

Natural Approaches to Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). The disease is characterized by loss of myelin, the fatty tissue that surrounds and protects nerve fibers allowing them to conduct electrical impulses. In MS, scar tissue, or sclerosis, forms at the sites of demyelination, with destruction of neuronal axons and progressive neurologic disability. The National Multiple Sclerosis Society estimates that 400,000 individuals in the United States have MS.¹

Etiology and Epidemiology

The etiology of MS is unknown, but evidence suggests that genetic, environmental, and immunologic factors and infectious agents may be involved. Currently, MS is presumed to be an autoimmune disease that develops in genetically susceptible individuals upon activation by some unknown environmental trigger.

Several risk factors have been associated with MS. Tobacco smoking significantly increases the odds of developing MS.² So do other lifestyle factors, such as drinking coffee and alcohol.³ Women are 2–3 times more likely to develop MS than men, and Caucasians, particularly those of Northern European descent, are more likely to develop MS than other ethnic groups. Individuals living at northern latitudes are also at increased risk, suggesting a possible link with vitamin D and sun exposure. In addition, migration from one geographic area to another changes an individual's risk for MS. Individuals who move before the age of 15 take on the risk associated with their new geographical location. If an individual migrates after the age of 15, the change in risk is seen in the next generation.³

It is apparent that genetics plays a role in the etiology of MS, given the increased risk of the disease in siblings of individuals with MS, as well as a greater concordance rate in monozygotic compared to dizygotic twins.⁴ In addition, research indicates that first-degree relatives of individuals with MS have a sevenfold greater than average risk of developing the disease.⁵ Considerable research is being done to determine the gene or genes that cause(s) susceptibility to MS, and currently, the most consistent finding involves the major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) system. A specific finding is

that a variant in the HLA-DRB1 allele is linked to an increased risk of MS. Most recently, scientists have also found that variants of the gene for the alpha chain of the interleukin (IL)-7 receptor and the gene for the alpha chain of the interleukin IL-2 receptor are associated with an increased risk of MS.⁶

Numerous infectious agents have also been associated with MS and are currently being investigated. Evidence indicates that infectious mononucleosis caused by the Epstein-Barr virus increases the risk of MS, and that this increased risk persists for at least 30 years after infection.⁷ Research also shows that infectious mononucleosis in adolescence or young adulthood increases the risk of MS by 2.3-fold.⁸ Among other findings, *Varicella zoster* viral DNA has been detected more frequently than average in individuals with MS, and is found in 43.5% of individuals with relapsing–remitting MS. The results of this same study demonstrated active replication of JC virus and human herpes virus-6 (HHV-6) in the CNS of some individuals with MS.⁹ Some research also suggests that there is a link between the recombinant hepatitis B vaccine and increased risk of developing MS.¹⁰

Studies of pregnancy in women with MS also suggest a role of hormones in the disease. Of the women studied, 75% showed a distinct shift from a Th2 cytokine bias during pregnancy to a Th1 cytokine bias postpartum.¹¹

Pathology

Individuals with MS experience a variety of symptoms, and can have a relapsing–remitting course of disease; or a primary progressive course; or a relapsing–remitting followed by a progressive course; or what is known as a secondary-progressive course; or a progressive-relapsing course. Relapses of MS are defined as the appearance of new or worsening neurologic symptoms lasting longer than 24 hours. These symptoms usually evolve over a period of 24–48 hours, plateau for several weeks, and may resolve over periods ranging from weeks to several months. Common symptoms of MS include fatigue, visual changes, numbness, weakness, muscle spasticity, and depression. Additional symptoms may include difficulty with walking, problems with balance and coordination, dizziness or vertigo, emotional changes, cognitive impairment, bladder or bowel problems, pain, and tremor. The most common presenting symptoms of MS are diplopia, numbness and tingling in the extremities, and unilateral loss of vision from optic neuritis.

The pathology of MS includes dysfunction in both the immune and nervous systems. Inflammatory cytokines, macrophages, microglia, antibodies, and free radicals may all cause damage to myelin and axons. Degenerative changes are characteristic of progressive forms of MS, while inflammatory changes within the CNS are characteristic of the relapsing–remitting form of the disease. Large numbers of inflammatory cells are seen in new lesions, while fewer are seen in chronic lesions.

