CHAPTER 32

Multiple Sclerosis

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Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS), which predominantly affects white matter, though gray matter involvement also occurs. It is a progressive neurodegenerative condition; early axonal loss has been identified.[1] MS causes demyelination and scarring of myelin, resulting in plaques visible on MRI and in histopathologic specimens. The manifestations of the disease vary from an insidious progressive to a rapidly progressive and disabling illness that has a profound effect on physical function and quality of life.[2] See Figure 32-1.

The classification of MS is based on its variable clinical courses (see Table 32-1). These courses are defined by periods of relapse, remission, and chronic progression.[4] The etiology of MS is unknown, although it is hypothesized that a virus may precipitate an autoimmune response in a genetically susceptible individual with certain environmental exposures. MS has been called the disease of young adults because the highest rate of incidence is between the ages of 20 and 50 years. In fact, it is the most common nontraumatic cause of neurologic disability in young adults.[5] Recent research suggests that low vitamin D levels, smoking, and Epstein–Barr virus infections are associated with increased risk of MS.[6]

There are more than 4,00,000 cases of MS in the United States,[1] with women being affected at least three times as frequently as men. Whites are affected more frequently than any other racial group. The lifetime risk of MS in the general population is approximately 0.1%, but children of a parent with MS have a 3% risk, thus supporting genetic susceptibility theories. There have been many susceptibility loci identified through genetic studies in recent years.[6] Epidemiologic studies report that MS is more prevalent in the colder northern latitudes, though there may be an attenuation in latitude gradient that suggests other environmental associative factors. In general, MS is more common in Europe, the United States, Canada, New Zealand, and Southern Australia than in more tropical regions. Moving to a warmer climate before the age of 15 years confers a lower risk of climate influence.

The course of MS is unpredictable even within each subtype. Cohort studies have provided broad prognostic factors. Younger age at onset, female gender, monosymptomatic presentation, complete relapse recovery, long interval between first and second relapses, few relapses, and a relapsing rather than a progressive course are factors associated with a better prognosis. In addition to male gender, poorer prognosis is associated with age of onset over 40 years; initial presentation of motor, cerebellar, or sphincter symptoms or polysymptomatic presentation; frequent attacks in the first 5 years; and a short interval between attacks.[6]

PATHOGENESIS AND PATHOPHYSIOLOGY

The inflammation in the brain and spinal cord in MS begins because of a complex interplay of genetic, environmental, and immunologic factors. The traditionally accepted model of inflammation is based on the animal model of experimental autoimmune encephalitis (EAE). It begins with peripheral activation and proliferation of T cells by an antigen-presenting complex (APC) in the periphery, causing the expression of inflammatory cytokines and matrix metalloproteinases (MMPs). MMPs disrupt the blood–brain barrier, allowing proinflammatory cells (T cells, B cells, and macrophages) to enter the CNS. Once inside the CNS, T cells are reactivated by myelin antigens. Inflammation continues with recruitment of other cytokines, causing demyelination and axonal loss. B cells are also involved, secreting antibodies directed against myelin. These antibodies are found in the CSF and are called oligoclonal bands. The suspected mechanism of action (MOA) of current disease-modifying therapies is a shift from proinflammatory T cells, interleukins, and other cytokines, to an anti-inflammatory milieu.[4]

The pathologic hallmark of MS is demyelinated lesions or plaques, which are sharply demarcated areas easily distinguishable from surrounding white matter.[2] They appear as bright spots on T2-weighted MRI images (see Fig. 32-2). Newer MRI techniques have exposed MS lesions in gray matter. The composition of a lesion varies depending on its age. In an acute lesion, there is partial or complete damage to the myelin, called *vesicular demyelination.* The damage consists of a breakdown of the myelin sheath that surrounds axon cylinders. As the lesion evolves, there is a proliferation of astrocytes and oligodendrocytes (myelin-producing cells), although many oligodendrocytes are destroyed by the cellular infiltrates of T cells and macrophages. Acute MS plaques will be seen as bright white lesions on T1-weighted gadolinium (contrast)-enhanced MRI images (see Fig. 32-2). The surviving oligodendrocytes may partially remyelinate the affected areas. Long-standing lesions are composed of thick, matted, relatively acellular fibroglial tissue. Long-standing lesions may appear as dark areas, sometimes termed "black holes," on T1-weighted MRI images (Fig. 32-2). Wallerian degeneration does occur in MS as axonal transection is present even early in the disease. Axonal loss is visible in normal-appearing white matter of histopathological specimens.[4] Lesions have an affinity for the optic nerves, periventricular white matter, brainstem, cerebellum, and spinal cord white matter. The plaques vary in diameter from 1 to 2 mm to several centimeters.[7]

MS affects primarily the white matter of the brain and spinal cord by causing scattered, demyelinated lesions, preventing or impeding conduction of normal nerve impulse through the demyelinated

