studied because baseline atrophy is ignored.

Brain atrophy is often present in mild-to-moderate multiple sclerosis. Atrophy is most likely to progress when there are Gd-enhancing lesions at baseline (Simon et al 2000). Ventricles in relapsing-remitting multiple sclerosis increase in size by 5% per year, compared to 1% to 2% in normal controls. In most cases of multiple sclerosis that come to medical attention, disease activity never sleeps, and atrophy progresses relentlessly in all multiple sclerosis subtypes. However, there are a large number of subclinical cases with benign courses and presumably much milder inflammation.

Advanced MRI techniques should aid in measuring CNS lesions. Three-dimensional FLAIR increases sensitivity and contrast; magnetic resonance frequency shifts can measure tissue architecture in new lesions; MRI texture analysis quantitates changes in local image intensity; double inversion recovery (DIR reveals intracortical lesions not seen on FLAIR); 7-Tesla imaging shows the expanding inflammation as a hypointense rim and improves detection of cortical lesions; injection of albumin-binding gadolinium with a 4-hour delay increases signal and decreases noise; [11C]PK11195 binding to a mitochondrial translator protein on PET scans correlates with disability, likely from microglial activation.

Magnetic (motor) and electric evoked potentials do not correlate with disability at first presentation. However, abnormal evoked potentials do predict disability at 2 years (r = 0.6 with motor and visual potentials) (Fuhr et al 2001) and at 5 years (r = 0.5 with motor and sensory) (Kallmann et al 2006).

CSF with a high white cell count predicts future Gd+ MRI lesions (Rudick et al 1999). CSF with high numbers of natural killer cells and monocytes augurs slower progression (Cepok et al 2001), although subsets of both of these cell types can damage oligodendroglia. High levels of IgG predict faster progression. B cells and plasma cells and a high B cell to monocyte ratio in CSF predict faster progression, as do increased myelin basic protein, increased IgM oligoclonal bands, homozygous HLA-DRB1*1501, and polymorphisms in multiple genes (Frohman et al 2005). Antibodies to myelin basic protein in clinically isolated syndromes were highly predictive for development of multiple sclerosis in one study, but other labs have not been able to replicate these findings. Conversely, the 10% of multiple sclerosis patients with negative oligoclonal bands in CSF are more likely to have progressive forms of multiple sclerosis, non-specific “supratentorial” symptoms, lower cells and IgG in CSF, and less well-defined MRI lesions (Siritho and Freedman 2009).

Other markers may be helpful in the future. Some of these include molecular indicators of interferon efficacy, B7 costimulatory molecules (CD8, CD86, PD-1, PD-L1) and adhesion molecule expression on mononuclear cells, serum cytokines or cytokine receptors, kallikrein proteases and matrix metalloproteases, IgM antibodies to glycans (anti-GAGA4), antibodies to CNS proteins (galactocerebroside, myelin basic protein, myelin-oligodendrocyte glycoprotein, neurofilaments, proteolipid protein), heat shock proteins, increased CSF 14-3-3 protein (neuronal loss) and myelin basic protein (oligodendrocyte damage), and CSF or serum soluble intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM) (correlate with MRI activity).

The lifetime cost of multiple sclerosis in the United States is high compared to other neurologic diseases. Several years
after the first disease-modifying drugs for multiple sclerosis were introduced, multiple sclerosis had a total lifetime cost of $2,200,000 and an annual cost of $34,000 to $47,000. Multiple sclerosis therapy was more expensive than ischemic stroke ($100,000 lifetime) and Alzheimer disease ($49,000 to $490,000 lifetime) (Whetten-Goldstein et al 1998). Expense in diseases of long duration accrues from earnings lost, rehabilitation, drug therapy, “shadow costs” in monitoring the therapy, medical equipment, and formal and informal care. Fifty-three percent is direct (40% drugs, 3% inpatient hospital care), 10% is informal care, and 37% is productivity loss (reduced work time and retirement) (Kobelt et al 2006). Costs increase dramatically with more severe disease. A British cost-effectiveness analysis suggests that each relapse avoided during interferon therapy costs 28,700 British pounds (Parkin et al 2000). Relapses are easy to count, but have weak correlation with progression—a better indicator of disability. Longer survival with interferon beta-1b has not yet been factored into these analyses.

**Clinical vignette**

A 28-year-old woman began to stumble when walking. Her right leg was slightly stiff and was weak, especially after exercise and hot showers. These symptoms developed over 3 days and gradually disappeared over 4 weeks.

She was on the college swim team before these symptoms arose. When she was 21 years old, she developed a unique and extreme type of fatigue that differed from the usual fatigue after intense swimming workouts. The extreme fatigue disappeared after several weeks, but reappeared again when she was 28 years of age. A maternal aunt had multiple sclerosis.

An MRI scan showed multiple periventricular lesions. Her spinal fluid had elevated IgG levels and 3 oligoclonal bands (normal, less than 2).

One year later, 10 days after a “cold,” she developed blurred vision in her right eye and her visual acuity dropped to 20/200. She had moderate pain behind her eye when she looked to either side. The pain and visual loss gradually disappeared over 6 weeks. Two years later, both legs gradually became weaker and spastic, and she was sprinting to the washroom nearly every hour to urinate. These symptoms slowly progressed over the next 10 years, with occasional exacerbations affecting other areas of the brain. IFN-beta was begun in the middle of the relapsing and progressive phase, and the frequency of attacks and rate of progression slowed. She is now walking with the help of bilateral ankle and foot orthoses. She has been aided by minor modifications of her workplace and by treatment of multiple sclerosis symptoms, and she continues to work as a business executive.

**Prevention**

There is no known cause for multiple sclerosis. Viruses are often implicated as the primary cause, but in no case has this been substantiated. There is no apparent risk of transmitting multiple sclerosis to spouses or medical personnel.

Symptoms and exacerbations frequently follow virus infections (Sibley et al 1985; Panitch et al 1991; Edwards et al 1998), bacterial and bladder infections (Rapp et al 1995), prostatitis, and decayed or missing teeth (Craelius 1978). Exacerbations during systemic infections are twice as likely to lead to sustained clinical deficits, though there is no difference on MRI (Buljevac et al 2002). It is wise to prevent immune activation with good bladder and dental hygiene and by minimizing exposure to people with upper respiratory infections.

There is a 1.6 relative risk of development of multiple sclerosis in cigarette smokers (Hernan et al 2001). Smokers are more likely to develop a progressive course (Durfee et al 2008), possibly from an effect on the blood-brain barrier or an influence of chronic bronchitis. Smoking increases the exacerbation rate by 60% and doubles the rate of brain atrophy. This raises an ethical question—should a person who refuses to stop smoking be placed on a $50,000.00 per year disease-modifying therapy, which will be cancelled by the smoking?

Vaccinations and immunizations usually do not cause exacerbations of multiple sclerosis (Sibley et al 1985; Ascherio et al 2001) and may actually reduce exacerbations, with relative risk of 0.71 following vaccination for tetanus and hepatitis B (Confavreux et al 2001). Measles, mumps, rubella, and human papilloma virus vaccines are considered safe. Tetanus and diphtheria vaccinations are associated with a reduced chance of developing multiple sclerosis (0.67) (Hernan et al 2006), as is Bacille Calmette-Guérin vaccine (Ristori et al 2014). Influenza vaccination should be encouraged in order to obviate the risk of exacerbation during virus infections.

There is debate about exacerbations from recombinant hepatitis B vaccine (Hernan et al 2004). Live virus vaccines,
however, are likely to induce a cytokine storm and should be administered with caution. Yellow fever vaccinations, for instance, increase the risk of exacerbations 9-fold in relapsing-remitting multiple sclerosis. Some multiple sclerosis therapies reduce responses to H1N1 swine flu vaccination. Protective levels are reached in 44% of controls, and multiple sclerosis patients on IFN-beta therapy, compared to 24% on natalizumab, 22% on glatiramer, and 0% on mitoxantrone (Olberg et al 2014). Fingolimod induces a normal percentage of protection above threshold, but overall titers are reduced by 60%.

Diet and environment appear to affect the development and course of multiple sclerosis. In Norway, cod liver oil and fish intake (omega-3 fatty acids) reduces risk of developing multiple sclerosis (Kampman and Steffensen 2010). High-risk groups such as unaffected relatives of multiple sclerosis patients could benefit from a dirty environment, a diet rich in polyunsaturated fats (evening primrose and flaxseed oil), weight loss, not smoking, sunlight, and vitamin D (Bielby personal communication 2005; Ponsonby et al 2005).

Theoretical reasons exist to avoid several drugs, but therapeutic need may outweigh theory. Cimetidine, a histamine H2 blocker (Anlar 1993), and melatonin (Constantinescu 1995) enhance immune function, and may oppose the ability of H1 agonists to reduce blood-brain barrier permeability. Beta-adrenergic blockers inhibit suppressor cell function (Karaszewski et al 1991). Occasional patients worsen with fluoroquinolone antibiotics (eg, ciprofloxacin), which induce inflammatory cytokines in addition to their antibacterial effects (Riesbeck 2002). Some patients are extremely sensitive to low doses of carbamazepine; weakness is probably caused by blockade of Na+ channels in demyelinated axons.

Stress does not provoke attacks of multiple sclerosis in controlled trials, despite widespread anecdotes of stress worsening multiple sclerosis (above).

Exercise, physical therapy, dancing, social contacts, better diet, and drug treatment of symptoms can improve motor function and coordination, and quality of life. All of these interventions allow patients to realize that they can control some of the symptoms of multiple sclerosis.

**Differential diagnosis**

Monosymptomatic illnesses from focal or multifocal CNS insults can mimic the first attack of multiple sclerosis. These illnesses and cover a wide spectrum of neurologic diseases.

Postinfectious and postvaccinal encephalomyelitis follow inflammation-induced sensitization to myelin antigens. These reactions cause inflammatory demyelination that is localized (eg, transverse myelitis, optic neuritis) or diffuse (eg, encephalomyelitis). Symptoms often develop after upper respiratory tract infections (usually viral or mycoplasma) or vaccinations, leading to acute disseminated encephalomyelitis. CSF oligoclonal bands are less common than in multiple sclerosis and, if present, often disappear. MRI lesions should all be of the same age at onset, but several weeks afterward, partially-resolved lesions can appear to be different ages. The perivascular inflammation and demyelination is similar to the histopathology in multiple sclerosis, but these fever-associated disorders are monophasic (Tselis and Lisak 1995).

Experimental allergic encephalomyelitis is the animal model for postinfectious encephalomyelitis. Multiple sclerosis patients vaccinated with porcine myelin basic protein can develop encephalomyelitis. This non-recurring demyelinating disease suggests (1) a primary response to the antigen and (2) that myelin basic protein does not trigger multiple sclerosis.

