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Multiple sclerosis:
Managing patients in primary care

Abstract: In this era of the Patient Centered Medical Home model of care, chronic diseases such as multiple sclerosis (MS) are managed in partnership with specialty care practices. For the patient and family living with MS, assuring that patients get proper care when and where they need it requires that nurse practitioners understand their role in assessing and managing complex chronic diseases.

By Heidi Wynn Maloni, PhD, ANP-BC, CNRN, MSCN

Multiple sclerosis (MS) is a chronic, degenerative, neurologic disease of the central nervous system (CNS).[1] MS, characterized by unpredictable relapses and remissions of neurologic events, is the most common cause of nontraumatic disability in young adults, affecting those in their most productive years.[2-4] Nurse practitioners (NPs) in pediatric and primary care settings may be the first to recognize motor, sensory, and cognitive deficits that may help establish a diagnosis of MS. A timely referral to a neurologist follows the assessment in the pediatric or primary care setting. Patients with chronic illness will often return to the primary care setting for management. The NP is well-positioned to manage individuals with MS. Similar to other chronic diseases, treating and managing relapses, modifying the course of disease, managing symptoms, and improving health-related quality of life (HRQOL) is familiar to NP practice. The purpose of this article is to familiarize NPs with MS, its treatments, and to offer practical management strategies to enhance the capacity for health in individuals living with MS.

Epidemiology

MS affects about 400,000 individuals in the United States and 2.5 million around the world.[5] Prevalence rates are higher in northern Europe, southern Australia, and northern parts of North America. The risk of developing MS increases for those living in latitudes farther from the equator, suggesting that geography plays a role in disease susceptibility.[5,9]

Recent studies implicate the role of sunshine and vitamin D exposure, either in birth month or in childhood, as predictive of risk for MS diagnosis.[6] MS is more common in those of northern European descent but is also seen in those of African, Asian, and Hispanic ancestry. MS rates have been increasing in many groups over the past few decades felt to be at low risk for the disease, including Blacks, populations in the Middle East, and Asia.[7,9]

The average age of diagnosis is 32 years. Typically, the diagnosis is made in individuals between the ages of 20 and 50.[5] However, older adults and children are diagnosed with MS. There are more than 10,000 children in the United States with an MS diagnosis, and another 15,000 have experienced at least one symptom suggestive of MS.[12] The risk of developing MS is 1:750 in the general population and is three times more common in women than men. Environmental agents are thought to play a major role in MS susceptibility with genetic susceptibility playing a more minor role. Infectious agents, particularly viruses, have long been implicated as MS triggers due to their affinity for nervous system tissue. Epstein-Barr virus infection has been implicated as important in the development of MS. However, no virus or environmental agent has been confirmed to trigger the onset of MS in humans.[5-9,11]

To date, no single gene has been identified as a direct link to MS, however, the human leukocyte antigen (HLA) exerts a strong influence on the development of this disease. This makes sense, as MS is an immune-mediated disease, and the HLA alleles distinguish self from nonself. The evidence for genetic factors is demonstrated among monozygotic twins,

Illustration by Steve Oh, M.S./Phototake ©

Key words: chronic diseases, immunomodulatory drugs, multiple sclerosis, nurse practitioners

where disease concordance rates are maximal at 30%. The absolute risk of MS in a first-degree relative of a person with MS is less than 5%, but this risk is 20 to 40 times the risk in the general population.[2,5,10,11] MS is thought to be an immune-mediated disease likely precipitated by early exposure to unknown environmental factors in genetically susceptible individuals.

