

Multiple Sclerosis  
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## ABSTRACTS

Folate, vitamin B12, and neuropsychiatric disorders.

Bottiglieri T.

*Nutr Rev.* 1996 Dec; 54(12):382-90.

Folate and vitamin B12 are required both in the methylation of homocysteine to methionine and in the synthesis of S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurologic and psychiatric disturbances including depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatry of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and vitamin B12 deficiency

1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis.

Cantorna MT, Hayes CE, DeLuca HF.

*Proc Natl Acad Sci U S A.* 1996 Jul 23; 93(15):7861-4.

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease multiple sclerosis (MS). Induced by immunizing B10.PL mice with myelin basic protein (MBP), EAE was completely prevented by the administration of 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3]. 1,25-(OH)2D3 could also prevent the progression of EAE when administered at the appearance of the first disability symptoms. Withdrawal of 1,25-(OH)2D3 resulted in a resumption of the progression of EAE. Thus, the block by 1,25-(OH)2D3 is reversible. A deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, 1,25-(OH)2D3 or its analogs are potentially important for treatment of MS

Exogenous lipids in myelination and myelination.

Di Biase A, Salvati S.

*Kaohsiung J Med Sci.* 1997 Jan; 13(1):19-29.

Myelinogenesis is a scheduled process that depends on both the intrinsic properties of the cell and extracellular signals. In rat brain, myelin development is an essentially postnatal event and environmental interferences could affect myelin synthesis. Nutrition plays an important role, since severe postnatal malnutrition and essential fatty acid (EFA) deficiency cause hypomyelination. Even though the dietary effects are more pronounced in the postnatal period, dietary lipids can affect myelin development also in the postweaning period. Rats fed with diets rich in polyunsaturated n3 fatty acids showed a decrease of the relative amount of myelin basic protein (MBP) and a CNPase activity indicating a delay in myelin deposition and/or an instability of its structure. Our recent studies have shown that dietary fatty acids can be positively involved in the control of central nervous system (CNS) myelinogenesis. Offspring of rats fed diets containing odd chain fatty acid during pregnancy and lactation show an early development of behavioral reflexes linked to myelination compared to controls fed a diet containing margarine. Subsequent studies have shown that the expression of myelin proteins is higher in test than in control animals, but the mechanism of the action of fatty acids is still unknown. Also human brain myelinogenesis can be affected by environmental factors. EFA deficiency has been well studied for the important role of C22:6 (a C18:3 metabolite) in the vision system development. The observation that dietary fatty acids can affect membrane composition has led to the use of modified diets in some CNS pathological conditions. For example, preterm infants characterized by low levels of C22:6 and fed with formulae diets enriched in this fatty acid, show a recovery of visual function. The administration of C22:6 has also been tested in patients affected by peroxisomal biogenesis disorders which are associated with very low levels of this fatty acid in the brain. During the treatment, C22:6 content increases in red blood cells, and probably in the brain membranes, as considerable neurologic and

electrophysiological improvement suggest. A mixture of glyceryltriheptanoate and glyceryltrioleate has been tested in the demyelinating disease Adrenoleukodystrophy which is characterized by an abnormal accumulation of very long chain fatty acids (VLCFA) in tissues and fluids. The diet is able to lower VLCFA levels in plasma, but its efficacy for myelin damage is debated. Lastly, a diet which reduces the intake of saturated fatty acid and increases the quantity of polyunsaturates is suggested for multiple sclerosis patients since a decrease of linoleic acid in their plasma and erythrocytes has been observed. Such a diet seems able to reduce the severity of the attacks

Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada.

Ghadirian P, Jain M, Ducic S, et al.

*Int J Epidemiol.* 1998 Oct; 27(5):845-52.

**BACKGROUND:** It has been suggested that nutrition and food patterns, particularly high consumption of animal fat and low intake of fish products, may play a role in the aetiology of multiple sclerosis (MS). **METHODS:** The relation between nutritional factors and MS was studied among 197 incident cases and 202 frequency matched controls in metropolitan Montreal during 1992-1995. Dietary information was collected by employing a 164-item food frequency questionnaire in a face-to-face interview. **RESULTS:** An inverse association was observed between high body mass index (BMI) and the risk of MS, with an odds ratio (OR) of 0.76 (95% confidence interval [CI]: 0.61-0.95), per 5-unit increase in BMI, both sexes combined. In addition, taller women showed a greater risk for MS; the OR per 10 cm increase in height was 1.58 (95% CI: 1.06-2.35). In continuous variable analyses, using the difference between the lowest and highest quartile of intake as a unit, a positive association was observed with energy and animal fat intake. The OR per 897 kcal increase was 2.03 (95% CI: 1.13-3.67) and 1.99 (95% CI: 1.12-3.54) per 33 g of animal fat intake above the baseline. A significant protective effect was observed with other nutrients, including vegetable protein, dietary fibre, cereal fibre, vitamin C, thiamin, riboflavin, calcium, and potassium. Similar trends were seen for males and females when analysed separately. With respect to specific foods (as opposed to nutrients), a higher intake of fruit juices was inversely associated with risk (OR = 0.82; 95% CI: 0.74-0.92). A protective effect was also observed with cereal/breads intake for all cases combined (OR = 0.62; 95% CI: 0.40-0.97) and for fish among women only; pork/hot dogs (OR = 1.24; 95% CI: 1.02-1.51) and sweets/candy (OR = 1.29; 95% CI: 1.07-1.55) were positively associated with risk. **CONCLUSION:** The study generally supports a protective role for components commonly found in plants (fruit/vegetables and grains) and an increased risk with high energy and animal food intake

Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D.

Goldberg P, Fleming MC, Picard EH.

*Med Hypotheses.* 1986 Oct; 21(2):193-200.

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin

Vitamin D and multiple sclerosis.

Hayes CE, Cantorna MT, DeLuca HF.

*Proc Soc Exp Biol Med.* 1997 Oct; 216(1):21-7.

Recently, it has been clearly demonstrated that exogenous 1,25-dihydroxyvitamin D<sub>3</sub>, the hormonal form of vitamin D<sub>3</sub>, can completely prevent experimental autoimmune encephalomyelitis (EAE), a widely accepted mouse model of human multiple sclerosis (MS). This finding has focused attention on the possible relationship of this disease to vitamin D. Although genetic traits certainly contribute to MS susceptibility, an environmental factor is also clearly involved. It is our hypothesis that one crucial environmental factor is the degree of sunlight exposure catalyzing the production of vitamin D<sub>3</sub> in skin, and, further, that the hormonal form of vitamin D<sub>3</sub> is a selective immune system regulator inhibiting this autoimmune disease. Thus, under low-sunlight conditions, insufficient vitamin D<sub>3</sub> is produced, limiting production of 1,25-dihydroxyvitamin D<sub>3</sub>, providing a risk for MS. Although the evidence that vitamin D<sub>3</sub> is a protective environmental factor against MS is circumstantial, it is compelling. This theory can explain the striking geographic distribution of MS, which is nearly zero in equatorial regions and increases dramatically with latitude in both hemispheres. It can also explain two peculiar geographic anomalies, one in Switzerland with high MS rates at low altitudes and low MS rates at high altitudes, and one in Norway with a high MS prevalence inland and a lower MS prevalence along the coast. Ultraviolet (UV) light intensity is higher at high altitudes, resulting in a greater vitamin D<sub>3</sub>

synthetic rate, thereby accounting for low MS rates at higher altitudes. On the Norwegian coast, fish is consumed at high rates and fish oils are rich in vitamin D3. Further, experimental work on EAE provides strong support for the importance of vitamin D3 in reducing the risk and susceptibility for MS. If this hypothesis is correct, then 1,25-dihydroxyvitamin D3 or its analogs may have great therapeutic potential in patients with MS. More importantly, current research together with data from migration studies opens the possibility that MS may be preventable in genetically susceptible individuals with early intervention strategies that provide adequate levels of hormonally active 1,25-dihydroxyvitamin D3 or its analogs

The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis.

Johnson S.

*Med Hypotheses*. 2000 Sep; 55(3):239-41.

Multiple sclerosis (MS) has a much higher incidence among caucasians than in any other race. Furthermore: females are much more susceptible than males and white females living in colder, wetter areas are much more susceptible than those living in warmer areas. On the other hand, menstruating women have increased copper (Cu) absorption and half-life, so they tend to accumulate more Cu than males. Moreover, rapidly growing girls have an increased demand for zinc (Zn), but their rapidly decreasing production of melatonin results in impaired Zn absorption, which is exacerbated by the high Cu levels. The low Zn levels result in deficient CuZnSuperoxide dismutase (CuZnSOD), which in turn leads to increased levels of superoxide. Menstruating females also often present with low magnesium (Mg) and vitamin B6 levels. Vitamin B6 moderates intracellular nitric oxide (NO) production and extracellular Mg is required for NO release from the cell, so that a deficiency of these nutrients results in increased NO production in the cell and reduced release from the cell. The trapped NO combines with superoxide to form peroxynitrite, an extremely powerful free radical that leads to the myelin damage of MS. Iron (Fe), molybdenum (Mo) and cadmium (Cd) accumulation also increase superoxide production. Which explains MS in males, who tend to accumulate Fe much faster and Cu much less rapidly than females. Since vitamin D is paramount for Mg absorption, the much reduced exposure to sunlight in the higher latitudes may account for the higher incidence in these areas. Moreover, vitamin B2 is a cofactor for xanthine oxidase, and its deficiency exacerbates the low levels of uric acid caused by high Cu levels, resulting in myelin degeneration. Finally Selenium (Se) and vitamin E prevent lipid peroxidation and EPA and DHA upregulate CuZnSOD. Therefore, supplementation with 100 mg MG, 25 mg vit B6, 10 mg vit B2, 15 mg Zn and 400 IU vit D and E, 100 microg Se, 180 mg EPA and 120 mg DHA per day between 14 and 16 years of age may prevent MS