Immune Dysfunction

The immune response plays a key role in the pathogenesis of MS. T-lymphocytes are implicated in the disease process. The activation of CD4 + T-cells and their differentiation into T-helper-1 (Th1) cells are critical events in the initial steps of MS, and these cells are probably also important mediators in the long-term progression of the disease. Cytokines secreted by Th1 cells, such as IL-12, interferon (IFN)–gamma, tumor necrosis factor (TNF)–alpha, and IL-2, are believed to be involved in the pathology of MS. Th2 cytokines suppress Th1 activity and include IL-4, IL-10, and transforming growth factor (TGF)–beta. MS patients have increased circulating T-cell and antibody reactivity to the myelin proteins and gangliosides that are essential to the structural integrity of the myelin sheath. The pathogenesis of MS involves a breakdown in T-cell tolerance to myelin proteins, such as myelin basic protein (MBP).

Free Radicals

Free radicals are believed to play a role in the pathogenesis of MS. Persons with MS have elevated concentrations of markers of nitric oxide (NO) production, including nitrate and nitrite, in their cerebrospinal fluid (CSF), blood, and urine. Research suggests that NO has a role in the axonal degeneration and impairment of axonal conduction, disruption of the blood–brain barrier, and oligodendrocyte injury and demyelination in MS.¹² NO is also found in increased concentrations in inflammatory MS lesions, possibly as the result of increased expression of inducible nitric oxide synthase (iNOS) by astrocytes and macrophages. Astrocytes, macrophages, and oligodendrocytes in these lesions have also shown elevated levels of nitrotyrosine, indicating the presence of peroxynitrite, a highly reactive metabolite of NO, that may be the primary source of injury of oligodendrocytes in MS patients.¹³ A study of CSF levels of nitrate and nitrite in MS patients over a period of 3 years found increased CSF levels of nitrate and nitrite in mildly disabled individuals, which correlated with the volume of lesions found on magnetic resonance imaging (MRI). Greater than normal levels of nitrate and nitrite in the CSF at the time of baseline examination of MS patients also correlated with clinical progression of the disease and with MRI results.¹⁴

Neurologic Dysfunction

Abnormalities in the concentrations and relative concentrations of various neurotransmitters are thought to play a part in the pathogenesis of MS. Research has found that persons with MS have

increased levels of CSF and the excitatory neurotransmitters glutamate, aspartate, and noradrenaline. Increased blood levels of glutamine, asparagine, and glycine were also found in these patients.¹⁵ Further suggesting neuronal and axonal dysfunction in MS is the finding of altered levels of myoinositol, creatine, choline, glutamate, glutamine, and N-acetyl-aspartate in surrounding white and gray matter.¹⁶

Diagnosis

No specific test or set of criteria now exists for making a definitive diagnosis of MS. The current, generally accepted diagnostic standard, known as the revised McDonald criteria, was first described in 2005 and is based on the patient's history, diagnostic tests, results of neurologic examination, and findings on MRI. A positive diagnosis requires at least two distinct, CNS-related neurologic symptoms occurring in different anatomical locations and on different occasions, which are not caused by another disease process. An MRI scan performed at least 30 days after the onset of symptoms and showing lesions compatible with MS can be used to establish a second episode of the disease in the absence of prior clinical evidence of its presence. Further tests for the diagnosis of MS may include analysis of the CSF to detect an elevated immunoglobulin (Ig)G index, and/or the finding on protein electrophoresis of bands indicating oligoclonal IgG in the CSF but not in the serum. An electroencephalogram may show a greater than normal number of evoked potentials. Additional testing may be needed to exclude other causes, such as chronic infectious disease, of clinical symptoms often seen in MS.

Conventional Therapies

IFN-beta (IFN-B) (e.g., IFNA beta-1b, *Betaseron*; IFN beta-1a, *Avonex*; and IFN beta-1a, *Rebif*)¹⁷ is used to modify the immune response in MS. IFN-B affects the immune system by inhibiting T-cell stimulation and increasing the activity of CD8 suppressor lymphocytes. IFN-B also regulates the production of IFN-gamma. The net effect is to reduce the overall immune response to myelin in MS. Also, IFN-B restores the integrity of the blood–brain barrier, decreasing T-cell migration into the brain.