Recurrent symptoms that mimic relapsing-remitting multiple sclerosis may be caused by focal repetitive insults such as transient ischemic attacks or exacerbations of connective tissue disease. Vascular insults usually have a rapid onset (Hamamcioglu and Reder 2005). In hypertensive vascular disease, MRI lesions are in the centrum semiovale instead of periventricular sites, are not in cerebellar outflow pathways, and do not spare subcortical U fibers. Some authors have implicated antinuclear antibodies and granulomatous angiitis in multiple sclerosis-like syndromes. CADASIL,Binswanger disease, hemiplegic migraine, Sjögren syndrome, and Behçet disease can cause episodic, multifocal central nervous system lesions that can be confused with multiple sclerosis clinically and on MRI.

Progressive cord symptoms can be caused by subacute combined degeneration, adrenoleukodystrophy, chronic fatigue syndrome, and tropical spastic paraparesis from human T cell lymphotropic virus infection. Damage from a
spinal dural arteriovenous fistula, cavernous hemangioma, or tumor can cause indolent cord symptoms. Progressive symptoms also suggest metabolic problems (copper, vitamin B12, vitamin E, or folate deficiency—often from complications of gastric bypass surgery), genetic disorders (adrenoleukodystrophy and very high long chain unbranched fatty acids, sometimes with a late inflammatory phase; hereditary spastic paraplegia; Wilson disease), and mitochondrial disorders (Natowicz and Bejjani 1994). Magnetic resonance spectroscopy can help differentiate plaques from central nervous system tumors.

“Phenocopies” of multiple sclerosis appear on MRI scans. CADASIL, hypertensive vascular disease, Susac syndrome, leukodystrophies, vanishing white matter disease, Alexander disease, sarcoid, and migraine all overlap with the MRI appearance of multiple sclerosis.

Transverse myelitis can be an isolated event or the first sign of multiple sclerosis or neuromyelitis optica. The cord lesion in multiple sclerosis is more often partial, patchy, and asymmetric, but in idiopathic transverse myelitis it is symmetrical and bilateral and longitudinal demyelination may be extensive, and CSF abnormalities are less common than in multiple sclerosis.

Optic neuritis is often the first sign of multiple sclerosis. Isolated optic neuritis involves only the optic nerves, without dissemination of lesions in time and space. CSF oligoclonal bands are less common than in multiple sclerosis. Nonetheless, one third of patients with optic neuritis will eventually develop multiple sclerosis. Optic neuritis must be differentiated from ischemic optic neuropathy, increased intracranial pressure causing papilledema, vitamin B12 deficiency, vasculitis (temporal arteritis), viral infections, and Devic disease.

Conditions that can be confused with multiple sclerosis:

- Acoustic neuroma. Nerves VIII, V, and VII are compressed by slowly expanding neuroma or meningioma.

- Acute disseminated encephalomyelitis often follows an infection or vaccination (postinfectious or postvaccinal encephalomyelitis). ADEM is more likely to occur in children and to have a polysymptomatic or multifocal presentation, with systemic symptoms that are uncommon in multiple sclerosis. Patients develop sudden pyramidal symptoms, bilateral optic neuritis (unilateral optic neuritis is seldom or never seen and suggests multiple sclerosis). Importantly, there is also fever, headache, vomiting, shooting pains, meningismus, encephalopathy, altered consciousness, EEG changes, and blood and CSF pleocytosis. Oligoclonal bands in CSF are uncommon (0% to 30%), but protein is often greater than 100 mg/dl.

  MRI lesions are large, “fluffy,” enhancing, often in ring patterns, often in a diffuse bilateral pattern, often in the corpus callosum and thalamus (thalamic gray matter T2 lesions are rare in multiple sclerosis), seldom in a Dawson finger shape, less often periventricular, and seldom cause T1 black holes (Dale et al 2000). Macrophages and sleeves of (later) demyelination surround venules in many small and large inflammatory lesions. Axons are relatively preserved. Myelin loss is more pronounced in multiple sclerosis than in ADEM and experimental allergic encephalomyelitis. All lesions are approximately the same age in the initial attack. A storm of many cytokines appears, with high granulocyte colony stimulating factor, but no IL-17.

  ADEM is usually monophasic, and MRI lesions are of similar age. This basic form lasts up to 3 months. Symptoms can fluctuate, and MRI may transiently show Gd-enhancing and nonenhancing lesions as ADEM evolves. If similar lesions reappear 3 months later, it is termed “recurrent ADEM.” In “multiphasic ADEM,” new brain areas are involved during a second episode. It is possible that abrupt discontinuation of steroid therapy allows recrudescent lesions; in this case, the disease is not truly recurrent. Therapy with high-dose glucocorticoids and then a prolonged taper is advised in ADEM.

  Multiple sclerosis eventually develops in 20% to 33% of ADEM patients. Thus, most patients with ADEM (66% to 80%) do not develop multiple sclerosis and should not be treated for multiple sclerosis when oligoclonal bands are negative.

- Acute hemorrhagic leukoencephalitis of Weston Hurst appears to be a more severe form of ADEM but may have a distinct etiology. Polymorphonuclear infiltrates are common, and the histopathology differs.

- Acute ischemic optic neuropathy has a sudden onset, is usually painless, may progress over several days with an unremitting course, and is typically seen in patients 60 to 100 years old. Visual loss involves the central fixation area but is altitudinal, with sharp borders. Ischemic optic neuropathy is likely to cause disc swelling, pallor, arterial
• Acute necrotizing encephalopathy of childhood, seen in Asian countries, follows several days of fever with a respiratory or gastrointestinal virus infection. Lesions are hypointense on T1 and hyperintense on T2 MRI in the bilateral thalami (classic for this condition) but are not present in the basal ganglia and cerebral cortex.

• Adult onset autosomal dominant leukodystrophy from a lamin B1 mutation. Onset is at approximately 40 years, with autonomic symptoms and then cerebellar and pyramidal signs. T2 MRI shows symmetric fronto-parietal and cerebellar white matter lesions but sparing of the periventricular areas.

• Alexander disease can appear in adults (type II) with a myelopathy and medullary signs; MRI shows patchy medullary and brainstem lesions with atrophy of medulla and cord.

• Aminoaciduria: 3-methylglutaconic aciduria type I causes adult onset leukoencephalopathy.

• Amyloid angiopathy causes cerebral microhemorrhages but also a leukoencephalopathy that involves the U-fibers. Iron in lesions can be seen on T2-weighted MRI.

• Aneurysm of intracranial blood vessels.

• Atopic myelitis, idiopathic eosinophilic myelitis, hyperIgEaemic myelitis.

• Autoimmune thyroid disease--often familial, causes tremor, and seizures. Spinal cord involvement may suggest overlap with neuromyelitis optica.

• Balo concentric sclerosis has large concentric lesions with centrifugal waves of demyelination and remyelination. MRI shows ring enhancement with Gd, increased signal on FLAIR, ring lesions on diffusion-weighted imaging, and related changes in apparent diffusion coefficient imaging. There is loss of myelin-associated glycoprotein and oligodendrocyte apoptosis. Demyelinated areas are high in nitric oxide synthetase (iNOS). Hypoxic conditioning may explain the rings, where sublethal hypoxia provides resistance to later injury. Hypoxia-inducible factor1alpha is increased in the outer edge of preserved tissue (Stadelmann et al 2005); it is also increased in normal-appearing white matter in multiple sclerosis.

• Behçet disease -- CSF pleocytosis, large MRI lesions in upper brainstem and basal ganglia, and occasional punctuate parenchymal enhancement. Behçet disease causes intermittent cranial nerve deficits. Biopsies show polymorphonuclear cells and eosinophils surrounding arterioles. It is associated with genital and oral ulcers, uveitis, and meningoencephalitis. Optic neuropathy is relatively rare in Behçet disease. Twenty percent of patients with Reiter syndrome (reactive arthritis) have uveitis.

• CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a mutation of the Notch3 gene. Notch controls oligodendrocyte maturation and lymphocyte development. The intermittent strokes in midlife on a background of patchy MRI T1 holes plus diffuse increased white matter T2 signal can be confused with multiple sclerosis. T2 lesions are large and confluent and often significant in the anterior temporal lobes. It is diagnosed with a forearm skin biopsy for granular osmiophilic material in arterioles or with DNA analysis for the Notch mutation. Related syndromes include autosomal dominant retinal vasculopathy with cerebral leukodystrophy, hereditary cerebral amyloid angiopathy (CAA), COL4A1 angiopathy, and vascular leukoencephalopathy mapping to chromosome 20q13.

• Cancer--primary and secondary brain tumors. Hemophagocytic lymphohistiocytosis, Langerhans cell histiocytosis, and neoplastic angioendotheliosis can be confused with multiple sclerosis.

• CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a mutation of the HTRA1 gene, which codes for a serine protease that controls TGF-beta signaling. MRI and presentation is similar to CADASIL.

• Carcinomatous polyradiculopathy is associated with adenocarcinoma of breast and lung, lymphoma, or melanoma.

• Cavernous sinus thrombosis affects cranial nerves III, IV, V, and VI.
• Celiac disease can cause myelopathy and encephalopathy. Celiac disease was increased in relapsing multiple sclerosis patients (11%, which is 5x above normal) and families (“32%”) (Rodrigo et al 2011). Many autoantibodies, as well as anti-tissue transglutaminase-2, were elevated in 8 of 72 multiple sclerosis patients, but only one had diarrhea and 5 were constipated. This study needs replication.

• Cerebellar degeneration and Friedreich ataxia can mimic progressive cord symptoms.

• Cerebrotendinous xanthomatosis (progressive myelopathy in a young patient, but with cataracts, diarrhea, ankle tendon xanthomas, and cerebellar dentate lesions on MRI).

• Cervical compression (disc, spondylosis, or tumor) can cause a progressive paraparesis, gait disorder, and bladder dysfunction.

• Charcot-Marie-Tooth disease (brain MRI lesions and progressive course).

• Chemotherapy can cause a leukoencephalopathy and cognitive decline (Ara-C, cisplatin, 5-fluorouracil, 5-flourauracil+levamisol); neurotoxicity is worse with radiotherapy and progresses over time.

• Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with optic neuritis.

• Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPTERS) has enhancing lesions centered in the pons, sometimes with spread to cord with extensive lesions, also cerebellum, basal ganglia, and small juxtacortical lesions. Severe, approximately biannual attacks cause brainstem and cerebellar, and sometimes cord, symptoms. CD4 T cells infiltrate the lesions in this non-demyelinating disorder of unknown etiology. One patient has developed CLIPTERS after natalizumab withdrawal.

• Cogan syndrome (vestibulo-auditory problems). Inflammation is predominantly CD4 T cells.

