Multiple Sclerosis

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DIAGNOSTIC SUMMARY

- Episodic neurological symptoms, depending on the parts of the central nervous system (CNS) affected
- Typical onset in adults between ages 20 and 55 years
- Symptomatology not consistent with a single neurological lesion
- Diagnosis made based on clinical symptoms, magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analysis

GENERAL CONSIDERATIONS

Multiple sclerosis (MS) is a disabling disease of the CNS that commonly affects young and middle-aged adults.[1] Physicians have recognized MS since the mid-19th century, and although there were initially no management options, there has been significant therapeutic advancement since the 1990s with multiple effective disease-modifying therapies (DMTs) now available to treat MS.

In MS, the dysregulated immune system attacks the protective sheath (myelin) that covers nerve fibers in multiple locations through the CNS, referred to as areas of demyelination. MS pathology primarily consists of these multifocal areas of demyelination (plaques) in the brain, spinal cord, and optic nerves. In addition to the areas of demyelination, significant axonal damage affecting the CNS can also occur in severe forms of MS. Frequently, the nerves are permanently damaged or deteriorate concurrently with damage to myelin. Inflammatory cells composed predominantly of macrophages and lymphocytes are present when there is active demyelination within MS plaques, indicating that MS is an inflammatory disease.

MRI provides a means of visualizing MS lesions within the brain and spinal cord (Fig. 199.1). MS signs and symptoms depend on the parts of the CNS affected, and patients have varying levels of permanent disability depending on the degree of inflammation and resultant damage. Clinically, MS can cause a variety of neurological problems, depending

primarily on the location and severity of MS plaques (Table 199.1). Many MS symptoms, such as fatigue, cognitive impairment, and heat sensitivity, however, are not easily localized anatomically and are not well understood. In about 85% of cases, MS starts with a relapsing-remitting course.[2] Patients experience relapses or attacks of MS during which they develop a new neurological problem or worsening of preexisting symptoms. Relapses develop over a few days or weeks, followed by a period of improvement and stability, and typically last for more than 48 hours. In between relapses, patients are in remission and clinically stable, although they may have residual permanent neurological signs and symptoms from previous relapses. Relapses that cause symptoms represent only the "tip of the iceberg" of disease activity at this stage of the illness. Serial MRI studies in patients with MS have disclosed that new, asymptomatic MS lesions appear within the brain 5 to 10 times more commonly than symptomatic lesions, causing permanent damage that contributes to the overall MS disease burden.[3]

According to the natural history data, about 50% of patients with relapsing-remitting MS (RRMS) enter a progressive phase of the disease 10 to 15 years after onset. This progressive phase, called secondary progressive MS (SPMS), is characterized by a steady worsening of signs and symptoms. Patients with SPMS may or may not continue to have relapses. About 15% of MS patients have progressive worsening from the onset of their illness, a form of MS referred to as primary progressive MS (PPMS). Although MS is rarely fatal, it is often disabling. The natural history of MS suggested relatively quick progression of the disease from onset to having ambulation difficulty and walking with a cane occurring over a median of approximately 15 years. More recent studies report a significantly longer time to reaching this disability milestone, with a median time from onset to cane of 30 years.[4,5] Early studies of PPMS also reported short median time from disease onset to cane of less than 10 years. However, more recent studies show the median time of progression to be closer to 15 years. The widespread
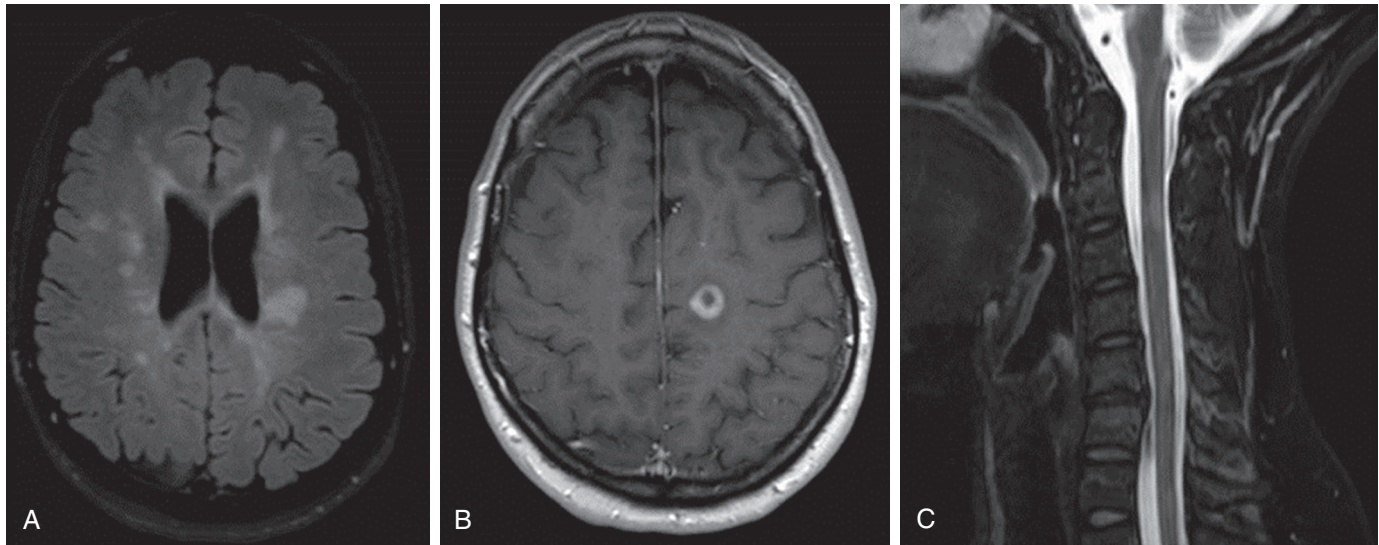
Fig. 199.1 Magnetic resonance imaging (MRI) of the brain and cervical spine of a patient with multiple sclerosis (MS). A, Axial T2 MRI brain with large areas of increased signal intensity adjacent to the lateral ventricles in the classic distribution typical for MS. B, Axial T1 MRI brain after gadolinium contrast agent with a ring-enhancing lesion in left centrum semiovale. C, Multiple cervical spine lesions, T2 sequence with increased signal intensity at multiple levels.

TABLE 199.1   Symptoms of Multiple Sclerosis and Their Localization

Location of Lesion	Symptoms
Cortical	Cognitive problems
Optic nerve	Vision loss
Brainstem	Diplopia
	Facial sensory loss
	Facial weakness
	Respiratory irregularities
Cerebellum	Imbalance
	Incoordination
	Vertigo
Spinal cord	Numbness, paresthesias, and/or weakness from level down
	Stiffness in limbs
	Constipation
	Urinary urgency, retention, incontinence

availability and use of immune-modulating medications for relapsing MS likely have played a role in the improved long-term MS prognosis.[6]

Up to 15% of patients with MS never develop any overt permanent disability. Most patients, however, develop varying degrees of permanent neurological disability. Although it can be difficult to predict which patients will progress and which patients will have benign MS, several prognostic factors for unfavorable clinical outcomes have been identified. Some of these factors include older age at onset; initial symptoms involving motor function; higher initial clinical activity, including high relapse rate; and increased disease progression in the first 5 years. Smoking tobacco and low serum vitamin D levels have also been determined to be predictors of poorer long-term outcome.

Epidemiology

It is estimated that MS affects approximately 2.5 million people worldwide and 400,000 people in the United States.[6] MS affects about 1 out of 1000 persons in the United States, Canada, and northern Europe. MS typically begins between the ages of 20 and 40 but may occur at any age.