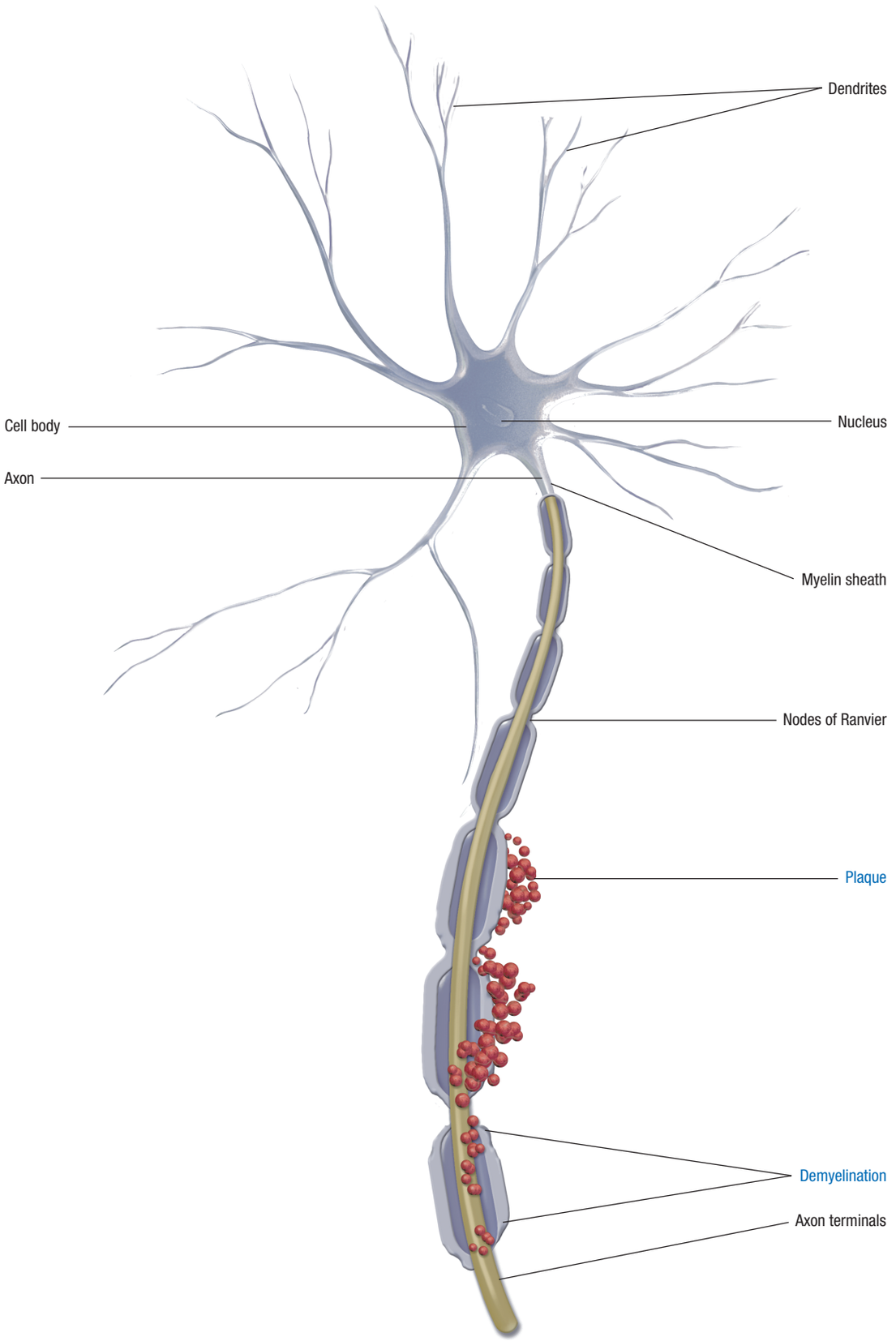

Figure 32-1 ■ Myelin destruction in multiple sclerosis. Asset provided by Anatomical Chart Co.

TABLE 32-1 FOUR CATEGORIES OF MULTIPLE SCLEROSIS (MS) BASED ON CLINICAL COURSE

TYPE	DESCRIPTION
Radiologically isolated syndrome (RIS)	Incidental brain MRI findings suggestive of demyelinating disease in patients who had brain imaging for reasons other than the suspicion of MS.[3]
Clinically Isolated Syndrome (CIS)	A single neurologic episode consistent with CNS inflammation or demyelination; may be monofocal or multifocal; examples include optic neuritis, transverse myelitis, and brainstem or cerebellar syndromes; a high risk of developing MS is present.
Relapsing–remitting MS (RRMS) (80% of all cases)	Characterized by recurrent attacks of neurological dysfunction which evolve over days to weeks and may be followed by complete, partial, or no recovery; there is no progression of symptoms between attacks; this pattern is often seen in the early course of the disease and is the most common form seen.
Secondary progressive MS (SPMS)	Gradual neurological deterioration with or without acute relapses, minor remissions, and plateaus in a patient who previously had RRMS.
Progressive-relapsing MS (PRMS)	From the onset, there is gradual progression of disability; unlike RRMS, there is continuing disease progression without stabilization of the disease
Primary progressive MS (PPMS)	A pattern of gradual neurological deterioration from the onset of symptoms, but with superimposed relapses noted.

zone. Conduction blocks occur when the nerve impulse is unable to move across a demyelinated segment. This is caused by a resting axon membrane that becomes hyperpolarized due to the exposure of voltage-dependent potassium channels (normally located under the myelin sheath). A temporary conduction block often follows a demyelinating event before the sodium channels (originally concentrated at the nodes) have undergone a redistribution that allows the continuous propagation of nerve action potentials through the demyelinated segment. However, the leakage currents are too large for the nerve impulse to jump the internode distance and conduction fails.[1] These variations in conduction help to explain the variations in symptoms that occur with MS throughout a day or a week and in relationship to activity or illness.

Remission or improvement of symptoms may occur with MS as the result of healing or in response to the conclusion of an acute inflammatory event. Eventually, the axonal cylinder of the neuron may become affected, so that disabilities increase and become permanent, or symptoms worsen. At autopsy, MS plaques are scattered throughout the white matter of the brain and cord. Plaque distribution differs from patient to patient, accounting for the variety of symptoms experienced by patients. Some cases of MS are clinically silent, and the presence of the disease process is identified incidentally at autopsy, or when MRI imaging of the brain or spinal cord is performed for another reason.

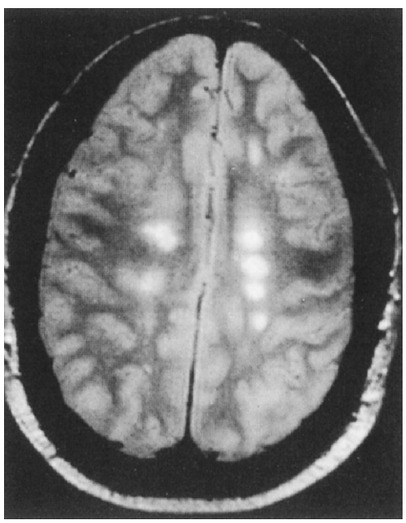

Figure 32-2 ■ Axial T2-weighted image shows ovoid hyperintense lesions in both hemispheres.

Signs and Symptoms

The signs and symptoms of MS vary greatly from patient to patient and can vary over time in the same patient. The most common initial symptoms are sensory loss (37%), optic neuritis (36%), weakness (35%), paresthesias (24%), diplopia (15%), ataxia (11%), and vertigo (6%).[8] Other symptoms mentioned below may occur paroxysmally throughout the course of disease or with a relapse. The multiple signs and symptoms of MS may include the following.