• Combined central and peripheral demyelination and encephalomyeloneuropathy appears in multiple hereditary and degenerative diseases. Many patients with combined central and peripheral demyelination have antibodies to neurofascin, a CNS and PNS adhesion molecule in the nodes of Ranvier and paranodes. Others have antibodies to neutral glycosphingolipids.

• Congenital adrenal hyperplasia (diffuse brain white matter and corpus callosum abnormalities).

• Connective tissue diseases can mimic multiple sclerosis. They can cause vasculitis with neuropathy, cranial nerve damage, and CNS destruction. Systemic lupus erythematosus causes a severe, progressive thoracic myelopathy also called “lupoid sclerosis” or “acute lupus myelopathy.” It is acute or subacute with scattered white matter lesions in the cortical or subcortical junction but can affect gray and white matter. Twenty percent of patients have optic neuropathy in one or both eyes. When the cord is involved, the damage extends over many segments or the entire cord. This historic entity is likely to have been from neuromyelitis optica associated with connective tissue disease.

Most patients with systemic lupus erythematosus, however, have no cord lesions. Treatment of connective tissue disorders diametrically differs from multiple sclerosis therapy, as interferons could cause worsening. (Sjögren syndrome is described below.) Craniofacial scleroderma is associated with bilateral-enhancing MRI lesions and oligoclonal bands.

• Copper deficiency causes a progressive myelopathy and neuropathy, often related to gastrointestinal disorders, post-gastric bypass, and zinc excess (similar to the cuprizone model in rodents).

• Cortical blindness must be discriminated from optic neuritis.

• Cranial arteritis (temporal arteritis) can affect the posterior optic nerve, without papilledema, in 70- to 80-year-old patients. It causes devastating visual loss; temporal pain, fever, weight loss, headache, fever, and high erythrocyte sedimentation rate and is linked to polymyalgia rheumatica.

• Devic disease, or neuromyelitis optica, is a demyelinating, sometimes necrotic, inflammatory disease of the spinal cord and the optic nerves. Attacks are more severe and more frequent than in multiple sclerosis. In Asia and South America and in Native American Indians, Devic disease is more common than multiple sclerosis. In Europe and the
United States, multiple sclerosis is far more common. Devic disease traditionally accounted for less than 1% of occidental demyelinating disease, but a test (NMO-IgG) suggests that approximately 5% of “multiple sclerosis” cases with optic neuritis and longitudinal cord lesions are the Devic variant.

This IgG1 neuromyelitis optica antibody recognizes aquaporin-4, a water transport channel that is localized in astrocyte foot processes over paranodal axons and near blood vessels. Aquaporin-4 is present in high levels in renal tubules, possibly explaining the low glomerular filtration rate in progressive multiple sclerosis (Calabresi et al 2002). Antibodies to aquaporin predict development of Devic disease and a more severe course. Although this antibody is present at all times, the attacks are intermittent.

Devic disease is associated with connective tissue disease, rheumatoid arthritis, pernicious anemia, hypothyroidism and antibodies to thyroid antigen, and myasthenia gravis. The odds ratio of having another autoimmune disease is 10. Linkage of multiple sclerosis to these autoimmune disorders becomes unlikely when Devic disease cases are eliminated from the “multiple sclerosis” pool. CNS Sjögren disease is similar to Devic disease (detailed below), but only 40% are NMO-IgG positive.

Devic disease is monophasic in one third of patients (Wingerchuk et al 1999). In the remaining two thirds, Devic disease has severe and frequent relapses and does not become progressive. The damage in the optic nerves and cord is diffuse, often total, and includes significant axonal loss. Because axons are lost out of proportion to the demyelination, lesions cause pronounced clinical symptoms, but heat sensitivity is less prominent than in multiple sclerosis. Lesions are sometimes cavitary and necrotic and are often hypointense on T1-weighted MRI scans. The MRI lesions only infrequently surround veins, unlike multiple sclerosis, where more than 95% have a clearly-seen central vein. Importantly, the spinal lesions in Devic disease extend over more than 2 vertebral segments and are usually cervical. Cervical MRI images in Devic disease are similar to CNS Sjögren disease. In the early, strict definition, MRI scans of the brain are normal, and there is no demyelination in the brain, brainstem, or cerebellum (Mandler et al 1993). However, 20% later evince large brainstem and hypothalamic lesions that sometimes enhance on MRI. CSF protein and neurofilament heavy chain levels are elevated. Seventy-five percent of patients have CSF pleocytosis, and 35% have greater than 50 cells/mm3; polymorphonuclear cells are often present. CSF IgG synthesis is usually normal, and CSF IgG1 is not elevated (it is elevated in multiple sclerosis). Oligoclonal bands are less common (40% or less) than in multiple sclerosis (97%) and can disappear over time.

Lesions in parenchyma and meninges have more IgM than IgG. There are few T cells but prominent eosinophils and granulocytes, likely related to excess IL-17 (Ishizu et al 2005). CD8 cells that produce Th1-like cytokines are elevated in optico-spinal multiple sclerosis (Ochi et al 2001). Aquaporin-4 is modulated off the astrocyte foot processes in Devic disease but not in multiple sclerosis.

Rituximab was therapeutic in a series of 8 patients (Cree et al 2005). Plasmapheresis may also reduce symptoms. Interferon therapy, however, may cause worsening (Javed and Reder 2006; Wang et al 2006; Warabi et al 2007), but because this disease is so active, adverse interferon effects could be spurious.

• Eales disease, a syndrome of retinal perivasculitis and recurrent intraocular hemorrhages, is infrequently associated with neurologic abnormalities (7 of 17 patients).

• Encephalitis (anti-NMDA receptor encephalitis), in 3% of cases, has prominent MRI or clinical features of multiple sclerosis or neuromyelitis optica.

• Erdheim-Chester disease causes sclerosis and bone pain, diabetes insipidus, and histiocytic infiltration of the meninges, and T2 positive, enhancing lesions of cerebellum and brainstem. It is very sensitive to interferon-alpha therapy.

• Folate deficiency can cause encephalopathy and spastic paraparesis.

• Fragile X-associated tremor ataxia syndrome, from an FMR1 gene CGG repeat expansion, causes tremor, ataxia, and a sensory peripheral neuropathy. MRI has hyperintensity of the corpus callosum, splenium, and the middle cerebellar peduncle in two thirds.

• Gadolinium encephalopathy (MRI lesions).
• Genetic—see storage disease plus other genetic disorders.

• Gerstmann-Sträussler-Scheinker syndrome is a prion disease that can cause ataxia, MRI, and CSF findings similar to multiple sclerosis.

• Guillain-Barré syndrome, Miller Fisher variant (below).

• Hemophagocytic lymphohistiocytosis (associated with Epstein-Barr virus or a perforin mutation). Loss of perforin function prevents termination of immune response and inflammation of brain and peripheral nerves.

• Hepatic encephalopathy, with symmetric high MRI T1 signal in the globi pallidi, likely from manganese deposition.

• Hereditary diffuse leukoencephalopathy with axonal spheroids is from mutations in the CSF1R gene, causing depression, progressive loss of memory and executive function, seizures, tremor, bradykinesia, apraxia, rigidity, and gait dysfunction. MRI shows confluent frontoparietal periventricular T2 lesions that spare U fibers and cortex, plus corpus callosum lesions. Possibly related to POLD.

• Hereditary spastic paraplegia (versus primary progressive multiple sclerosis ).

• Hypothyroidism--can cause constipation and fatigue even though the motivation to act remains. In multiple sclerosis, abulia is sometimes associated with fatigue.

• IgG4-related disease cause progressive spasticity and dementia, plus cortical and subcortical MRI lesions.

• Increased intracranial pressure and normal pressure hydrocephalus can cause visual and long tract findings.

• Infection. Tuberculosis, tuberculomas, sarcoidosis, fungus such as Cryptococcus, syphilis, Lyme disease (Borrelia burgdorferi), chlamydia, mycoplasma, toxoplasmosis (in 80% of French, 30% world-wide), brucellosis (abscesses, occasionally intramedullary, can involve spinal cord), familial Mediterranean fever, Listeria monocytogenes (cervical cord lesions), CNS Whipple disease, toxocariasis, purulent leptomeningitis, or intraocular inflammation. Inflammation of the paranasal sinuses seldom causes optic nerve inflammation.

• Inflammatory bowel disease with brain lesions.

• Leber hereditary optic neuropathy is a hereditary, maternally transmitted mitochondrial disease (base pair 11778 of mitochondrial DNA, causing loss of function of the reduced form of nicotinamide adenine dinucleotide dehydrogenase 4). It causes bilateral, often sequential, painless visual loss. In females, but not in males, it is sometimes indistinguishable from multiple sclerosis because of associated multiple sclerosis-like symptoms, destructive white matter lesions containing macrophages and CD8 T cells, widespread and periventricular white matter lesions on MRI, abnormal visual evoked potentials, and sometimes abnormal CSF (Harding et al 1992; Kovacs et al 2005). In men, diffuse white matter lesions are not present, but affected optic nerves show abnormalities on short-term inversion recovery MRI. The symptoms are often unilateral but eventually are bilateral. Visual loss is permanent and untreatable. Although neurons (third-order retinal neurons) are the main targets in Leber disease, a parallel mitochondrial defect theoretically also could make oligodendroglia more susceptible to damage in multiple sclerosis. Other ocular disorders include Eales disease and retrobulbar vasculopathy of Susac (Weinshenker and Lucchinetti 1998; Susac et al 2003).

• Leukoencephalopathy with vanishing white matter in adults causes slow neurologic deterioration and white matter lesions. Autosomal recessive mutation in eukaryotic initiation factor 2B (eIF2b) increases unfolded proteins and cell death. It occurs rarely in adults, with progressive symptoms. White matter signal is diffusely increased on T2 and FLAIR and low on apparent diffusion coefficient MRI.

• Lyme disease is occasionally associated with unilateral or bilateral optic neuritis or ischemic optic neuropathy (in addition to retinal vasculitis), internuclear ophthalmoplegia, deafness, and multiple other neurologic signs.

• Lymphoma can form white matter MRI lesions. Tumor-filled centrum ovale venous streaks can occur on MRI. Intravascular large B cell lymphoma, angioendotheliomatosis proliferans sytematica is a non-Hodgkin variant that infiltrates CNS and skin.

• Maculopathy or macular degeneration.
• Macrophage activation syndromes can be confused with multiple sclerosis in very young patients and include familial hemolymphphagocytic lymphohistiocytosis, Chediak-Higashi disease, Griscelli disease, and Purtillo syndrome. Crystal-storing histiocytosis can mimic multiple sclerosis in adults.