Immunopathology

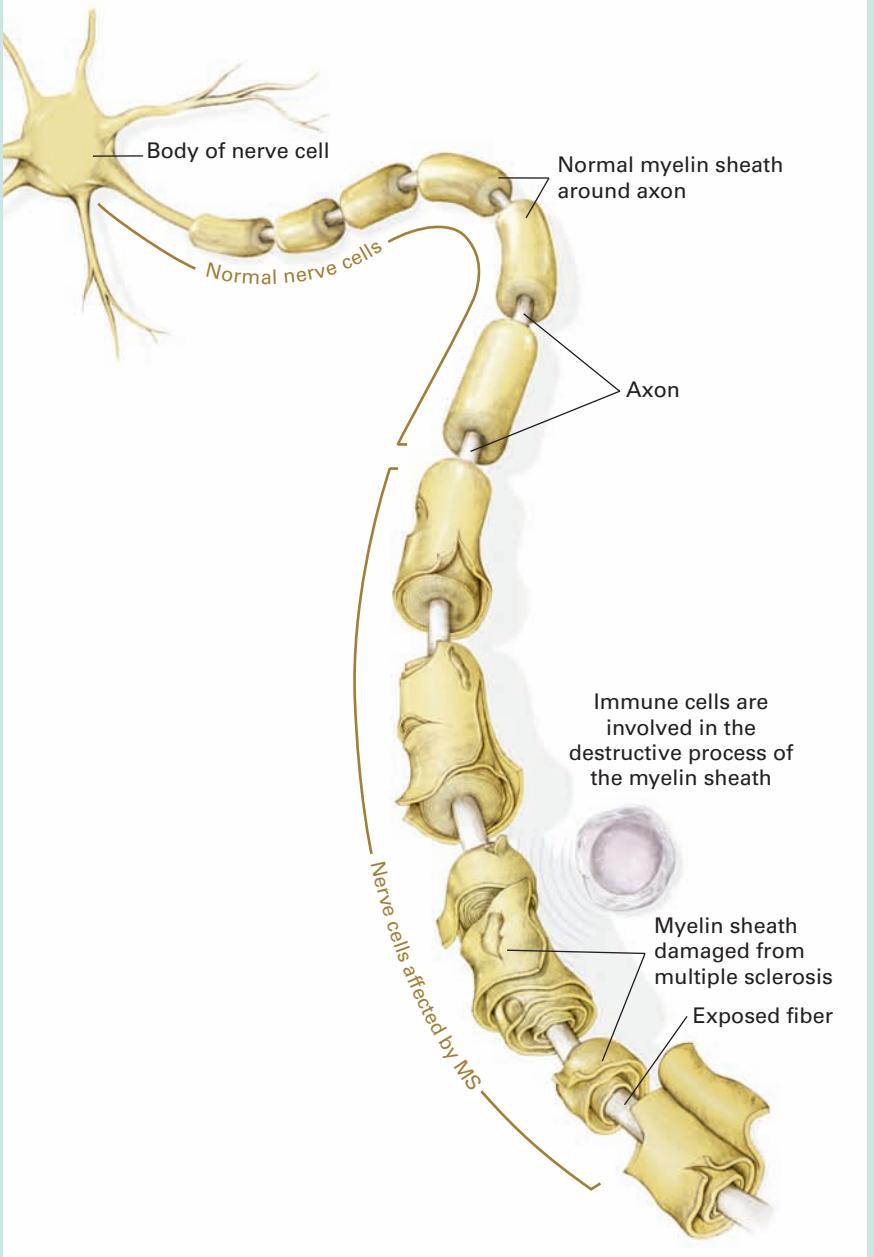
The pathologic hallmarks of MS are inflammatory, demyelinating plaques and axonal loss in the CNS. Pathology reflects two distinct processes: inflammation and neurodegeneration with subsequent tissue volume loss.[14] MS has an extensive effect on CNS white matter, and more recent findings suggest lesions are seen in gray matter.[13,14] Inflammation leads to degeneration of the myelin sheath (see *Pathologic changes in MS*). The denuded axon begins to disintegrate, resulting in axonal loss and brain atrophy.

Motor, sensory, and cognitive symptoms are thought to be the consequences of myelin loss, leading to slowed or blocked conduction. The resolution of inflammation and associated edema along with compensatory remyelination are thought responsible for the remission of symptoms.[13]

MS is a heterogeneous disease reflecting CNS lesion differences related to MS subset and age, among several other factors.[14] CNS damage is mediated by a number of immune and inflammatory factors. There is wide variability among patients clinically, pathologically, and on magnetic resonance imaging (MRI). Several pathogenic mechanisms may be implicated in tissue damage, influencing MS treatment. More than one approach to disease management may be necessary.[3,14,15]

A major part of the inflammatory disease component in MS resides in autoreactive T cells stimulated in the periphery that have access to the blood-brain barrier, cross into the CNS, and organize an immune response to myelin. T cells are activated by macrophages that present an autoantigen or non-self-antigen. Activation allows