- **Sensory symptoms:** numbness or sensory loss; paresthesia (burning, prickling, tingling); pain; decreased proprioception and perception of temperature, depth, and vibration.
- **Motor symptoms:** paresis, paralysis, dragging of foot; spasticity; diplopia; bladder and bowel dysfunction (incontinence or retention).
- **Cerebellar symptoms:** ataxia; loss of balance and coordination; nystagmus; speech disturbances (dysarthria, dystonia, scanning speech, slurred speech); tremors (intentional tremors, described as tremors that increase when a purposeful act is initiated); vertigo.
- **Other symptoms:** fatigue; optic neuritis; eye movement disorders; tremor; respiratory disturbance; dysphagia; sleep disorders; neurogenic bowel or bladder; impotence or decreased genital sensation and sexual dysfunction; cognitive dysfunction; neurobehavioral disorders such as depression, anxiety, or euphoria. Less common symptoms include tonic spasms, visual loss, trigeminal neuralgia, facial palsy, and impotence.

Sensory Symptoms

Sensory loss and tingling on the face or involved extremities are common and may be painful. Loss of proprioception and joint sensation may be accompanied by edema of the limb or feelings of constriction. Fifty percent of patients develop objective sensory loss (position, vibration, shape, texture). Pain is not uncommon; it can be complex and either acute or chronic. **Lhermitte's sign** is described as an electric or shock-like sensation that extends down the arms, back, or lower trunk bilaterally upon flexion of the neck.

The sensation probably results from the buckling effect on the dorsal roots of the posterior columns from sclerotic plaques, and is an example of acute pain. Chronic pain can be related to dysesthesias, band-like pain around the torso or limbs, musculoskeletal conditions or radiculopathies, or headache. Sensory symptoms can contribute to disorders of gait and balance.

Motor Symptoms

Motor symptoms often begin with weakness in an extremity and complaint of a feeling of heaviness or uselessness of the involved limb. Hemibody weakness or paraparesis may occur. Spasticity, with its usual concurrent hyperreflexia, is common. The presence of spasticity often interferes with ambulation, ADLs, and sleep. The decline in motor function may last from minutes to hours and is therefore not always observed by the physician. Motor function can worsen spontaneously after strenuous exercise, fever, or a hot shower or hot tub bath. This response is called **Uhtoff's phenomenon**, and is thought to be due to heat-related nerve conduction block.

Incoordination is another frequent symptom and may be manifested on examination as ataxia of the limbs or tremor. Various types of tremors may occur in MS with the upper extremities usually affected. An **action tremor** (previously called intentional tremor), produced by voluntary muscle contraction, is the most commonly reported type. The finer the required movement, the greater the tremor will be…Spastic weakness or ataxia of the muscles of speech is responsible for the dysarthria common in MS. Speech may be slurred (dysarthric). In later stages, speech may be explosive or staccato and unintelligible. **Scanning speech**—slow and measured with pauses between syllables—is seen sometimes with bulbar involvement, if cerebellar ataxia is prominent.

Ocular, Vestibular, and Auditory Symptoms

Optic neuritis, a common presenting event, is evidenced by visual clouding, visual field (often central) deficits, and pain with eye movement; pallor of the optic discs is usually noted. Optic neuritis may cause optic neuropathy, or permanent visual loss to varying degrees, but good visual acuity is usually regained after the first attack. Measurement of decreased retinal nerve fiber layer thickness by optical coherence tomography and abnormal visual evoked potentials may occur even in individuals without a history of optic neuritis. On examination, a patient may have an afferent pupillary defect, also known as a *Marcus Gunn pupil.*

Diplopia and **nystagmus** are common as a result of brainstem lesions. Internuclear ophthalmoplegia of lateral gaze, when noted, strongly suggests MS. **Vertigo** is a common symptom usually noted as instability of gait or sensations of movement. Vomiting and nystagmus can accompany the vertigo. Deafness is a rare finding.

Paroxysmal Symptoms

Paroxysmal symptoms, which are less common but can occur in MS, include focal or generalized epilepsy, tonic seizures, trigeminal neuralgia, and occasionally, paroxysmal (tonic) spasms. The spasms are described as contractions of the hands or feet into a dystonic, sustained, abnormal position and can be very painful.

Neurobehavioral Disorders

Neurobehavioral disorders associated with MS include emotional lability (pseudobulbar affect), irritability, apathy, inattentiveness, poor judgment, euphoria, dementia, and cognitive impairment. Depression is very common occurring in 30% to 50% of patients. Less common are extreme anxiety, bipolar disease, and psychosis.

Other Symptoms

Fatigue is a very common symptom in MS, can range from mild to severe disabling, and is often the reason people with MS leave the workforce. The basis for fatigue is unknown. Bladder, bowel, and sexual dysfunction are common. Bladder dysfunction is caused by detrusor hyperreflexia (failure to store), detrusor sphincter dyssynergia (failure to empty), or a combination of the two. Constipation is the most common bowel complaint, with fecal incontinence occurring less frequently. Sexual dysfunction is caused by loss of sensation; fatigue, weakness, pain, or spasticity in the legs; erectile dysfunction and/or ejaculatory dysfunction in men; loss of lubrication and/or orgasm in women; medication side effects; psychologic effect; or loss of libido.

Course of the Illness

The course of MS (see Table 32-1) is varied and unpredictable. Symptom clusters have been noted when a particular area of the brain is involved. For example, **Charcot's triad**, which includes nystagmus, intentional tremors, and staccato speech, occurs with brainstem involvement. Typically, MS is a disease manifested by periods of relapse and remission early, with gradual accumulation of disability later. Conversion from RRMS to SPMS occurs in about 25 years for 79% of people. Periods of remission are interspersed with paroxysmal increases in symptom severity or neurologic symptoms that are present daily. Events that may precipitate increased symptomatic complaints include menstruation, emotional stress, humid, hot weather; hot baths, heat exposure or overheating due to activity, fever, and fatigue.

A relapse, also called an attack or an exacerbation, is defined as a new neurologic symptom, or worsening of an existing previously stable symptom, lasting for more than 24 hours and not having an alternative explanation for its cause. A pseudorelapse is a worsening of an existing symptom that is referable to infection, fatigue, fever, heat exposure, or over exertion. Relapses last a few days to a few weeks, after which there is complete or incomplete reversal of symptoms. Deficits present after 3 months are usually permanent. Pseudorelapses resolve with treatment of the underlying condition. Prediction of when the next relapse will occur is impossible. Some patients may experience another attack in a few weeks, whereas others may be spared for many years. The average number of relapses per year has been estimated between 0.1 and more than 1.