• The Marburg variant of multiple sclerosis has axonal loss and severe widespread diffuse or multifocal demyelination. Lesions can be of different ages and contain massive macrophage and CD8 cell infiltrates; in one case, inflammation preceded the demyelination. Several cases showed active vasculitis including polymorphonuclear cells, suggesting overlap with acute hemorrhagic leukencephalitis. Death is within a year. Death in 1 month is frequent, often from brainstem or upper cord lesions. Steroids and chemotherapy prolong life to 3 months; plasmapheresis may be helpful. Large tumefactive lesions may be confused with the Marburg variant.

• Marchiafava-Bignami disease causes demyelination of the corpus callosum, usually the medial sector. There is a clinical pattern of hemispheric disconnection.

• Metastasis from cancer.

• Metronidazole causes transient cerebellar dentate lesions.

• Migraine can cause visual disturbances, vertebrobasilar symptoms, and disseminated T2 lesions on MRI. In women, when migraines are frequent and associated with aura, MRIs show small cerebellar infarcts—the location is more lateral than the cerebellar peduncle lesions of multiple sclerosis. Occasionally deep white matter lesions are seen in the centrum semiovale, likely from associated hypertensive disease (Kruit et al 2004). One third of headache patients with MRI lesions actually fit the McDonald criteria for multiple sclerosis. Importantly, they do not have multiple sclerosis symptoms.

• Miller Fisher syndrome (subacute ataxia and ophthalmoplegia from Guillain-Barré syndrome) affects cranial nerves and eye movements. There are rare cases of this disorder and chronic inflammatory demyelinating polyneuropathy along with multiple sclerosis.

• Mitochondrial disorders. Genetic mitochondrial syndromes can cause strokes, diffuse periventricular T1 holes and T2 white matter lesions, including the spinal cord. Non-syndromic mitochondrial disorders can cause scattered white matter lesions on FLAIR MRI. Intrinsic mitochondrial defects could affect onset or course of multiple sclerosis.

• Myasthenia gravis can cause diplopia and muscle weakness.

• Myotonic dystrophy types 1 and 2 (brain white matter lesions on MRI).

• Neoplastic (lymphoma, intravascular lymphoma, primary or metastatic central nervous system tumor; can involve eyes also).

• Neuroretinitis. This is a form of papillitis with associated deposits of lipids and protein. These deposits radiate from the macula and form a stellate pattern at the macula or a half star between the macula and the disc. The "macular star" is formed as fluid from leaking disc capillaries accumulates within the Henle layer around the fovea. The macular star may take up to 2 weeks to form after the onset of papillitis. Symptoms are similar to those in typical optic neuritis, but neuroretinitis seldom progresses to multiple sclerosis, suggesting that another etiology has been confused with multiple sclerosis.

• Nutritional neuropathy includes Jamaican neuropathy and Cuban epidemic neuropathy.

• Optic nerve glioma ("benign" glioma of childhood-a pilocytic astrocytoma; malignant glioblastoma is more common in adults).

• Orbital pseudotumor with proptosis, pain, and ophthalmoplegia, but infrequent visual loss.

• Paraneoplastic: anti-CV2 antibodies for optic neuritis. Also possible are limbic encephalitis, brainstem encephalitis, cerebellar degeneration, and lobar encephalopathy with large MRI lesions.

• Parasites can migrate into the CNS and cause focal symptoms and must be excluded in patients from endemic areas, eg, cysticercosis.
• Pelizaeus-Mertbacher disease (brain MRI lesions and progressive course), including proteolipid protein-1 (PLP-1) mutation.

• Pigmented orthochromatic leukodystrophy mutations (POLG-1 = mitochondrial DNA polymerase gamma; the CSF1 receptor is also implicated) can cause progressive CNS signs in childhood or late teens, psychiatric symptoms, and bilateral periventricular lesions on MRI similar to leukoariosis. The CSF-1R mutation also causes hereditary diffuse leukoencephalopathy with axonal spheroids.

• Polyglucosan body disease in adults begins at approximately 50 years and causes neurogenic bladder, spastic paraplegia with vibration loss, and a peripheral axonal neuropathy (Mochel et al 2012). A glycogen-branching enzyme mutation causes accumulation of polyglucosan bodies throughout the nervous system and cerebral myelin loss. T2 and FLAIR MRI shows symmetrical white matter lesions in periventricular areas, posterior internal capsule, external capsule and medial lemniscus of pons with atrophy of medulla and spinal cord. There is a mutation in glycogen branching enzyme.

• Porphyria. Hereditary coproporphyria can cause progressive CNS and PNS symptoms.

• Posterior reversible leukoencephalopathy. Increased T2 MRI signal in white more than gray matter. Triggers include eclampsia, acute renal failure, hypertensive encephalopathy, and immunosuppressive drugs such as cyclosporin (high dose) and methotrexate.

• Progressive multifocal leukoencephalopathy. Progressive symptoms such as cognitive loss, occipital visual loss, and hemiparesis. MRI lesions are usually large and rarely enhance. Optic neuritis or cord lesions are very likely.

• Progressive necrotizing myelopathy provoked by mycoplasma pneumoniae, m Tb. In rats with experimental allergic encephalomyelitis, it is provoked by tilorone, an IFN-alpha/beta inducer.

• Pseudotumor cerebri (visual loss).

• Pseudoxanthoma elasticum (brain MRI lesions and vascular disease).

• Psychogenic. Multiple sclerosis symptoms are often confusing to patient and doctor because they are generated by aberrant CNS conduction and can be elaborated or misreported. Actual psychogenic symptoms can easily be confused as multiple sclerosis, but can also be difficult to challenge when the patient is invested in the diagnosis of multiple sclerosis. “Pseudo-multiple sclerosis” or “therapeutic mislabeling” should not be supported by the neurologist (Boissy and Ford 2012).

• Radiation necrosis. Possibly treated with corticosteroids and hyperbaric oxygen.

• Raeder paratrigeminal syndrome is unilateral facial pain in the V1 and V2 branches of the trigeminal nerve; it is associated with ptosis and miosis from a parasellar mass and must be differentiated from trigeminal neuralgia due to multiple sclerosis.

• Sarcoidosis can involve single or multiple cranial and peripheral nerves, the brainstem, hypothalamus, and meninges.

• Schilder disease (diffuse sclerosis) causes large hemispheral demyelinating lesions.

• Sjögren syndrome. When associated with central and peripheral nervous system lesions, classic Sjögren symptoms (sicca and rheumatic) are less common than in primary Sjögren disease. Serum antibodies to Sjögren syndrome A and B proteins (SSA and SSB) are positive in only one third of patients and are more often negative than in Sjögren disease without neurologic symptoms. A lip or parotid biopsy is needed to clinch the diagnosis (Alexander et al 1986; Sandberg-Wollheim et al 1992; Javed and Reder 2006).

In CNS Sjögren syndrome, one third have MRI, CSF, or evoked potential evidence of cerebral abnormalities; one third have longitudinal spinal cord lesions; the rest have optic neuritis and diffuse symptoms such as seizures, cognitive loss, and encephalopathy (Delalande et al 2004). There are small white matter MRI lesions in two thirds (occasionally in basal ganglia, infrequently in corpus callosum), oligoclonal bands in one third, and abnormal visual evoked potentials in about two thirds (de Seze et al 2003). PNS Sjögren disease can cause sensory ganglionitis, painful sensory
neuropathy, and distal sensory-motor axonopathy.

Adil Javed has described a new Sjögren-related entity, seen predominantly in young black women (Javed et al 2008). Patients with severe destruction from optic neuritis and longitudinal cervical cord lesions resemble patients with Devic disease, but NMO-IgG levels are positive in only 40%. However, minor salivary gland biopsy is positive for Sjögren disease: inflammation grade 4+/4 in 85%, and 2+ in 100%, often when SSA and SSB serology is negative. Other autoimmune diseases (myasthenia gravis, primary biliary cirrhosis) are often associated. Treatment differs from multiple sclerosis therapy, as interferons may cause worsening. Mycophenolate mofetil provides some benefit, but the best responses are with rituximab (Javed personal communication 2007).

• Storage disorders and other genetic diseases versus childhood multiple sclerosis. Leukodystrophies are usually confluent and bilateral on MRI. Juvenile metachromatic leukodystrophy and late onset Tay-Sachs disease have MRI signatures that could be confused with multiple sclerosis. Also to be considered are Alexander disease (frontal, cerebellar, brainstem, and spinal cord T2 MRI lesions), childhood ataxia with cerebral hypomyelination (eIF2b mutation), late-onset Canavan disease (mutations of aspartoacylase gene, restricted to oligodendrocytes, with accumulation of the substrate molecule N-acetyl-aspartate), Fabry disease (periventricular lesions, but non-multiple sclerosis clinical symptoms), globoid cell leukodystrophy/Krabbe disease, hereditary diffuse leukoencephalopathy with axonal spheroids (see above), Pelizaeus-Merzbacher disease (PLP mutation and dysmyelination; “jimpy” mouse is model), Refsum disease (ataxia and MRI lesions), and Wilson disease.

• Susac syndrome. Retrobulbar vasculopathy of Susac causes encephalopathy, branch (distal) retinal artery occlusions, and hearing loss (Weinshenker and Lucchinetti 1998). It affects 20- to 40-year-old women and is associated with headaches, hearing loss, tinnitus, pseudobulbar speech, and encephalopathy. There are microangiopathic infarcts in gray and white matter, and bilateral branch artery occlusions in the retina. MRI shows many multifocal white matter lesions of the central corpus callosum, plus lesions in deep gray, posterior fossa, brain parenchyma, and occasionally the leptomeninges. Acute large “snowballs” and multiple older small “punched-out” areas riddle the central corpus callosum (Susac et al 2003). Lesions are less likely to have a central vein than in multiple sclerosis. Intravenous immunoglobulin and corticosteroids improve hearing and MRI.

• Syphilis also has huge variety in its presentation.

• Thyroid ophthalmopathy can cause diplopia.

• Tobacco-alcohol amblyopia.

• Tolosa-Hunt syndrome. Painful ophthalmoplegia with subacute boring eye pain, palsy of extraocular muscles, V1 sensory loss, sympathetic denervation of pupils, and rapid response to 100 mg prednisone.

• Trauma; direct or after anterofrontal deceleration.

• Tuberculomas in the brain parenchyma.

• Tuberous sclerosis can cause subcortical tubers that appear in white matter on MRI.

• Tumor necrosis factor receptor-1-associated periodic syndrome (familial Hibernian fever) is from a mutation in the p55 receptor for TNF. It occasionally has onset and MRI features similar to multiple sclerosis (Kumpfel et al 2008). It does not respond to multiple sclerosis therapies but improves with anti-TNF therapy.

• Vaccination (polio and possibly influenza). The associations reported in a few papers are likely spurious, as the vast majority of studies find no link. Some find a 3-fold increase in the incidence of multiple sclerosis after vaccination with recombinant hepatitis B vaccine but not with vaccines against other viruses (Hernan et al 2004), yet others report no increase. Confusion clouds this issue from statistical and reporting problems--combining data on recombinant and nonrecombinant vaccines, written versus computer records, and date of onset versus date of diagnosis. Most experts
urge caution with live virus vaccines (measles, mumps, rubella, varicella/zoster, and yellow fever vaccines).

