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Why we should offer routine vitamin D supplementation in pregnancy and childhood to prevent multiple sclerosis

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Summary Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that runs a chronic course and disables young people. The disease is more prevalent in the geographic areas that are farthest from the equator. No form of treatment is known to be effective in preventing MS or its disabling complications. A number of epidemiological studies have shown a protective effect of exposure to sunlight during early life and a recent longitudinal study confirmed that vitamin D supplementation reduced life-time prevalence of MS in women. Very little is known regarding the role of vitamin D on the developing brain but experimental data suggest that cerebral white matter is vitamin D responsive and oligodendrocytes in the brain and spinal cord and express vitamin D receptors. It is possible that differentiation and axonal adhesion of oligodendrocytes are influenced by vitamin D level during brain development and a relative lack of vitamin D may increase oligodendroglial apoptosis. The age effect of migration on susceptibility to develop MS could be explained by a role of vitamin D on brain development. In areas of high MS prevalence, dietary supplementation of vitamin D in early life may reduce the incidence of MS. In addition, like folic acid, vitamin D supplementation should also be routinely recommended in pregnancy. Prevention of MS by modifying an important environmental factor (sunlight exposure and vitamin D level) offers a practical and cost-effective way to reduce the burden of the disease in the future generations.

Introduction

The cause and the exact pathogenesis of multiple sclerosis (MS) are unknown [1]. The pathological hallmark of MS is confluent and multi-focal demyelination in association with progressive neuronal loss. In the past, most researchers assumed an autoimmune mechanism of demyelination in MS driven by T-lymphocytes sensitised to one or more target epitopes in the myelin protein [2,3]. However, it is acknowledged even by the ardent followers of autoimmunity that there exists no reproducible and specific immunological marker for MS [3]. Experimental allergic encephalomyelitis (EAE) is an animal model of demyelination induced by artificial T-cell sensitisation to myelin basic protein. Clinically and pathologically, EAE bears only superficial resemblance to MS and most treatments that work in EAE are not considered to be safe or effec-

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tive in the human trials of MS [1]. Morbidity and occasional mortality from immunological treatments in MS are of significant concern, especially because these treatments do not prevent the disease or its progression over the years. Pathological findings in newly forming acute demyelinating lesions may be characterised by virtual absence of lymphocytes or myelin phagocytes that bear no resemblance with the histology of EAE [4]. There is a growing controversy at present whether the primary disease process in MS is autoimmune [5,6].

One of the most valid criticisms of the autoimmune mechanism and the EAE model in MS is that these assumptions cannot explain either the geographic distribution or the effect of early life migration on the prevalence of MS. Exposure to sunlight during early life is considered to have a protective effect on the disease [7]. Seasonal fluctuations in the vitamin D level have been associated with MS relapses [8,9] and a prospective longitudinal study in women recently found that dietary vitamin D supplementation significantly reduced the incidence of MS [10]. Here, I suggest that vitamin D supplementation in pregnancy and early life may prevent the symptomatic manifestation of MS later in life. Vitamin D supplementation in pregnant women should be considered as a public health policy similar to maternal folic acid supplementation that is currently recommended to prevent neuralp tube defects.

The present review is based on our reading of the existing medical texts and a search of the PubMed and Medline for articles combining (a) multiple sclerosis and vitamin D; (b) season of birth and multiple sclerosis; (c) migration and multiple sclerosis; (d) vitamin D and population; and (e) myelin and/or oligodendrocytes and vitamin D and/vitamin D receptor published by March 2004. Only articles in English were considered and where appropriate, original articles cited in the published reference lists were traced.

Physiology of vitamin D

Vitamin D (Fig. 1) is a steroid hormone in structure and function. The dietary form of vitamin D is an essential nutrient only if humans are not sufficiently exposed to sunlight. With adequate exposure to solar ultraviolet B radiation, vitamin D is synthesised in the skin and no dietary supplement is needed. The biologically active form of vitamin D requires successive hydroxylations in the liver and kidneys before it enters the circulation. Active vitamin D, i.e., 1,25 dihydroxyvitamin D_3, is recognised by target tissues that possess a specific nuclear receptor (vitamin D receptor or VDR). VDR is a member of the steroid superfamily of receptors. Interaction between VDR and active vitamin D results in the phosphorylation of the 1,25 dihydroxyvitamin D_3-VDR complex. This phosphorylated complex then combines with the retinoic acid receptor to form a heterodimer that, in turn, interacts with a specific vitamin D responsive element in the target nuclei, leading to the mRNA synthesis for proteins such as osteopontin and osteocalcin.

