

Multiple Sclerosis

An update on environmental factors and treatments

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Introduction

Multiple sclerosis (MS) is a neurological disorder affecting anywhere from 250,000 to 450,000 people in the U.S. [1] MS is a chronic inflammatory disease of the central nervous system (CNS) with underlying immune. [2] The disease is more common in women than men and peaks at age 20-40. Multiple sclerosis presents differently in different patients with the symptoms ranging from mild neurological impairments to debilitating deficits of motor, cognitive and visual function. Multiple sclerosis pathogenesis is believed to involve an autoimmune response within the CNS, resulting in demyelination and axonal injury. Inflammation and demyelination seem to be the primary pathology in the relapsing forms of MS, whereas neurodegeneration seems to dominate in the progressive forms of the disease. [3] There is no definitive cause or cure for MS and multiple etiologies are discussed in the literature.

Etiology

The cause of multiple sclerosis is not known. There is data to support both genetic and environmental influences and new research to support new thoughts on the etiology. *Genetic predisposition* has been established by an association with human leukocyte antigen (HLA) DR2. 60% of patients with MS are HLA DR2 positive. [4] The exact mode of inheritance is unknown. There is also an increase risk of MS in someone with a first degree relative who has the disorder and this risk is unexplained by shared environment. [4] Half-siblings of affected persons have half the risk of full siblings of developing MS and adopted siblings have no greater risk than the general population. [5] There is clearly some underlying genetic component.

Smoking is an environmental risk factor for MS that contributes to both increased disease susceptibility and more rapid disease advancement. The relative risk for MS development is approximately 1.5 for smokers compared with nonsmokers. [6] The link between cigarette smoking and MS was established years ago. Smoking cessation is an important aspect to managing patients with MS.

Latitude and vitamin-D levels are also well established factors in the development of multiple sclerosis. A recent meta-analysis confirms an association of increase risk of MS in persons living in northern latitude around the globe. [7] This association is linked to decreased exposure to ultraviolet radiation (UVR)/vitamin D. Persons with MS have low serum levels Vitamin D and periods of low Vitamin D exposure precede occurrence of high lesion activity on MRI images and periods of high Vitamin D precede low lesion activity in people with MS. [8] Vitamin D supplementation may play a role in decreasing the risk of MS. [9] The role of vitamin D in the treatment of people with MS needs to be clarified in larger clinical trials.

Viruses are another known factor in the development of MS supported by the presence of bands of oligoclonal IgG (OCBs) in MS brain and cerebral spinal fluid (CSF) that persist throughout the lifetime of the patient. No single virus has been connected to the disease and some researchers believe that more than one infectious agent causes or triggers disease. The varicella zoster virus (VZV), and Epstein-barr virus (EBV) have been implicated. The detection of VZV

in CSF and peripheral blood mononuclear cells (MNCs) of MS patients suggested a link between VZV infection and MS and was reinforced by the presence of herpesvirions and VZV in CSF and peripheral blood within one week after exacerbations of patients with relapsing-remitting MS. [10] Epidemiological studies have revealed an increased risk for MS in EBV-seropositive individuals. Serum and CSF of MS patients show enhanced immunoreactivity to the EBV-specific proteins of MS patients and EBV has been found in the postmortem brain of patients with MS. [10,11] There is limited information on the benefit of using anti-viral medication or herbs in managing MS.

Hormones play a role in the development of multiple sclerosis as evidence by the increase rates of MS in women than men, and a decrease in MS symptoms in pregnant women, especially in the third trimester. A later onset of disease in male patients compared to female patients coincides with a decline in testosterone in men. In women with MS, late pregnancy is associated with a significant reduction in relapses, while there is a rebound increase in relapses postpartum. [12] One study followed 254 women with MS to one year post delivery and showed that relapse rates were reduced by nearly 80% during the third trimester. [13] But whether or not hormones can be used in the treatment of MS is still evolving. A recent study used 8mg a day of estriol in women with MS for 6 months to observe the effects of estrogen treatment. The dose yielded estriol levels in the blood that approximated 6-month pregnancy levels in humans. The results showed that relapsing remitting patients treated with oral estriol (8 mg/day) demonstrated decreased gadolinium enhancing lesion numbers and volumes on MRI. When estriol treatment was stopped, enhancing lesions increased to pretreatment levels. [13] When estriol treatment was reinstated, enhancing lesions again were significantly decreased. Estriol treatment also significantly increased cognitive function. In another study, ten male MS patients were treated with 10 g of gel containing 100 mg of testosterone in a cross-over design for 12 months. All patients had improvement in cognitive performance and slowing of brain atrophy as measured by MRI. There was no significant effect of testosterone treatment on gadolinium-enhancing lesions on MRI. [12] Animal models of multiple sclerosis also support the role of estrogen and testosterone therapy in the management of the disease.