• Vascular disease lesions are usually spherical and tend to be located in the centrum semiovale instead of “fingers” radiating outward from the corpus callosum. Lacunes are common in the basal ganglia but not in the corpus callosum. Some lesions in hypertensive elderly patients are periventricular and are quite similar to multiple sclerosis lesions. Vascular lesions with aging tend to be smaller and random but sometimes symmetrically involve the periventricular white matter in confluent posterior ischemic damage (Arnold and Matthews 2002). Vascular malformations and cavernous hemangiomas show persistent Gd enhancement. Moyamoya syndrome has paroxysmal symptoms and can be confused with multiple sclerosis on MRI.

• Vasculitis (temporal arteritis, angiitis, cranial arteritis, Churg-Strauss syndrome). Isolated angiitis can occur in children.

• Viruses or viral encephalitis (EBV, chickenpox, cytomegalovirus, hepatitis A and B, HHV-6 encephalomyelitis, HHV-7, VZV, herpes zoster vasculopathy, acute HIV infection, HTLV-I (also associated with Sjögren syndrome), infectious mononucleosis, Japanese encephalitis (a flavivirus with bilateral thalamic lesions and polio-like flaccid paralysis), measles, mumps, rubella, post-measles autoimmunity and subacute sclerosing panencephalitis, poliomyelitis (central cord lesions on MRI), West Nile virus (flavivirus) with a polio-like presentation. Note, HIV patients, usually on highly-active retrovirus therapy, have a reduced risk of multiple sclerosis. Japanese macaque encephalitis causes multifocal inflammatory demyelinating plaques of varying ages. It is caused by a gamma-2 herpesvirus with 50% homology to human Kaposi sarcoma-associated virus.

• Vitamin B12 deficiency causes subacute combined degeneration with centrocecal scotomata, optic atrophy, MRI lesions around the corpus callosum (not Dawson fingers), partially reversible leukoencephalopathy, and long tract signs from cord degeneration. Methionine synthase deficiency is a rare cause of similar symptoms with symmetric periventricular leukoencephalopathy.

• Vitamin E deficiency causes ataxia, myelopathy, and neuropathy.

**Diagnostic workup**

Multiple sclerosis is traditionally described as clinical symptoms or signs of two CNS lesions separated in time and space that are not caused by another CNS disease. These lesions are detected with a history and neurologic examination—the sine qua non of a diagnosis of multiple sclerosis. MRI and CSF analysis strengthen the diagnosis (Poser et al 1983; McDonald et al 2001) and are each abnormal in more than 95% of definite multiple sclerosis cases. MRI is essential to rule out mimics of multiple sclerosis. A standardized brain and cord imaging and reporting protocol from the (Consortium of Multiple Sclerosis Centers) (CSMC) enhances diagnosis, clinical trial assessment, and monitoring of disease activity and damage (Simon et al 2006). CSF shows ongoing inflammation and oligoclonal bands, and it can exclude alternate causes.

Criteria that define “multiple sclerosis” have been revised several times: 2001, 2005, and 2010 (Polman et al 2011). Criteria now allow diagnosis of multiple sclerosis when a new MRI lesion defines separation in time and space. Initial criteria included a new T2 MRI lesion more than 30 days or enhancement more than 3 months after the initial event (McDonald et al 2001). In 2010, this was revised so that enhancing and non-enhancing lesions on one scan could show dissemination in time.

New criteria allow for early diagnosis at time of first attack, with caveats when pronouncing that 1 Gd+ and 1 Gd- lesion on a single scan equals “separation in time.” There is temporal variation in the duration of enhancement, plus some regional differences that interfere with comparison of Gd+ and Gd- lesions. For instance, Gd+ MRI lesions in white matter are easier to see than lesions in the cortical gray matter. Similarly, Gd enhancement lasts 2 weeks (median) to 3 weeks (mean) (Cotton et al 2003), but there is temporal variation in the duration of enhancement. Gd+ ring-enhancing lesions with central pallor correlate with disease severity and are larger and last longer than homogenously enhancing lesions. With this temporal variation, there could be a tail of enhancing lesions several weeks after a clinically isolated syndrome or ADEM, so “old” and “new” lesions could still be from the initial insult.

Widened inclusion criteria for a diagnosis of multiple sclerosis after a clinically isolated demyelinating syndrome lead to spurious improvement in prognosis, the “Will Rogers phenomenon” (Sormani et al 2008). The new criteria also
affect clinical trials. Patients with milder disease have been allowed into recent studies, necessitating larger patient cohorts to see any drug benefit. Drugs that benefit MRI more than clinical activity will seem to be more effective. Furthermore, drug efficacy can be measured by induction of a “disease activity free” state that can be achieved in a subset of patients, but not all. This state is much more dependent on MRI than clinical activity and is more stringent when scans are frequent, with triple-dose gadolinium, and on high-Tesla MRI magnets. Importantly, drug effects on MRI do not necessarily correlate with clinical relapses or with long-term prognosis (Arnason 1999).

**MRI in diagnosis.** On monthly scans, 90% of untreated relapsing-remitting patients will have MRI activity over 9 months (Li and Paty 1999). Early, active MRI lesions are typically hyperintense on T2 with a hypointense ring, possibly containing activated macrophages. Large, fluffy T2 lesions often have preserved axons and repletion of oligodendroglia. Some acute plaques enhance with gadolinium, but early on, they can be almost isointense on T2 MRI (Bruck et al 1997). Late active lesions are less hyperintense on T2 and sometimes hypointense on T1-weighted images (“black holes”). Inactive lesions (demyelinated or myelinating) are hypointense on T2 scans and normal or hypointense on T1 scans. Black holes are not uniform. They range from slightly hypointense (“gray holes” would be more apt) to CSF-like hypointense (black), indicating a spectrum of axonal loss and demyelination. Variation in blackness is not usually analyzed.

Certain MRI features are typical of multiple sclerosis, such as multiple ovoid-shaped bright lesions on T2-weighted MRI, abrupt loss of T2 signal as a lesion approaches the gray matter (“open ring”), and periventricular lesions, often radiating up from the corpus callosum or out from the ventricle (called “Dawson fingers”), especially near the body and posterior horn of the lateral ventricle. Other typical features are a lesion greater than 5 mm; lesions in the corpus callosum, brainstem, or cortical gray matter; and lesions below the tentorium, especially in the cerebellar peduncle (Offenbacher et al 1993). Corpus callosum lesions can also be caused by vascular disease, CADASIL, Susac syndrome, tumor, Marchiafava-Bignami disease, echovirus 9, and adrenoleukodystrophy.

Twenty percent of Gd+ lesions are reoccurrences at prior sites; these are larger and have lower magnetization transfer values than new lesions. T2 volume, MRI “burden of disease,” increases by 5% to 10% per year.

A leak through the tight junctions of the blood-brain barrier is usually invoked as the cause of Gd enhancement. It is also likely that T cells constantly activate endothelial cells. Activated, enlarged endothelial cells can pinocytose gadolinium and gadolinium-protein complexes and could cause a capillary blush on MRI (Brown 1978; McDonald and Barnes 1989; Claudio et al 1995). Treatment with glucocorticoids blocks MRI enhancement, probably through a direct effect on endothelial cells. IFN-beta and antibodies to VLA-4 also block gadolinium enhancement, interrupting T cell-endothelial interaction.

Perivenular spaces are prominent due to inflammation (lymphocyte cuffing) (Ge et al 2005). A “sand-like appearance” of the high convexity white matter is from dilated Virchow-Robin spaces (Achiron and Faibel 2002). These dilated spaces correlate with Gd+ lesions (Wuerfel et al 2008), suggesting diffuse activation of multiple areas of the brain.

Spinal cord lesions are usually only 1 to 2 segments long, often multiple, and predominantly cervical (66%) (Bot et al 2004). They are diffuse in only 13% and are most likely in chronic multiple sclerosis. Almost all are peripherally located, not in the central cord, perhaps related to inflammation near pial veins. In recently diagnosed multiple sclerosis, cord lesions help define dissemination in space (85% are positive with brain plus cord MRI versus 66% using brain MRI alone). The cord is often a target primary progressive multiple sclerosis, but over 90% of these patients also have brain lesions.

Normal-appearing white matter evinces slight abnormalities on MRI and MR spectroscopy and also more cerebral perfusion several months before overt MRI lesions appear (Goodkin et al 1998; Filippi et al 1999; Wuerfel et al 2004). MR spectroscopy (MRS) shows biochemically abnormal lipid peaks in gray matter. Scans with 8 Tesla magnets reveal multiple lesions in gray matter and many in subpial and periventricular locations (Rammohan 2003). PET scans show decreased cerebral glucose utilization in frontal and parietal cortex, and this correlates with low NAA/Cr ratios on magnetic resonance spectroscopy and low oxygen use on MRI. Resting-state networks also have decreased functional connectivity on fMRI, affecting vision, working memory, and sensorimotor function. These measures decline over time in multiple sclerosis and suggest hypometabolism and mitochondrial respiratory dysfunction.

Magnetization transfer (MTR) values in normal-appearing white matter are lowest in chronic progressive multiple
Lesions in arcuate U fibers below gyri are bright on T2. These arcs form an "open ring" and are a strong indicator of demyelinating disease. Antibody and complement in plaques (Lucchinetti type II) causes a T1 Gd-enhancing ring and hypointense T2 ring (Konig et al 2008). Restricted apparent diffusion coefficient (ADC) on MRI is more common in demyelinating disease than in tumors or abscesses.

Brain atrophy is present in early multiple sclerosis and averages 0.9% per year, versus 0.1% to 0.2% in healthy controls. It evolves 5 times more rapidly than in normal brains, and up to 14 times faster during active secondary progressive multiple sclerosis. Atrophy is largely from axonal loss but also from demyelination and contraction of the neuropil. Axonal loss and T2 lesion volume are only partially correlated. White mater loss is best seen as thinning of the corpus callosum. Gray matter volume loss appears at first presentation in the thalamus and putamen, caudate, cerebellum, and cortex. White and gray matter atrophy correlate with cognitive decline and can be measured with third ventricular volume, a reflection of thalamic loss. CNS atrophy can also be measured with transcranial sonography of the third ventricle (width versus disability is inversely correlated at r = -0.6). Cerebellar gray atrophy correlates with loss of locomotion. Brain atrophy correlates better with changes in disability than T2 MRI lesions do and is most predictive in the cervical cord (Zivadinov and Bakshi 2004). Cervical cord atrophy is pronounced in primary and secondary progressive multiple sclerosis. Eventual atrophy is predicted by the presence of early T2 hypointensity and T1 Gd+ lesions (Simon et al 2000), T1 “black holes,” and low brain volume in some studies. T2 hypointensity is likely from iron deposition (perhaps neurotoxic) and correlates with later brain atrophy. IFN-beta and glatiramer therapy do slow atrophy. Atrophy is slower with weekly IFN-beta than with high-dose, high-frequency interferon, possibly because the latter reduces inflammation (“pseudoatrophy”) or because there are differences in neurotrophin induction.

