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Is there a link between vitamin B and multiple sclerosis?

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Abstract: Damage to the myelin sheath (demyelination) is one of the main manifestations of multiple sclerosis (MS). Interestingly, both MS and vitamin B deficiency results in severe myelin degeneration that leads to loss in neuronal signal transmission. Deficiency in vitamin B complex vary, although common symptoms include fatigue, increased oxidative stress, inflammation and demyelination. In particular, vitamin B12 (cobalamin) has triggered an increased attention for its role in the methylation process, involvement in myelination and re-myelination and reversal of MS symptoms. Here we discuss the role of vitamin B complex (B1, B2, B3, B4, B5, B6, B7, B9, B12) in MS. The anti-inflammatory and re-myelinating attributes of vitamin B complex members are promising, although with limited clinical studies. Hence, there is an urgent need for larger scope studies to determine the role of vitamin B supplementation alone, or in combination with other therapeutic agents, in prevention or reversal of MS and aid in improved quality of life of MS patients.

1. INTRODUCTION

Multiple sclerosis (MS) is an autoimmune neurodegenerative disorder associated with chronic inflammation of the central nervous systems (CNS) leading to axonal loss and demyelination [1]. Activated macrophages, autoreactive CD4 T cells, antibodies, Th1 cytokines, T regulatory cells and Th17 cells against protein constituents of the myelin sheath (myelin basic protein, MBP; proteolipid protein, PLP; myelin oligodendrocyte protein, MOG) have been implicated in the pathogenesis of MS [2]. The onset of MS usually occurs in young individuals, aged 25-35 years and is more common (2:1) in females than males [2]. The disease manifests itself in a series of time-varying MS attacks where there are alterations/abnormalities in sensory, motor and/or cognitive function. Most symptoms are a result of axonal damage and neuronal loss as is seen in advanced and progressive stages of the disease, where myelin is destroyed in discrete areas of the brain or spinal cord (plaques of demyelination), resulting in impairment of axonal signalling and miscommunication [3].

MS is divided into 4 types, (i) relapsing-remitting (RR), (ii) primary-progressive (PP), (iii) secondary-progressive (SP), (iv) progressive-relapsing (PR) [4]. RR is characterized by defined attacks of worsening neurologic function (relapses), followed by partial or complete recovery periods (remission). Almost 85 % of individuals diagnosed with MS are RR type and 10 % with PP type. PP is characterized by steady worsening of neurologic function from the initial diagnosis with no distinct relapses and remissions. Approximately 2/3 of patients with RR MS will eventually develop SP MS, that progresses more steadily with or without relapses. The least common type of MS is PR, and is characterized by the steady progression of the disease from the beginning with occasional violent exacerbations [4].

In MS, damage to the myelin fibre (demyelination) is the most common outcome, where severe degeneration could lead to a block in neuronal communication and loss of conductance. The symptoms are variable amongst each patient and are largely dependent on the location and the severity of the demyelinated plaque [1]. The most common sites of demyelination are within the optic chiasm and nerves, the brainstem, cerebellum, upper spinal cord and cerebrum; periventricular, pericallosal and subcortical being common lesion locations. As a result, immobility, spasticity and motor-sensory problems become an issue. Complete axonal degeneration occurs in the later chronic progressive stage (PR) of the disease resulting in permanent disability [5].

Interestingly, vitamin B is a broadly available potent modulator of the re-myelination process and its deficiency could possibly have detrimental effects in MS progression. There is increasing interest towards the link between vitamin B deficiency and its involvement in MS development and progression. Herein, we review the putative role of vitamin B group in the prevention of MS development and progression.

2. VITAMIN B AND HEALTH

Vitamin B constitutes a collection of water soluble B vitamins including, B1 (thiamine), B2 (riboflavin), B3 (nicotinamide), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid), B12 (cyanocobalamine) and each with distinct functions. Vitamin B is required for proper functioning of the methionine and folate cycles, methylation cycle, monoamine oxidase production, DNA synthesis, repair and maintenance of lipids including myelin [6-9]. The methylation cycle is responsible for detoxification, immune function, mood and controlling inflammation. A defect in methylation function contributes to numerous chronic conditions, including, neurological conditions [7-9]. Monoamine oxidase plays a vital role in the inactivation of neurotransmitters and a dysfunction in monoamine oxidase is thought to be responsible for a number of psychiatric and neurological disorders, including schizophrenia, depression and MS [7, 10-12]. It is apparent that vitamin B plays a role in the maintenance of human neurophysiology and has an important regulatory role in MS.

3. WHAT ROLE DOES VITAMIN B PLAY IN MS?

Despite current advances in MS research, the disease aetiology remains unknown, although genetic susceptibility to disease, mimicry between viruses and proteins within the myelin sheath, immune cells (i.e. Th1, Th17 antibodies), vitamin D deficiency, insufficient

nutrition, stress and demographics have been suggested, Fig. (1) [13-18]. Prevention of acute inflammatory myelin damage at early, as well as at the late stage, and, promotion of neuro-regeneration can provide better quality of life to MS patients regardless of the type and stage of disease [19].