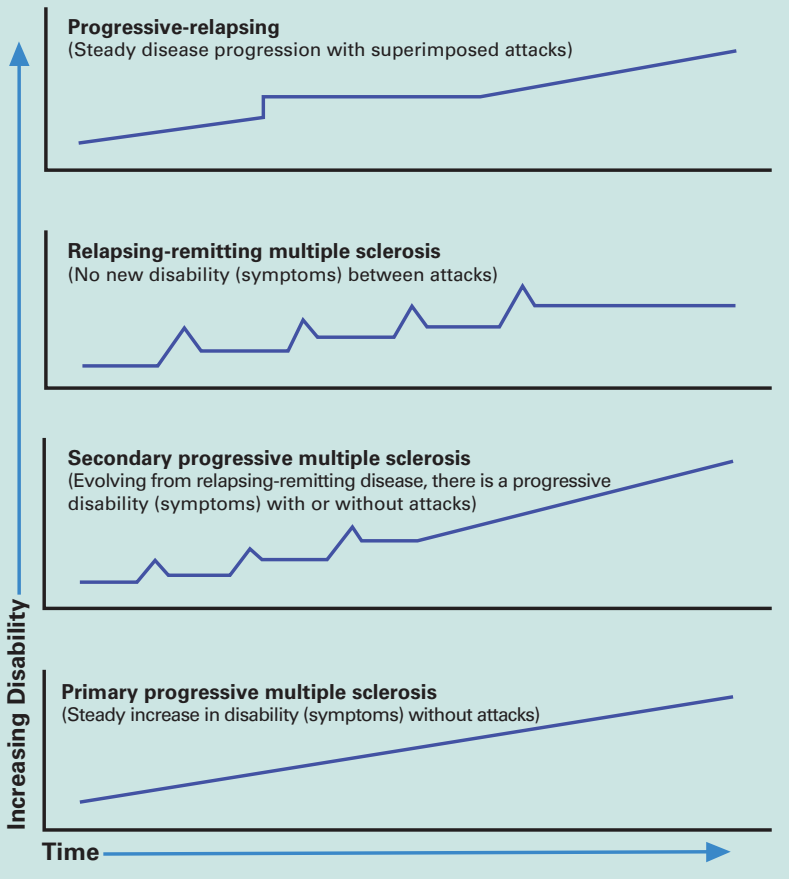
Pathologic changes in MS



Source: Anatomical Chart Company. *Diseases & Disorders.* 3rd. ed. Skokie, IL: Wolters Kluwer/Lippincott Williams & Wilkins; 2008:7.

for adhesion molecule presentation on the T-cell surface stimulating attraction to the endothelium of the blood-brain barrier. This attraction facilitates access of proinflammatory cells across the blood-brain barrier and into the CNS. Once in the CNS, these autoreactive T cells are presented with recognizable antigens, and an inflammatory response follows, characterized by inflammation, demyelination, irreversible axonal injury, scarring, and loss of cells that make myelin, the oligodendrocyte.[16] B cells, plasma cells, and autoreactive antibodies are involved in the inflammatory response and myelin destruction. B cells are present in the brain and spinal fluid of MS patients. This process explains the progressive loss of neurologic function in MS. It does not explain disease variability or predict disability. Axonal destruction occurs early and is observed on MRI in clinically and radiologically isolated syndromes even before the MS diagnosis is made.[16-20]

Clinical disease subtypes



Source: Anatomical Chart Company. *Diseases & Disorders.* 3rd. ed. Skokie, IL: Wolters Kluwer/Lippincott Williams & Wilkins; 2008:7.

Disease characteristics

Four subtypes or phenotypes characterize the clinical disease course. Approximately 80% of those diagnosed with MS present with relapsing remitting MS (RRMS).[29] Remissions can be complete to baseline or evidence incremental accrual of disability over time. About half of those diagnosed with RRMS will transition to secondary progressive MS (SPMS) in 10 years. Transition to SPMS is typified by progression of disability without clear evidence of neurologic events, decreasing number of gadolinium-enhancing lesions, and increase in T1 black holes (representing axonal loss) on MRI. SPMS is typically seen in those with advancing age and greater duration of disease[29] (see *Clinical disease subtypes*). However, SPMS is not a homogenous phenotype, and relapses can occur in this subgroup.

Primary progressive MS (PPMS) occurs in about 10% of those who experience progression of disease from the time of diagnosis without evidence of acute attacks. Progressive relapsing MS (PRMS) includes about 5% who experience steady neurologic disease progression and, with time, experience superimposed attacks or exacerbations.[29]

The relapse rate (or attacks) in untreated RRMS is approximately one to two relapses a year; relapse rates correlate with disability. There is evidence to support early treatment to slow or prevent worsening of disability.[30] Disease characteristics are important to treatment decisions.

Diagnosis

Immune pathology occurs early in the disease process and may be associated with irreversible damage in the absence of clinical symptoms. Early diagnosis is important to early treatment that may slow the progression of nervous system damage.[18] The diagnosis of MS may not be readily apparent, as it can take years to establish the diagnosis.

However, there are clues that help NPs assess and make the diagnosis of MS. No single test, no lab analysis, or definitive diagnostic test alone can make the diagnosis. The diagnosis of MS remains a clinical diagnosis with evidence on history and neurologic exam of two episodes of neurologic symptoms referable to the CNS, separated in space and in time.[18-22]

The *2010 Revised McDonald Diagnostic Criteria for MS*[20] is helpful in making a diagnosis when the patient presents

with a clinically isolated syndrome (CIS), a first clinical or neurologic event suggestive of MS in one or more sites in the CNS, or progression without evidence of relapse. The criteria are a sensitive and specific tool for rapid diagnosis using even a single MRI to establish dissemination of lesions in space and time.[18,20,21]

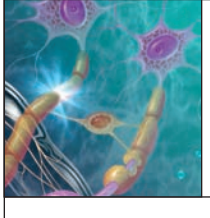
Subjective data

When a patient presents with neurological complaints, age, ethnicity, and gender can increase the suspicion of a diagnosis of MS.[19,22] The most common presenting symptom, occurring 33% at the time of diagnosis, is sensory.[24] Unilateral visual loss is another commonly occurring symptom in 16% at the time of diagnosis.[24] The lack of findings in the history to indicate dissemination of neurologic events over time and in space, onset of symptoms before age 10 or after age 55, normal bowel and bladder symptoms, progressive myelopathy, localized disease, peripheral neuropathy, prominent uveitis, impaired level of consciousness, early dementia, seizure, aphasia, and extrapyramidal features (parkinsonian movement disorders) decrease the suspicion of MS diagnosis.[19,22]