In inflammatory conditions in the CNS such as multiple sclerosis or experimental autoimmune encephalomyelitis (EAE), circulating lymphocytes and monocytes/macrophages readily cross the blood–brain barrier and gain access to the CNS leading to edema, inflammation, and demyelination. Also often used to modify the disease process in MS is glatiramer acetate, a mixture of synthetic polypeptides composed of four amino acids, and based on the structure of MBP, which is believed to inhibit the T-cell response to multiple antigens in myelin. Glatiramer acetate induces T-regulatory cells known as GA-specific regulatory CD4+ and CD8+ lymphocytes, as well as causing a

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shift from Th1 to Th2 activity, increasing the secretion of anti-inflammatory cytokines and suppressing the autoimmunity led by Th1 cells.¹⁸

When IFNs and glatiramer acetate do not effectively control MS, immunosuppressant drugs are often used. The most commonly used such agents are azathioprine, cyclophosphamide, methotrexate, and mitoxantrone. Mitoxantrone (Novantrone) is often used to reduce neurologic disability and/or the frequency of clinical relapses in secondary progressive, progressive-relapsing, and worsening relapsing–remitting MS. This agent acts by suppressing lymphocyte production in bone marrow, decreasing T-cell and B-cell numbers.¹⁹

High-dose corticosteroids are used to manage acute relapses. Intravenous methylprednisolone is the standard treatment for MS relapses and elicits rapid reduction of gadolinium enhancing (Gd+) lesions seen on brain MRIs of patients with MS.²⁰ Natalizumab (Tysabri) is a recombinant humanized anti- α -4 integrin monoclonal antibody approved for use in relapsing–remitting MS patients. It decreases leukocyte migration from peripheral blood into the CNS.²¹

Natural Therapies

Vitamin D

Research has found that higher serum levels of 25-hydroxyvitamin D are associated with a decreased risk of developing MS,²² and animal models of the disease indicate that supplementation with vitamin D reduces the frequency of MS and retards its progression. A study of vitamin D supplementation showed it to be associated with a 40% reduction in MS risk,²³ and another study found a strong association between reduced exposure to sunlight, decreased vitamin D levels, and greater disability in persons with MS.²⁴ It has also been found that vitamin D levels are lower during relapses of MS than during remission periods, suggesting a possible role of vitamin D on the course of the disease,²⁵ and the finding that concentrations of 25-hydroxyvitamin D are lower and those of intact parathyroid hormone are higher during relapses than during remissions suggests that altered calcium metabolism may also play a role in the course of MS.²⁶

Alpha Lipoic Acid

Alpha lipoic acid (ALA) is a potent antioxidant and coenzyme required for numerous biochemical pathways. Studies with animal models of MS indicate that supplementation with ALA retards progression of the disease and decreases demyelination and T-cell and macrophage infiltration into the CNS.²⁷ Additional research with animal models indicates that ALA decreases T-cell migration and stabilizes the dysfunctional blood–brain barrier in MS, as well as inhibiting damage to the barrier caused by reactive oxygen species (ROS).²⁸ Human studies indicate that ALA is well tolerated in MS, and decreases the concentrations of such markers of inflammation as matrix metalloproteinase-9 (MMP-9) and soluble intercellular adhesion molecule-1 (sICAMP-1).²⁹ Additionally, ALA enhances immunomodulatory activity by increasing the concentration of cyclic adenosine monophosphate (cAMP) in human T-cells and natural killer cells.³⁰



Canola plants.

Essential Fatty Acids

Supplementation with essential fatty acids (EFAs) has proven beneficial in MS. EFAs compete with proinflammatory metabolic processes to decrease the synthesis of inflammatory mediators, in addition to suppressing B- and T-lymphocyte proliferation and decreasing antibody production. The two EFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in high concentrations in fatty fish such as cod, salmon, and mackerel. The combination of a low-fat diet and supplementation with omega-3 fatty acids was found to decrease fatigue in patients with MS and to decrease the relapse rate in the disease.³¹

Alpha-linolenic acid, an omega-3 fatty acid commonly found in *Linum usitatissimum* (flax), canola, and *Glycine max* (soy) beans, can be taken as a supplement, although this is considered a secondary choice by many clinicians since alpha-linolenic acid does not appear to be as therapeutically efficient as EPA and DHA supplementation. Studies have also found that treatment of microglial cultures with either omega-3 fatty acids or fish oil inhibits the production of the myelin toxin MMP-9,³² and that supplementation with omega-3 polyunsaturated fatty acids positively affects cytokines in MS patients. The latter study found a decrease in IL-1beta, TNF-alpha, IL-2, and IFN-gamma in association with such supplementation, and a diminished production of the proinflammatory eicosanoids prostaglandin E2 and leukotriene B4.³³



Olive oil.