Women are more commonly affected than men, with about 60% of cases being female. A strong racial influence on the risk of developing MS exists: it is most common among individuals of white and Caucasian backgrounds, particularly those of northern European descent.[7,8] Typical MS is rare among Asians and black Africans but is relatively common among black Americans. The racial predilection of MS is one piece of evidence indicating the strong influence of genes on the risk of developing MS. In addition to racial influences, there is also an interesting geographical distribution of the disease. Areas with the highest prevalence are located in higher latitudes, in both the northern and southern hemispheres.[9,10] These high-risk areas include the northern United States, Canada, Great Britain, Scandinavia, northern Europe, New Zealand, and Tasmania.[11,12]

Pathogenesis

Experts agree that MS results from an acquired immune dysregulation and aberrant immune activation, leading to inflammatory processes driven by macrophages and B and T lymphocytes in the CNS that result in demyelination and axonal damage. Activated T cells produce proinflammatory cytokines, which additionally contribute to tissue damage. Increased levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon (IFN)-γ, and interleukin (IL)-2, have been found in the peripheral blood, CSF, and brain lesions of patients with MS.[13–18] Numerous reports document the association between these cytokines and disease activity, thus implicating them as mediators of the immunopathogenesis of MS.[13,15–17] Anti-inflammatory cytokines IL-4, IL-5, IL-10, and IL-13 and transforming growth factor beta-1 (TGF-β1)[19] have down-regulatory effects on the immune system and are thought to be beneficial in MS.[20] Besides the role of macrophages, lymphocytes, and cytokines, other biomarkers, such as enzymes, can play an important role in MS pathogenesis. Matrix metallopeptidase-9 (MMP-9) is a group of enzymes responsible for the migration of immune cells to sites of inflammation as well as remodeling extracellular matrix, basement membrane, and other tissues in the body by breaking down collagen components in these tissues. MMP-9s are thought to play a significant role in the transmigration of inflammatory cells into the CNS by aiding in the disruption of the blood–brain barrier.[21,22] Several studies have shown higher serum levels of MMP-9 in patients with MS.[23–25]

MS pathology is defined as having three different categories of acute white-matter demyelination (The figure discussed in this section is under Reference 1 and could not be included due to copyright concerns.).[26] The most common types (patterns I and II) show a background of mononuclear phagocytes with perivascular and parenchymal T-cell infiltration. Pattern II is also characterized by immunoglobulin and complement deposition of antimyelin antibodies that can damage myelin either by initiating complement-mediated demyelination or assisting the phagocytosis of myelin by macrophages. Pattern III is seen in approximately 25% of biopsied active lesions and consists of oligodendrocyte apoptosis, and these lesions are similar to viral, toxic, and ischemic processes suggesting a "dying-back" phenomenon. This model of the acute MS lesion appears consistent with the most prevalent theory about MS, namely, that it is an immune-mediated disease. Less understood is what happens chronically after the acute phase: whether there is persistent myelin degeneration (smoldering), inflammation resolves without inflammation (chronic inactive), or if lesions are invested with a thin myelin sheath (remyelinated).

Risk Factors
Genes
Substantial evidence indicates that genetic and racial background influence the risk of developing MS.[27,28] Caucasian and African American populations appear to be at a much higher risk of developing MS than Asians. Having a first-order relative (parent or sibling) with MS increases the risk of developing the disease by five- to twentyfold. Perhaps the most compelling evidence of the genetic influence on the risk of developing MS comes from studies of twins where at least one twin has MS.[29] Among nonidentical twins, the chances of the second twin having MS are 1% to 2%, which is similar to the risk of nontwin sibling pairs. Among identical twins, the chance of the second twin having MS is only 25%, indicating the strong influence of environmental factors besides the genetic background. Although the cause of MS remains unknown, more than 100 genes are thought to affect the risk of developing MS.[30] The human leukocyte antigen (HLA) genes are thought to have the strongest association with MS risk, with the most evidence for HLA-DRB1.[31]

Infections
Considerable interest lies in identifying the target(s) of the pernicious inflammatory response in MS.[29] Viruses and microbial agents have been postulated to be associated with an increased risk of developing MS. For decades there has been interest in the possibility that one or more viruses or other microbial infections might cause MS. This interest stems from the inflammatory nature of MS and the apparent influence of the environment on the risk of developing MS, both suggesting the possibility of an infectious etiology. In addition, a spontaneous inflammatory demyelinating disease, called Japanese macaque encephalomyelitis (JME), has been observed in a colony of Japanese macaques at the Oregon National Primate Research Center. This disease appears remarkably similar to MS, with similar MRI white-matter lesions, clinical findings, and pathological findings. The JME white-matter lesions were cultured and revealed a previously undescribed herpesvirus.[32]

Although various infectious agents have been reported to be associated with MS—including measles, Epstein–Barr virus, distemper virus, coronavirus, retrovirus, herpes simplex, human herpesvirus-6, and *Chlamydia pneumoniae*—there is no convincing evidence at present of a linkage between any infectious agent and MS.[33] The lack of evidence does not exclude the possibility that an infectious agent causes MS, but currently, there is no widely accepted evidence associating MS with any specific virus or other microbe.

Environment
Geographical and seasonal influences. The association
with latitude and MS prevalence has shown mixed results and is confounded by factors that include migration, lifestyle habits, and biological and social influences. In general, there is an increased prevalence of MS in northern latitudes (high risk) and a decreased prevalence in southern latitudes (low risk). People who move from a low-risk to a high-risk area before age 15 acquire a higher risk of developing MS, whereas those who make the same move after adolescence retain a lower risk.[12,34] These observations suggest that an environmental exposure in the first two decades of life can influence the risk of developing MS. They also suggest that early sunlight exposure, which is correlated to serum vitamin D levels, may influence the risk for developing MS.[35]

Although not consistent to all geographical areas, there are several European epidemiological studies showing an association between season of birth and the risk of developing MS.[36–38] These studies indicate that there appears to be a lower risk for MS for births occurring after summer and a higher risk for MS for births occurring after winter. The authors reporting these findings suggest that maternal levels of vitamin D during the third trimester of pregnancy may influence the risk for MS, with a lower risk when maternal vitamin D levels are high (summer months) and a higher risk when maternal vitamin D levels are low (winter months). Taken together, there is some evidence to suggest that sunlight exposure and vitamin D levels at a young age may have an influential role in the risk of developing MS.

Diet. Diet has been investigated as a risk factor for acquiring
MS. An association was first suspected based on the observation that inland farming communities in Norway had a higher incidence of MS than areas near the coastline. It was discovered that the diets of the farmers were much higher in animal and dairy products than the diets of the coastal dwellers, whose diet was enriched by cold-water fish.[39] Additional studies have since correlated consumption of animal fat, animal protein, and meat from nonmarine mammals with the risk for MS.[40] Individual dietary components may also affect MS pathogenesis. One example is the discovery of molecular mimicry between myelin and some dietary proteins, such as butyrophilin protein in cow's milk, inducing antibodies targeted against myelin oligodendrocyte glycoprotein (MOG). High salt intake was recently postulated as a risk factor for MS development and to have an association with increased relapses in people with MS. However, this association has not been validated.[41]

An epidemiological review evaluating the relationship between diet and MS from 1952 through 1995 suggested that the risk of MS is significantly correlated with the following parameters: consumption of animal fat, animal protein, and meat from nonmarine mammals.[40] However, a large prospective cohort study using data from the Nurses' Health Study and Nurses' Health Study II found no evidence linking the risk of MS with the intake of saturated fats. The authors did note, however, that intake of linolenic acid, an omega-3 fatty acid (O3FA), but not fish oils or docosahexaenoic acid, was associated with a trend toward a lower risk for MS.[42]

Using data from the same cohorts, this same group also found no relationship between intake of fruits and vegetables and the risk of MS.[43] A case-control study in Canada assessing the relationship between nutritional factors and the risk of MS in 197 incident cases of MS and 202 frequency-matched controls found a positive association between animal fat intake and the risk of MS.[44]

Recent data highlight that vascular disease risk factors such as obesity, hypertension, hyperlipidemia, heart disease, and diabetes can deleteriously affect MS progression. The presence of obesity as a child and in early adulthood has been associated with a greater risk of developing MS.[41] Because most of the vascular disease risk factors, including

obesity, are influenced by dietary habits, these studies suggest that there likely is an influence of diet on the risk of developing MS.

Gut microbiome. The gut microbiome is an ecosystem of commensal, symbiotic, and pathogenic microorganisms that outnumber their host's genes by more than 100 times.[45] The gut microbiome and its relationship with health and disease have been subject to extensive research, and the gut microbiome has been shown to be involved in maintaining human metabolism, nutrition, physiology, immune function, and mental health. The gut–brain axis is a bidirectional neurohumoral communication system that integrates neural, hormonal, and immunological signaling between the host gut and brain activities.[46] Commensal, probiotic, and pathogenic bacteria in the gastrointestinal tract can activate neural pathways and CNS signaling systems and can influence the development of anxiety and depression.[47] The bidirectional relationship is reflected in the observation that stress can influence the integrity of the gut epithelium and can alter peristalsis, secretions, and mucin production, promoting changes in microbial composition.[45] The concept of a gut–brain axis suggests that modulation of the gut microbiota may be a feasible approach to the management of CNS disorders with significantly less toxicity than many of the pharmaceuticals used currently.