Vitamin B12 metabolism and massive-dose methyl vitamin B12 therapy in Japanese patients with multiple sclerosis.

Kira J, Tobimatsu S, Goto I.

*Intern Med*. 1994 Feb; 33(2):82-6.

Serum vitamin B12 levels and unsaturated vitamin B12 binding capacities were measured in 24 patients with multiple sclerosis (MS), 73 patients with other neurological disorders and 21 healthy subjects. There was no decrease in the vitamin B12 levels, however, a significant decrease in the unsaturated vitamin B12 binding capacities was observed in patients with MS when compared with other groups. A massive dose of methyl vitamin B12 (60 mg every day for 6 months) was administered to 6 patients with chronic progressive MS, a disease which usually had a morbid prognosis and widespread demyelination in the central nervous system. Although the motor disability did not improve clinically, the abnormalities in both the visual and brainstem auditory evoked potentials improved more frequently during the therapy than in the pre-treatment period. We therefore consider that a massive dose methyl vitamin B12 therapy may be useful as an adjunct to immunosuppressive treatment for chronic progressive MS

Trace metals in multiple sclerosis.

Mauch E.

*Neurol Psychiatry Brain Res*. 1995; 3(3):149-54.

Clinical correspondence: the effect of magnesium oral therapy on spasticity in a patient with multiple sclerosis.

Rossier P.

*Eur J Neurol*. 2000; 7(6):741-4.

Vitamin B12 and its relationship to age of onset of multiple sclerosis.

Sandyk R, Awerbuch GI.

*Int J Neurosci.* 1993 Jul; 71(1-4):93-9.

Attention has been focused recently on the association between vitamin B12 metabolism and the pathogenesis of multiple sclerosis (MS). Several recent reports have documented vitamin B12 deficiency in patients with MS. The etiology of this deficiency in MS is unknown. The majority of these patients do not have pernicious anemia and serum levels of the vitamin are unrelated to the course or chronicity of the disease. Moreover, vitamin B12 does not reverse the associated macrocytic anemia nor are the neurological deficits of MS improved following supplementation with vitamin B12. It has been suggested that vitamin B12 deficiency may render the patient more vulnerable to the putative viral and/or immunologic mechanisms widely suspected in MS. In the present communication, we report that serum vitamin B12 levels in MS patients are related to the age of onset of the disease. Specifically, we found in 45 MS patients that vitamin B12 levels were significantly lower in those who experienced the onset of first neurological symptoms prior to age 18 years (N = 10) compared to patients in whom the disease first manifested after age 18 (N = 35). In contrast, serum folate levels were unrelated to age of onset of the disease. As vitamin B12 levels were statistically unrelated to chronicity of illness, these findings suggest a specific association between the timing of onset of first neurological symptoms of MS and vitamin B12 metabolism. In addition, since vitamin B12 is required for the formation of myelin and for immune mechanisms, we propose that its deficiency in MS is of critical pathogenetic significance

A prospective study of physical trauma and multiple sclerosis.

Sibley WA, Bamford CR, Clark K, et al.

*J Neurol Neurosurg Psychiatry.* 1991 Jul; 54(7):584-9.

During an eight year period 170 multiple sclerosis (MS) patients and 134 controls without physical impairment were followed closely to record all episodes of physical trauma and to measure their effect on exacerbation rate and progression of MS. There was a total of 1407 instances of trauma, which were sorted into various categories. Overall there was no significant correlation between all-traumas and disease activity. There was, however, a statistically significant negative correlation between traumatic episodes and exacerbations in 95 patients who had exacerbations during the programme, due primarily to less activity of the disease during a three month period following surgical procedures and fractures. Electrical injury had a significant positive association with exacerbation using a three month at-risk period, but there were no other significant positive correlations in any other category of trauma, including minor head injuries; there were no cases of head injury with prolonged unconsciousness. There was no linkage between the frequency of trauma and progression of disability. MS patients had two to three times more trauma than controls

Trauma and multiple sclerosis: a population-based cohort study from Olmsted County, Minnesota.

Siva A, Radhakrishnan K, Kurland LT, et al.