Whilst each vitamin B has a role in human health, the general association of vitamin B deficiency in MS patients is often linked with chronic fatigue, inflammatory diseases and neuronal demyelination. Vitamin B complex has been implicated to have a modulatory role in the pathophysiological process of MS, Fig. (1) (see below sections 3.1-3.8).

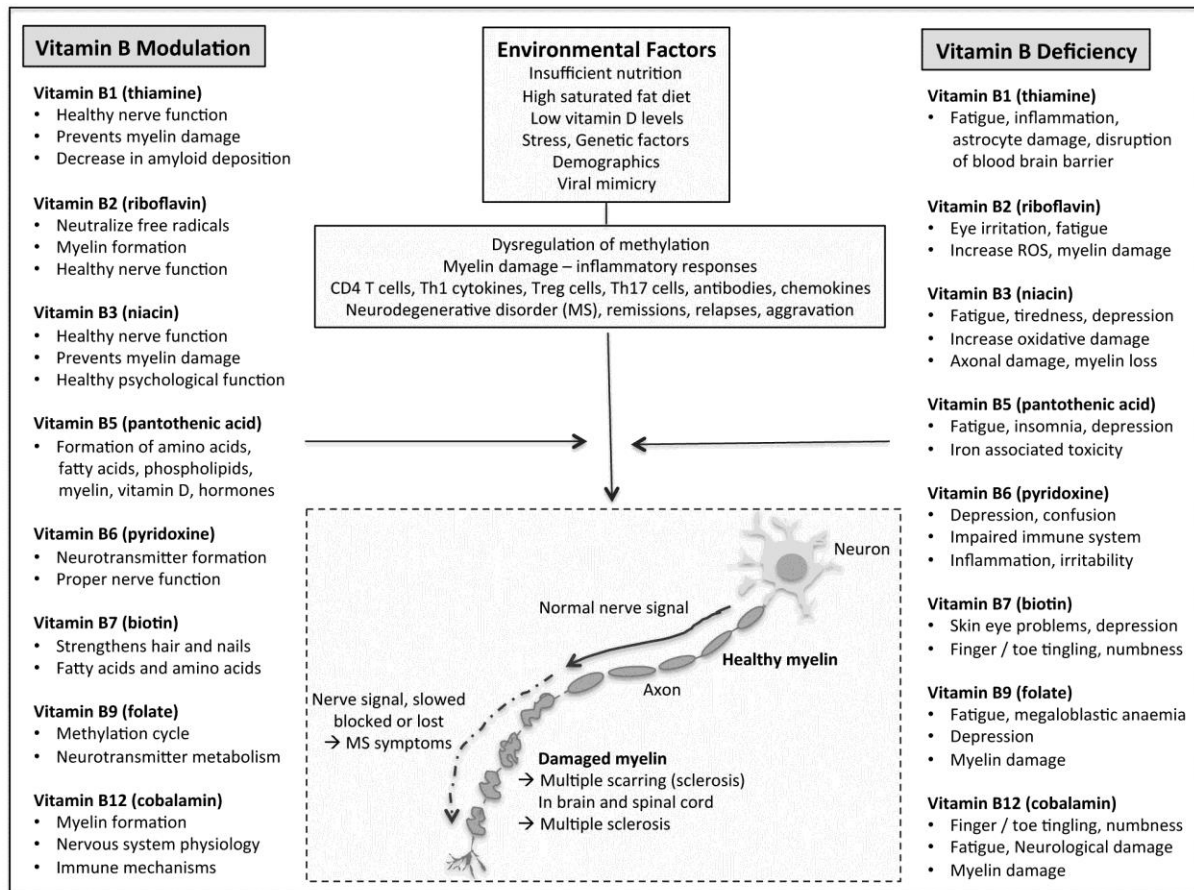


Fig. (1). Vitamin B complex modulation of MS: MS is associated with genetic and environmental factors, which appear to be controlled by epigenetic regulation of the methylation process. Vitamin B complex are all involved directly or indirectly in neurodegenerative disease prevention.

3.1. The role of vitamin B1 (thiamine) in MS

Vitamin B1 (thiamine) is present in most foods, such as, brewer’s yeast, meat, tuna, cereals, breads, legumes, nuts. Thiamine is required to process carbohydrates into energy, as well as, RNA and DNA production, and psychological and nerve function [20]. Patients with MS experience fatigue which has been linked to intracellular thiamine deficiency. Indeed, in a pilot study, 15 patients with MS in remitting phase who showed fatigue, administration of high doses of thiamine (600 – 1,500 mg/day; 1.2 mg is the recommended daily intake) resulted in fatigue regression as evaluated by the fatigue severity scale [21]; despite having