B Vitamins

Several vitamins have been shown to be present in suboptimal concentrations in patients with MS. Vitamin B12, which is important for myelin formation as well as for immunomodulatory activity, may be among these vitamins.³⁴ Significantly lower serum levels of vitamin B12 have been found in persons in whom symptoms of MS appear before the age of 18 than in patients with symptoms of later onset.³⁵ In addition to serum B12 deficiency, evidence also indicates decreased levels of red blood cell folate in patients with MS.³⁶

However, at least one study, rather than finding overtly decreased levels of vitamin B12 in MS patients, found that the binding capacity for unsaturated vitamin B12 was significantly decreased in these patients as compared to controls and individuals with other neurologic disorders. When the scientists went on to provide massive supplemental doses of 60 mg daily of methyl-vitamin B12 for 6 months to a small group of patients with chronic progressive MS, the scientists found that abnormalities in visual and brainstem auditory evoked potentials improved more often during the therapy than in the period before supplementation.³⁷ Researchers have suggested that vitamin B12 deficiency may make an individual more susceptible to immunologic or viral insults.

Antioxidants

ROS appear to play a role in the pathology of MS. Epigallocatechin-3-gallate (EGCG), a constituent of *Camellia sinensis* (green tea) known for its antioxidant activity, reduced the clinical severity of experimental autoimmune encephalomyelitis (EAE) in mice when given at or after the onset of EAE in the animals, by limiting brain inflammation and reducing neuronal damage. EAE is the animal model used to study MS as this condition can be induced in laboratory animals. EAE is a demyelinating disease in which the myelin is damaged and exhibits similar clinical progression. EGCG also directly inhibited the formation of neurotoxic ROS in neurons.³⁸ Curcumin, a constituent of *Curcuma longa* (turmeric) with potent antioxidant activity, is also known for its anti-inflammatory activity. Supplementation with curcumin in animal models of MS decreased the duration and severity of the disease by decreasing secretion of the proinflammatory cytokine IL-12 from monocytes and microglial cells resulting in decreased T-cell proliferation and Th1 differentiation.³⁹

Another supplement with antioxidant properties is *Ginkgo biloba* (ginkgo) extract. When given at a dose of 240 mg per day to persons with MS, this was found to decrease fatigue and improve functionality over that of controls.⁴⁰ Treatment of animal models of MS with the antioxidant supplement N-acetyl-L-cysteine (NAC) was also found to attenuate clinical disease, increase the concentrations of anti-inflammatory cytokines such as IL-10, and decrease both nitrite production and the Th1-cell secretion of IFN-gamma.⁴¹

Quercetin, a dietary flavonoid found in many plants and known for its anti-inflammatory and antioxidant activity, was found to attenuate EAE, and decrease IL-12-induced T-cell proliferation and Th1-cell differentiation.⁴² A further finding in MS has been that of low levels of the antioxidant nutrients beta carotene, retinol, alpha-tocopherol, and ascorbic acid in serum or CSF.⁴³

Carnitine

The results of a randomized, double-blind, crossover study have suggested that acetyl-L-carnitine given supplementally at 1 g twice daily is better tolerated and more effective than amantadine for the treatment of MS-related fatigue as evaluated with the Fatigue Severity Scale.⁴⁴ Additional studies have found lower carnitine levels in patients treated for MS than in untreated MS patients or controls. When levocarnitine was given orally as a supplement at a dose of 3–6 g per day, 63% of MS patients undergoing immunosuppressive or immunomodulatory therapy exhibited reductions in the intensity of their fatigue.⁴⁵

Additional Nutrients

Two further nutrients investigated in MS have been glucosamine and retinoic acid. Supplementation with glucosamine in animal models of MS was found to increase levels of Th2 cytokines and suppress the Th1 response. Inflammation and demyelination in the CNS were decreased and EAE was suppressed.⁴⁶ This suggests that supplemental glucosamine may act as both an immunosuppressant and immunomodulating agent in MS.⁴⁶