During the history, the patient may report Lhermitte sign, a brief electric shock-like sensation down the spine, radiating into the arms and legs, occurring when the neck is flexed toward the chest. Lhermitte is typical, not specific to MS, and correlates with active inflammation usually of the cervical cord.[24]

Objective data: The neurologic exam

It is highly atypical to find a normal neurologic exam in MS. Neurologic exam findings may include the following: localized weakness, focal sensory disturbance with a decrease in proprioception and vibration, an increase in tone and spastic catch on rapid flexion and extension, hyperreflexia, clonus, and upgoing toes.[25] Exam of cranial nerves may reveal a pale optic disk, poor visual acuity, a field cut, or red color desaturation (CN II); extraocular movements (CN III, IV, VI) indicating a lesion involving afferent pathways termed a relative afferent pupillary defect (APD) or efferent pathway defect characterized by diplopia, oscillopsia, and nystagmus. Double vision or diplopia relates to an internuclear ophthalmoplegia (INO) and seen objectively as the affected eye (ipsilateral) is unable to fully adduct, and the contralateral eye exhibits horizontal nystagmus. Bilateral INO is highly diagnostic of MS.[25] Other diagnostic clues include action or cerebellar tremor, one that increases as the finger reaches the target on finger-to-nose testing. Dysmetria or clumsiness also refers to cerebellar dysfunction. A positive Romberg test or poor balance when visual cues fail to "ground" suggests proprioceptive impairment.[26] In summary, signs consistent with an MS diagnosis are nystagmus, cerebellar tremor, decreased perception of pain, temperature, vibration, hyperreflexia, spasticity, Babinski sign, or upgoing toes. Eye findings such as INO, red color desaturation, and APD are often pathognomonic of MS.[24-26]



The risk of developing MS is 1:750 and is three times more common in women than men.

Objective data: Lab and diagnostic testing

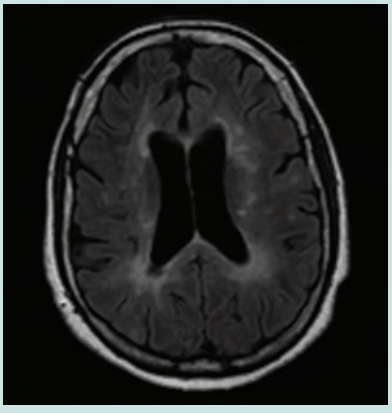
Lab and diagnostic testing includes supportive and confirmatory paraclinical exams of MRI, cerebrospinal fluid (CSF) analysis, and evoked potential testing, including visual evoked potential, somatosensory evoked potential, and brainstem auditory evoked responses (BAER). CSF may provide supporting evidence for a diagnosis of MS when positive for oligoclonal IgG bands in the CSF (and not in the serum), elevated IgG index, and mild leukocytosis. It should be noted that a negative result can occur in someone with a definite diagnosis of MS.[18,19,23] There are no blood tests that are diagnostic of MS. Lab data are gathered to exclude other diseases.[19,21] MRI of the brain can be useful in making the diagnosis in absence of clinical episodes. MRI can establish dissemination in time, detect subclinical lesions, and identify active inflammation with gadolinium contrast enhancement.[18-20] The diagnosis can be made without CSF analysis and evoked potential testing. Their utility may be in lending support to the diagnosis when clinical and radiologic findings are equivocal. Ultimately, there must be no better explanation for the diagnosis than MS.

MRI primer

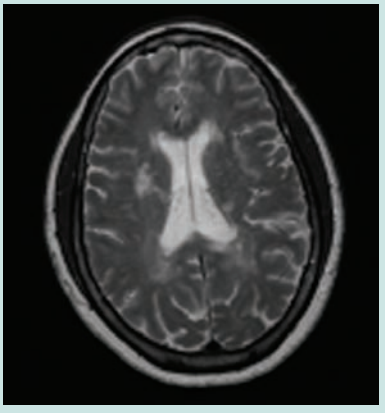
The advent of MRI has made a dramatic impact on MS. MRI increases confidence in the diagnosis of MS, allowing for earlier diagnosis. It is used as an outcome measure in clinical trials and as a surrogate biomarker for disease. MRI is important in assessing disease activity that may drive treatment decisions. Inflammation in the brain is visualized on MRI and represents the dispersal of proinflammatory T cells into the brain and spinal cord.[34] Although there is no "typical" MS lesion, MS plaques or lesions are usually oval or elliptical in shape with distinct margins.[34] MS lesions are found anywhere in the brain's white matter, with 15%

MRI findings

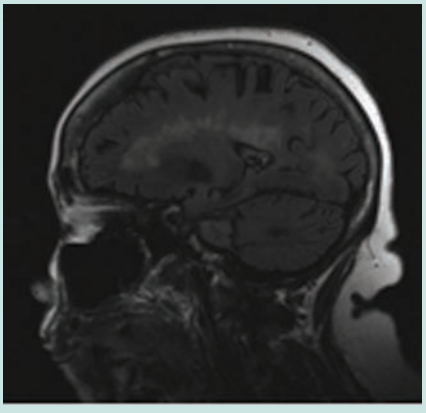
T2 W FLAIR with extensive white matter lesions and enlarged ventricles and sulci-indication of brain atrophy.