The bioactive form of vitamin D (1,25 dihydroxyvitamin D_3) is produced not only in the kidneys but also in the placenta during pregnancy. Receptors for 1,25 dihydroxyvitamin D_3 are present in bone and the best understood function of vitamin D is in relation to its role in calcium and phosphate homeostasis and to bone formation and maintenance. Other than bone, VDR is expressed widely in the intestine, skin, kidneys, pituitary, parathyroids, pancreatic beta cells, gonads, skeletal muscles, circulating monocytes and activated T and B lymphocytes [11].

As compared to the knowledge of vitamin D in calcium homeostasis and skeletal growth, very little is known about its role in the central nervous system. The evidence for a neurobiological effect of vitamin D came in 1991 when the regulatory effect of 1,25 dihydroxyvitamin D_3 on nerve growth factor was first reported [12]. Studies have since shown that bioactive vitamin D may modulate the production of neurotrophins, growth factors and neurotransmitters in the mammalian brain [13].

Dietary requirement of vitamin D

It is not a current recommendation, at least in the United Kingdom, that vitamin D supplementation should be routinely offered either during pregnancy or childhood unless there are concerns about nutritional deficiency or malabsorption. It is generally accepted that simple vitamin D deficiency can be prevented by dietary supplementation of 400 units (800 units in Asians and in the elderly) every day [14]. In England, a daily requirement of 100 units was considered adequate in the adults on the basis of its effect in only 7 women all of whom had severe nutritional osteomalacia [15]. However, a daily intake of 200 units of vitamin D, the currently