The gut microbiome has been implicated in the induction of autoimmune conditions in human diseases and experimental animal models, including inflammatory bowel disease, ankylosing spondylitis, uveitis, rheumatoid arthritis, type 1 diabetes, and experimental autoimmune encephalomyelitis (EAE).[48–50] Current methodologies investigating gut microbial diversity, such as next-generation, 16S rRNA gene-sequencing technologies, suggest a "dysbiotic" gut microbiota in both adult and pediatric subjects with MS.[51–53] An alteration in gut microbiota has also been apparent in subjects with MS on DMTs such as glatiramer acetate and interferons.[53] Additionally, alterations in gut microbiota appear to be associated with relapse risk in pediatric and adult MS subjects.[51,53] The current, but limited, knowledge of gut microbiome changes in MS are intriguing, and it remains unclear if alterations in the gut microbiome precede or are a consequence of MS pathogenesis. University of California–San Francisco (UCSF) researchers suggested a causal relationship of gut microbiota and MS in a study where transplanting microbiota from MS subjects was found to exacerbate symptoms in mice with EAE.[54,55] The same group evaluated 34 sets of twins discordant for MS, revealing that transplanting gut microbiota from the MS-affected twins into transgenic mice induced CNS-specific autoimmunity at a higher incidence than microbiota taken from the healthy twins.[56] Although human and mouse microbiota are not directly comparable, the biological pathways represented by MS-associated bacterial taxa largely overlap.

Many factors, both nonmodifiable and modifiable, can influence the composition of an individual's gut microbiome. These include genotype, age, sex, disease modifying therapies (DMTs) for MS such as interferon and glatiramer acetate, antibiotics, and diet. An animal model of the gut microbiome suggests that diet can rapidly influence the gut microbiome, with changes occurring within a single day of diet change from a low-fat, plant-polysaccharide–rich diet to a high-fat, high-sugar diet.[57,58] Analysis of the fecal microbiome of a high-fiber diet compared with a Western diet revealed underrepresentation of Enterobacteriaceae (*Shigella* and *Escherichia*) with an abundance of bacteria from the genus *Prevotella* and *Xylanibacter,* known to contain a set of bacterial genes for cellulose and xylan hydrolysis, useful in digestion in a predominantly plant-based diet.[58,59] The Enterobacteriaceae family members associated with a Western diet have been shown to exacerbate small intestinal inflammation, whereas the bacteria associated with high-fiber diets, including *Prevotella* and *Xylanibacter,* are associated with a protective role against gut inflammation.

Toxins and toxicants. All environmental pollutants have demonstrated prooxidant activity, with the most toxic compounds causing the most oxidative damage. These toxicants also typically deplete the level of reduced glutathione in the brain tissue and inhibit the function of the antioxidant enzymes. Both reactive oxygen and reactive nitrogen species (ROS and RNS) can directly oxidize and damage DNA, protein, and lipids in the brain, leading to neurodegeneration. Neurons are directly affected by this oxidative stress, as are the glial cells. Oxidative stress activates the glial cells, leading to an increased production and release of the proinflammatory chemicals interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-10 (IL-10); gamma-interferon (IFN-γ); and TNF-α.

The resulting neuroinflammation is a key component in the pathobiology of multiple sclerosis.[60] Activated glial cells and mast cells both appear to be responsible for the release of the proinflammatory chemical soup that fuels neuroinflammation. Glial cell activation has been implicated in the pathogenesis of epilepsy, Alzheimer's and Parkinson's diseases, MS, motor neuron diseases (amyotrophic lateral sclerosis [ALS]), stroke, and mood disorders.[61] Neuroinflammation is triggered by traumatic brain injury, endotoxicity (circulating levels of lipopolysaccharides), elevated blood sugar (glycation end products), stress, and a host of environmental toxicants, including air pollutants, heavy metals, and organophosphate pesticides.[62]

In a case-control study of children with MS having a father who worked in a gardening-related occupation (odds ratio [OR] = 2.18, 95% confidence interval [CI]: 1.14–4.16) or any household use of pesticide-related products (OR = 1.73, 95% CI; 1.06–2.81) were both associated with an increased risk of developing pediatric MS.[63] An Italian case-control study indicated that occupational solvent exposures could be related to the risk of MS, as both shoe/leather workers and mechanical manufacturing industry workers were found to have a twofold increase in the odds of developing MS.[64]

Summary of Risk Factors

Although there is general agreement that MS is an immune-mediated disease, why people develop MS remains uncertain. Epidemiological studies suggest a complex relationship between genetic and environmental factors that can influence both the risk of acquiring MS and disease progression in MS.

DIAGNOSTIC CONSIDERATIONS

MS remains a clinical diagnosis.[1] No single test (e.g., blood test, MRI examination, CSF study) is adequate to diagnose MS. The diagnosis relies on a knowledgeable physician taking a detailed history, performing a neurological examination, conducting various tests, and then making a diagnosis on the basis of all the data. Among the various practitioners, trained and experienced neurologists usually accurately diagnose MS. Even among neurologists, the rate of misdiagnosis of MS can be high because there are many mimics that appear similar to MS.[65] The diagnosis of MS rests on the *objective* demonstration of two or more areas of demyelination in the CNS that have occurred more than one time, and a diagnosis cannot be based only on a patient's symptoms.

Means of "objective" demonstration of areas of demyelination include the neurological examination; MRI of the brain and spinal cord; CSF examination; and electrophysiological tests (called evoked potentials) that assess visual, auditory, and somatosensory pathways. Evaluation of the CSF in a patient with suspected MS includes the presence of immunoglobulin G (IgG) production within the CNS, as seen by qualitative (oligoclonal bands) and quantitative (total IgG,

TABLE 199.2 Differential Diagnosis for Multiple Sclerosis

Infections of the central nervous system (CNS)	Syphilis
	Progressive multifocal leukoencephalopathy (PML)
	Lyme disease
	Human immunodeficiency virus (HIV)
	Human T-cell lymphotropic virus-1 (HTLV-1)
Inflammatory disorders of the CNS	Sjogren's syndrome
	Vasculitis
	Systemic lupus erythematosus (SLE)
	Neurosarcoidosis
	Behçet's disease
Genetic disorders	Hereditary myelopathies
	Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
	Leukodystrophies
	Hereditary cerebellar degeneration
	Mitochondrial disease
Brain tumors	Metastases
	Lymphoma
Deficiencies	Copper deficiency
	Vitamin B_{12} deficiency
Structural damage in brain or spinal cord	Cervical spondylosis
	Herniated disc
	Chiari's malformation
Other non-MS demyelinating disorders	Neuromyelitis optica (NMO)
	Acute disseminated encephalomyelitis (ADEM)

IgG index, and IgG synthesis rate) IgG changes. Excluding other disorders that can masquerade as MS is critical; these include unusual causes of stroke; nutritional deficiencies; genetic leukodystrophies or leukoencephalopathies; cancer; spinal cord compression from tumors, herniated disks, or spinal canal stenosis; vascular malformations of the spinal cord; infectious etiologies; and various other inflammatory disorders of the CNS (see Table 199.2 for a list). Although MS was formerly difficult to diagnose, MRI scanning has significantly improved the ability to diagnose MS in its early stages because it allows imaging of areas of demyelination in the brain and spinal cord and also helps exclude the presence of other diseases that might explain the patient's symptoms. The criteria used to diagnose MS are summarized in the revised 2017 McDonald criteria table (Table 199.3).

THERAPEUTIC CONSIDERATIONS

Disease Modifying Therapies (DMTs)

The conventional approach to treating MS includes the use of medications to control disease activity and some symptoms and rehabilitation interventions to alleviate symptoms resulting from damage to the CNS. Medications that help decrease MS disease activity are referred to as disease-modifying agents, or DMTs. (See Table 199.4 for a complete list.) Most of the DMTs are approved by the U.S. Food and Drug Administration (FDA) for relapsing forms of MS. These DMTs can broadly be broken down into route of delivery, including injectable medications, oral medications, and infusions. Compared with a placebo, these medications decrease the relapse rate by 30% to 67%, decrease new lesion formation in the brain as detected by MRI, and decrease the risk of developing a permanent neurological disability.