T2 weighted image



T2 FLAIR image showing Dawson's Fingers and brain atrophy in a 46-year old Female



Source: International Association of Multiple Sclerosis Nurses slide deck used with permission: http://www.urmc.rochester.edu/smd/rad/neurocases/Neurocase20.htm

to 37% located in the gray matter.[13,34] Plaques are often observed near or around the ventricles, termed periventricular. Lesions in the corpus callosum are highly suggestive of a MS diagnosis. When observed on sagittal imaging, these lesions are referred to as "Dawson fingers"[34] (see *MRI findings*). Lesions are generally nonspecific and usually cannot be referred to specific symptoms. However, lesions in the brainstem, optic nerve, spinal cord, trigeminal nerve, and cerebellum can often be directly associated with symptoms.[35]

A contrast material, gadolinium, is used to identify active inflammation. The influx of inflammatory cells into the brain causes the blood-brain barrier to break down and allow entrance to this large molecule. Gadolinium is attracted to fluid-filled areas of inflammation (pathologic/diseased tissue has high-water content) and allows visualization of new inflammatory lesions. This bright, hypointense signal is known as a gadolinium enhancing lesion and indicates newly active lesions on T1 (longitudinal relaxation time) imaging.[36] MRI signal sequences help differentiate disease activity and conventionally consist of T1-weighted (severe hypointense representing axonal loss), T2-weighted (representing burden of disease), and fluid attenuated inversion recovery (FLAIR) images, which provide greater contrast between CSF and lesions. Brain atrophy is a biomarker, or surrogate, for axonal loss and disease progression.[37]

Differential diagnosis

The diagnosis of MS may be confounded by "MS mimics" or diseases that have similar presenting characteristics. These diseases are considered in the differential diagnosis (see *Differential diagnosis: MS mimics*) as well as lab data to rule out MS mimics (see *Lab analysis to rule out MS mimics*).

Treatment of symptoms

MS symptoms include motor, sensory, emotional, and cognitive manifestations. Symptoms are unpredictable and may remain, fluctuate, or progress. Symptoms that are related directly to a lesion in the CNS are considered primary symptoms. Common primary symptoms include sensory disturbances of numbness, tingling, burning, and pain; visual disturbance (blurred vision or diplopia), weakness and poor walking endurance, fatigue, bowel and bladder dysfunction; spasticity, ataxia, cognitive dysfunction with short-term memory loss most prominent, and tremor. Heat intolerance, Lhermitte's sign, trigeminal neuralgia, seizures, vertigo, and migraine may be present and represent CNS dysfunction. It is important to note that symptoms vary between patients. There are certainly commonalities of symptoms experienced, but not all symptoms are experienced by all individuals with MS. Secondary symptoms occur as a consequence of poorly managed primary symptoms. Secondary symptoms of infections, falls, skin breakdown, injuries, and contractures contribute to disability and impact HRQOL. Loss of job, loss of intimacy, role changes, family disruption, social isolation, dependency, loss of self-esteem, and all possible consequences of chronic disease are considered tertiary symptoms of MS.[30]

NPs will recognize the need to address MS symptoms and make necessary referrals to healthcare colleagues.

Managing MS symptoms requires a team approach involving social work, mental healthcare professionals, and rehabilitation, to name a few. Physical and occupational therapists assist with safety concerns, energy conservation measures, optimization of function, and prevention of secondary symptoms, such as pressure ulcers with concern for wheelchair seating and positioning.[30]

Treatment of disease: Immunomodulatory drugs

There are currently nine U.S. FDA-approved immunomodulatory drugs (IMDs) to treat relapsing remitting and relapsing forms of SPMS. There are no FDA-approved IMDs to treat PPMS. IMDs have shown effectiveness in limiting relapses, disease progression, and inflammatory lesions seen on MRI.[40] (See *IMDs*.)