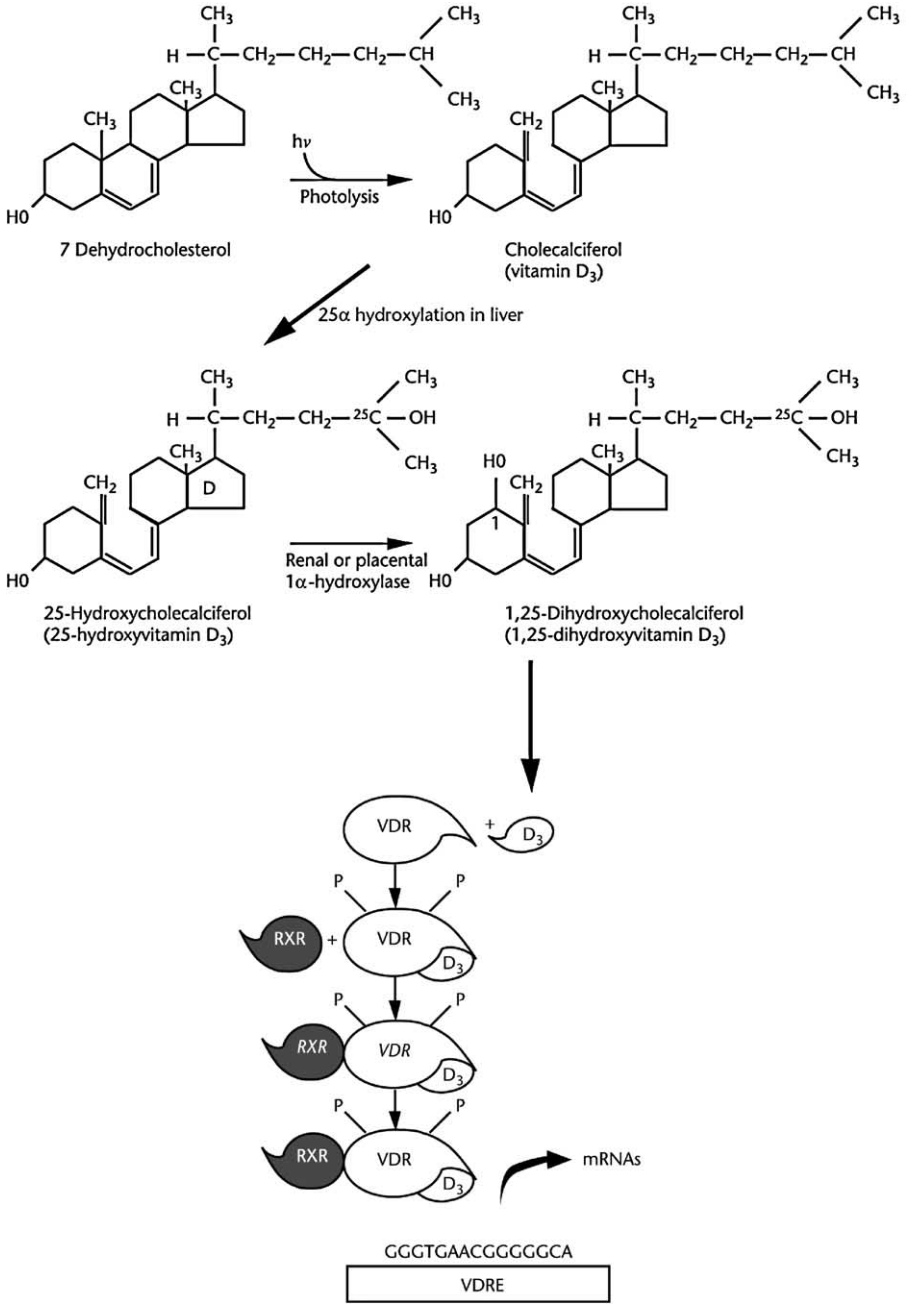

Figure 1 Biosynthesis and nuclear target of vitamin D. VDR: vitamin D receptor; VDRE: vitamin D responsive (nuclear) element; RXR: retinoic acid receptor.

recommended adult dietary allowance, may not be adequate to influence serum vitamin D levels [16]. It is estimated that submarine sailors are deprived of environmentally acquired vitamin D equivalent of 800—2000 units every day. However, total-body sun exposure provides the equivalent of 10,000 units of vitamin D/day, a level that is considered to be the upper physiologic limit [16]. A daily intake of vitamin D above 2000 units has been avoided because of potential risk of toxicity despite the fact that vitamin D has a wide therapeutic window and significant risk of toxicity has been observed with daily doses above 40,000 units.

The reason as to why the naturally controlled level of vitamin D synthesis from sunlight exposure (up to 10,000 units/day) is many folds higher than what is required to prevent simple rickets or osteomalacia (100 units/day) is not known. However, ethnic populations living in geographic areas with high levels of solar exposure throughout the year (Asians

or Africans) have coloured skin, a feature associated with reduced rate of cutaneous vitamin D synthesis (but still considerably higher than the recommended dose of 200 units/day). In areas of high latitudes where MS is common, ultraviolet radiation is too low to produce sufficient vitamin D in fair-skinned population throughout the year. Vitamin D is not synthesised in latitudes of ~42° N or higher during the winter months [17]. The biological half-life of 25 hydroxyvitamin D is 19 days [18], therefore those with low dietary intake remain at a high risk of vitamin D deficiency throughout the autumn and the winter seasons. While the recommended dietary allowance of vitamin D may prevent osteomalacia in adults, we do not have sufficient knowledge to set the physiological vitamin D level for its putative extra-skeletal functions. Indeed, it has been suggested that the currently accepted limit of 2000 units/day may be ''too low by at least 5-fold'' [16].

Vitamin D levels in population

Longitudinal evaluation of vitamin D status in healthy subjects suggest that there are marked seasonal and gender differences in the vitamin D levels [19,20]. The Third National Health and Nutrition Examination Survey (NHANES III, 1988—1994) in the United States surveyed 18,875 young adults and adolescents and measured serum vitamin D levels. Vitamin D insufficiency was common in all groups of adolescents and adults in the winter/lower latitude subpopulation even though the studied subjects lived considerably south of 42° N. Vitamin D insufficiency was also common in certain groups of adults even in the summer/higher latitude subpopulations and ethnic minorities had a higher level of vitamin D insufficiency [19]. In a study from Southern Italy, young healthy women were found to have a high prevalence of subclinical vitamin D deficiency. Significant gender-specific seasonal variations were also observed in this population [20]. Biochemical evidence of hypovitaminosis D was present in over a quarter of all healthy women in winter (27.8%) but relatively few were affected in summer (3.4%). Men, however, did not show much evidence of hypovitaminosis D or seasonal variation [20]. There is a concern that some younger individuals may experience multiple cycles of temporary vitamin D deficiency during winter months with an unknown potential, cumulative impact [19].

Epidemiological studies agree on the observation that MS is nearly twice as common in women as in men and typically manifests during the reproductive age (15—45 years). It is also well recognised that women of child bearing age are most affected by low vitamin D levels. The risk is higher among migrant women with coloured skin (because of a lower rate of photoconversion of endogenous pro-vitamin D). Between 4% and 40% of women in the age group of 15—49 years have hypovitaminosis D [21] and the risk is particularly high (50—80%) in migrant pregnant women living in cold climates who are dark-skinned or veiled [22,23]. The increased physiological needs in pregnancy and more indoor activity (less outdoor exposure to sunlight) are also important risk factors increasing the vulnerability to vitamin D deficiency in pregnancy. The only source of vitamin D in developing foetus is maternal. Placental vitamin D synthesis is exclusively regulated by maternal factors (dietary level and sunlight exposure).