Solvent exposure has been linked to multiple sclerosis in several studies. A meta-analysis of 13 studies of organic solvents and the risk of MS found that organic solvents may cause MS. [14] An occupational study on solvent exposure and MS found that painters, construction and food processing workers who were exposed to solvent had increased risk for MS. [15] Another study looked at nurse anesthetists exposure to solvents and their risk of developing MS. The incidence of MS was higher in the nurse anesthetist group when compared with both the other nurse and teacher groups respectively. [16] The study included exposure to volatile anesthetic agents used prior to 1985 before more stringent restrictions to solvent exposure were in place. Most studies on solvents and MS are related to occupational exposure. There is a strong need for research on low-dose solvent exposure from common household sources and the risk of MS. It is fairly easy to test patients for solvent exposure in the blood and urine. Detoxification methods including sauna therapy have shown a reduction of solvents in the body. [17]

Heavy metals have been implicated in risk for multiple sclerosis. A 2007 meta-analysis review of articles published from 1996-2006 showed an increase between mercury amalgam use and risk of MS. [18] Also, serum mercury levels were correlated to MS in the general population in Iran.

74 patients with MS were compared to 74 age matched controls. Serum mercury level in MS patients was significantly higher than controls revealing that high mercury levels in serum might enhance MS development in susceptible individuals. [19] There is one published case of a patient with MS undergoing heavy metal urine challenge testing with EDTA revealing elevated aluminum, lead and mercury in the urine. After undergoing EDTA chelation treatments twice a month (totaling 60 treatments) the patients' symptoms of MS improved. [20]

Stress has an impact on health for both the general population and for people with multiple sclerosis. A meta-analysis of 20 studies showed that stressful events in life are associated with an increased risk for MS for exacerbations. [21] In patients with MS, the experience of at least one stressful event during a period of four weeks was associated with double the risk of an exacerbation within the next week. [22] The results of a recent 2011 study do not support a major role of stress in the development of the disease, just in exacerbation of symptoms. [23] However, older studies do suggest a link between stressful event and the development of the disease. A 1982 study showed more MS patients had unwanted stress in the 2 yrs before onset than controls [24] A study done in 1989 showed MS patients had more life threatening events 6 months before onset than controls. [25] There are benefits in educating patients with MS in stress management techniques and coping skills. In a randomized controlled trial of relapsing-remitting MS patients, an 8-week stress management program decreased both the number of weekly symptoms and the mean intensity per symptom. [26] Another study on teaching MS patients stress management and coping techniques showed a decrease in new lesions on MRI. [27]

Celiac disease (CD) is a systemic disease related to intolerance to gluten and is often associated with different autoimmune and neurological diseases. A link between MS and celiac has been postulated for some time. Some patients with MS show high levels of anti-tissue transglutaminase-2 (TGt-2) antibodies, which is an important serological marker in the diagnosis of celiac disease. 98 patients with multiple sclerosis were found to have increase in titers of immunoglobulin G antibodies against gliadin and tissue transglutaminase compared to controls. [28] Another study looked at the prevalence of celiac disease in Multiple Sclerosis patients and their first-degree relatives. It found an increased prevalence of CD in 8 of 72 MS patients (11.1%) and also in their first-degree relatives based on duodenal biopsy and blood tests. [29] All eight of the MS patients were female. All had a positive response to a gluten free diet in MS symptoms. However, some studies do not show a link between gluten sensitivity, celiac disease and multiple sclerosis. 217 patients with multiple sclerosis (MS) were evaluated for the presence of IgA and IgG celiac disease-related antibodies and compared to a sample of 200 controls not affected by neurological disorders. None of the 217 patients with MS presented IgG and IgA anti-gliadin, anti-endomysial antibodies, anti-tissue transglutaminase and anti-reticulin. [30] This study did not show an increased frequency of celiac disease among patients with MS. The conflicting evidence means this area requires more investigation. Testing MS patients for celiac could prove beneficial if it means early detection and possible improvement of symptoms on a gluten-free diet.

Air pollution and poor air quality is related to the risk of multiple sclerosis in women as well as exacerbation of symptoms. A study of outdoor air particulate matter (PM) in the Atlanta area linked PM-10 to etiology of MS in women. [31] This is coarse particulate matter from smoke, dirt and dust from factories, farming and roads, mold, spores, and pollen. PM-10 has an influence

on systemic immune response and inflammation. Ambient air pollutants are known to induce systemic immune responses and to enhance existing peripheral inflammation. Ambient air quality and monthly MS relapse occurrence in south-western Finland were compared showing the risk of a relapse was over fourfold when the concentration of PM-10 was at the highest quartile. [32] Some medications can protect against the effects of poor air quality in MS patients. Beta-interferon is a common treatment for MS due to its immune-modulating properties. PM-10 can affect the immune system making those exposed more susceptible to infections. In patients not using beta-interferon, MS relapses were more frequent, than those using beta-interferon, 1-month following the episodes when PM-10 was in the highest quartile in the air. [33] Instead of using beta-interferon to protect MS patients against poor air quality, another option would be tighter regulations of industries and diesel trucks responsible for polluting the air with PM-10.