MS does not affect a woman's fertility or pregnancy outcome. In fact, women with MS typically do not have relapses during pregnancy because of changes in hormone levels and circulating proteins. There is an approximate 20% to 40% risk of relapse in the first trimester postpartum. In general, risk of relapse following pregnancy is related to the degree of disease activity before becoming pregnant.[9] Relapse postpartum have not been associated with an increased risk of long-term disability. The effect of pregnancy on MS has led to modern studies of the effects of hormones on the course of the disease. Pregnancy should be discussed carefully with a woman who has either severe disease related to frequent exacerbations or significant disability. Women of childbearing age should be counseled that the majority of the medications used to modify the disease and to treat its symptoms are not safe for use during

pregnancy. Family planning discussions are important for these reasons.

Clinical Pearl: MS is usually characterized by periods of relapse and remission, however, symptoms of MS may occur daily, and disease progression occurs over time.

Diagnosis

The neurological history and examination are cornerstones for diagnosis along with imaging studies. The MRI, especially with gadolinium enhancement, has revolutionized the diagnosis of MS. Different MR imaging techniques show chronic lesions, areas of acute inflammation, atrophy, and areas of tissue loss. MRI is useful not only for initial diagnosis, but also for monitoring changes during treatment. The Schumacher criteria and revised McDonald criteria are the commonly used criteria for diagnosis of MS.[10,11] The Schumacher criteria are based on the neurological history and examination and includes the following.

- Neurological examination that reveals objective abnormalities attributable to the CNS
- White matter involvement
- Two or more sites of CNS involvement
- Relapsing–remitting or chronic (>6 months) progressive course, each lasting 24 hours and at least 1 month apart, or a gradual or stepwise progression over at least 6 months
- Age at onset of 10 to 50 years
- No better explanation of symptoms

The McDonald criteria, published in 2000 and revised in 2005 and 2010, are based on the number of clinical attacks, and the number, location, and timing of objective lesions noted on MRI (Table 32-2). In some cases, cerebrospinal fluid (CSF) findings are used to support the diagnosis. The 2010 revision of the McDonald criteria, developed through the consensus of the International Panel on the Diagnosis of MS, is currently the most commonly used diagnostic criteria.[11] See Figure 32-3.

MRI and Evoked Potentials

The MRI is a sensitive diagnostic test and has greatly improved the ability to make an accurate and early diagnosis of clinically isolated syndrome (CIS) or MS. Multiple hyperintense lesions, which are best seen on the T2-weighted images, represent multiple plaques in MS (see Fig. 32-2). Gadolinium-enhanced lesions represent areas of acute inflammation. Hypointense lesions on T1-weighted images represent tissue loss. Newer MRI techniques are allowing scientists to evaluate the presence of MS in gray matter, as well as determine better ways to measure brain atrophy. Evoked potential assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways. In MS, evoked potentials are characterized as slow or abnormal conduction patterns on visual, auditory, somatosensory, or motor pathways. Visual evoked potentials are evaluated most frequently.

TABLE 32-2 2010 REVISED MCDONALD MULTIPLE SCLEROSIS DIAGNOSTIC CRITERIA[12]

Diagnosis of MS requires elimination of more likely diagnoses and demonstrations of dissemination of lesion in space (DIS) and time (DIT)

CLINICAL (ATTACKS)	LESIONS	ADDITIONAL CRITERIA TO MAKE DIAGNOSIS
2 or more	Objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack.	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	DIS; or await further clinical attack implicating a different CNS site
1	Objective clinical evidence of ≥2 lesions	DIT; or await a second clinical attack
1	Objective clinical evidence of 1 lesion	DIS or await further clinical attack implicating a different CNS site and DIT; or await a second clinical attack
0		One year of disease progression (retrospective or prospective) and at least two of DIS in the brain based on ≥1 T2 lesion in periventricular, juxtacortical, or infratentorial regions; DIS in the spinal cord based on ≥2 T2 lesions; or positive CSF.

Paraclinical Evidence In MS Diagnosis	
Evidence for dissemination of lesions in space (DIS) ≥1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord. • Gadolinium enhancement of lesions is not required for DIS • If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count	Evidence for dissemination of lesions in time (DIT) • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.
Evidence for positive CSF Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index	

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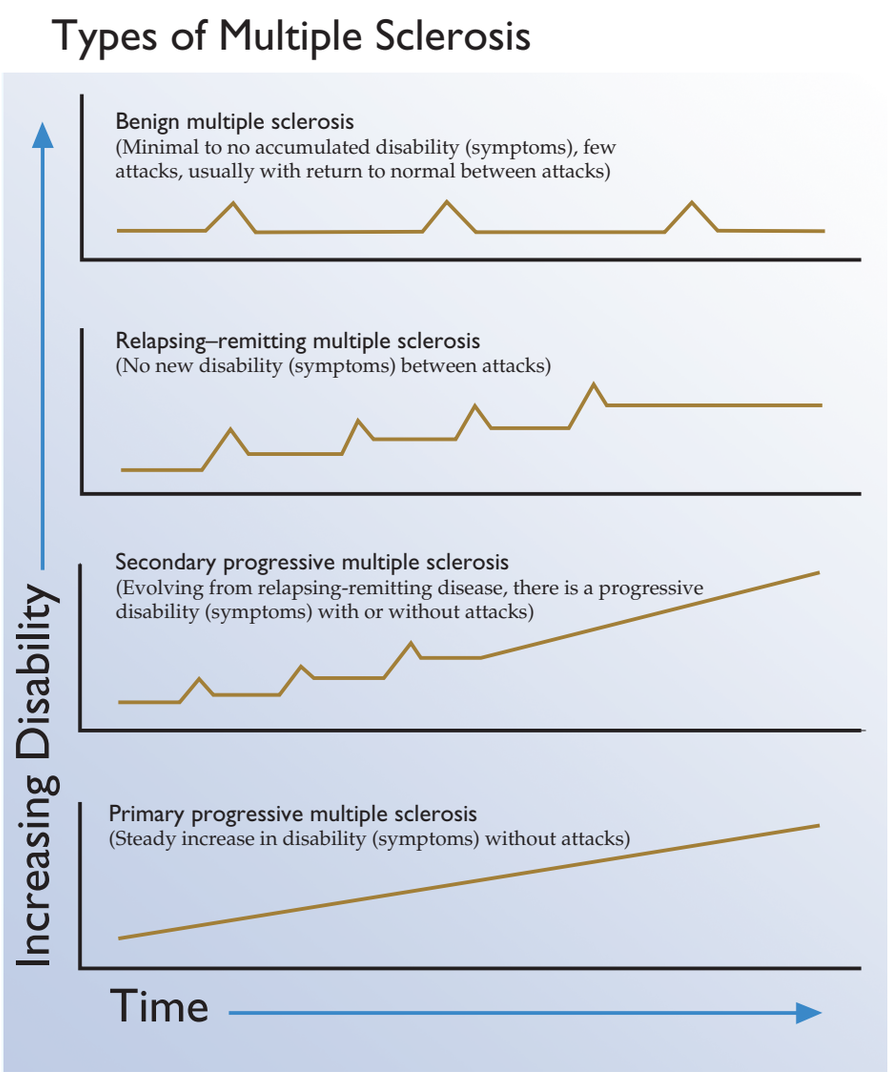