blood thiamine and thiamine pyrophosphate levels within the normal range. Importantly, despite the high dose of thiamine used no side effects were reported. Thiamine deficiency causes impaired oxidative metabolism due to poor enzymatic activity of thiamine-dependent proteins causing a series of symptoms, such as, decreased energy, increase in oxidative stress, lactic acidosis, astrocyte dysfunction, disruption of the blood-brain barrier, decreased cellular glucose uptake and chronic inflammation [22]; interestingly, these are also symptoms of MS. In a mouse model of MS, experimental autoimmune encephalomyelitis (EAE) induced by, myelin oligodendrocyte glycoprotein encephalitogenic peptide, MOG₃₅₋₅₅, the disease severity is exacerbated in thiamine deficient mice compared to non-thiamine deficient mice. The deficient mice showed pathologic alterations in the spinal cord, microglial activation and increased Th1 and Th17 cell infiltration and increased expression of chemokine, CCL2, and its receptor in the spinal cord [23]. Thus, there is preliminary evidence that suggests some potential role of thiamine in MS, however these need to be substantiated in larger studies.

3.2. The role of vitamin B2 (riboflavin) in MS

Vitamin B2 is present in yeast, liver, milk, meat, eggs, green vegetables and fortified cereals. Its main function is to convert carbohydrates into glucose, neutralize free radicals, such as reactive oxygen species (ROS) and maintain normal vision, normal red blood cells, normal function of the nervous system and myelin formation in nerve cells. In addition, riboflavin interacts with vitamin B6 and B9 converting them into their active forms. Riboflavin deficiency is usually associated with fatigue, eye irritation and sore throat [20].

ROS are chemically reactive molecules containing oxygen ions and peroxides and are involved in normal homeostasis. However, during stress the levels of ROS increases dramatically leading to oxidative damage to neuronal membrane lipids, proteins, RNA and DNA [24]. In MS, this contributes to initiation and persistence of lesions, by disrupting the blood–brain barrier, increasing inflammation and demyelination. Indeed, in active demyelinating lesions, there is extensive oxidative damage primarily to astrocytes and myelin-laden macrophages which can be reversed by endogenous antioxidant enzymes [24]. Riboflavin exhibits anti-inflammatory and antioxidant properties and its protective effect against MS was noted in a study of 197 MS patients [25]. In this case-controlled study 197 patients with MS and 202 matched control subjects underwent a 164-item food frequency questionnaire. An inverse association was noted between higher body mass index and the incidence of MS, as well as significant protective effect with intake of vegetable protein, thiamine, riboflavin, calcium and potassium. Hence, nutritional factors in this cohort appear to be associated with risk/aetiology of MS. However, in a randomized double blind controlled study where 29 patients with MS received riboflavin (10 mg) for 6 months and compared to a placebo group, there were no improved effects noted to MS symptoms was noted [26]. It is difficult to compare these 2 studies, as the population cohort were different, different metrics outcomes were assessed and one assessed food intake whereas the other determined the effects of riboflavin supplementation over 6 months. Of relevance, in EAE, an animal model of MS, brain-derived neurotrophic factor and protein levels were increased in the brain and spinal cord of mice treated with riboflavin for 2 weeks, and daily clinical scores were significantly reduced, compared to sham or interferon beta-1a treated mice [27]. Hence,

riboflavin appears to have immunomodulatory effects, exerts protective effects against oxidative damage and demyelination; however, further research is required to ascertain its role in MS.

3.3. The role of vitamin B3 (niacin) in MS

Vitamin B3, or niacin, is found in 2 forms, nicotinamide and nicotinic acid. The synthesis of niacin requires tryptophan, which is obtained from foods, mostly seafood or by dietary supplements [28]. Niacin is also found in yeast, liver, chicken, red meat, legumes and nuts [20]. Interestingly, coffee also provides significant amounts of nicotinic acid, and one cup of coffee provides the daily allowance of vitamin B3. Niacin acts as a co-factor for the conversion of carbohydrates into glucose, aids in the production of fatty acids and cholesterol, repairs DNA damage, provides normal psychological and biochemical functions of the nervous system. Its deficiency is associated with fatigue, tiredness, dementia and depression [20].

Interestingly, over 40 years ago, observational studies by a physician where he administered large doses of nicotinamide (100 mg, 30 minutes before meals and bed) and thiamine (300 - 500 mg, 30 minutes before meals and bed) to patients with MS was able to arrest and reverse MS symptoms and repair damaged nerve cells [29]. Recently, the interest in using vitamins to treat MS has resurfaced. Interestingly, a Mongolian patient with MS, had severe deficiency of micronutrients, including that of niacin which may have played some role to his MS diagnosis [30]; albeit weak evidence with only one patient. In animal models of MOG-induced and PLP induced EAE, daily injections of 500 mg/kg of nicotinamide significantly improved behavioural scores and clinical features with delayed onset and lower clinical scores of EAE. Histologically, mice injected with nicotinamide showed significantly reduced areas of immune cell infiltration and demyelination. Furthermore, nicotinamide protected against axonal damage in an *in vitro* model for microglia-mediated neurotoxicity (lipopolysaccharide activated microglia). Hence, together the *in vivo* and *in vitro* data suggests that nicotinamide has a direct neuroprotective role. Moreover, in a therapeutic setting of EAE, where nicotinamide (500 mg/kg) was administered into mice which had already developed EAE, areas of inflammation and demyelination were reduced, axonal loss was significantly prevented and the behavioral score was significantly reduced compared to control mice [31]. These studies suggest the possibility of using nicotinamide as a treatment for EAE in mice. Further research is required to underpin the role of niacin in MS; however, nutritional treatment using niacin may be an effective approach to alleviating disease outcomes or protecting against MS.