Differential diagnosis: MS mimics[19,22]

- **Infection**
  Lyme, syphilis, progressive multifocal leukoencephalopathy (PML), human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV-1)
- **Inflammatory and autoimmune**
  Systemic lupus erythematosus (SLE), Sjögren syndrome, vasculitis, sarcoidosis, Behcet disease
- **Metabolic**
  B-12 deficiency, rare familial diseases
- **CNS lymphoma**
- **Degenerative spinal disease**
- **Motor neuron disease**

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Lab analysis to rule out MS mimics[22]

- B-12, folate
- Rapid plasma reagin (RPR), The fluorescent treponemal antibody absorbed (FTA-ABS)
- HIV
- HTLV-1
- Antineuclear antibody (ANA), Anti-SS-A, Anti-SS-B (Sjogren's Syndrome antibodies)
- Antiphospholipid antibodies
- Erythrocyte sedimentation rate (ESR), C-reactive protein
- Thyroid function
- Angiotensin-converting enzyme
- Anti-acetylcholine receptor antibodies
- Long-chain fatty acids
- Lyme titer

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The National Multiple Sclerosis Society (NMSS) National Clinical Advisory Board recommends that IMDs be initiated as soon as possible following diagnosis and should remain in place unless there is lack of clear benefit, intolerable adverse reactions, or a better therapy emerges. The NMSS advisory board states that individuals qualifying for IMDs should not be denied access to drugs by insurance companies due to frequency of relapses, age, or level of disability.[41,42]

Clinical trials of IMDs utilize important endpoints, such as preventing relapses, slowing disability progression, decreasing MRI activity, and improving HRQOL.[42,43] Recent MS natural history (untreated disease) studies revealed wide variation in time to disability in this cohort. Time to disability, or time to require a cane to ambulate, ranged from 15 to 32 years from diagnosis.[44] Comparison studies of long-term disease progression in natural history patients versus IMD users have not been conducted.[44] Long-term benefits of IMD therapy have not been established. However, the pathogenicity of disease is influenced by immunomodulation, typically in early disease. The MS scientific community recognizes the importance of IMDs in disease management.[41] NPs need to convey information critical to disease outcomes to patients. NPs can optimize IMD use through ongoing communication and education to recognize and manage adverse IMD effects. Perceived lack of efficacy, drug adverse reactions, and injection site reactions are common reasons for lack of adherence.[45] An explanation of the efficacy and safety of IMDs from clinical trial data can help frame realistic expectations. Patients should be disabused of the notion that IMDs will improve their condition. The use of IMDs is analogous to using an umbrella in a storm. Limiting attacks, progression of disease, and new lesions seen on MRI is the expected goal of IMD therapy. When patients understand realistic therapy goals, are educated to make informed therapy choices, and feel a true partnership in care, adherence to therapy has greater probability.

Treatment of relapses

A new onset of symptoms may indicate a relapse or pseudo-relapse. A relapse is defined as an episode of focal neurologic disturbance lasting more than 24 hours, without an alternate explanation, and with a preceding period of clinical stability lasting at least 30 days.[27] A pseudo-relapse has characteristics of transient worsening or return of neurologic symptoms that can be attributable to environmental, systemic, or other influences, such as infection, increase in core or environmental temperature, stress, anxiety, or worsening symptoms related to the menstrual cycle.[28] An example of pseudo-relapse would be blurred vision associated with exercise. This phenomenon is known as Uhthoff

IMDs[51]

The following are FDA approved drugs and one drug with pending approval for treating MS. Consult the manufacturer's prescribing label for each individual drug for complete prescribing and dosage information.

Drug and indications	Contraindications	Adverse reactions	Precautions and warnings
Interferon beta-1a Interferon beta-1b Indications: Relapsing remitting and relapsing forms, CIS	Known hypersensitivity to the drug, albumin, or drug components	• Flulike symptoms • Headache • Depression • Mild anemia • Elevated liver enzymes • Injection site reaction with subcutaneous injections	• Pregnancy: Category C • Monitor for depression, suicide ideation, seizure disorder, rare allergic reaction • Monitor those with a history of cardiovascular disease for heart failure (HF), and dysrhythmias • Monitor CBC, thyroid-stimulating hormone, and hepatic function with liver function test (LFT): baseline, 1 month, 3 months, and every 6 months
Glatiramer acetate Indications: RRMS, CIS	Known hypersensitivity to the drug or mannitol	• Injection site reactions (lipoatrophy and skin necrosis) • Postinjection reaction—rare (anxiety, chest pain, palpitations, dyspnea, flushing) • Vasodilation—rare	• Pregnancy: Category B • Immediate postinjection reaction (16% experience); transient chest pain; lipoatrophy, lymphadenopathy
fingolimod Indications: Relapsing forms	Recent (within the last 6 months: myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated or Class III/IV heart failure (HF) History or presence of Mobitz type II or third degree AV block, sick sinus syndrome, baseline QTc interval 500 ms or greater, treatment with Class Ia or Class III antiarrhythmics	• Bradycardia • Infections (herpes viral, bronchitis, tinea, influenza) • Macular edema • Respiratory (cough) and hepatic effects (LFT elevation) • Headache • Dizziness • Diarrhea • Back pain	• Pregnancy: Category C • Varicella vaccine prior to treatment if lack of antibodies to varicella • Obtain a baseline ECG (if not done within last 6 months), and monitor for bradycardia before and after first dose for 6 hours • Labs: LFT & lymphocyte monitoring; vision testing for macular edema recommended at baseline and 3 months.
Mitoxantrone Indications: Worsening RRMS SPMS PRMS	Known hypersensitivity to the drug	• Blue-green urine post infusion for 24 hours • bone marrow suppression • infection, urinary tract infection • nausea, gingivitis • alopecia	• Pregnancy: Category D • Cardiac toxicity: MUGA testing for ejection fraction baseline and after each treatment and annually to rule out HF • Risk for acute myelogenous leukemia
Natalizumab Indication: Monotherapy for relapsing forms; for those with inadequate response to or inability to tolerate injectable agents	Patients who have or have had PML or hypersensitivity to the drug	• Hypersensitivity reactions: Urticaria systemic signs and symptoms, edema/swelling, rashes, difficulty breathing, angioedema, cardiac symptoms • Infusion reactions: Headache, nausea, sweats, dizziness, fatigue, rigors • Elevated LFT • Possible multiple myeloma	• Pregnancy: Category C • Must be TOUCH program enrolled • Risk for: PML—caused by common JC virus—personality or behavioral changes, changes in thinking, seizure, disturbance in vision, hemiparesis • JC virus antibody testing available to stratify risk • Risk increases with increase doses • Risk for liver damage