Figure 32-3 ■ Types of multiple sclerosis. Asset provided by Anatomical Chart Co.

Laboratory Studies

Laboratory tests may help to establish the diagnosis of MS. More importantly, serum laboratory studies help to rule out MS mimickers such as vitamin deficiencies, neurosarcoidosis, other autoimmune diseases that affect the CNS, and Lyme disease.

CSF testing is often used to strengthen an MS diagnosis. Three CSF abnormalities may be noted: mononuclear cell pleocytosis, an elevation in the total immunoglobulin (Ig), and presence of oligoclonal Ig. The *mononuclear cell pleocytosis* is usually less than 50 cells/mm.[12] In rapid progressive MS, the level may reach 100 cells/mm.[4] The proportion of gamma globulin (mostly IgG) is increased to values greater than 12% of total protein in about two thirds of patients. The *IgG synthesis rate* represents a calculation of the level of IgG within the intrathecal space. It is increased to more than 3 mg/day in 80% to 90% of MS patients. This rate is a reflection of MRI plaque burden. The *IgG index* indicates the proportion of IgG in the intrathecal space. It is increased to a value greater than 0.7 in 86% to 94% of MS patients.[13]

Oligoclonal bands are discrete electrophoretic bands that are frequently found in the CSF of almost all (90% to 97%) of the MS patients. The bands of MS are found only in the CSF when concurrent CSF and serum samples are evaluated simultaneously, and differ from the pattern seen in other inflammatory neuropathies, neoplasms, and systemic immune responses.

Many diseases mimic MS. As such, MS is considered a diagnosis of exclusion. The aforementioned clinical and paraclinical data are used to ensure there is no better explanation for the neurological presentation.[14]

Clinical Pearl: MS is a diagnosis of exclusion based on a clinical history, neurologic examination, and paraclinical data.

Treatment

In the last few years, development in drug therapy options for MS patients has been significant, and research continues on other possible avenues of treatment. The Kurtzke Expanded Disability Status Score (EDSS), the most widely accepted measure of neurological impairment in MS,[15] is used to compare the clinical effect of

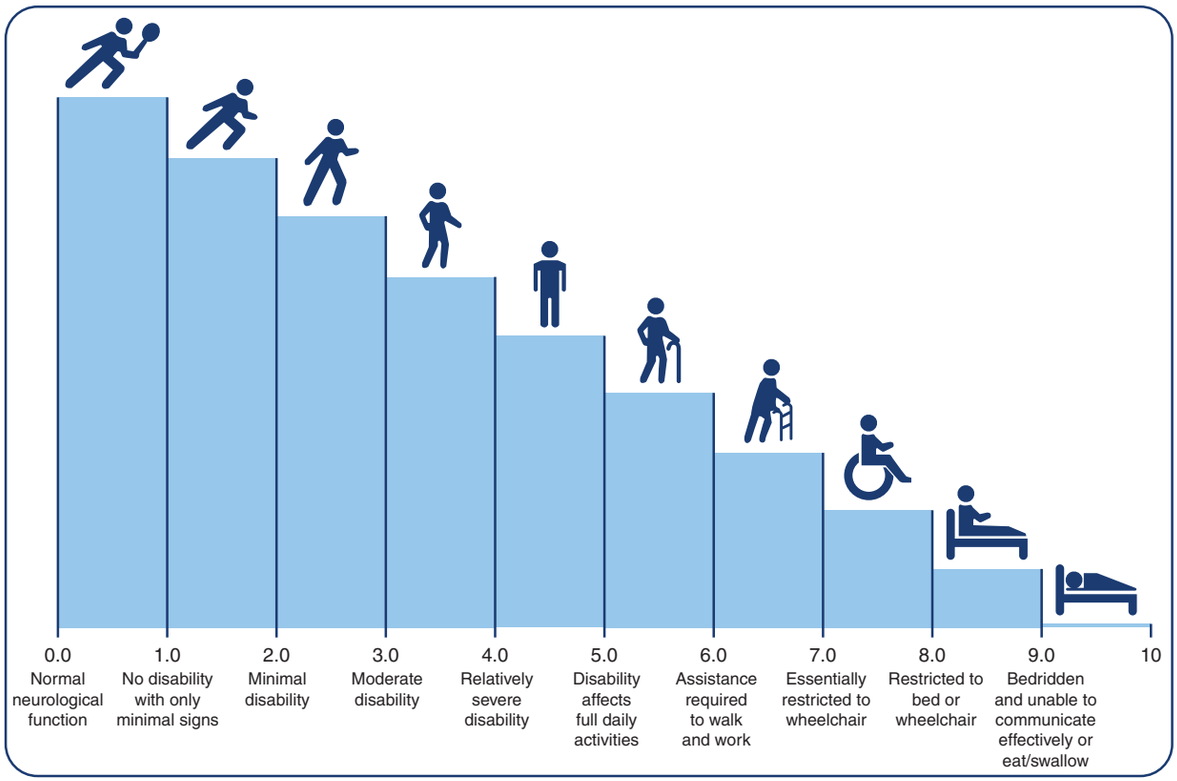

Figure 32-4 ■ Kurtzke Expanded Disability Status Score (EDSS). Image provided by My-MS.org, with permission.

current and proposed drugs for treatment of MS (see Fig. 32-4). The MS Functional Composite (MSFC) was developed in the late 1990s as a standardized measure of cognitive function for use in clinical trials.[16] There are two categories of treatment for MS: treatment to arrest the disease process and treatment for symptom management.