3.4. The role of vitamin B4 (choline) in MS

Vitamin B4 (referred to the distinct chemicals, choline, adenine, carnitine) is classed with B vitamins based on its chemical structure, is a crucial component of myelin, but its main action is as a cholinergic substance and the primary constituent of the neurotransmitter acetylcholine. Acetylcholine is predominantly involved in parasympathetic nervous system function and is found at preganglionic neurons and neuromuscular junctions. Interestingly,

acetylcholine supplementation alleviates injury and alters spinal cord lipid content in MOG induced EAE mice [32]. Furthermore, choline plays an important role in cell signalling and function and is important in cell membrane structure and plasma lipoproteins. Choline is significantly elevated in patients with RRMS which is involved in inflammation and demyelination [33] as well as being increased in pre-lesional normal appearing white matter in MS [34]. A mechanism to enhance myelin repair via the choline pathway was identified [35], where choline exerted neuroprotective and regenerative properties in 2 EAE animal models. It was noted that clinical symptoms in a MOG induced EAE model were reduced when injected prior to EAE induction but not once EAE was induced; suggesting a role of choline in protecting against disease initiation. However, in the cuprizone model where immune cells are not the primary effectors in EAE, choline enhanced myelin repair and reversed motor coordination deficits. In addition, choline was shown to increase the proliferation of oligodendrocyte precursor cells (OPC) *in vitro* [35, 36]. In fact, for remyelination to occur effectively, recruitment of oligodendrocyte progenitor cells (OPC) need to occur at lesion sites, they must differentiate into mature cells capable of undergoing the process of myelination and repair of the demyelinated axon [37]. In the quest to enhance myelination therapeutically for patients with MS, much attention has concentrated on promoting endogenous repair mechanism either via control of OPC proliferation, maturation and differentiation, or by transplanting myelinating cells directly into lesions, although the later poses some ethical concern as the process uses stem cells therapy [38]. It is apparent that choline has therapeutic potential against MS, however further research is required to ascertain the role of choline in MS.

3.5. The role of vitamin B5 (pantothenic acid) in MS

Pantothenic acid (or pantothenate, vitamin B5) is found in all foods (small quantities); however high quantities are primarily in yeast and organ meats (ie. liver, brain, kidneys, heart), and to a certain extent in avocado, eggs, milk, legumes and fortified cereals [20]. Pantothenic acid is the immediate precursor to co-enzyme A and is involved in metabolism of fats, carbohydrates and protein for energy generation [39]. It is involved in the formation of red blood cells, amino acids, fatty acids, cholesterol, phospholipids, vitamin D, sex hormones and aids in healthy mental performance. Pantothenic acid deficiency is rare and has not been thoroughly studied, however in the few cases studied (ie extreme starvation or malnutrition) symptoms include fatigue, insomnia, depression and respiratory infections [20].

Regulation of iron by pantothenic acid, and formation of circulating vitamin B5, 4'-phosphopantothenate, is essential for oxygen transport in the brain, electron transfer, neurotransmitter synthesis, myelin production and facilitates myelin regeneration. However, high levels of iron can be detrimental leading to free radical production and neurotoxicity. High iron levels in the brain have been noted in a number of neurological disorders, including, Parkinson's disease, Alzheimer's diseases and MS, even though the underlying pathological process in the brain is not well understood [40]. In light of the beneficial and detrimental properties of iron in MS, and pantothenic acid is required for the regulation of iron, sufficient iron levels are required for re-myelination and repair whilst avoiding excess that might contribute to damage [41]. Further research is required to determine the role of

pantothenic acid in relieving MS symptoms and whether pantothenic acid has a direct or indirect effect.