(continued)

IMDs (*Continued*)

Drug and indications	Contraindications	Adverse reactions	Precautions and warnings
Teriflunomide Indications: Relapsing forms of MS	Severe hepatic impariment, pregnancy or patients who are currently on leflunomide therapy Black box warning for hepatotoxicity and teratogenicity	• Increase in alanine aminotransferase • Diarrhea • Nausea • Paresthesia • Alopecia • Influenza	• Pregnancy Category: X • Elimination accelerated by administration of cholestyramine or activated charcoal for 11 days • Screen for TB • Monitor for infection (obtain CBC before starting drug), hyperkalemia, acute renal failure, blood pressure, peripheral neuropathy, severe skin reactions
Dimethyl fumarate* (*FDA approval is pending, and was scheduled for March 31, 2013 at press time.*) Indications: Relapsing forms of MS		• Flushing • Nausea • Diarrhea • Upper abdominal pain • Decrease lymphocyte count • Elevated LFTs • Proteinuria • Pruritus	• Pregnancy Category: C • Monitor for infection: upper respiratory tract, urinary tract infection, influenza, nasopharyngitis • Monitor: CBC & LFT at baseline, one month and every six months for the first year of dosing

* Biogen idec. Press release details. Oral BG-12 (Dimethyl Fumarate) significantly reduced multiple sclerosis (MS) relapses and disability progression in Define Phase 3 Clinical Trial. http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1619878.

syndrome. Uhthoff was a French neurologist in the 19th century who recognized that heat (fever, increase in ambient temperature, or exercise) caused conduction block in demyelinated axons.[29]

Acute relapses are treated with glucocorticosteroids. The aim of these powerful anti-inflammatory agents is to limit the severity of relapses and speed the rate of recovery of active CNS lesions. Corticosteroids have little effect on long-term clinical outcome or disability.[28]

Expert opinion on acute relapse treatment suggests the use of high-dose I.V. corticosteroids for 3 to 5 days with or without an oral corticosteroid taper (patient or provider's preference).[27] An equivalent dose of oral prednisone daily for 3 to 7 days may be convenient and cost-effective.[27,28] Dexamethasone oral or I.V., due to its limited mineralocorticoid effect, may be better tolerated.[39]

Adverse reactions of corticosteroid treatment include risk of infection due to immunosuppression. Immediate concerns are for hypersensitivity reactions, fluid retention, hypertension, hyperglycemia, hypokalemia, hypernatremia, insomnia, psychiatric/behavioral manifestations, dyspepsia, and elevated BP. Long-term risks for weight gain, cataracts, avascular necrosis, and osteoporosis are considered.[27]

Complementary and alternative medicine(CAM)

Outside the realm of conventional medications, 75% of people with MS use CAMs.[52] Exercise, yoga, acupuncture, vitamin D, calcium psyllium for constipation, valerian, cranberry for urinary tract infection, prophylaxis, omega 3, and omega 6 fatty acids are beneficial on symptom management and quality of life as seen in some small studies.[32] The NP should be aware that substances that activate the immune system should be avoided in MS (Echinacea, zinc, Asian ginseng, garlic, alfalfa, astragalus, melatonin, and DHEA).[52] Bee sting therapy, chelation therapy, hyperbaric oxygen, Prokarin, magnets, and having amalgam fillings removed have no effect on MS.[53] There are no diets that have been shown to change disease outcomes.[53] The NMSS Consensus Statement of the use of cannabis states there is insufficient data to recommend marijuana or its derivatives as a treatment for MS symptoms.[54] Medical marijuana use is legal in 16 states and the District of Columbia. However, risks associated with long-term use may outweigh perceived benefit. Clinical trial data indicate that MS marijuana smokers had poorer cognitive function than people with MS who did not smoke marijuana.[55] Cannabis therapy for MS is approved as an oromucosal spray in Canada. The question about the impact of marijuana on MS symptoms will continue to be of interest to patients. Further clinical trial data may reveal its importance in immune modulation and symptom management. Low-dose naltrexone (LDN), chronic cerebrospinal venous insufficiency (CCSVI), hematopoietic stem cell transplantation (HSCT), and remyelination are of high interest to people with MS. Study data on LDN showed that 4.5 mg