Treatment to Arrest the Disease Process

In the United States, seven FDA-approved drugs are approved to modify MS disease process for relapsing–remitting or relapsing forms of MS (including SPMS with relapses): interferon beta-1a (Avonex 30 mcg IM QW; Rebif 22 mcg and 44 mcg SC TIW; interferon beta-1b (Betaseron 8MU SC EOD; Extavia 8MU SC EOD); glatiramer acetate (Copaxone 20 mg SC daily); fingolimod (Gilenya 0.5 mg PO daily); and natalizumab (Tysabri 300 mg IV monthly).[17,18] Mitoxantrone (Novantrone) is approved to treat relapsing forms of MS that have not responded to traditional therapies, however, is no longer widely used because of the risk of cardiotoxicity.[19] The approved indications, efficacy, most common side effects and adverse events, and monitoring parameters of these medications are outlined in Table 32-3. See also Table 12-9 in Chapter 12.

The injectable disease-modifying therapies (DMTs) are considered safe based on long-term postmarketing safety data. The specific MOAs of interferon beta and glatiramir acetate are unknown. In general, these DMTs induce an anti-inflammatory shift in T cells and cytokines in the CNS. These medications reduce the 2-year relapse rate in a statistically significant manner when compared to placebo. Additionally, if indicated and prescribed for CIS, they reduce the conversion to clinically definite MS (CDMS) at 5 years in a statistically significant manner.[6]

Natalizumab is a monoclonal antibody that blocks activated lymphocytes from adhering to blood vessel endothelium and entering the CNS by binding to the α4 subunit of α4β1 and α4β7 integrins. Natalizumab has been associated with a disabling and potentially fatal illness, progressive multifocal leukoencephalopathy (PML), caused by the James Cunningham (JC) virus. The risk of PML increases with duration of natalizumab use and with prior immunosuppressant exposure. Current data suggest that the risk of PML is greatest after 24 months of exposure to natalizumab. Risk management strategies are in place to monitor persons with MS on natalizumab, including a recently approved serum test for the antibody to the JC virus.

Fingolimod is a sphingosine-1 receptor modulator that sequesters lymphocytes in the lymph nodes, preventing their egress into the lymphatic system, and thus, into the CNS. Fingolimod decreases circulating lymphocytes by 20% to 30%. This drug requires first-dose monitoring because of the risk of bradycardia. Additionally, before beginning therapy, a person with MS is recommended to have a baseline CBC, LFT (and GGT), a negative serum pregnancy test, a normal ECG, positive antibodies to the varicella zoster virus (VZV), and an ophthalmologic examination without evidence of macular disease.

Teriflunomide inhibits dihydroorotate dehydrogenase, an enzyme involved in pyrimidine synthesis. It has both anti-inflammatory and immunomodulatory properties, but the exact mechanism of action is unknown. It carries boxed warnings for liver toxicity and teratogenicity, and should not be given to people with severe hepatic impairment, pregnant women, or women of childbearing age not using reliable contraception. The most common side effects are elevated ALT, alopecia, diarrhea, influenza, nausea, and paresthesia. Prior to giving teriflunomide, the patient should have a CBC, LFT, and TB test, as cases of TB have been reported. Decreases in white

TABLE 32-3 DRUG TREATMENT OPTIONS FOR MULTIPLE SCLEROSIS

DRUG	DOSE	SIDE EFFECTS
Relapsing Forms of MS and CIS (When Noted); Relapse Rate (RR) Decrease Compared to Placebo		
Interferon beta-1b (Betaseron; Extavia) Approved for relapsing forms, CIS. 34% decrease in RR	8 million IU SC q.i.d.	Flu-like symptoms following injection, which lessen over time for many patients; injection site reactions, of which 5% need treatment; rarer findings: elevated liver enzymes, low white blood count; can cause abortion in pregnant woman
Interferon beta-1a (Avonex) Approved for relapsing forms of MS, CIS. 32% decrease in RR	30 mcg IM q/wk	Flu-like symptoms of muscle ache, fever, and chills; pain, weakness; rarely, mild anemia, elevated liver enzymes
Glatiramer acetate (Copaxone) Approved for RRMS, CIS. 29% decrease in RR	20 mcg SC daily	Injection site reaction; rarer, an immediate postinjection reaction of anxiety, chest tightness, shortness of breath, and flushing that lasts 15–30 min
High-dose interferon beta-1a (Rebif) Approved for relapsing forms of MS. 27–32% decrease in RR Natalizumab (Tysabri) Approved for relapsing forms of MS. 68% decrease in RR Fingolimod (Gilenya) Teriflunomide (Aubagio); 31% decrease in RR Dimehtyl fumarate (Tecfidera); 53% decrease in RR Approved for relapsing forms of MS. 54% decrease in RR	22 mcg or 44 mcg SC t.i.d. 300 mg IV monthly 0.5 mg PO daily 7 mg or 14 mg PO daily 240 mg PO BID	Injection site reactions and flu-like symptoms most common adverse effects; elevated liver enzymes Infections, liver enzyme abnormalities, postinfusion reactions including hypersensitivity and anaphylaxis, PML, headache, fatigue, UTI Bradycardia, increased risk of serious infection, decreased lymphocyte count, macular edema, breathing problems, liver enzyme abnormalities, increase in blood pressure, headache, flu, diarrhea, back pain, cough Liver toxicity, teratogenicity, alopecia, diarrhea, influenza, nausea, paresthesia Leukopenia, flushing, abdominal pain, diarrhea, nausea, vomiting, dyspepsia
For Secondary Progressive MS (SPMS) and Worsening Relapsing Forms of MS		
Mitoxantrone (sometimes listed as an "off-label" treatment option)	Several administration schedules reported in the literature; one example is 5–12 mg/m^2 of body surface IV q/3/mo for 2 yrs.	Cardiotoxicity, neutropenia, amenorrhea, alopecia, nausea/diarrhea, respiratory and urinary infections, anemia, and decreased white blood count.
For Primary Progressive MS (PPMS)		
None; offer symptom management therapy		

blood cell counts and platelets may occur, as may transient acute renal failure and hyperkalemia. If an adverse event occurs, rapid elimination of the drug can occur by administering activated charcoal or cholestyramine.