TABLE 199.3 2017 Revised McDonald MS Diagnostic Criteria

Clinical Presentation (Attacks)	Lesions (Objective Clinical Evidence or MRI)	Additional Data Needed to Make MS Diagnosis
≥2	≥2	None. Dissemination in space (DIS) and dissemination in time (DIT) have been met
≥2	1	One of these criteria: • DIS: additional clinical attack implicating different CNS site • DIS: ≥1 MS-typical T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial or spinal cord
1	≥2	One of these criteria: • DIT: additional clinical attack • DIT: simultaneous presence of both enhancing and nonenhancing MS-typical MRI lesion • DIT: new lesion or enhancing MRI lesion compared with baseline scan • CSF-specific oligoclonal bands
1	1	DIS: additional clinical attack implicating a different CNS site or by ≥1 MRI -typical lesion in ≥2 areas of CNS AND one of these criteria: • DIT: additional clinical attack or by MRI • DIT: simultaneous presence of both enhancing and nonenhancing MS-typical MRI lesion • DIT: new lesion or enhancing MRI lesion compared with baseline scan • CSF-specific oligoclonal bands
0 (progression from onset)		1 year of disability progression (retrospective or prospective) AND two of these criteria: • ≥1 symptomatic or asymptomatic MS-typical lesion • ≥2 spinal cord lesions • CSF-specific oligoclonal bands

CFS, Cerebrospinal fluid; CNS, central nervous system; MRI, magnetic resonance imaging; MS, multiple sclerosis.
If the 2017 McDonald criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If MS is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald criteria are not completely met, the diagnosis is possible MS. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis.

TABLE 199.4 Disease Modifying Therapies for Multiple Sclerosis

	Drug	FDA Approval	Dosing	AEs	FDA Warnings/Monitoring
Injectable	Interferon beta-1a (Avonex, Rebif, Plegridy: pegylated interferon)	Avonex: RMS, CIS 1996 Rebif: RMS 2002 Plegridy: RMS 2014	Avonex: 30 mcg IM once weekly Rebif: 22 mcg or 44 mcg SQ three times a week Plegridy: 125 mcg SQ every 14 days	Flu-like symptoms (chills, fever, muscle pain, fatigue, weakness) after injection, headache, injection-site reactions (swelling redness, pain)	• Monitor closely if history of depression, seizures, cardiac problems • Rare allergic reactions **Monitoring:** • Baseline and periodic LFTs • Periodic CBC due to lowering of WBCs, RBCs, platelets
	Interferon beta-1b (Betaseron or Extavia)	Betaseron: RMS 1993 Extavia: RMS, CIS 2009	0.25 mg SQ every other day	Flu-like symptoms after injection, headache, injection-site reactions (swelling redness, pain), injection-site skin breakdown	• Monitor closely if history of depression, seizures, cardiac problems • Rare allergic reactions • Possible skin damage and infection **Monitoring:** • Baseline and periodic LFTs • Periodic CBC due to lowering of WBCs, RBCs, platelets
	Glatiramer acetate (Copaxone, generic)	RMS 1996	20 mg SQ every day, or 40 mg subcutaneously three times per week	Injection-site reactions (redness, pain, swelling), flushing, shortness of breath, rash, chest pain	• ~16% postinjection reaction, including flushing, chest pain, palpitations, anxiety, shortness of breath, constriction of the throat, and transient skin eruptions; resolves after 15 min • Lipoatrophy (skin depressions) at injection sites, skin damage • Careful rotation of injection sites **Monitoring** • No screening labs required
	Daclizumab (Zinbryta)	RMS 2016 **Withdrawn from market March 2, 2018**	150 mg SQ once a month	Colds, upper respiratory tract infections, rash, flu, rash, throat pain, bronchitis, eczema, depression, swollen lymph nodes	• Risk for severe liver injury • Immune-mediated disorders **Monitoring** • Baseline LFTs and monthly during treatment up to 6 months after last dose
Oral	Teriflunomide (Aubagio)	RMS 2012	7- or 14-mg pill once daily	Headache, hair thinning, diarrhea, nausea, abnormal liver tests	• Can cause major birth defects up to 2 years after discontinuation **Monitoring** • Baseline LFTs and monthly during first 6 mo, then routinely • CBC at baseline and routinely due to lowering WBCs and increased risk for infection • Screen for TB • Renal function tests routinely
	Fingolimod (Gilenya)	RMS 2010	0.5-mg capsule once daily	Headache, flu, diarrhea, back pain, liver enzyme elevations, sinusitis, abdominal pain, pain in extremities and cough	• Risk of macular edema • Lowers heart rate • Cryptococcal meningitis **Monitoring** • Vision test before and 3 months after starting • Requires a first-dose observation, ECG before first dose • CBC at baseline and routinely; consider discontinuation if ALC <200 • Increased risk for PML • VZV (chickenpox/shingles) antibody, if negative—recommend VZV vaccination 6 wk before start
	Dimethyl fumarate (Tecfidera)	RMS 2013	120-mg capsule taken twice daily for 1 week, followed by 240-mg capsule taken twice daily thereafter	Flushing (sensation of heat or itching and a blush on the skin), gastrointestinal issues (nausea, diarrhea, abdominal pain)	• Can cause severe allergic reactions **Monitoring** • CBC at baseline and routinely, at least 6 months initially; consider discontinuation if ALC <600 • Some cases of PML

TABLE 199.4 Disease Modifying Therapies for Multiple Sclerosis—cont'd

	Drug	FDA Approval	Dosing	AEs	FDA Warnings/Monitoring
Infusion	Natalizumab (Tysabri)	RMS 2006	300 mg IV once every 28 days	Headache, fatigue, joint pain, chest discomfort, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash.	• Increases risk of PML • Liver damage risk • Anaphylaxis and other allergic reactions • Risk of infections, meningitis, and encephalitis **Monitoring** • JCV antibody at least every 6 mo • Baseline and periodic LFTs
	Alemtuzumab (Lemtrada)	RMS (if inadequate response to ≥2 DMTs)	12 mg IV per day for 5 consecutive days, followed by 12 mg per day on 3 consecutive days 1 year later	Rash, headache, fever, nasal congestion, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infections, hives, itching, thyroid gland disorders, fungal infection, pain in joints, extremities and back, diarrhea, vomiting, flushing Infusion reactions (including nausea, hives, itching, insomnia, chills, flushing, fatigue, shortness of breath, changes in the sense of taste, indigestion, dizziness, pain) are also common while the medication is being administered and for 24 hours or more after the infusion is over	• Serious, sometimes fatal autoimmune conditions (ITP, autoimmune renal disease) • Risk of infusion reactions, steroids given before and during first 3 days after infusion • Increases risk of malignancies (thyroid cancer, melanoma, blood cancers) • Skin testing before and yearly • Thyroid disorders • No live vaccinations **Monitoring** • CBC, kidney tests, UA before and every month until 48 months after last infusion • Thyroid testing every 3 months until 48 months after last infusion • VZV antibody, may require vaccination 6 wk before start
	Mitoxantrone (Novantrone)	RMS, SPMS 2000	12 mg/m² IV every 3 months Lifetime cumulative dose limit of approximately 8–12 doses over 2–3 years (140 mg/m²)	Nausea, hair loss, menstrual change, upper respiratory infection, urinary tract infection, mouth sores, irregular heartbeat, diarrhea, constipation, back pain, sinusitis, headache, blue-green urine	• AML, can be fatal • Risk of heart damage • Contraindicated if preexisting heart problems, liver disease, and certain blood disorders **Monitoring** • Tests of heart function before each dose and periodically after treatment has ended • Baseline and periodic LFTs
	Ocrelizumab (Ocrevus)	RMS, PPMS 2017	600 mg every 6 months (first dose: 300 mg IV on day 1 and 300 mg IV 2 weeks later)	Infusion reactions (most commonly itchy skin, rash, throat irritation, flushed face or fever, headache), which in rare instances may be life threatening; increased risk of infections, including respiratory tract infections and herpes infections; possible increase in malignancies, including breast cancer	• Infusion reactions • Chronic hepatitis B reactivation • Increases risk of infection • Vaccinations 6 wk before infusion **Monitoring** • Hepatitis B antibody screening • An increased risk of breast cancer may exist; follow standard breast cancer screening guidelines

AE, Adverse effect; ALC, absolute lymphocyte count; AML, acute myeloid leukemia; CBC, complete blood count; CIS, clinically isolated syndrome; ECG, electrocardiogram; FDA, U.S. Food and Drug Administration; IM, intramuscular; ITP, immune thrombocytopenia; IV, intravenous; JCV, John Cunningham virus; LFT, liver function tests; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RBC, red blood cell; RMS, relapsing multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SQ, subcutaneous; TB, tuberculosis; UA, urinalysis; VZV, varicella zoster virus; WBC, white blood cell.