The effect of reduced maternal vitamin D levels on developing foetal brain in humans has not been studied. The first experimental study in animals was only published last year [24]. Female rats deprived of vitamin D gave birth to pups with significantly abnormal brain. The cortex of the newborn rats was thinner and longer with enlarged lateral ventricles. There was more cell proliferation in the brain with reduction in the brain content of nerve growth factor and the glia-cell derived neurotrophic factor. The main limitation in extrapolating the study to humans is that the level of vitamin D deficiency induced in female rats was severe. However, the gestation period in rats is considerably short (3 weeks) and it is therefore difficult to speculate the effect of less severe vitamin D deficiency over a longer period of brain development time in humans.

Season of birth and life time risk of multiple sclerosis

In 1950s, it was observed among the US veterans that the average annual hours of sunshine and the winter daily solar radiation at places of births strongly and inversely correlated with the life-time incidence of MS [25]. Subsequent studies in Australia in 1962 [26] and among immigrants in Israel in 1967 [27] also confirmed these findings. In 1991, a retrospective study from Denmark observed that the season of births of people who were later diagnosed with MS differed significantly from that of the general population [28]. In this study, the peak excess months of birth were March to June. Monthly distribution of births of people who were later diagnosed to have MS did not differ significantly from the general pop-

ulation in a report from British Columbia (Canada) [29]; however, statistical reanalysis of the data indicated that the rates of MS were significantly higher in those born between months of January to June as compared to the remainder of the year [30]. An epidemiological study from Hungary observed that patients reliably diagnosed with MS were born in greater numbers in April and October than at other months in the rest of the year [31]. In a review of existing seasonal birth studies in neurological disorders, the association of an excess of seasonal births during spring with MS was reconfirmed [32]. However, a subsequent study from Sicily reported an excess of births of MS patients in the summer [33]. Although there was no plausible explanation for a lower incidence of MS in winter born people, the seasonality of MS births seem to suggest an apparently higher risk if the first or second trimesters of pregnancy were either during the autumn or winter months, the seasons of low or absent endogenous vitamin D synthesis in mothers living in moderate to high latitudes.

Maternal contribution to the risk of MS

There is a substantially higher risk of MS in children born to parents with MS [34]. Part of this risk is certainly genetic but it seems that the risk may also be modified by environmental factors. This is because if the risk was purely genetic, then a similar proportion of children born to either of the affected parents (mother or father) would develop MS provided there were no other significant difference among these children with respect to the environmental risk factors after birth (e.g. infection). While no epidemiological study has directly addressed this issue, in those families with a parental history of MS, more children who later developed MS were born from affected mothers than fathers [35] (73% and 27%, respectively; λ^2 test p-value: 0.001). In addition, sons of affected men had almost twice the chance of not having a relapsing-remitting form of MS and were more likely to have a primary progressive form of MS that is characterised by a delayed onset and slower progression of disability. One interpretation of the disproportionately higher number of children developing relapsing-remitting MS being born to affected mothers is that maternal environment during pregnancy not only increases the expression of genetic risk, but also modifies the disease phenotype of MS (relapsing-remitting as opposed to primary progressive).

Another interesting observation is that the incidence of MS among second-generation migrants in European countries, i.e., children born to mothers arriving from areas of lower disease prevalence in Asia or Africa, is similar to the expected prevalence in the ethnic population. This increased risk is likely to be environmental and while endemic infections (e.g. Epstein Barr virus) may be a plausible explanation, pregnant women from non-ethnic minorities are also known have a higher risk of subnormal vitamin D levels [22,23].

Seasonal incidence of MS and vitamin D levels

Changes in the brain lesion volumes as detected by the gadolinium enhanced MRI are related to the seasonal fluctuations in the vitamin D levels, with the low levels preceding high lesion activity and high levels associated with low activity [8,9]. A large, population based prospective study in Stockholm, Sweden, observed a seasonal pattern of monosymptomatic optic neuritis, with highest incidence (31%) during spring and the lowest incidence (17%) during winter ($p = 0.007$; C.I. 1.13—3.01) [36]. Like seasonal births, later-life incidence of demyelination in MS appears to parallel seasonal fluctuations in vitamin D level.