Dimethyl fumarate activates the Nrf2 pathway, which is involved in oxidative cellular stress. The exact mechanism of action is unknown. The most common adverse events are leukopenia, flushing, and GI events. Flushing and GI events improve within the first two months of taking the medication. A CBC should be drawn prior to initiation, and regularly thereafter.

The goal of disease-modifying therapy in MS is to treat early in order to reduce the frequency and severity of exacerbations, reduce new or enhancing brain lesions, reduce brain atrophy, and delay disability progression. Providing therapy that is well tolerated and has an acceptable benefit to risk ratio may enhance treatment adherence. The best person to make treatment decisions is a clinician with expertise in MS, particularly with the advent of new therapies with novel mechanisms of action and unknown long-term safety. Careful patient selection and monitoring are critical to patient management.[6]

Clinical Pearl: Disease-modifying therapies are available to decrease the frequency and severity of relapses, decrease the number of lesions seen on MRI, and decrease the progression of disability.

Drug Therapy for Acute Relapses/Exacerbations

A short course of corticosteroids may be given to treat acute relapses and accelerate recovery. The determining factor in prescribing corticosteroids is the presence of functionally disabling symptoms with objective evidence of neurological impairment. The preferred treatment is a short course of methylprednisolone, 1 g intravenously daily for 3 to 5 days. This may be followed by a short oral prednisone taper. A prednisone taper may begin with 60 mg every day for 3 days followed by decreases in dosage by increments of 10 mg/day. Selection of appropriate drug therapy depends on the severity of the relapse and the resources available to treat the patient with intravenous therapy. Higher doses of oral prednisone or dexamethasone may also be prescribed. Adrenocorticotropic hormone (ACTH, or Acthar) 80 mg SC daily for 5 days is another option.

The long-term use of high-dose corticosteroids is associated with an increased risk for metabolic derangements including overweight, diabetes, and dyslipidemia, as well as osteoporosis and cataracts. It is important to monitor people using steroids frequently for these comorbidities, and to reinforce the need for age-appropriate preventive health screenings with a primary care provider.[4]

Symptom Management

The management of symptoms associated with MS often requires a collaborative multidisciplinary approach. The major problems

requiring management include spasticity, sensory symptoms, weakness, bowel and bladder problems, pain, fatigue, cognitive dysfunction, and depression. Drug management begins with an initial dose and is titrated to symptom control and tolerance of side effects. Therefore, close management and follow-up is necessary to achieve optimal results. In addition, patient and family education is very important to manage symptoms and to maintain a reasonable quality of life. Both nonpharmacologic and pharmacologic strategies are cornerstones of symptom management.[4,5] The goal of care is to keep the patient as independent and functional for as long as possible.

Motor symptoms require a physical therapy program using exercise and ambulatory assistive devices to enhance or maintain function. Such programs are cornerstones of physical management of MS whether or not the person with MS has motor loss. The physical therapist can recommend a brace or support device (e.g., cane, walker), as necessary, to maintain ambulation and independence. In 2010, dalfampridine (Ampyra) was approved to improve walking speed in MS. It was the first drug approved specifically for a symptom related to MS.[20,21]

If leg spasticity develops, gait retraining designed to develop alternative muscles may be helpful. Stretching exercises are effective for both spastic arms and legs. With severe spasticity, drugs such as baclofen (Lioresal), tizanidine (Zanaflex), or diazepam (Valium) may be beneficial in improving motor function. Baclofen may be given intrathecally using an infusion pump with very good effect. Botulinum toxin (Botox) or surgical procedures may be necessary for some patients. To prevent muscle shortening and joint contractures, passive range-of-motion exercises must be a daily part of any patient activity. The patient who is ataxic may be helped by means of gait retraining or by use of a weighted cane or walker to widen the base of support. Weighted bracelets on either extremity are also of value.

Occupational therapy (OT) provides education and therapy in maintaining ADLs and other instrumental activities of living. Occupational therapists can be most helpful for teaching methods to conserve energy when performing ADLs, therefore, decreasing severity of fatigue. Speech therapy is helpful for difficulty in articulation or staccato speech and dysphagia.

Patients with sensory loss must be taught to protect themselves from injury. The body must also be protected from trauma, heat, cold, and pressure. For patients with paresthesias (abnormal sensations such as burning or prickling), drug therapy may be helpful. Examples of drugs commonly used to treat this type of neuropathic pain are gabapentin (Neurontin), pregabalin (Lyrica), duloxetine (Cymbalta), and tricyclic antidepressants. Limb pain may be managed with exercise and pharmacologic agents.

Management of bowel and bladder symptoms requires a multifaceted approach. Bladder dysfunction may be a result of a failure to store, a failure to empty, or a combination of these problems. It can be managed with medication, behavioral therapy, and bladder training. If these things are ineffective, discussion regarding catheterization is required. Urinary tract infections are more common in people living with MS, and can be a cause of a pseudoexacerbation. UTI surveillance is important. The most common bowel symptom in MS is constipation. Diarrhea and involuntary bowel due to diminished sphincter control or a hyperreflexic bowel may also occur. An evaluation of diet and fluid intake, activity, and lifestyle is required to determine appropriate interventions for bowel dysfunction. Sexual dysfunction can be related to lesion location and referable symptoms of MS, medication side effects, or psychological issues. Behavioral measures, psychotherapy, and certain medications may be helpful.

Finally, cognitive dysfunction, fatigue, and depression are very common. Fatigue is particularly disabling. It contributes to social isolation and depression. Exploration for contributing factors to fatigue helps to identify patterns that may be ameliorated. Risk modification, along with drug therapy, is useful to decrease fatigue. Cognitive rehabilitation may be helpful for people with cognitive dysfunction. There are no pharmacologic therapies known to ameliorate this problem, however, behavioral measures can be quite helpful.