The injectable medications form the platform therapies and include human recombinant interferon-β (Avonex, Betaseron, Rebif, and Plegridy) and glatiramer acetate (Copaxone, Glatopa). Interferons (IFNs) are cytokines that mediate antiviral, antiproliferative, and immunomodulatory processes. There are three major forms of IFNs: alpha (α), beta (β), and gamma (γ), which have some overlaps in function yet are distinct, with IFN-β showing benefit in the management of MS. Although the precise mechanism by which IFN-β works in MS is not certain, the immunomodulatory effects proposed to occur include inhibition of proinflammatory T-cell activation and proliferation, destruction of autoreactive T cells, cytokine modulation, and prevention of migration across the blood–brain barrier.[19,66] IFN-β therapy has been found to decrease annualized relapse rates by 27% to 36% and reduce disability progression by 30% to 38% in various clinical trials. Glatiramer acetate is a random polymer of four amino acids that stimulates protective T cells and is the safest option of the DMTs. In multiple randomized trials, glatiramer was shown to reduce the relapse rate by 28% and reduce disability accumulation (risk ratio of 0.6) compared with placebo.[67] Glatiramer acetate and IFN-β therapies are frequently used as first-line therapy for MS due to an excellent safety profile. Another injectable, daclizumab (Zynbryta), has been taken off the market due to hepatitis risk.

The oral medications include three medications, fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera). The mechanism of action of fingolimod involves the reduction of CNS inflammation and axonal damage by retaining lymphocytes in the lymph nodes so that fewer are able to enter the CNS.[68,69] Fingolimod has been shown to reduce relapse rates by 50%, decrease the rate of disease progression, and decrease disease activity (MRI lesions).[68,69]

Teriflunomide prevents the division of active immune cells, including T and B lymphocytes.[19,70] Teriflunomide has been shown to reduce relapse rates by 36% compared with placebo and to decrease the rate of brain atrophy as assessed by MRI. Teriflunomide remains in the bloodstream for up to 2 years after discontinuation and is associated with fetal complications in pregnancy when taken by either males or females.[19]

Dimethyl fumarate is based on a German psoriasis treatment that may enhance Th2 cellular response through the activation of intracellular nuclear pathways.[71] Dimethyl fumarate affects transcription pathways that change the balance of T helper cell profiles, causing immunosuppression. Dimethyl fumarate decreases the absolute relapse risk by 56% compared with placebo, decreases the number of new lesions on MRI, and decreases the rate of confirmed disability progression.[71]

The FDA approved-infusions include natalizumab (Tysabri), alemtuzumab (Lemtrada), and ocrelizumab (Ocrevus). Natalizumab is a monoclonal antibody against α-4 integrin that prevents inflammatory cells from entering the CNS and has been shown to decrease the annualized relapse rate by 68% and reduce disease activity (new or enlarging MRI lesions) by 83% over 2 years compared with placebo.[72,73] The main risk with natalizumab is the possibility of developing progressive multifocal leukoencephalopathy (PML), which is associated with exposure to John Cunningham virus (JCV). Natalizumab was taken off the market shortly after its release due to the development of PML before reintroduction with recommendations to monitor JCV antibody, which correlates with risk of PML development.[19]

Alemtuzumab is a monoclonal antibody to CD-52 that is present on most immune cells in the body and was approved by the FDA in 2014 for relapsing MS. Alemtuzumab is given as two annual infusions and has been shown to reduce relapses by 55% compared with the use of IFN-β-1a.[74]

Ocrelizumab is a monoclonal antibody directed at B-lymphocytes and was approved by the FDA in 2017 for both primary progressive MS and relapsing forms of MS. Ocrelizumab has been shown to reduce annual relapses by 50% compared with IFN-β-1a, with a 95% reduction in new active MRI lesions compared with IFN-β-1a.[74] Ocrelizumab, in addition to being approved for the management of relapsing MS, has been shown to be effective in decreasing the accumulation of disability in patients with primary progressive MS and is the only FDA-approved drug for this indication. Ocrelizumab reduced confirmed disability progression by 24% compared with a placebo in those with primary progressive MS.[74]

Although conventional DMTs are able to reduce disease activity in relapsing forms of MS, they have limitations, which include only a modest effect on prolonging time to disability, rising costs (average cost is more than $60,000 per year), and side effects (e.g., injection-site reactions and neutralizing antibodies for IFN-β; bradycardia and arrhythmia for fingolimod; birth defects with teriflunomide; flushing and diarrhea with dimethyl fumarate).

Corticosteroids, such as methylprednisolone, given in high doses can decrease the duration of relapses of MS but do not affect the degree of eventual recovery after relapses.[75] A number of different medications are useful for treating various symptoms of MS, such as fatigue, bladder dysfunction, and spasticity, but these medications do not reverse the damage that has already occurred or decrease disease activity. Given these considerations, an effort to identify natural therapies that have benefit for people with MS is warranted.

Natural Medicine Therapeutic Considerations

From a natural medicine standpoint, there are four major approaches to treating MS:
- Diet
- Nutritional supplements
- Exercise
- Stress management

Including all four provides the most comprehensive natural medicine treatment plan, and it is recommended that these should be used in combination with appropriate conventional therapies.

Diet

Diet is one way to influence general health, which is important to maintain in people with a chronic disease such as MS. There is no panacea diet for MS. However, various health factors, particularly vascular disease risk factors such as hypertension, hyperlipidemia, salt intake, diabetes, and obesity, can contribute to MS disability progression.[41] These vascular risk factors are readily influenced by diet and can be modulated with intervention.

Low-Saturated-Fat Diets

Swank diet. The Swank diet is one of the oldest and most well known dietary interventions used by people with MS. Dr. Roy Swank reported that a diet low in saturated fats maintained over a long period of time tends to slow disease progression, reduce the number of attacks, and decrease mortality.[76,77] Swank began treating patients with his low-fat diet in 1948. The approach to using a low-fat diet supplemented with cod liver oil is based on epidemiological studies that found a decreased incidence of MS in populations that had a low consumption of animal fats with a high consumption of cold-water fish.

Based on current knowledge of the pathogenesis of MS, the rationale of using the Swank diet or other diets low in saturated fats in patients with MS relates to the general health benefits of such a diet and the anti-inflammatory and perhaps neuron membrane–stabilizing effects

of a diet enriched with O3FAs. Although the consumption of red meat is significantly restricted on the Swank diet, fish appears to be particularly indicated because of its excellent protein content and, perhaps more importantly, its high content of O3FAs. Cold-water fish such as mackerel, salmon, and herring are rich in O3FAs, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). As reviewed in the "Nutritional Supplements" section, O3FAs have anti-inflammatory effects that may be of benefit in MS. In addition, because optimal neuronal functioning depends on cell membrane fluidity, which in turn depends on lipid composition, optimal essential fatty acid (EFA) levels may be important in exerting neuroprotective effects by maintaining healthy neuronal functioning.[77,78] Decreasing animal fats and increasing O3FAs in the diet thus may improve neuronal function by modulating neuronal lipid composition.

Since Dr. Swank's observational studies, two pilot studies evaluating diet in MS have been conducted. An open-label study evaluated the effects of a diet low in saturated fats combined with fish-oil supplementation and vitamin B complex and vitamin C in newly diagnosed RRMS.[79] Beside dietary modifications, subjects were advised to reduce their intake of sugar, coffee, tea, and alcohol and to stop smoking. Diet was monitored over 2 years by a 4-day dietary record at the end of each year, and plasma fatty acid levels were monitored at baseline, year 1, and year 2.

A significant increase occurred in the intake of fish, and a reduction in food items containing saturated fats occurred after 2 years. A significant increase occurred in plasma levels of O3FAs, and a significant decrease occurred in plasma omega-6 fatty acids (O6FAs). Over the 2 years of the study, patients had significant reductions in both relapse rates and disability. This study, however, had significant limitations because there was no comparison group.

Although caution is warranted in interpreting the results of this small open-label study, its outcome does concur with Dr. Swank's long-term studies on diet and fish-oil supplementation for people with MS.