nightly is safe, improves QOL, but has no effect on symptoms, relapse rate, or disease progression.[56] CCSVI, a novel concept, proposes that the cause of MS is not an immune system abnormality but rather an abnormality of the venous system. It is posited that CCSVI, by causing venous backpressure and iron deposition, secondarily activates an immune response. The excitement of CCSVI relates to its possible cure, as veins undergo angioplasty to improve venous flow of blood in the CNS. Safety and efficacy of CCSVI is currently under investigation. Several studies have not supported initial findings of venous anomalies. The stenting of jugular veins carries risk. Well-designed clinical trials are warranted. The NMSS has committed $2.4 million to CCSVI research. It may be several years until we know if CCSVI has any place in the armamentarium of MS treatments.[57] Lastly, stem cell research in MS, the purging of the immune system with chemotherapeutic agents (followed by the regeneration of healthy immune cells), or resetting the immune system as treatment has risk of mortality and little reported gain for patients. Small clinical trials have shown an effect on limiting inflammation and new lesion development but have not shown an effect on disease progression. HSCT may be effective in those with less disease burden.[58] Remyelination remains an in vitro endeavor.[58]

Women and MS

Because MS is most prevalent in woman of child bearing potential, it is important for NPs to tell female patients there is no evidence that MS has an effect on fertility or that pregnancy has an effect on the long-term clinical course of MS.[46] MS does not affect pregnancy outcomes, and pregnancy does not negatively impact MS. In fact, the number of MS relapses often decreases during pregnancy, especially in the second and third trimester, due to the protective effect of pregnancy hormones on the immune system.[47] If a relapse occurs, corticosteroids are shown to be safe during pregnancy. Obstetric care, labor, and delivery, including the use of all forms of anesthesia used at the time of delivery, are similar for women with MS and their non-MS counterparts. IMDs are not approved for use during pregnancy and not recommended during breastfeeding.[48] Relapse risk increases after delivery and may be mitigated by breastfeeding, use of corticosteroids, or use of IMDs.[49,50]

Emerging therapies

Barring a cure, safe and effective therapies with tolerable adverse reactions are the ideal treatment regime. While ongoing research exists to study disease causes and strategies to "reset" the immune system, such as stem cell transplantation or neuroregeneration, these strategies are exploratory and carry risk.[58] Emerging drugs hold promise.

Organizations supporting MS patients, caregivers, and professionals

National Multiple Society
www.nationalMSsociety.org

The Consortium of Multiple Sclerosis Centers
www.mscare.org

Can Do Multiple Sclerosis
http://www.mscando.org/

Veterans Affairs Medical Center Multiple Sclerosis Center of Excellence
www.va.gov/ms

The International Organization of Multiple Sclerosis Nurses
www.iomsn.org

Multiple Sclerosis Association of America
www.msassociation.org

Multiple Sclerosis Foundation
www.msfocus.org

Industry sponsored support
www.msactivesource.com
www.mslifelines.com
www.betaseron.com
www.sharedsolutions.com

Some of these drugs in clinical trials are oral agents (such as laquinimod) that may optimize treatment outcomes by improving long-term adherence.[59] Monoclonal antibodies such as alemtuzumab, daclizumab, ocrelizumab, and rituximab (given parenterally) are in late-stage development.[59] Some of the new drugs are showing significant efficacy in clinical trials. However, there are greater safety concerns than with the existing injectable, first-line therapies.[59] New agents will likely be approved as second-line therapies. Helping patients understand therapy risks and benefits is important to adherence and outcomes. Offering written information and guidance on reliable websites is important to decision making and patient autonomy.

Moving forward

MS is a disease affecting those in their most productive years. MS not only impacts the person diagnosed but family members and society as well. Living with a chronic, unpredictable, and progressive disease comes at a price. The payer is the patient who risks social, financial, and personal loss. The economic impact of MS is enormous. The per patient lifetime cost in the United States–both opportunity costs from loss of productivity (work) and the cost of disease maintenance–is upward of $2 million.[60,61] IMDs aim at improving disease, and

ultimately, lowering the economic burden. While the use of disease modulating therapies in MS results in health gains, these therapies come at a very high cost–$800,000/quality-adjusted life-years and relapse-free years.[62] MS disease management means ongoing education of patients and families when weighing the risks/benefits of drugs, recognizing the importance of symptom management, offering nonpharmacologic management strategies, and rehabilitation while treating acute relapses. NPs who are knowledgeable about the epidemiology, immunopathology, diagnosis, and disease modulation are able to manage MS in the patient's medical home–the primary care NP practice. Several organizations support people living with MS and their families through research, education, and advocacy (see *Organizations supporting MS patients, caregivers, and professionals*). There are many organizations that offer an abundant resource for the NP and patient with MS. NP

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