Treatments

Multiple sclerosis is a chronic disabling disease affecting thousands of people in the USA. Many people with MS utilize conventional drug therapies and explore integrative modalities as well. Surveys suggest that up to 70% of people with MS have tried one or more alternative medicine, or integrative medicine, treatments to help control their MS symptoms. [1] In addition to treatments already discussed, several other etiologies and integrative therapies for MS will be reviewed.

Resveratrol

Resveratrol is a polyphenolic compound produced by the skin of red grapes, peanuts, and other fruits. Most research on resveratrol has been conducted in cultured cells and animals. Recently its effect in mice with multiple sclerosis has been investigated. Optic neuritis is an inflammatory demyelinating disease of the optic nerve and often occurs as an acute episode of MS. A pharmaceutical-grade formulation of resveratrol was administered to mice with experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The results showed resveratrol prevented neuronal loss during optic neuritis. This is significant as treatments that prevent neuronal damage during optic neuritis may have potential to prevent long-term visual loss and may have neuroprotective effects for other MS lesions. [2] A second study further investigated the mechanism of resveratrol's neuroprotective effect and found in animal models of MS it can prevent neuronal loss without immunosuppression. In addition to preventing loss of neurons, at daily doses of 250 mg/kg, resveratrol delayed the development of neurologic dysfunction in mice with EAE. [3] The use of resveratrol in persons with multiple sclerosis sounds promising however studies need to be conducted on its use in humans.

Inosine

It has been shown that lower serum uric acid (UA) levels in MS patients are associated with relapse and that serum uric acid might serve as a possible marker of disease activity in MS. [4] Raising uric acid levels can be beneficial in the treatment of MS and inosine supplementation is emerging as a method of achieving this goal. After oral administration of uric acid failed to increase low serum UA levels, evidently due to its degradation by gastrointestinal bacteria, researchers turned to its precursor inosine. In a small study, 3 of 11 patients with MS given inosine showed evidence of clinical improvement and there was no sign of new lesions on MRI in the remaining patients.[5] Inosine is a purine nucleoside. After oral ingestion it produces uric acid which has peroxynitrite scavenging activity. Peroxynitrite, a toxic product of the free radicals nitric oxide and superoxide, has been implicated in the pathogenesis of CNS inflammatory

diseases, including multiple sclerosis. [6] Inosine is often used by body builders and athletes for its supposed effects of energy and performance. More research is evolving in the use of inosine with persons with MS. In a double blind randomized control trial of 16 patients with MS, oral administration of inosine raised uric acid levels which was correlated with decreased gadolinium-enhanced lesions and MS symptoms. Raising UA levels decreased serum nitrotyrosine while increasing the ratio of Th2 to Th1 cytokines in circulating cells. The only side-effect was kidney stone formation in 4/16 subjects. [7] These are small yet promising studies on the use of inosine for treating MS.

Green Tea

Green tea properties are being studied for their effects in several disease process and conditions. The main constituent of green tea is epigallocatechin-3-gallate (EGCG). In animal models of multiple sclerosis, called experimental autoimmune encephalomyelitis (EAE), green tea reduced clinical severity when given at initiation or after the onset of EAE by both limiting brain inflammation and reducing neuronal damage. [8] Green tea has both anti-inflammatory and neuroprotective effects. The human dosage equivalent to what was used in this study is contained in 3 liters of conventionally brewed green tea. A more recent study combined green tea with a common conventional medication for MS, Glatiramer acetate (GA). In an animal model of MS the combination of green tea extract plus GA delayed disease onset, strongly reduced clinical severity, even after onset of symptoms and reduced inflammatory infiltrates. [9] Epigallocatechin-3-gallate (EGCG) in green tea has immunomodulatory and neuroprotective effects that may be beneficial in the management of MS.