A partially blinded, randomized controlled study evaluated the effect of low-fat dietary intervention with O3FA supplementation in 31 subjects with RRMS.[80] The intervention lasted for 12 months, and the primary outcome was quality of life, evaluated using the Short Form Health Survey Questionnaire (SF-36). Subjects were randomized into one of two groups: the low-fat diet/fish-oil group and the diet/olive-oil group. The low-fat diet/fish-oil group followed a diet that did not exceed 15% of saturated fats (percentage of total daily calorie intake) plus fish-oil capsules (daily doses of EPA 1.98 g and DHA 1.32 g). The diet/olive-oil group followed the American Heart Association's Step I diet, 30% saturated fats (percentage of total daily calorie intake) plus olive-oil capsules (6 capsules of 1 g of olive oil per day). The subjects were followed for an average of 11 ± 2.9 months, and the low-fat diet/fish-oil group maintained better quality-of-life scores for physical well-being (although not statistically significant) than the group using olive-oil supplementation. The scores on the mental health component were similar in the two intervention groups. At the 6-month time point, the olive-oil group reported an improvement in fatigue compared with the fish-oil group ($P = 0.035$), which continued for 12 months. For both intervention groups, relapse rates were reduced compared with the year before entering the study. This study suggests that a diet low in saturated fats with fish-oil supplementation might promote better physical and mental health for people with MS. Because all subjects improved after 12 months, the study also suggests that diet modification in addition to supplementation with a "good oil" (fish oil or olive oil) may be beneficial in people with MS.

The epidemiological studies suggesting a link between a high-fat diet and an increased risk of MS coupled with the results from the three low-fat-diet studies reviewed show a consistency in identifying a low-fat diet as a therapy that may benefit people with MS. A person with MS following a low-fat diet will gain general health benefits.

McDougall diet. The McDougall diet is a very low-fat, strictly plant-based diet that is based mainly on complex carbohydrates as the main source of energy. This diet is based on starch, with 10% of calories derived from fat, 14% from protein, and 76% from carbohydrates. Animal-derived products, dairy products, and oils are restricted from the McDougall diet.

Paleolithic diet. The Paleolithic (Paleo) diet is based on the idea that humans are better equipped to handle the diet consumed by their Paleolithic ancestors. The Paleo diet is a component of the Wahls protocol for MS management developed by Dr. Terry Wahls. The diet consists of nondomesticated lean meats and plant-based foods except fruits, nuts, roots, and legumes. The ratio of saturated to polyunsaturated fatty acids is 1.4 to 2.0:1. The diet consists of three cups of green leafy vegetables, three cups of sulfur-rich vegetables, and three cups of intensely colored vegetables daily. In addition, two tablespoons of O3FAs and 4 oz or more each of animal protein and plant protein is to be consumed daily. No more than two servings per week of gluten-free grains/starchy foods are recommended, and gluten, dairy, and eggs are prohibited.

Small open-label studies have been conducted in subjects with secondary progressive MS with a multimodal intervention consisting of diet, massage, acupuncture, meditation, and implementation of the Paleo diet. These limited studies showed the diet was well tolerated, and although adherence to the diet was not consistent, participants had improved fatigue. The fatigue changes were not clinically significant, and the results were further diluted by the fact that additional interventions were employed rather than just the diet. The Paleo diet also has the added risk of nutritional deficiencies, including folic acid, vitamin B_1, and vitamin B_6, from the decreased intake of fortified cereals, as well as calcium and vitamin D deficiency from the lack of dairy intake.[41]

Caloric Restriction

Diet can lead to inflammation via oxidative stress based on the type and amount of food that is consumed. Increases in caloric intake and glycemic load, and a high intake of saturated fat, trans fat, or O6FAs can lead to postprandial inflammation. Inflammation is decreased by the consumption of polyphenols, O3FAs, caloric restriction, and exercise. Caloric restriction has shown beneficial effects on disease activity in mouse models of MS.

A pilot study evaluating the effect of restricting the diet to 1700 to 1800 kcal was performed in 33 subjects with RRMS and 10 subjects with PPMS. Although there were no differences in neurological examination results in the follow-up period of 6 months, there was a 59% reduction of activated MMP-9 in subjects with PPMS and 51% reduction in subjects with RRMS.[81] In another study, 60 subjects with RRMS were randomized to one of three parallel groups: one group that continued a usual diet, one group with a usual diet enhanced by an initial 7-day fasting episode, and one group with ketogenic diet over the course of 6 months. Subjects were asked to complete the Multiple Sclerosis Quality of Life-54 Questionnaire (MS-54). The subjects who were on the ketogenic diet and those on the initial fasting diet showed an improvement in the MS-54.[82]

Nutritional Supplements

Essential fatty acids. O3FAs are found in both plant and animal forms, with alpha-linolenic acid (ALA) being found in plant foods and EPA and DHA being found in marine foods. O6FAs include linoleic acid, which is found in vegetable oils, nuts, and seeds, and arachidonic

acid, which is found in meat and eggs. The body can synthesize most of the fats needed from the diet. There are two essential fatty acids (EFAs) that cannot be synthesized in the body and must be obtained from food: ALA (an O3FA) and linoleic acid (an O6FA). Omega-9 fatty acids (O9FAs) are monounsaturated fats, are made in the body, and are considered nonessential.

Omega-3 fatty acids. There have been multiple studies evaluating O3FAs in RRMS. One open-label study in RRMS patients ($n = 10$) showed a significant decrease in MMP-9 levels secreted from unstimulated immune cells after supplementing with fish-oil concentrate at 8 g/day (containing 2.9 g EPA and 1.9 g DHA) for 3 months. All subjects showed a decrease in MMP-9 levels whether or not they were on MS disease-modifying medication.[83]

O3FAs have been shown to have immunomodulatory effects. In vitro, animal, and ex vivo human studies have reported a decrease in mRNA and protein levels of a number of cytokines, including TNF-α, IFN-γ, IL-1, IL-2, and VCAM-1. One published study documented the effects of supplementation with fish oils enriched with the O3FAs EPA and DHA on cytokine secretion in MS.[84] In this study, levels of IL-1-β, TNF-α, IL-2, IFN-γ, prostaglandin E2 (PGE2), and LTB4 secreted from unstimulated and stimulated immune cells in people with MS and healthy controls were evaluated. Twenty subjects with MS and 15 age-matched healthy controls were supplemented with 6 g/day of fish oil containing 3 g EPA and 1.8 g DHA for 6 months. All subjects with MS had a stable course of MS for at least 3 months before enrollment, had not modified their diet as a consequence of developing MS, and were not on any DMTs.

Outcome measures compared baseline levels of the cytokines mentioned to levels after 3 and 6 months of supplementation in both subjects with MS and healthy controls. After 3 and 6 months of fish-oil supplementation, there was a significant decrease in the levels of soluble IL-1β ($P = 0.03$), TNF-α ($P = 0.02$), IL-2 ($P = 0.002$), and IFN-γ ($P = 0.01$) in the unstimulated peripheral blood mononuclear cells (PBMCs) of both groups. A significant difference was observed after 3 and 6 months of supplementation in the levels of soluble IL-1β ($P = 0.01$), TNF-α ($P = 0.02$), IL-2 ($P = 0.003$), and IFN-γ ($P = 0.005$) from stimulated immune cells of both groups. Cytokine levels returned to baseline values after a 3-month washout period.

One study has examined the use of O3FA supplementation in MS.[85] This was a large ($n = 312$) double-blind, placebo-controlled trial in which patients with MS were randomized to receive either 20 capsules of fish oil per day or olive oil containing 72% oleic acid for 2 years. The total daily dose of EPA was 1.71 g, and the total daily dose of DHA was 1.41 g. This study reported a trend in improvement in the O3FA–treated subjects compared with controls; however, these results did not achieve statistical significance ($P = 0.07$). There are some criticisms of the study design, including that both groups in the study were advised to follow a diet low in animal fats and high in polyunsaturated fatty acids. Importantly, both groups developed changes in serum fatty acid content over the 2 years of the study. The lack of a comparison of fish-oil supplementation with a placebo in patients who did not have other dietary modifications may have affected the ability of the study to detect a statistically significant therapeutic benefit of O3FA supplementation.