T2 lesion volume has a weak correlation with disability (r = 0.2 to 0.3). T1 holes correlate more strongly, especially in secondary progressive multiple sclerosis (approximately 0.8). Without treatment, 56% of acute black holes will remain as permanent black holes. Callosal atrophy is a poor prognostic sign.

Rare patients can develop nephrogenic systemic fibrosis (NSF) from certain preparations of gadolinium. NSF is more common with low glomerular filtration rate and diabetes, and it can be diagnosed with a skin biopsy.

**CSF in diagnosis.** The CSF is the best non-MRI marker of multiple sclerosis. Analysis of CSF is helpful when patients have atypical clinical symptoms or MRI appearances, or early or late onset of disease. CSF reflects CNS inflammation and detects blood-brain barrier leaks (Freedman et al 2005). The CSF, in order of increasing frequency and importance for a diagnosis of multiple sclerosis, shows elevated protein, a moderate increase in white blood cells, increased IgG, IgG/albumin index, IgG synthesis rate (Tourtellotte or Link formulas), and oligoclonal bands (OGCB). {embed="pagecomponents/media_embed" entry_id="12223"} IgA and IgM OGCB provide limited additional information.

Bands are present in 95% of multiple sclerosis patients but only 80% of primary progressive patients (Siritho and Freedman 2009; Freedman personal communication 2011). The index, synthesis rate, and oligoclonal bands are increased in black compared to white patients by 30% to 40%, suggesting more active inflammation (Rinker et al 2007). The IgG index correlates with CSF IL-10 and IL6 levels. A positive MRI and CSF oligoclonal bands in clinically isolated syndromes predict conversion to definite multiple sclerosis in 90% of patients, at 9 times the rate with negative tests, perhaps more predictive than dissemination in space on MRI.

When suspected cases of multiple sclerosis have no CSF IgG bands, a repeat study will show new bands in half of them (Thompson and Freedman 2006). With only one CSF band, 1 in 3 later develops more oligoclonal bands, and 1 in 27 has cerebral lymphoma (Davies et al 2003). Patients with diagnosed multiple sclerosis who have negative oligoclonal
bands are less likely to develop more bands over time (Siritho and Freedman 2009). Serum bands are increased in 44% of multiple sclerosis patients and are 10 times more common in women than in men (Thompson and Freedman 2006). Inflammatory conditions such as SSPE, Lyme disease, syphilis, Behçet disease, lupus, and adrenoleukodystrophy also often have unique CSF bands.

Intrathecal synthesis of antibodies to measles was described in 1962. Many other viruses, such as HHV-6, are also targets of a polyspecific B cell response. An index of CSF antibodies to measles, rubella, and herpes zoster (the MRZ reaction) improves sensitivity (Felgenhauer 1992) and is low or absent in neumyelitis optica. Antibodies to galactocerebroside, triose-phosphate isomerase, and glyceraldehyde-3-phosphate are elevated. These antibodies inhibit glycolytic enzyme activity and could disrupt neuroaxonal function. Reports of CSF antibodies to MOG and MBP have not been replicated, perhaps because of assay difficulty from conformational changes in the protein.

The CSF cell count is often slightly elevated at 5 to 10 per cubic um. Eighty percent are T cells in stable multiple sclerosis and in healthy controls; T cells rise to 90% in active multiple sclerosis (Reder and Arnason 1985). CSF white blood cells are 90% CD3+ T cells (70% CD4, 20% CD8), 3% natural killer, 4% macrophages, and 5% B cells (Cepok et al 2001). The CD4/CD8 ratio reflects the blood (2/1) in relapsing-remitting multiple sclerosis, but CSF CD8 cells fall in progressive disease. Many CSF T and B lymphocytes are activated blasts (Noronha et al 1980). B cells are at lower levels than in blood. A high CSF B cell to monocyte ratio in CSF correlates with IgG levels and with rapid disease progression in relapsing and progressive multiple sclerosis (Cepok et al 2001).

Potential biomarkers in CSF, reflecting damage to brain cells and inflammation, include the following: proteins from axon cytoskeleton (neurofilament light chains, present in first multiple sclerosis attacks; neurofilament heavy chains, highest in secondary progressive multiple sclerosis, but present even in clinically isolated syndromes; actin; NAA; tau; and tubulin), neurons and axons (fetuin-A, NOGO receptor), astrocytes (GFAP), membranes (24S-hydroxycholesterol, apoE4, NCAM-1), glia (GFAP, S-100b), endothelial cells (endothelin, e-Selectin, PECAM-1, VCAM-1), immune cells (ICAM-1, cytokines, MMP, GM1 allotype of immunoglobulin), and amyloid precursor protein (Teunissen et al 2009). microRNAs, miR 155, miR 338 and miR 491, which regulate neurosteroid production in the brain are elevated in progressive multiple sclerosis brains; also miR922, miR181c, and miR633 are elevated in CSF and help differentiate between forms of multiple sclerosis.

N-acetyl aspartate (NAA) is abundant enough in neurons (10 mM) to be detectable with magnetic resonance spectroscopy. NAA decreases in CSF during secondary progressive multiple sclerosis as neurons die or lose function. Tau protein, a marker of axonal damage, increases 2-fold in progressive multiple sclerosis but also increases in other inflammatory diseases, and levels correlate with the IgG index. 14-3-3, a neuronal, axonal, and glial protein, is present in 10% of patients with transverse myelitis and multiple sclerosis (de Seze et al 2002). In clinically isolated syndromes, 14-3-3 predicts an earlier conversion to multiple sclerosis. It is also elevated in various dementias after extensive damage of the brain, especially in Creutzfeldt-Jacob disease where levels are high. Reduced ATP metabolites, perhaps reflecting high energy demand, correlate with more severe multiple sclerosis progression. Cystatin C may be uniquely cleaved by endogenous CSF proteases. A high level of myelin basic protein (MBP) in CSF and MBP-like material in the urine reflects damage to myelin and oligodendroglia in progressive multiple sclerosis (Whitaker et al 1995) and correlates with the number of MRI T1 black holes. S-100b protein increases during flares. None of these is diagnostic in itself, but multiplex analysis coupled with reliable assays may be used in the future.

CSF neurotrophic factors also rise during different phases of multiple sclerosis. Neural cell adhesion molecule (N-CAM) and ciliary neurotrophic factor (CNTF) increase in serum during recovery from exacerbations. Nerve growth factor (NGF) sometimes increases during exacerbations, although levels fall as the disease becomes advanced. Dj-1 (PARK7) in astrocytes and neurons stabilizes neuroprotectant Nrf2. Dj-1 is elevated 6-fold in relapsing-remitting Japanese multiple sclerosis versus non-inflammatory disease and correlates well with the multiple sclerosis severity scale (MSSS; r = 0.509) (Hirotani et al 2008). Other growth factors are reduced. Growth hormone, which is neuroprotective and induces insulin-like growth factor-1 and remyelination, is at low levels in the CSF.

Evoked potentials in diagnosis. Evoked potentials are occasionally needed to confirm multiple sclerosis (eg, when MRI and CSF are normal), but they should not be used for the routine diagnosis of multiple sclerosis. The frequency of abnormal evoked potentials in definitive multiple sclerosis is visual=90%, auditory=80%, and somatosensory=70%. Visual evoked potentials become less variable 4 weeks after the onset of optic neuritis and are now quite standardized compared to the pre-MRI era. Visual evoked potentials latency reflects demyelination and has less spontaneous recovery than other visual measures such as fields and acuity. Auditory evoked potentials are seldom helpful in
making the diagnosis. Neurophysiological studies such as vestibular evoked myogenic potentials, multifocal visual evoked potentials, motor (magnetic) evoked potentials, and the P300 event-related potential could also provide information about central nervous system function and prognosis (Leocani and Comi 2000).

**Serum tests in diagnosis.** Erythrocyte sedimentation rate or C-reactive protein, antinuclear and anticytoplasmic antibodies (Cuadrado et al 2000), Sjögren syndrome A and B antibodies, angiotensin converting enzyme, vitamin B12 and methylmalonate, and vitamin D levels should be ordered when appropriate. CRP, a marker for inflammation from many etiologies, has a modest correlation with relapses, progression, and MRI activity.

DNA transcription from many genes is controlled by methylation. Circulating methylated DNA profiles are highly abnormal in multiple sclerosis plasma (Liggett et al 2010).

**Ophthalmologic diagnosis.** The optic neuritis workup is funduscopy, visual acuity, perhaps optical coherence tomography (below), a neurologic examination, MRI, and possibly lumbar puncture. Perimetry shows a scotoma that is typically central or diffuse but sometimes is peripheral. Low-contrast Sloan letter charts are more sensitive than the standard Snellen measure of visual acuity. A loss of one line of low-contrast acuity correlates with a 3 mm2 increase in MRI T2 lesion volume; one line of high-contrast loss correlates with a 6 mm2 increase in MRI T2 lesions (Wu et al 2007). Loss of acuity can also reflect post-geniculate white matter damage.

Visual evoked potentials are often abnormal in the affected eye but return to normal within 2 years in one third of eyes. Visual evoked potentials are more sensitive than optical coherence tomography (Naismith et al 2009). Multiple sclerosis patients with normal visual acuity but no history of optic neuritis will have subclinical optic tract lesions detected with visual evoked potentials (82%), contrast sensitivity (73%), OCT (60%), pupillary light reflex (52%), flight of colors (36%), and color vision (Ishihara plates) (32%) (van Diemen et al 1992; Naismith et al 2009). Low contrast visual evoked potentials stimulation (just as with visual acuity tests) and multifocal visual evoked potentials (which correlate with retinal nerve fiber layer thickness) are more sensitive than conventional tests. Electoretinograms measure macular function. The optic nerve head component of the ERG measures the transition from membrane to saltatory conduction at the optic nerve head, and it is abnormal in multiple sclerosis.