3.6. The role of vitamin B6 (pyridoxine) in MS

Vitamin B6 constitutes 3 interrelated isoforms, pyridoxine, pyridoxal, and pyridoxamine. All 3 pyrimidine derivatives are naturally occurring that are endogenously converted to pyridoxal 5'-phosphate [42]. Pyridoxine is found in chicken, liver, pork, fish, nuts, bread, cereals [20, 43]. Pyridoxine assists in the synthesis of haemoglobin which is important for red blood cells, aids in the production of hormones (serotonin, melatonin and dopamine) which influence mood, and melatonin which helps regulate the circadian rhythm. It is known for its involvement in neurotransmitter formation and is an essential nutrient in regulation of neuronal activities and integrity [44]. However, high supplementation levels may cause sensory nerve damage. Pyridoxine deficiency is uncommon; however, people with such deficiency present with nervous system disorders (depression, confusion, irritability), impaired immune system and inflammation [20]. In infants fed with autoclaved formula, where pyridoxine is destroyed, hyper-irritability and epileptic-type seizures were reported; administration of the vitamin reversed symptoms [45]. In addition, clinically low pyridoxine levels (< 20 nmol/L) are not uncommon in autoimmune disorders, as noted in rheumatoid arthritis [46] and type I diabetes [47]. In fact, in an observational cross-sectional study of 43 patients with rheumatoid arthritis, patients were put into 2 groups, (i) < 20 nmol/L (n=30, deficient levels) or (ii) > 20 nmol/L (n=13, adequate levels) pyridoxine levels. Those in the deficient pyridoxine group were reported to have high inflammation as measured by C-reactive protein and higher immune cell numbers (T cells) [46]. In addition, in 32 type I diabetic patients and 27 matched healthy controls it was noted that type I diabetes altered the metabolism of pyridoxine leading to increased risk of pyridoxine deficiency and diabetic complications [48]. Furthermore, studies conducted over 40 years ago demonstrated that pyridoxine deficiency directly lead to demyelination in animals models of mice and rats. In addition, impaired immune responses of MS patients and pyridoxine deficiency were intercorrelated in regards to impaired antibody and delayed hypersensitivity reactions [49]. Follow-up studies are considerably overdue, and a resurgence is required to determine the role of pyridoxine in MS.

3.7. The role of vitamin B7 (biotin) in MS

Vitamin B7 (biotin, coenzyme R, vitamin H) is found in yeast, peanuts, soybeans, almonds, walnuts, milk, raw egg yolk, liver, kidney and green leafy vegetables. Biotin is required for cell growth, maintenance of blood sugar levels, strengthening hair and nails and it is a coenzyme for carboxylase enzymes involved in the synthesis of fatty acids and amino acids. Biotin deficiency is extremely rare as biotin is synthesized by gut flora. However, when deficiency is present, symptoms include hair loss, dry skin, conjunctivitis, dry eyes, dermatitis, insomnia and neurological symptoms, i.e. depression, hallucinations, muscle pain and numbness and tingling of fingers and toes [20].

There is limited research in the MS field related to the role of biotin in MS. However, in serum and cerebrospinal fluid of 170 patients with various neurological disorders (33 MS,

13 motor neuron disease, 13 with dementia, 17 with epilepsy, 18 with polyneuropathy and the remainder were grouped as various neurological disorders group) and 68 age and sex matched controls significant differences were noted in biotin levels. Only patients with MS (79 ± 28 mg/L) or epileptics (82 ± 21 mg/L) showed significant reduced levels of biotin in cerebrospinal fluid compared to controls (136 ± 75 mg/L; $p=0.001$) [50]. In addition, supplementation with high doses of biotin (MD1003; 100-300 mg) in an open label pilot study in 23 patients with primary and secondary progressive MS, showed positive effects with a treatment period of 3-12 months. Effects included, improvement of neurological disability, even after a long period of motor deficit, significant improvement in visual acuity, and, improvement in the homonymous lateral hemianopia [51]. Furthermore, in a randomized double blind placebo controlled clinical study in 154 patients with progressive MS, high dose of MD1003 (100 mg) resulted in reduced Expanded Disability Status Scale (EDSS) progression and improved clinical impression of change compared to placebo group. MD1003 was shown to be safe and achieved sustained reversal of MS related disability in 13 patients with progressive MS [52]. These studies suggest that biotin plays a role in MS; however, further research is required to determine the role of biotin deficiency in MS and the mechanism of action of high dose biotin supplementation in MS patients.

3.8. The role of vitamin B9 (folate) in MS

Vitamin B9 (folate, folic acid, vitamin M, vitamin BC) from the Latin word ‘folium’ meaning ‘leaf’ is found in dark green leafy vegetables, as well as, in beans, wheat, yeast, eggs, milk and orange juice [20]. Folate, or folic acid, is required in the methylation of homocysteine to methionine and in the synthesis of S-adenosyl-methionine. S-adenosyl-methionine is involved in the methylation reactions of proteins, DNA, lipids and neurotransmitter metabolism. Insufficient folate levels is best known to cause deformation of the newborn although, other symptoms include fatigue, megaloblastic anemia and aggravates depressive disorders.