Omega-6 fatty acids. There is some experimental basis for considering supplementation with O6FAs. Two studies in an animal model of MS reported that supplementation with linoleic acid, which is rich in O6FAs, decreased the severity of disease[86] and reduced inflammation in the CNS.[87]

O6FA (linoleic acid) supplementation for the treatment of MS has been investigated in at least three double-blind clinical trials.[88–90] O6FA spread (11–23 g/day linoleic acid) was provided in comparison

with oleic acid (control). Disability progression at 24 months was provided from two trials encompassing 144 patients and did not show a difference. Two additional studies evaluated relapse risk in 132 subjects with RRMS and showed a small decrease in relapse rate at 24 months (weighted mean difference [WMD] of 0.79, CI 0.63–1.00, $p = 0.05$). Linoleic acid (2.9–3.4 g/day) did not show a significant decrease in the rate of progression in 65 subjects with progressive MS.[19]

Evening primrose oil, which is rich in the O6FA gamma-linoleic acid, is commonly used by patients with MS. Gamma-linolenic acid might be more effective than linoleic acid because of its easier incorporation into brain lipids and its possibly greater effect on immune function.[91] However, evening primrose oil contains low levels of gamma-linolenic acid, and the product is relatively expensive. Large and prohibitively expensive amounts of evening primrose oil would have to be used to obtain adequate supplementation. In addition, a single pilot trial of evening primrose oil in MS failed to demonstrate any benefit.[88] Despite its common use by patients with MS, supplementation with evening primrose oil is not recommended.[92] The data to support O3FA or O6FA supplementation are lacking, and although there may be no harm in the use of EFAs, there is no major effect on disease progression in MS.

Vitamin D. Epidemiological studies have found that low vitamin D intake and low serum levels of vitamin D may increase the risk of MS.[93,94] A retrospective study of serum levels of vitamin D in people with MS ($n = 199$) found 84% of them to be deficient.[95] Studies of vitamin D in animal models of MS have shown that vitamin D has the ability to decrease immune cell–mediated inflammation and prevent disease.[96,97] MS studies in animal models suggest that vitamin D may have a beneficial role in MS by affecting the ability of inflammatory cells to enter the CNS.[98]

Numerous human studies have evaluated both vitamin D supplementation and associations between serum vitamin D levels and biomarkers of MS disease progression. One open-label study ($N = 16$ subjects with MS) using oral calcitriol at a target dose of 2.5 mcg/dL found the intervention safe and tolerable up to a year of supplementation.[99] Another study examined the seasonal variation in the serum levels of vitamin D in people with MS ($n = 103$) and healthy controls ($n = 110$) and found these levels to be significantly higher in the summer compared with the winter in both cohorts.[99] This study also observed that higher circulating levels of vitamin D in women were correlated with lower MS-related disability. A pilot study evaluating 29 subjects with RRMS found a positive correlation between serum vitamin D levels and levels of the anti-inflammatory cytokine IL-4.[100] In another 1-year prospective study, vitamin D supplementation and increases in serum vitamin D concentrations resulted in a significant decrease in annual relapses in MS subjects. This was observed in subjects who had vitamin D levels below 50 nmol/L.[19]

Thus emerging evidence from both animal studies and human studies suggests that vitamin D may have potential beneficial effects in MS. Given that 30% to 50% of the general population may be deficient in vitamin D,[101] experts believe that serum levels of vitamin D should be evaluated to assess and treat vitamin D deficiency in MS. Experts recommend vitamin D supplementation to target a serum level of (40–60 ng/mL or 75–150 nmol/L).[19]

Lipoic acid. Oral lipoic acid (LA) is an over-the-counter supplement that has been investigated as an antioxidant, anti-inflammatory, and neuroprotective agent in MS. LA and its reduced form, dihydrolipoic acid (DHLA), are potent antioxidants with multiple modes of action. LA/DHLA can regenerate other antioxidants, such as glutathione, vitamin C, and vitamin E; serve as an ROS scavenger; repair oxidative damage; and chelate metallic ions involved in oxidative injury. DHLA acts by restoring reduced levels of other antioxidants, such as glutathione,

and by repairing oxidative damage.[102–104] LA is absorbed from the diet and synthesized de novo; it readily converts intracellularly to DHLA. Both LA and DHLA are present in both extracellular and intracellular environments.[105] In an animal model of MS, LA has been shown to suppress the development of disease by preventing inflammatory T cells from entering the CNS.[106–108] The immunomodulatory effects of LA include inhibition of T-cell production of MMP-9, inhibition of the expression of the adhesion molecules ICAM-1 and VCAM-1, and stimulation of cAMP by the prostaglandin receptors EP2 and EP4.[106,107,109]

One small double-blind, placebo-controlled study evaluated the optimal dosing of oral LA in RRMS.[110] In this study, 37 subjects were randomized to one of four groups: (1) placebo, (2) LA 600 mg twice a day, (3) LA 1200 mg once a day, and (4) LA 1200 mg twice a day. The study found that LA given at 600 mg twice a day was barely measurable in serum, whereas LA given at the dose of 1200 mg once daily showed significantly higher serum levels. The study also found an association between higher LA serum levels and lower MMP-9 levels and higher LA serum levels with lower soluble ICAM-1 levels. The investigators concluded that oral LA between 600 and 1200 mg can be measured in serum and that higher serum levels of LA are associated with an increased immunomodulatory activity that may benefit people with MS.

A pilot double-blind, placebo-controlled study of daily oral 1200 mg LA in 51 patients with SPMS revealed a decreased annualized rate of brain volume over the course of 2 years in the LA-treated subjects.[111] There was also a trend of improved 25-foot walk time in the group that received LA. Larger studies are under way to further investigate the association of LA and whole-brain atrophy in progressive MS.

Biotin. Biotin, also known as vitamin H or vitamin B$_7$, is a water-soluble B vitamin that is taken orally and is known to have multiple functions in energy metabolism and fatty acid synthesis. It is known to participate in myelin synthesis by activating the enzyme acetyl-CoA carboxylase. High-dose biotin (300–600 mg daily) has been studied in both primary and secondary progressive MS. An initial pilot study of 23 patients with progressive MS was performed, and 91.3% of the patients had an improvement in clinical measurements.[112]

Patients with MS with a progressive decline in disability score over the previous 2 years were randomized to either placebo or a formulation termed MD10003, a highly concentrated oral form of biotin.[113] MD10003 was given at 100 mg three times daily over a 12-month period, and 12.6% of treated patients had an improvement in disability score by 1 point on the Expanded Disability Status Scale (EDSS), versus none of the placebo group.

Although these studies have revealed promising results, there have been negative results associated with biotin. A study completed in Italy including 41 patients with progressive MS treated with high-dose biotin resulted in a significant increase in relapse rate.[114] Many of these patients had PPMS and had never experienced an MS relapse before. High-dose biotin has also been shown to interfere with various laboratory tests, resulting in a number of adverse events, including at least one death.[115] Some of the laboratory values affected include measures of cardiac injury and thyroid function.[116]

Botanical Medicines
Ginkgo biloba

Cognitive impairment affects up to 40% to 50% of people with MS,[117,118] and there are currently no effective symptomatic therapies for cognitive dysfunction in MS. *Ginkgo biloba* has been evaluated for cognitive impairment in Alzheimer's disease, with mixed findings. A recent meta-analysis of these studies reports that *G. biloba* is safe, but the benefits for cognitive impairment and dementia are not predictable.[119]

There is one randomized, placebo-controlled pilot study evaluating the effects of a standardized *G. biloba* extract on cognitive performance in 43 subjects with MS.[120] Subjects were randomized to receive 120 mg of *G. biloba* twice a day or placebo for 12 weeks. The outcomes of the study included several neuropsychological tests, including the Stroop test, which is a measure of attention and executive function. Subjects receiving *G. biloba* showed significantly improved performance on the Stroop test as well as improvement in subjective reports of cognitive deficits compared with the placebo group. This pilot study also showed that *G. biloba* extract was safe and well tolerated. Although the studies evaluating *G. biloba* in people with dementia have shown mixed results, this supplement has been shown to be safe and well tolerated in many clinical trials. The pilot study in MS also demonstrated that *G. biloba* standardized extract given at 120 mg twice a day for 12 weeks was safe in people with MS. Given its safety profile and limited evidence on improving attention and executive function in MS, *G. biloba* standardized extract may benefit MS patients with cognitive impairment.

Cannabinoids

Cannabinoids are a group of compounds found in the plant cannabis, also known as marijuana. The major psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol (THC). THC binds to cannabinoid receptors (CB) in the CNS and acts as a partial agonist to both CB1 and CB2 receptors. Cannabidiol (CBD) is a nonpsychoactive constituent in cannabis and the major constituent in the plant. It is thought to decrease the clearance of THC by affecting liver metabolism. It binds to both CB1 and CB2 receptors in the CNS, with a higher affinity to the CB2 receptor. Cannabinoids can be delivered orally (e.g., cannabis extract, synthetic THC), through mucosa (e.g., cannabis extract oral spray, nabiximols [Sativex]), and smoked.