*Neurology.* 1993 Oct; 43(10):1878-82.

Utilizing the Olmsted County, Minnesota, population-based records-linkage resource at Mayo Clinic, we identified an incidence and a prevalence cohort with multiple sclerosis (MS), a head injury cohort, and a lumbar disk surgery cohort to evaluate the association between mechanical trauma and MS onset or exacerbation. The MS cohorts consisted of 225 incidence cases (1905 to 1991) and 164 prevalence cases (December 1, 1991) of definite MS in the population of Olmsted County. We assessed the effect of mechanical trauma in the form of spinal injury or extremity fracture with regard to precipitation of MS or exacerbation of an existing neurologic deficit. Fifty-four episodes of trauma, as defined, occurred among 39 MS prevalence cases; most occurred 10 years or more after the onset of disease and were associated with existing MS-related disability. We compared the final disability status of the groups with and without trauma. We found no correlation between the occurrence of peripheral fractures and the onset of MS, exacerbation of MS, or final disability due to MS in the prevalence cohort. In a cohort of 819 head injury cases from the Olmsted County population, none developed MS within 6 months of the trauma. In a lumbar disk surgery cohort of 942 local residents, there were five with MS, but onset of MS had preceded the spinal surgery in four of the five. Thus, we found no association of head injury and spinal disk surgery with onset of MS

Multiple sclerosis: the lipid relationship.

Swank RL, Grimsgaard A.

*Am J Clin Nutr.* 1988 Dec; 48(6):1387-93.

Between 1949 and 1984, 150 multiple sclerosis patients consumed low-fat diets. Fats, oils, and protein intakes; disability; and deaths were determined. On daily fat consumption of less than 20.1 g (average 17 g), 31% died and deterioration was slight. Daily intakes of greater than 20 g (average of either 25 or 41 g) were attended by serious disability and deaths of 79% and 81%, respectively. Oil intakes bore an indirect relationship to fat consumption. Treatment early and before severe disability developed improved prognosis, and females tended to do better than males. High sensitivity to fats suggests they are involved in the genesis of multiple sclerosis

[The use of alternative medicine by multiple sclerosis patients--patient characteristics and patterns of use].

Winterholler M, Erbguth F, Neundorfer B.

*Fortschr Neurol Psychiatr.* 1997 Dec; 65(12):555-61.

The use of alternative medicine is growing in all Western countries. Little is known about the modalities and patterns of use of alternative medicine by patients suffering from multiple sclerosis. **PATIENTS AND METHODS:** We analysed an anonymous questionnaire that was sent to and answered by 129 former inpatients who had multiple sclerosis diagnosed by typical clinical and laboratory findings. **RESULTS:** 82 of 129 patients (63.6%) have been using alternative therapies. They were treated with a total of 87 different alternative healing methods or substances. Some patients used up to 9 different methods. The mean duration of the alternative treatment was 2.6 (0-20) years. Most patients used homoeopathy (n = 35), herbs (29 different substances, 32 users), different relaxation methods like yoga (n = 38) and various diets (n = 21). The most important motivation to look for alternative medicine was the aim to participate actively in the healing process. Most patients thought that there was some positive effect from the alternative treatment but did not inform their general practitioner or neurologist about it. **DISCUSSION:** Like in other chronic diseases many MS-patients use alternative medicine. The experiences of these treatments forms part of the patient's coping with the disease

Experimental and clinical studies on dysregulation of magnesium metabolism and the aetiopathogenesis of multiple sclerosis.

Yasui M, Ota K.

*Magnes Res.* 1992 Dec; 5(4):295-302.

The proposed aetiologies of multiple sclerosis (MS) have included immunological mechanisms, genetic factors, virus infection and direct or indirect action of minerals and/or metals. The processes of these aetiologies have implicated magnesium. Magnesium and zinc have been shown to be decreased in central nervous system (CNS) tissues of MS patients, especially tissues such as white matter where pathological changes have been observed. The calcium content of white matter has also been found to be decreased in MS patients. The interactions of minerals and/or metals such as calcium, magnesium, aluminium and zinc have also been evaluated in CNS tissues of experimental animal models. These data suggest that these elements are regulated by pooling of minerals and/or metals in bones. Biological actions of magnesium may affect the maintenance and function of nerve cells as well as the proliferation and synthesis of lymphocytes. A magnesium deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly, and thus magnesium depletion may be implicated in the aetiology of MS. The action of zinc helps to prevent virus infection, and zinc deficiency in CNS tissues of MS patients may also be relevant to its aetiology. Magnesium interacts with other minerals and/or metals such as calcium, zinc and aluminium in biological systems, affecting the immune system and influencing the content of these elements in CNS tissues. Because of these interactions, a magnesium deficit could also be a risk factor in the aetiology of MS

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