Serum and cerebrospinal fluid folate levels in 293 patients (with MS, Alzheimer’s type dementia, non-Alzheimer’s type dementia or myelopathy) and 157 control subjects, did not show significant differences between the various groups [53, 54]. However, it has been suggested that low or reduced levels of folate found in MS patients may be related to previous corticosteroid treatments [55]. In a cross-sectional study in 101 RR MS patients, nutritional status and its relationship with fatigue in MS was determined. Fatigue was measured using the Modified Fatigue Impact Scale (MFIS), dietary intake was measured via a 3-day food record questionnaire and compared to dietary reference intake (DRI) values. The data suggests that daily intake of folate as well as vitamin D, calcium and magnesium were significantly lower than the DRI in all patients and MFIS correlated with folate intake; suggesting that low folate diets correlate with high fatigue in patients with MS [56]. Interestingly, folic acid supplementation (200-300 μ g/day) to patients with MS improved the neurological status of patients, promoted myelin regeneration and the overall general condition and symptoms [57, 58]. Conversely, in the Kaiser Permanente study, 22 patients with MS received a short course of immunosuppression (cyclophosphamide 400-500 mg) and

was compared to 20 patients with MS who were supplemented with folic acid (1 mg, 5 times/week for 2 weeks), showed similar disease progression in both groups [59].

Undoubtedly, folate is an important regulatory molecule that could prevent methylation related alterations that contribute to demyelination. Insufficient research linking the association between folate and MS begs for more clinical investigations and opens a new outlook on folate / folic acid metabolism and its importance in neurodegenerative diseases, such as MS.

3.9. The role of vitamin B12 (cobalamin) in MS

Vitamin B12 comprises the only cobalt-containing molecules (cobalamin) that is associated with many biological functions. Cobalt gives vitamin B12 its red colour [20]. It is produced by microbial synthesis in the gut and the primary source of B12 is in organ meats (liver, kidney, heart); other sources include fish, eggs and milk. Even though B12 is synthesized in the gut, B12 intake from the diet is required. B12 is involved in cellular metabolism of carbohydrates, proteins and lipids, and acts as a co-factor in myelin formation and physiology of the nervous system and for immune mechanisms. Vitamin B12 also acts as co-enzyme for methionine synthase reaction with methylcobalamin and the methylmalonyl CoA mutase reaction with adenosylcobalamin. Low levels of B12 symptoms include, fatigue, nervousness, numbness or tingling of fingers and toes and in severe deficiency, neurological damage [20]. As B12 is not found in plant products or wheat, it makes B12 deficiency a concern in vegans.

3.9.1 Vitamin B12 deficiency

Between the 1950s - 1960s there was a vast interest in vitamin B12 levels and MS with > 15 papers published (Pubmed search term vitamin B12 and multiple sclerosis). The data was inconsistent, with studies showing lower B12 concentrations and others showing no difference in MS patients compared to controls. In the last decade, this interest has resurfaced.

In 35 MS patients during an acute attack, lower levels of serum vitamin B12 were noted compared to 30 healthy controls [60]. Likewise, in 75 patients with RRMS, serum B12 levels were significantly lower compared to 75 healthy controls [61]. In addition in another study, 10 MS patients were evaluated for B12 deficiency and there was a clear correlation [62]. However, in a Japanese cohort of 24 patients with MS and 73 patients with other neurological disorders there were no difference in B12 serum levels compared to 21 healthy controls [63]. Moreover, in 60 MS patients in remission there was no association between B12 deficiency and MS [64]. Cerebrospinal fluid levels of B12 in 293 neurological patients was correlated with low B12 concentrations in patients with Alzheimer's type dementia and MS [53]. Similarly, in a meta-analysis study in MS patients, raised homocysteine levels and low B12 levels were associated with the pathogenesis of MS (extracted from 8 reports on the role of homocysteine levels in MS and from 8 reports on the role of B12 levels in MS) [65]. There appears to be an association between the age of onset of MS and B12 deficiency; B12 deficiency was strongly correlated in MS patients where the onset of first neurological

symptoms was before 18 years, as compared to patients whose disease first manifested after the age of 18 [66].

3.9.2 Vitamin B12 supplementation

Methylcobalamin therapy may provide the basis for improved treatments for MS. In fact, using neurite outgrowth assays of neurons isolated from rats, culturing with high doses of methylcobalamin (100 nM) improves neurite outgrowth and neuronal survival *in vitro*, as well as improving nerve regeneration and functional recovery in regards to neuronal axonal length and thickness of re-myelination *in vivo* following high dose administration of methylcobalamin (1 mg/kg/day) without causing any side effects [67]. Vitamin B12 is required for the formation of methionine from homocysteine in the methylation cycle that involves methylation of DNA. Vitamin B12 enzyme, methionine synthase, is involved in catalyses of methyl group transfers from N5-methyltetrahydrofolate, resulting in synthesis of tetrahydrofolate and methionine. In addition, in mouse neuroblast cells, the addition of vitamin B12 into the media produced protective effects in cells subjected to stress stimulation [68]. Hence, B12 deficiency or lack of methionine synthase enzymatic activity can result in severe neurodegeneration and stress [69]. The proposed regenerative mechanism of vitamin B12 actions on the nervous system is shown in Fig. (2).