In a review of nine controlled studies evaluating a combination of THC and CBD (Marinol) for spasticity in MS, it was found that THC–CBD was well tolerated and improved patient self-reports of spasticity, although objective measures for spasticity such as the Ashworth score did not show significant improvement compared with a placebo.[121] The authors report that side effects were mild in both the treatment and placebo groups. The authors concluded that there was a significant improvement in patient-reported spasticity with the combination of THC–CBD and that THC–CBD was well tolerated in MS. Unlike the dietary supplements discussed, Marinol is a controlled substance and requires a prescription in the United States.

OTHER CONSIDERATIONS
Exercise

In the past, MS patients were often advised not to exercise because increased body temperature and nerve fiber fatigue resulting from exercise were thought to induce transient symptomatic worsening and provide no long-term benefit. However, research has since shown that regular exercise is beneficial for people with MS.[122–128] Four studies and two meta-analyses reported that compared with an MS nonexercise group, the MS exercise group demonstrated improvement in the subjects' reports of fatigue, quality of life, well-being, and walking ability.[123,124,127,129] A systemic review of 26 studies on the effects of exercise, physical activity, and physical fitness on cognitive-performance outcomes in people with MS suggested beneficial effects of physical fitness, physical activity, and regular exercise on cognitive performance in people with MS.[130] In addition to direct effects on MS, regular exercise provides benefits in multiple facets of health, including cardiovascular risk; metabolic functioning, including blood sugar maintenance; mental health and mood; bone

mineralization; and reduced risk for falls.[132] MS represents only one aspect of a person's health, and balancing other factors by maintaining a healthy lifestyle is crucial. In summary, evidence indicates that regular exercise is beneficial in MS and should be part of any natural medicine approach to treating MS.

Stress and Multiple Sclerosis

Patients with MS often report that stress worsens their MS symptoms and consequently triggers an exacerbation. In a review of the scientific literature reporting associations between psychological stress and worsening of MS symptoms, an expert panel concluded that there was a possible relationship between antecedent stress and either MS onset or exacerbations.[133] A prospective longitudinal study of patients with MS designed to examine the relationship between stressful life events, psychological stress, and disease activity as measured by MRI found that increased conflicts and disruptions in routine were followed by an increased risk of developing new brain lesions 8 weeks later.[134] Perceived stress in patients with MS has been associated with MS exacerbations in a number of studies.[135]

Given the emerging evidence that antecedent stressors may contribute to the development of new lesions in MS and that perceived stress is associated with MS exacerbations, therapies that reduce stress are highly recommended in MS.

Mind–Body

There are very few scientific studies evaluating mind–body interventions such as yoga, meditation, and prayer in MS.[136] Mind–body techniques using meditation, yoga, and slowed breathing to reduce stress in cancer patients have shown that these therapies are effective in decreasing stress, improving quality of life, and improving sleep.[137]

Stress Management Therapy

A randomized controlled study investigated the effect of stress management therapy (SMT) in MRI outcomes in people with MS.[130] Experienced therapists administered 16 individual 50-minute SMT sessions over a 24-week period followed by a 24-week period of observation. SMT first consisted of six sessions focused on relaxation, teaching problem-solving skills, cognitive restructuring, and enhancement of social support. Participants were then able to tailor their treatment using option modules, including management of cognitive problems, communication, assertiveness, fatigue management, anxiety reduction, management of sexual dysfunction, and management of insomnia. MRIs were obtained at 8-week intervals during the 24-week active-treatment period. Although the study was underpowered and enrolled fewer patients than originally planned, significantly more patients who underwent SMT (76.8%) were free of lesions versus the controls (54.7%).

Tai Chi

There are two reported pilot studies evaluating the use of Tai Chi in people with MS.[125,126] To evaluate the effects of training in the principles of "mindfulness of movement" from tai chi/qi gong in MS, 16 patients with secondary progressive MS were divided into 8 matched pairs. Each pair was randomized into a mindfulness group or a usual-care group (i.e., standard medical care for MS). Although there was no difference between groups in measures of balance, there was a significant improvement in the mindfulness group in self-reported measures of MS-related symptoms.[125] In a nonrandomized uncontrolled pilot study, 19 people with MS underwent tai chi training twice weekly for 8 weeks. Outcomes measures compared pretraining with posttraining scores. Posttraining outcomes demonstrated an improvement in walking speed, hamstring flexibility, and subjects' reports of well-being and quality of life.[126]

Yoga

There has been one randomized controlled study evaluating yoga in MS.[138] Sixty-nine subjects were randomized to one of three groups: (1) wait-list control ($n = 22$), (2) exercise ($n = 26$), and (3) yoga ($n = 21$). Those in the yoga group showed significant improvements in quality of life and physical measures compared with those randomized to the exercise or wait-list control group.

Mindfulness-Based Intervention

There has been one randomized study evaluating a mindfulness-based intervention (MBI) in MS.[139] One hundred and fifty subjects were randomized to an MBI ($n = 76$) or usual care ($n = 74$), with an intervention period of 8 weeks and a 6-month postintervention follow-up. Subjects randomized to MBI underwent training that included a 2½ hour session, once a week, for 8 weeks and one 7-hour session on Saturdays (Jon Kabat-Zinn's Mindfulness-Based Stress Reduction Program).[140] Subjects receiving usual care were offered MBI training after completing outcome assessments at the time equivalent of the MBI intervention and at 6 months postintervention. Compared with the usual-care group, subjects randomized to MBI showed significant improvements in quality of life, fatigue, anxiety, and depression. Mind–body interventions show promise of benefit in MS and offer a nonpharmacological therapy that can be effective in reducing stress, improving fatigue, and improving quality of life in MS.

THERAPEUTIC APPROACH

We believe that a natural medicine approach to MS management should be personalized for each individual, including dietary modification, nutritional supplementation, incorporation of exercise, and stress reduction techniques, complementary to the conventional medical approach including the use of DMT. Although the data supporting the benefits of each of these individual complementary therapies in MS management are limited, natural medicine approaches when used in conjunction with the approved MS DMTs have the potential to improve the general health of patients and may provide specific benefit in helping control the disease and improve symptoms.

Diet

Although there is no one diet for MS that has a proven efficacy, a few diets, such as the Swank diet (low saturated fat, with 15 g/day or less of saturated fat intake; unsaturated fat intake of a minimum of 20 g/day and maximum of 50 g/day; other details as described earlier), McDougall diet (very low-fat, strictly plant-based diet primarily based on starch, with ~10% of calories to be derived from fat, 14% from protein, and 76% from carbohydrates), and modified Paleo diet (nondomesticated, lean meats and plant-based foods except fruits, nuts, roots, and legumes; three cups each of green leafy, sulfur-rich, and intensely colored vegetables daily, two tablespoons of O3FAs, 4 oz or more each of animal and plant protein to be consumed daily) have some limited evidence of benefit with fatigue, quality of life, and possibly mortality (long-term Swank diet studies) in MS. The common theme of all of these diets is that patients with MS should limit processed foods and consume fresh, high-quality, whole foods. The key difference between the McDougall diet and the modified Paleo diet is the consumption of animal food, which is an area of unresolved controversy.

Nutritional Supplements

Various oral supplements have been studied in MS, including fish oils, vitamin C, vitamin D, biotin, lipoic acid, and *G. biloba*. Except for the stronger data showing possible beneficial effects of vitamin D supplementation, other supplements have not yet shown convincing benefit in MS management. Biotin supplementation remains currently under investigation, and because of its potential to cause interference with certain blood-based laboratory tests, careful use in clinical practice is warranted. An antioxidant, lipoic acid has convincing potential to decrease the rate of brain-volume loss in those with SPMS, and hence its supplementation may be considered. Our recommendation for vitamin D_3 and lipoic acid supplementation is as follows:

- Vitamin D_3: 2000 to 8000 Units/day with the goal of achieving blood levels at an ideal range of 40 to 60 ng/mL 25-hydroxy D3 (supplementing with vitamin D requires attention to vitamins A and K2).
- Consider lipoic acid 1200 mg daily.

Exercise

The type and amount of exercise should be tailored to the patient. Mild to moderate exercise for at least 30 minutes three times a week is recommended for most people with MS. Types of exercise recommended for MS can include walking, stretching, bicycling, low-impact aerobics, stationary cycling, swimming or water aerobics, yoga, and tai chi. Strategies to prevent overheating can include the use of air-conditioning and a cooling vest that can prevent temporary worsening of MS symptoms.

Stress Reduction

As with exercise, the therapies used for stress should also be tailored to the individual person with MS. Broadly, key stress-reduction therapies recommended for MS are yoga, exercise, meditation, deep breathing or breathing exercises, and prayer.

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