Retinoic acid has been shown to inhibit clinical signs of MS in animal models by preferentially inducing Th2 cytokines over those secreted by Th1 cells.⁴⁷ Research has also found that 9-*cis*-

retinoic acid inhibits the production of NO and proinflammatory cytokines by microglia and astrocytes, which are processes implicated in the pathology of MS.⁴⁸ In other research, the combination of IFN-B-1b with all-*trans*-retinoic acid inhibited IFN-gamma secreting cells, enhanced T-suppressor-cell activity, and decreased T-cell proliferation to a greater degree than did either treatment alone.⁴⁹

In addition, significantly decreased levels of manganese and increased levels of copper have been found in the CSF of MS patients as compared to controls.⁵⁰

Diet

Evidence suggests that specific dietary modifications may be beneficial in MS. The Swank diet advocates a low intake of saturated fat of less than 15 g per day and relatively high intake of polyunsaturated oil. Other recommendations of the diet are an unsaturated fat intake of 20–50 g per day; abstention from red meat including pork for the first year, followed by a maximum 3 oz of red meat per week thereafter; consumption of dairy products having no fat or less than 1% butterfat; no use of processed food containing saturated fat; an unlimited intake of fruits and vegetables; and supplementation with cod liver oil at 1 tsp daily.⁵¹ Butter, margarine, lard, shortening, cocoa butter, coconut oil, hydrogenated oil, palm oil, and imitation dairy products must be avoided.

Swank followed a group of patients for 34 years and demonstrated relative success with his low-fat diet. His study showed that patients who adhered to the recommendation of 20 g of fat per day or less experienced significantly less deterioration and had much lower death rates than subjects who consumed greater fat than this per day. Persons with minimum disability at the beginning of the trial experienced the greatest benefit.⁵²

A study compared a diet with 15% fat and fish oil supplementation with a diet of 30% fat and olive oil supplementation in individuals with relapsing–remitting MS. The patients had moderate clinical improvements with the former as compared with the latter regimen as measured with the Physical Components Summary Scale and the Short Health Status Questionnaire. The relapse rate in both groups was decreased.³¹ A further study found that consumption of liquid cow's milk was significantly associated with an increased prevalence of MS worldwide, with a weaker correlation for consumption of butter and cream.⁵³

Hormone Balancing

Research suggests that hormones influence the duration and severity of autoimmunity affecting the CNS. One study found abnormally low levels of testosterone in human males with MS, and animal models of MS have shown low levels of testosterone and increased levels of luteinizing hormone,⁵⁴ as well as an inverse relationship between testosterone levels and levels of inflammatory mediators.⁵⁴ Another study showed improvement in cognitive performance, a slowing of brain atrophy, and increased lean body mass upon supplementation with a gel containing 100 mg of testosterone given daily to men with relapsing–remitting MS for a 12-month period.⁵⁵ However, the supplementation had no significant effect on the numbers or vol-

umes of sclerotic lesions.⁵⁵ Levels of the androgen dehydroepiandrosterone (DHEA) have also been found to be significantly lower in MS patients than in healthy individuals.⁵⁶

Estrogen levels also appear to play a role in the severity of MS symptoms. Among a group of menopausal women with MS, 82% reported premenstrually increased symptom severity, 54% reported a worsening of symptoms with menopause, and 75% of those who had tried hormone replacement therapy reported an improvement in symptoms.⁵⁷ Studies indicate that low-dose estradiol may be beneficial for women with MS. Animal models show that low-dose estradiol inhibits T-cell migration into the CNS and has neuroprotective effects that promote axon and myelin survival.⁵⁸ Estrogens have also been found to inhibit the production of proinflammatory Th1 cytokines such as IL-12, TNF-alpha, and IFN-gamma, and to stimulate the production of anti-inflammatory Th2 cytokines such as IL-10, IL-4, and TGF-beta. This may explain why estrogen modulates Th1- and Th2-mediated diseases such as MS.⁵⁹ Studies of pregnancy in women with MS also suggest a role of hormones in the disease. Of the women studied, 75% showed a distinct shift from a Th2 cytokine bias during pregnancy to a Th1 cytokine bias postpartum.⁶⁰ Clinical trials using daily doses of estriol that are equivalent to the amount produced during pregnancy have shown significant reduction in MS lesions in patients with the relapsing–remitting form of the disease.¹¹

Conclusion

MS is a complicated disease of unknown etiology, whose initiation and progression are affected by numerous factors. A number of natural therapies have been shown to benefit individuals with MS, and need to be more vigorously studied. □

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