Retinal tomographs (OCT) reproducibly measure retinal nerve fiber layer thickness, retinal ganglion cells, and macular volume. One third of macular volume is from neurons, and macular edema correlates with visual function. OCT can define acute optic neuritis, demonstrate a second lesion in clinically isolated syndromes, and monitor atrophy and progression as a surrogate marker to complement the neurologic examination. OCT usually shows retinal nerve fiber layer thinning 3 to 6 months after optic neuritis. OCT is abnormal in half of the “normal” fellow eyes in multiple sclerosis patients after an episode of optic neuritis. Thinning of retinal nerve fiber layer is faster in optic neuritis eye (69 µm) than in “normal fellow” eye (partially affected, at 95 µm) and healthy control eyes (103 µm) (Trip et al 2006). The temporal quadrant is affected most. Retinal nerve fiber layer loss occurs over time in some patients, even without symptoms of optic neuritis. Retinal nerve fiber layer and total macular volume is lower in progressive multiple sclerosis than in relapsing-remitting multiple sclerosis. The decline is faster in patients with more active disease. Loss is even worse in neuromyelitis optica, where it is more diffuse than in multiple sclerosis and affects the superior and inferior quadrants. However, change over time in multiple sclerosis may be too slow to use OCT as a measure in trials in relapsing/remitting multiple sclerosis.

Ocular nerve cross-sectional area on MRI correlates with retinal nerve fiber layer thickness (r = 0.66). OCT measures do correlate with visual evoked potential amplitude but not with latency. Retinal nerve fiber layer thickness atrophy is associated with motor disability (r = 0.2-0.4) and cognitive problems (r = 0.5) (Toledo et al 2008). Peripapillary retinal nerve fiber layer thickness, and also a composite of [ganglion cells + inner plexiform layers], correlate with cortical gray and caudate atrophy (Saidha et al 2013). However, correlations of RNFL with atrophy of the visual cortex that suggested trans-synaptic degeneration were not compared to atrophy of other cortical areas. Inner nuclear layer thickness correlates with FLAIR lesion volume. With current technology, however, OCT is not a replacement for visual evoked potentials and MRI, especially in clinically isolated syndromes, because it is less sensitive.

MRI studies show multiple cerebral white matter lesions in one fourth to three fourths of optic neuritis patients, depending on the series; most of the MRI lesions involve the visual radiations.

The spinal fluid in idiopathic optic neuritis contains elevated protein, mild lymphocytosis, elevated IgG index, and oligoclonal bands (50% to 70% vs. 95% in multiple sclerosis).
Quality of life scales in diagnosis. Quality of life scales are inexpensive, simple to administer, and measure a wide range of the problems seen in multiple sclerosis (Cella et al 1996; Cella et al 2012). They predict changes in disability and are objective measures of therapeutic outcomes. However, present scales are insensitive and have not contributed to trial monitoring.

Confusion in diagnosis and misdiagnosis. In some patients with clinically definite multiple sclerosis but negative MRI, other techniques such as evoked potentials or magnetic transfer imaging will show damage. When CSF has no oligoclonal bands, as in approximately 3% of patients, prognosis is better and brain MRI lesions are fewer. Four years after a diagnosis of multiple sclerosis, only half of these oligoclonal band-negative patients become positive (Zeman et al 1996). Similarly, one third of patients with one oligoclonal band will eventually develop multiple oligoclonal bands on follow-up (Davies et al 2003).

Incidental, unexpected multiple sclerosis-like lesions on an MRI scan, without symptoms or signs of multiple sclerosis, are often referred to neurologists (radiologically isolated syndrome). Autopsy studies mentioned above show a significant reservoir of undetected multiple sclerosis. However, multiple sclerosis-like MRI lesions could be from vascular disease, tumor, and possibly migraine headache; strokes without overt symptoms are 5 times as common as symptomatic strokes—the same ratio as in multiple sclerosis. Nonetheless, in 30 patients with incidental brain MRI lesions, 23 (77%) developed new MRI lesions by 6 months, and 11 (37%) had clinical conversion to multiple sclerosis (Lebrun et al 2008). In 41 patients (7 treated) followed for 2.7 years, 59% had new MRI lesions; 30% had clinical attacks at a median time of 5.4 years (Okuda et al 2009). Male sex doubles the chance of a second attack; cervical or thoracic lesions triple the risk. A quarter of radiologically isolated syndrome patients have cognitive impairment, 40% have frontotemporal cortical MRI lesions, and N-acetylaspartate levels are 2 standard deviations below normal in normal-appearing white matter (in 44% of radiologically isolated syndrome) and cortex (61%) (Stromillo et al 2013). Asymptomatic cord lesions, present in one third of patients with these brain lesions, predict a future attack or progression in 80%. Thus, early treatment is reasonable for some cases with MRI lesions only, but commitment to a therapy after a misdiagnosis is a danger.

MRI lesions can lead to MRI-supported misdiagnosis of multiple sclerosis. Patients may be treated with expensive and dangerous drugs, “therapeutic mislabeling.” Reluctance to reverse the misdiagnosis by neurologists raises ethical issues because continued therapy does not provide full disclosure of a patient’s condition.

Imaging is expensive and can lead to decisions that are not evidence-based. MRI-based decisions to change treatment to another partially effective therapy should be made with caution in patients with definite multiple sclerosis (eg, one new lesion after years of clinically stable disease). Premature termination of a quite effective therapy in this highly variable disease can potentially harm patients. Baseline activity can’t be ignored as it predicts future multiple sclerosis activity. For example, a patient who had 20 new lesions per year before therapy and who then has one new lesion per year and no clinical attacks should not be called a “non-responder” to therapy. Personalized medicine versus evidence-based decisions are discussed by Caplan (Caplan 2011).

A diagnosis of multiple sclerosis should be judiciously questioned when there are “red flags” such as:

- No eye findings (optic nerve or motility) or conversely, prominent uveitis or retinitis
- No remissions
- Localized disease
- Repeated episodes in the same part of the CNS
- Atypical clinical features: aphasia, altered consciousness, connective tissue disease symptoms, extrapyramidal symptoms, fevers, homonymous visual field defects, third nerve palsy, no fatigue or heat sensitivity, no long tract findings, no sensory or bladder symptoms, no constipation, progressive myelopathy without bladder involvement, peripheral neuropathy, late (older than 60 years) or early age of onset
- Very high sedimentation rate or CRP
- Normal CSF and no oligoclonal bands (Rudick et al 1986); high white count greater than 50 cells/µl or protein higher than 100 mg/dl
• Normal MRI of brain and spinal cord, or atypical MRI with small lesions (less than 3 mm), basal ganglia or internal capsule involvement, bilateral “mirror image” lesions, diffuse confluent white matter lesions, or longitudinal cord lesions spanning more than 2 vertebral segments.

These red flags should prompt confirmatory tests for multiple sclerosis, such as CSF analysis, evoked potentials, and eye OCT. In the absence of objective evidence for multiple sclerosis or other disease, follow-up investigations should be kept to a minimum.

**Special considerations**

**Pregnancy**

Pregnancy is as potent as any available therapy for multiple sclerosis. The exacerbation rate during pregnancy at 0.14 per year is less than baseline at 0.36 per year and is approximately 70% lower in the third trimester. The severity and rate of attacks increase during the 3 to 6 months postpartum (to 1.00 attacks per year) (Roulet et al 1993; Damek and Shuster 1997). The average exacerbation rate during the entire year (pregnancy and postpartum period) is equivalent to the baseline rate. Mothers who smoke while pregnant have a 3-fold increased risk of having children who will develop multiple sclerosis (Mueller et al 2013).

Multiple sclerosis is unlikely to appear de novo during pregnancy. Pregnancy decreases the later risk of a progressive course (Runmarker and Andersen 1995). Each baby and each further birth reduces the risk of multiple sclerosis by 50% (Ponsonby et al 2012). The decline in family size and later age at first birth may be linked to the increasing frequency of multiple sclerosis in women.

The decline in exacerbations during pregnancy is presumably due to a shift from Th1 to Th2 type immunity and to immunosuppressive factors such as IL-10 that prevent rejection of the placenta and fetus. Treg cells decline during pregnancy, suggesting that they are of little consequence in multiple sclerosis. Estrogens are also important, and include estrone (E1, with one OH group), estradiol (E2), and estriol (E3), which is being studied as a treatment for multiple sclerosis. Estriol has 1/50th the estrogenic effect of estradiol but appears to have stronger effects on immunity. Estriol progressively increases during pregnancy. The progesterone/17-beta-estradiol ratio falls during the third trimester of pregnancy, when clinical activity is low. A rebound in immune function after delivery exacerbates disease activity.

In vitro fertilization increases risk of exacerbation 7-fold and MRI activity 9-fold (Correale et al 2012). Gonadotrophin-releasing hormone induced IL-8, IL-12, TGF-beta, and IFN-gamma and facilitated transmigration across a blood-brain barrier model. It also induced 17-beta-estradiol, which increased anti-MOG antibody titers but did not affect cytokines. Interferon therapy enhances fertility, perhaps by enhancing implantation (Reeder and Feng 2014).

Female hormones affect disease activity; 82% of women report worse symptoms before menses (Smith and Studd 1992). The progesterone/17-beta-estradiol ratio increases during the luteal phase of the menstrual cycle, and this corresponds to higher MRI activity (Pozzilli et al 1999). MRI activity increases during ovulation when estradiol is high and progesterone is low (Bansil et al 1999). Catamenial symptoms improve with aspirin, and this does not appear to be from effects on body temperature. Birth control pills tend to reduce the incidence of multiple sclerosis in some studies.

Fifty-four percent of women have worse symptoms during menopause, and 75% feel symptoms improve with hormone replacement therapy of menopausal gonadotropin at very levels; effects may parallel those of in vitro fertilization. Progression may be more rapid at menopause. Menopause and removal of ovaries cause low-grade systemic inflammation, which can be prevented with low-dose estrogen replacement (Abu-Taha et al 2009). A small clinical trial suggests that estriol decreases relapses and MRI lesions.

Breastfeeding, which elevates prolactin, has no effect on the exacerbation rate in most studies (Nelson et al 1988). Some women breastfeed for several days after delivery and then stop in order to begin an immunomodulatory drug; these women are more likely to have had active disease before or during pregnancy. (Breast-pumping for 5 hours after injections to clear interferon from milk is described at the end of the interferon section.)

Mothers with multiple sclerosis in Norway had babies with slightly lower birth weights (Dahl et al 2005). They also needed more frequent induction and interventions during delivery but had no increase in birth defects or mortality.
Perhaps confounding the data, these mothers were two years older than the control group. Other studies show similar trends for adverse delivery outcomes in women with severe disability (Franklin and Tremlett 2009), but duration of hospitalization is not longer.

Multiple sclerosis therapies are classified as pregnancy category B (glatiramer), C (fingolimod, fumarate, interferons, natalizumab, alemtuzumab), X (teriflunomide), and D (mitoxantrone). Glucocorticoids rarely cause orofacial malformations. Interferons and glatiramer do not affect risk of fetal loss, although IFN-beta causes slightly smaller babies. IFN-beta and glatiramer should not cross the placenta; natalizumab does not in the early trimesters. However, fingolimod can cause cardiac malformations and teriflunomide is teratogenic for many organs. Both have long half-lives and cross the placenta. Dimethyl fumarate crosses the placenta but has a shorter half-life and causes small babies with delayed bone formation (Langer-Gould 2014).