Lipoic acid

Lipoic acid (LA) is a potent antioxidant with several reported benefits and uses. In a randomized double-blind placebo-controlled study, 37 patients with multiple sclerosis took lipoic acid for 2 weeks. Patients were divided into 4 groups; placebo, LA 600 mg twice a day, LA 1200 mg once a day and LA 1200 mg twice a day. The purpose of the study was to determine the effects of lipoic acid on matrix metalloproteinase-9 (MMP-9) and soluble intercellular adhesion molecule-1 (sICAM-1). High levels of these proteins are associated with relapsing-remitting MS. The results showed that patients taking 1200 mg LA had substantially higher peak serum LA levels than those taking 600 mg and that oral LA can reduce serum MMP-9 and sICAM-1 levels. Although this is a small study, lipoic acid may be useful in treating MS. [10] Other studies have shown that Lipoic acid is effective in treating experimental autoimmune encephalomyelitis (EAE), the animal model for multiple sclerosis (MS), and optic neuritis associated with MS. [11]

Omega-6 fatty acids

Gamma-linolenic acid (GLA) is an omega-6 essential fatty acid that must be obtained from the diet. Research has shown a disturbance in omega-6 fatty acid metabolism in patients with MS and a role for omega-6 supplementation. In a randomized double-blind placebo controlled trial of a high dose and low dose GLA rich oil and a placebo control, the high dose GLA significantly decreased the relapse rate and the progression of relapsing-remitting MS [12] Another study looked at the effects of oral feeding of omega-6 fatty acid gamma-linolenic acid from *Borago officinalis* to mice with MS and found protection from disease relapse. [13] Although GLA appears to be a promising addition to disease management, several other studies on omega-6 supplementation in patients with MS have provided mixed results.

Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids also commonly used in the management of patients with multiple sclerosis. Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are two omega-3 fatty acids that are synthesized from linolenic acid in humans. Linolenic acid conversion to EPA and DHA in humans results in a very low amounts of EPA and DHA, which is why most EPA and DHA is supplemented through eating fish or taking fish oil. Several studies have shown that supplementing EPA and DHA in patients with MS results in a decrease in inflammatory cytokines and matrix metalloproteinase-9 (MMP-9). Matrix metalloproteinase-9 appears to be important for T-cell migration into the CNS in MS. [14, 15] However, a recent randomized, double-blind, placebo-controlled clinical trial conducted from 2004 to 2008 looked at whether omega-3 fatty acids reduce magnetic resonance imaging (MRI) and clinical disease activity in patients with multiple sclerosis, both as monotherapy and in combination with interferon beta-1a treatment. The study concluded that no beneficial effects on disease activity occurred from omega-3 fatty acids when compared with placebo as monotherapy or in combination with interferon beta-1a. [16] While omega-3 fatty acid therapy has some benefits with MS, more research needs to be done.

GABA

There is some evidence to consider the role of GABA in patients with MS. GABA is the main inhibitory neurotransmitter in the central nervous system. GABA is converted from glutamic acid by the action of glutamic acid decarboxylase (GAD). MS may be associated with low serum levels of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD). One study showed that the level of GABA and the GAD activity in the blood serum of MS patients was reduced as compared to the controls. [17] This would make one wonder if manipulating GABA levels could be a possible treatment for MS. A 2010 study explored the use of GABAergic agents in a mouse model of MS, experimental autoimmune encephalomyelitis (EAE). It found that increasing GABAergic activity improves paralysis and the number of relapses in EAE by decreasing inflammation. GABAergic agents act to diminish inflammatory responses to myelin proteins. [18] The GABAergic agents used were vigabatrin and gabaculine, which increases GABA, topiramate, whose mechanism of action is unknown, and muscimol, a GABA structural analog. It appears by increasing GABA there was an improvement in MS in animal models due to GABA role in decreasing inflammation. This possibly opens the door to study the effects of GABA supplementation in humans with MS.

It is interesting to note that inflammation inhibits GABA transmission in multiple sclerosis. [19] Lower levels of the inhibitory neurotransmitter GABA can cause an increase in the excitatory neurotransmitter glutamate [20] which is known to be elevated in persons with MS. [21] The link between neurotransmitter changes and MS was noted years ago showing that people with MS have high levels of glutamate, noradrenaline, glutamine, asparagine and glycine. [22] There are several labs that test neurotransmitter levels in the saliva and urine and natural treatments to balance neurotransmitter levels is very effective.

Summary

Multiple sclerosis (MS) is a neurological disorder affecting hundreds of thousands of people in the U.S. MS involves an autoimmune response within the central nervous system with elements

of inflammation, demyelination and axonal injury. This MS update explored the link between the HLA DR2 gene, smoking, vitamin D, the varicella zoster and Epstein-barr virus, hormones, stress, celiac disease, heavy metals, solvents and ambient air pollution. The etiology of multiple sclerosis is multi-factorial with further evidence linking MS to uric acid and neurotransmitter levels, oxidation, inflammation and free radical damage. This review looked at additional non-pharmaceutical therapies for MS. New research has opened the door to explore integrative therapies such as botanicals, antioxidants, amino acids, vitamins, fatty acids, diet and lifestyle changes, detoxification, hormone and chelation therapy. Although multiple sclerosis is a chronic disease with no definitive cause or cure, it is important to examine new risk factors, etiologies and integrative treatments in an attempt to slow disease progression and manage symptoms so people with MS can have normal to near-normal function.

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