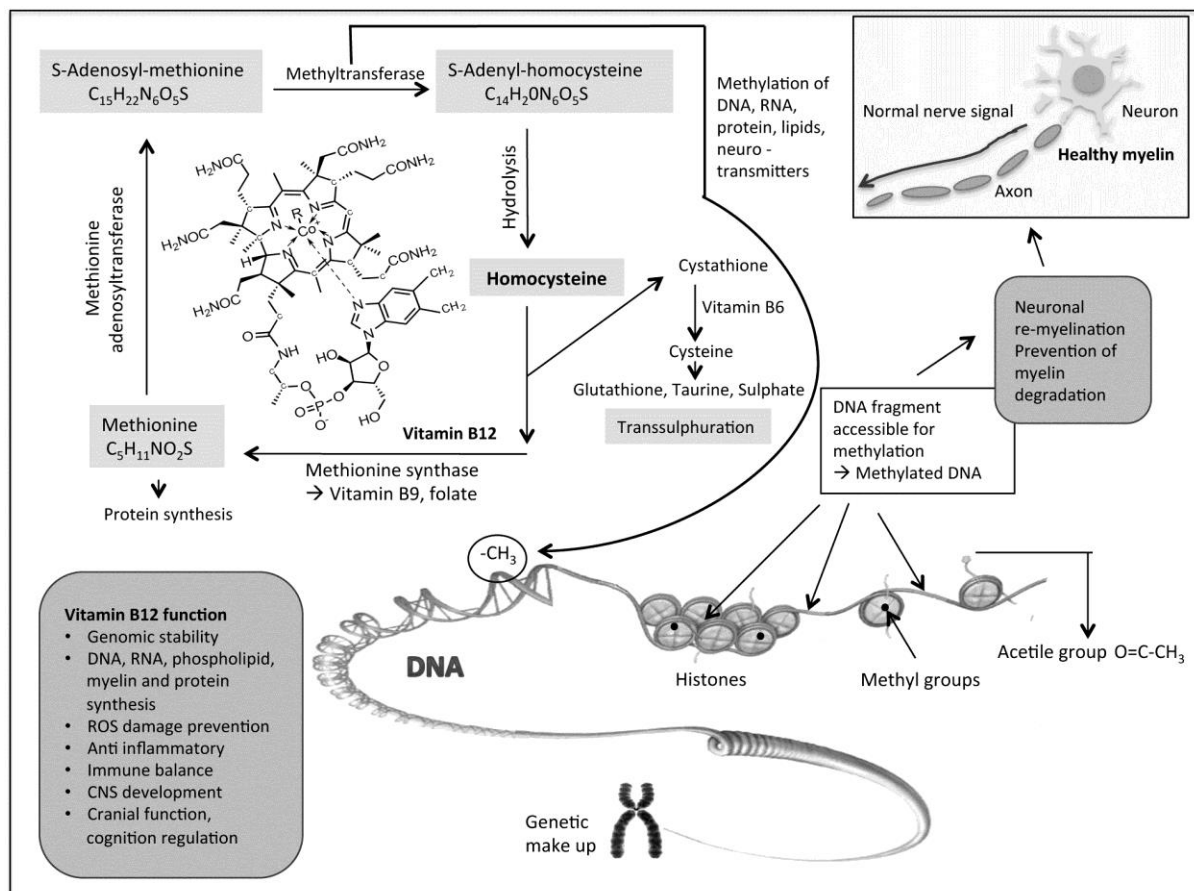


Fig. (2). Vitamin B 12 regulation of DNA methylation acetylation and re-myelination. Vitamin B12 activates methionine synthase, which catalyses the synthesis of methionine. Methionine is the precursor of S-adenosyl-methionine. S-adenosyl-methionine is the primary methyl donor in vitamin B12 metabolism, which

acts as methyl group donor for methylation of various molecules such as DNA, RNA, proteins, phospholipids (including myelin). S-adenosyl-methionine converts to S-adenyl-homocysteine and after hydrolysis, results in homocysteine. Homocysteine is usually at elevated levels and vitamin B12 at low levels in MS patients. DNA and various histone chemical modifications determine gene expression and disease progression. DNA present around histones determines gene expression that influences the re-myelination process. Gene expression modulation of re-myelination process can be activated or repressed by availability of the accessible DNA that involves the methylation process and availability of B12. Co⁺ = Cobalt; R = 5'-deoxyadenosyl,Me,OH,CN; Vitamin B12 (cobalamin) structure consists of Dimethylbenzimidazole and a Corrin ring with Cobalt ion.