Anesthesia

General anesthesia has no effect on multiple sclerosis (Bamford et al 1978). Direct trauma to the spinal cord or brain, barbotage, or intracerebral electrodes may predispose to lesions (Poser 1986), but there are also reports of multiple sclerosis patients with direct brain trauma and surgery that did not cause any plaque formation (Riechert et al 1975). Recent experience suggests that brain biopsy and thalamic stimulation do not induce plaques.

References cited


Banwell BL. Pediatric MS. Curr Neurol Neurosci Rep 2004;4:245-52. PMID 15102351


Clifford DB, Trotter JL. Pain in MS. Arch Neurol 1984;41:1270-2. PMID 6208884


Constantinescu CS. Melanin, melatonin, melanocyte-stimulating hormone, and the susceptibility to autoimmune demyelination: a rationale for light therapy in MS. Med Hypotheses 1995;45:455-8. PMID 8748085


Franklin GM, Tremlett H. MS and pregnancy: what should we be telling our patients. Neurology 2009;73(22):1820-2. PMID 19923551


Fuhr P, Borggreve-Chappuis A, Schindler C, Kappos L. Visual and motor evoked potentials in the course of MS. Brain
Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in MS. Muscle Nerve 2003;27:456-64. PMID 12661047


Gilbert JJ, Sadler M. Unsuspected MS. Arch Neurol 1983;40:533-6. PMID 6615282


Goodin DS, Reder AT, Cutter G. Treatment with interferon beta for multiple sclerosis. JAMA 2012a;308(16):1627; author reply 1627-8. PMID 23093155

Goodin DS, Reder AT, Ebers GC, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial. Neurology 2012b;78(17):1315-22. PMID 22496198

Goodkin DE, Hertsgaard D, Rudick RA. Exacerbation rates and adherence to disease type in a prospectively followed-up population with MS. Arch Neurol 1989;46:1107-12. PMID 2679508

Goodkin DE, Rooney WD, Sloan R. A serial study of new MS lesions and the white matter from which they arise. Neurology 1998;51:1689-97. PMID 9855524


Hamamcioglu K, Reder AT. Interferon-beta regulates cytokines and BDNF: greater effect in relapsing than in progressive MS. Mult Scler 2007;13(4):459-70. PMID 17463069


Hedstrom AK, Akerstedt T, Hillert J, Olsson T, Alfredsson L. Shift work at young age is associated with increased risk for MS. Ann Neurol 2011;70(5):733-741. PMID 22006815


Hulst HE, Schoonheim MM, Roosendaal SD, et al. Functional adaptive changes within the hippocampal memory system of patients with MS. Hum Brain Mapp 2012;33(10):2268-80. PMID 21898674

Ishizu T, Osoegawa M, Mei F, et al. Intrathecal activation of the IL-17/IL-8 axis in opticospinal MS. Brain 2005;128:988-1002. PMID 15743872


Kampman MT, Steffensen LH. The role of vitamin D in MS. J Photochem Photobiol B 2010;101(2):137-41. PMID 20471852


of impaired emotional reactivity. Ann Neurol 2004;56:787-95. PMID 15468096


Kurtzke JF. A reassessment of the distribution of MS. Acta Neurol Scand 1975;51:110-36. PMID 46682


McDonald WI, Barnes D. Lessons from magnetic resonance imaging in MS. Trends Neurosci 1989;12:376-9. PMID 2479134


Medaer R. Does the history of MS go back as far as the 14th century. Acta Neurol Scand 1979;60:189-92. PMID 390966


Noronha A, Richman DP, Arnason BG. Detection of in vivo stimulated cerebrospinal fluid lymphocytes by flow


Phadke JG. Clinical aspects of MS in north-east Scotland with particular reference to its course and prognosis. Brain 1990;113:1597-628. PMID 2276037


Rinker JR 2nd, Trinkaus K, Naismith RT, Cross AH. Higher IgG index found in African Americans versus Caucasians with MS. Neurology 2007;69:68-72. PMID 17606883


Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in MS. Brain 1995;118:253-61. PMID 7895009


Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in MS. Neurology 2011;77(13):1246-52. PMID 21917763


Stadelmann C, Ludwin S, Tabira T, et al. Tissue preconditioning may explain concentric lesions in Balo's type of MS.


Strasser-Fuchs S, Enzinger C, Ropele S, Wallner M, Fazekas F. Clinically benign MS despite large T2 lesion load: can we explain this paradox. Mult Scler 2008;14:205-11. PMID 17986507


Thompson EJ, Freedman MS. Cerebrospinal fluid analysis in the diagnosis of MS. Adv Neurol 2006;98:147-60. PMID 16400832


Trip SA, Schlottmann PG, Jones SJ, et al. Optic nerve atrophy and retinal nerve fibre layer thinning following optic neuritis: evidence that axonal loss is a substrate of MRI-detected atrophy. Neuroimage 2006;31:286-93. PMID 16446103


Warabi Y, Matsumoto Y, Hayashi H. Interferon beta-1b exacerbates MS with severe optic nerve and spinal cord demyelination. J Neurol Sci 2007;252:57-61. PMID 17125797


Whetten-Goldstein K, Sloan FA, Goldstein LB, Kulas ED. A comprehensive assessment of the cost of MS in the United
States. Milt Scler 1998;4:419-25. PMID 9839302


Wood DD, Bilbao JM, O'Connors P, Moscarello MA. Acute MS (Marburg type) is associated with developmentally immature myelin basic protein. Ann Neurol 1996;40:18-24. PMID 8687186


Zivadinov R, Bakshi R. Role of MRI in MS II: brain and spinal cord atrophy. Front Biosci 2004;9:647-64. PMID 14766398

**References especially recommended by the author or editor for general reading.

**ICD and OMIM codes

**ICD codes

ICD-9:
Multiple sclerosis: 340

ICD-10:
Multiple sclerosis: G35

**OMIM numbers

Multiple sclerosis: #126200

**Profile

**Age range of presentation

06-12 years
13-18 years
19-44 years
45-64 years

**Sex preponderance

female>male, >2:1 and ratio is increasing for the past 50 years, now up to 3.2:1 in Canada (Orton et al 2006)

**Family history

family history may be obtained
**Heredity**

heredity may be a factor

**Population groups selectively affected**

Caucasians
Northern Europeans

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

3-Methylglutaconic aciduria type I
Acute disseminated encephalomyelitis
Acute necrotizing hemorrhagic leukoencephalitis
Adrenoleukodystrophy
Adrenomyeloneuropathy
Alexander disease
Antiphospholipid antibody syndrome
Atopic myelitis, Idiopathic eosinophilic myelitis, HyperIgEaemic myelitis
Autoimmune thyroid encephalopathy
Balo concentric sclerosis
Behcet disease
Brainstem encephalitis
CADASIL
Canavan disease
Carbon monoxide poisoning
Carotid transient ischemic attacks
Cavernous malformations of the brainstem
Celiac disease (gluten ataxia)
Cerebral infarction (multiple)
Cerebrotendinous xanthomatosis
Cervical spondylotic myelopathy
Charcot-Marie-Tooth disease
Chiari malformation
Chlamydia
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyradiculoneuropathy with optic neuritis
Cogan syndrome
Congenital adrenal hyperplasia
Conversion disorder
Copper deficiency myelopathy (human swayback)
Creutzfeldt-Jacob disease
Cysticercosis
Devic disease
Eales disease
Episodic ataxia/Familial paroxysmal ataxia
Erdheim-Chester histiocytosis
Folate deficiency
Friedreich ataxia
Gliomatosis cerebri
Granulomatous angiitis
Guillain-Barré Syndrome, Fisher variant
Hashimoto encephalopathy
Hemophagocytic lymphohistiocytosis
HIV encephalopathy
HTLV-1 associated myelopathy
Ischemic optic neuropathy
Leber hereditary optic neuropathy
Lyme disease
Mad cow disease (variant spongiform encephalopathy)
Marburg variant of MS
Metachromatic leukodystrophy
Migraine (with multiple infarcts or MRI lesions)
Mitochondrial disorders
Myasthenia gravis
Myelinoclastic diffuse sclerosis
Myotonic dystrophy types 1 and 2
Neurofibroma
Neurologic disorders related to chemical and biological warfare agents
Neuromyelitis optica
Neurosarcoidosis
Neurosyphilis
Paraneoplastic limbic encephalitis, cerebellar degeneration, polymyoclonus/opsoclonus
Peroxisomal disorders
Post-chemotherapy leukoencephalopathy (see Neurologic complications of chemotherapy)
Postinfectious encephalomyelitis (see Acute disseminated encephalomyelitis)
Postpartum reversible posterior leukoencephalopathy (see Central neurologic complications of pregnancy)
Postvaccinal encephalomyelitis (see Acute disseminated encephalomyelitis)
Primary central nervous system lymphoma
Progressive multifocal leukoencephalopathy
Progressive necrotizing myelopathy (see Transverse myelitis)
Pseudoxanthoma elasticum
Schilder disease
Sjögren syndrome, including CNS Sjögren disease
Sjögren-Larsson syndrome
Spinal infarction (see Vascular disorders of the spinal cord)
Spinal meningioma
Subacute combined degeneration (see Vitamin B12 deficiency)
Subacute sclerosing panencephalitis
Susac syndrome
Syringomyelia or syringobulbia
Systemic lupus erythematosus
Transverse myelitis
Tropical spastic paraparesis
Tuberculosis of the central nervous system
Vasculitis (see Vasculitides presenting with dementia, Drug-induced cerebrovascular disease, Wegener granulomatosis, Cogan syndrome, Churg-Strauss syndrome)
Venous sinus thrombosis (see Cerebral venous thrombosis)
Vertebrobasilar transient ischemic attacks
Viral encephalitis
Vitamin B12 deficiency
Vitamin E deficiency (see Vitamin E in neurologic disorders)
Whipple disease
Wilson disease (cerebellar and brainstem)

Associated disorders

Optic neuritis
Pars planitis (peripheral uveitis)
Seizure disorder
Transverse myelitis
Trigeminal neuralgia
Uveitis

Other topics to consider

Affective disorders in neurologic disease
Baclofen
Clinical trials in neurology
Fatigue in multiple sclerosis
Glatiramer acetate
Hiccups
Interferon beta 1a
Interferon beta 1b
Intravenous immune globulin
Mitoxantrone
Multiple sclerosis: neurobehavioral aspects
Natalizumab
Sleep and multiple sclerosis
Spasticity
Vaccines for neurologic disorders

Copyright© 2001-2017 MedLink Corporation. All rights reserved.