Depression is very common in MS, and the patient, family, and health care providers must be vigilant for signs and symptoms. Approximately 25% to 55% of patients with MS are depressed, and the suicide rate is significantly higher than in the healthy population. The use of standardized depression scales plus monitoring of the patient provides the means for early identification and treatment. The newer generations of antidepressants, selective serotonin, and norepinephrine reuptake inhibitors are recommended for treatment.

Complementary and alternative medicine (CAM) techniques, such as acupuncture, massage therapy, and biofeedback, may also be helpful for MS symptom management. Patients should be counseled to discuss any supplement (vitamin, herb) or CAM use with their MS clinician prior to its initiation.

Clinical Pearl: Management of MS symptoms includes pharmacologic, rehabilitation, and behavioral measures.

RESEARCH

Current research in MS is directed at determining causative or predisposing factors of the disease, developing more effective therapies that have an acceptable risk–benefit ratio, identifying new imaging techniques, and developing better methods to manage symptoms from both the pharmacologic and rehabilitation perspectives. Recently, studies have provided information suggesting that high circulating levels of 25-hydroxyvitamin D are associated with a lower risk of MS in Caucasians; heavy smoking increases MS risk, and smoking with MS is associated with greater disability, number of lesions, and brain atrophy; MS risk is increased in those who developed clinical mononucleosis, supporting the involvement of the Epstein–Barr virus; and vascular comorbidities in people with MS are associated with increased disability progression.[22] There are also many promising ongoing phase 1 to 3 disease-modifying therapy studies, some of which predominantly target B cells instead of T cells.[6] Small studies using stem cell transplants are in process, as are studies attempting to identify biomarkers of the disease. It has been suggested that there are as many as 50 genes associated with genetic susceptibility in MS, and over 13 have already been identified. As genetic components of the disease become more apparent, scientists are searching for methods to identify those who may respond to one therapy better than others.

Nursing Management

Most patients with MS live normal lives between periods of relapses. When relapses occur, most patients are managed in the community by a primary care physician or a neurologist in a clinic. When the physical environment of the home has been adequately adapted, patients with permanent disabilities often live independently with

the aid of family members. Some patients with advanced disease are managed in nursing homes. When severe relapses or complications occur, patients are seen in the acute care setting where stays are usually short. Regardless of the setting in which the nurse comes in contact with the patient, it is important for the nurse to assess the patient's understanding of the illness, the factors related to relapse, and the need for lifestyle adaptation to live as independently and normally as possible. A teaching plan should be individualized according to the patient's needs.

The significant degree of psychosocial adaptation required of MS patients means that major adjustments must be made over the course of the illness. If permanent disabilities develop, the amount of support necessary from the nurse and other health care professionals increases. Many patients will note a decreased energy level, urinary tract problems, motor deficits, sexual dysfunction, changes in their social and recreational activities, and concerns about roles and employment. Most patients and families need support in their adjustment process. Some patients need counseling and psychotherapy to deal with behavioral and cognitive deficits. Cognitive-behavioral programs have improved outcomes for many patients, especially women.[23]

Nurses play an integral role in patient teaching about the disease, its course, and treatments including symptom management. Often, education about medication side effects and their management, necessary laboratory surveillance, and the importance of adherence is imparted by the nurse. A nurse may be required to teach appropriate injection technique of the available disease-modifying therapies. Additionally, a nurse may be asked for information regarding a risk–benefit ratio analysis of newer disease-modifying therapies. MS-certified nurses in the community can provide an excellent resource for education for the nursing community.

The nurse, as a member of the multidisciplinary team, plays a key role in patient/family education, symptom management, and support. Other members of this multidisciplinary team may include a neurologist, rehabilitation professionals, a psychiatrist and/or psychologist, a primary care provider, a urologist, a physiatrist, a social worker, an exercise specialist, a dietician, local community MS organizations, and a spiritual advisor.[24] The person living with MS may not need to access all specialists on a regular basis, but may need specialized care at some point along the continuum of the disease. It is important for the nurse to be knowledgeable about a referral base for these resources. The major patient problems and nursing diagnoses include the following.

- Knowledge Deficits related to lack of knowledge about MS, treatment options, course of illness, and available resources
- Impaired Physical Mobility related to muscle weakness and ataxia
- Self-Care Deficits related to muscle weakness, incoordination, sensory/perceptual deficits, and fatigue
- High Risk for Injury related to weakness, incoordination, and sensory/perceptual deficits
- Self-Concept Disturbance related to physical disabilities, altered role performance, and altered self-esteem
- Impaired Home Maintenance related to weakness, incoordination, sensory/perceptual deficits, and fatigue

For the patient with advanced disease, the use of braces and canes and, finally, confinement to a wheelchair may become a reality. These patients need instruction and help in modifying their lifestyles to maintain the greatest level of independence possible. In some instances, the patient will become bedridden. The nurse should modify care depending on the needs of the patient.

The nurse taking care of a person living with MS should foster a sense of empowerment and hope, and provide a wellness-focused plan of care. The role of the nurse is central to the multidisciplinary model of care of the person living with MS.[24]

Clinical Pearl: The role of the nurse taking care of the person living with MS involves wellness-centered education, empowerment, advocacy, and the instillment of hope.

Local and national resources are available to assist patients, families, and health care providers through the following organizations.

- The National Multiple Sclerosis Society, (800) 344-4867, http://www.nmss.org.
- The Multiple Sclerosis Association of America, (800) 833-4MSA, http://www.msaa.com.
- The Multiple Sclerosis Foundation, (800) 225-6495, http://www.msfocus.org
- The Consortium of MS Centers, (201) 487-1050, http://www.mscare.org
- International Organization of MS Nurses, (201) 487-1050, http://www.iomsn.org
- Veteran's Administration of America, http://www.va.gov

SUMMARY

MS is an autoimmune inflammatory disease of the CNS that predominantly affects white matter, though gray matter involvement also occurs. It is a progressive neurodegenerative condition. MS causes demyelination and scarring of myelin, resulting in plaques visible on MRI and in histopathologic specimens. The manifestations of the disease vary from an insidious progressive to a rapidly progressive and disabling illness that has a profound effect on physical function and quality of life. Patients must learn to manage their disease to optimize the quality of their life. The nurse works as a member of a collaborative health team member to educate and support the patient and family.

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