The effects of high methylcobalamin (B12) supplementation (60 mg/day for 6 months) in 6 patients with chronic progressive MS, resulted in improved visual and brainstem auditory evoked potentials [63]. In a randomized placebo controlled, double blind study in 138 patients with MS, B12 (1 mg) given intramuscularly for 24 weeks, improved by 2 Guy's neurological disability scale (GNDS) points which according to the scale this is a significant improvement [70]. The limited number of human studies using vitamin B12 supplementation in MS patients, places a question mark on what would happen if B12 would be routinely used for MS treatment and prevention. Likewise, in animal models of EAE, B12 supplementation with interferon-beta improves demyelination and reduces astrogliosis and results in near normal motor function [71]. Furthermore, B12 supplementation together with paclitaxel significantly reduced clinical signs of EAE in mice, astrogliosis reversed back to normal, interferon-gamma was reduced and T cell expansion was suppressed [72].

The continuous administration of high dose B12 should be further evaluated, as it aids in myelin recovery and other symptom improvement and may be beneficial to MS patients and may aid in the delay of relapses and disease progression associated with MS.

3.9.3 Vitamin B12 deficiency and MS symptoms: similarities and differences

Vitamin B12 deficiency is involved in a number of disorders, such as, peripheral neuropathy, autonomic nervous system dysfunction, optic nerve degeneration, depression, memory impairment, cognitive decline and mood and behavioral changes [73]. Patients with B12 deficiency also present with clinical and paraclinical characteristics that are similar to those seen in MS patients (**Table 1**). Vitamin B12 deficiency and MS are different clinical and pathological conditions, however, share similarity in loss of neuronal myelination and a range of other symptoms (**Table 1**). For example, B12 deficiency results in visual disturbances and brainstem auditory and somatosensory evoked responses which correlate with neurological dysfunction, similarly to the symptoms of MS patients [74]. Given the similarities in the clinical presentation and MRI findings, the differential diagnosis between B12 deficiency and MS may be difficult.

It is difficult to distinguish between the neurological dysfunction caused by MS or B12, and whether MS could be due to vitamin B12 deficiency. Perhaps, chronic vitamin B12 deficiency is a direct predisposition for MS development? Although other factors need to be considered, such as omega 3 and vitamin D deficiency (refer to paper by Simpson et al in this issue), environmental and genetic factors [75-78]. Nevertheless, further research is required to determine if there is a link between vitamin B12 and MS.

Table 1. Vitamin B12 deficiency versus MS symptoms.

Vitamin B12 deficiency	Reference	MS Symptoms	Reference
Sensory and motor function malfunction	[79-82]	Sensory and motor function malfunction	[83-85]
Vestibulocochlear damage, changes in auditory signal reception, balance problem, dizziness, nausea, vomiting	[86]	Vestibulocochlear damage, changes in auditory signal reception, balance problem, dizziness, nausea, vomiting	[83, 87, 88]
Visual impairment that causing double vision, inability to focus on the object, optical motor function dysregulation	[89]	Visual impairment that causing double vision, inability to focus on the object, optical motor function dysregulation	[90-92]
Cranial nerve damage, including thermoregulation, sensory, audio-optical-gustatory impairments, dysarthria	[89]	Cranial nerve damage, including thermoregulation, sensory, audio-optical-gustatory impairments, dysarthria	[93-96]
Tingling sensations, tremor, numbness of the limbs, involuntary movements	[97]	Tingling sensations, tremor, numbness of the limbs	[98-101]
Muscular pain and spasm	[97, 102]	Muscular pain and spasm	[3, 84]
Smooth muscles malfunction, including swallowing difficulty	[103]	Smooth muscles malfunction, including swallowing difficulty	[104, 105]
Fatigue, lack of energy and weakness	[106]	Fatigue, lack of energy and general weakness	[107-111]
Bladder and sexual incontinence	[112, 113]	Bladder and sexual dysfunctions	[114-117]
Cognitive deterioration, memory loss, dementia, language problems, emotional instability, irritability, depression.	[82, 118-126]	Cognitive impairments, such as memory problems, shortened attention span, language problems, emotional instability, irritability, depression	[127-130]
Macrocytic anemia, high homocysteine levels, memory loss, cognitive decline, paralysis	[131]	Macrocytic anemia, high homocysteine levels, memory loss, cognitive decline, paralysis	[60, 61]

The symptoms of vitamin B12 deficiency and MS are almost identical in description. It is not clear if these 2 conditions are interrelated or B12 deficiency has a role MS development and progression

4. CONCLUSION

A considerable amount of work is still required to completely understand the associated neurological degradation of MS and all ameliorating processes associated with it. Despite studies in the last century, MS patients are still experiencing progression of disease despite the number of new and improved treatment options available to them. It is necessary to identify the potent supplement that exerts neuronal recovery and accelerated re-myelination process. So far, vitamin B complex, appears to have the required actions that promote re-myelination and inhibits inflammation. However, the lack of detailed clinical studies, places a large demand on clinical studies to determine the role of vitamin B and MS, and its supplementation as a therapeutic against MS. Consequently, enrichment of food with

re-myelination promoting compounds, such as fish oil, vitamin B complex, vitamin D, elimination of psychological stressors, enhancing cognitive performances and improving blood/oxygen supply to the CNS could result in significant improvements in MS associated morbidity, mortality and quality of life.

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