Epidemiology of MS: relationship with solar exposure and early life migration

Several aspects of MS epidemiology may suggest a significant contribution of environment during the early life (childhood and adolescence) on the later-life risk of the disease. MS is uncommon in the topics and increases with distance from the equator in both hemispheres. A very important feature of the natural history of MS is that residency in a favourable geographic area (low disease prevalence) sometime before the age of 15 years can reduce the risk in individuals with higher genetic predisposition to the disease. Careful migration studies in South Africa and among immigrant West Indians in UK confirm that MS prevalence can vary with the place of residence early in life irrespective of the inherited genetic factors [37].

The unusual population composition of Israel (because of mass migration of Jews from several continents after the second World War) provided a unique opportunity to the epidemiologists to study the prevalence of MS. Population characteristics of MS in Israel was more suggestive of an association with an environmental factor. Analysing

the results of their study, Alter and colleagues commented that above 34° N latitude in Europe, prevalence rate of MS increased sharply, and that ''the causative agent of MS is about 34° N'' [38]. In the NHANES III study of vitamin D levels in seasonal subpopulations [19], the median cut-off for latitude in population where photoconversion of vitamin D was observed during winter months was ⩽34° N. Indeed, Alter's curve of MS prevalence rates becomes almost exponential at latitudes of ~42,° N and above, places in the continental Europe where cutaneous vitamin D synthesis is not possible during the winter months (Fig. 2).

The study of US veterans provides one of the best evidence to the increasing risk of MS by migration from low to high areas [39]. This and other epidemiological studies seem to suggest that acquisition of MS occurs between approximately between the ages of 10—15 years in the northern hemisphere [40,41]. However, the evidence of an age effect was not observed in the study of migrant population in Australia despite a strong correlation with latitude, the disease becoming increasingly prevalent with increasing south latitude [42]. The Australian study seemed to indicate that the age-risk of developing MS spans a wider age range during adolescence and early adult life, at least in the southern latitudes. A direct relationship between solar exposure in early life and MS has been documented in a number of epidemiological observations. In a case-control study, higher sun exposure during childhood and early adolescence was associated with a reduced risk of MS [7]. Early results from a large, multi-centre case control

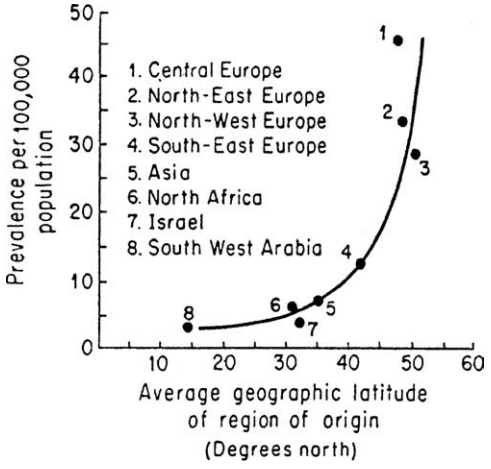

Figure 2 Prevalence of MS among people in Israel related to the latitude of the region of origin; note the steep rise in the northern European latitudes where winter synthesis of vitamin D is low or absent (graph adapted from Alter and others [38]).

study of MS patients in three different geographic areas of disease prevalence (Cuba, Sicily and Martinique) also indicate that, apart from family history, duration of skin exposure to sunlight before the age of 15 years is an important determinant of the disease risk [43]. Outdoor sports or duration of direct sunlight exposure in excess of one hour every week in childhood was found to confer protection against the disease in this study. It seems reasonable to infer from these data that sufficient endogenous bioactive vitamin D in early life may modify the genetic risk and significantly attenuate the life-time incidence of MS. Indeed, mortality from MS is strongly and negatively associated with residential and occupational sunlight exposure [44].

Vitamin D and MS

The suggestion that vitamin D may have a protective effect on MS is not new. It has been previously hypothesised that early life vitamin D deficiency may be a risk factor for various neurological and psychiatric diseases including MS [45] and that vitamin D is a natural inhibitor of MS [46]. A number of studies have also revealed that individuals with MS have insufficient vitamin D levels and there is higher prevalence of reduced bone mass [47], fracture history [48] and dental caries [49,50] among MS patients. Symptoms of MS in women worsen in the first three months after delivery [51] in parallel with the high maternal bone turnover and increased vitamin D requirement during late pregnancy and lactation [52]. Dietary supplementation with vitamin D, calcium and magnesium for a period of one to two years was found to decrease relapse rate in a group of young MS patients in the mid-1980s [53]. Incidence of MS is low in Greenland Eskimos possibly because of their diet contains high levels of fish oil that is rich in vitamin D.

First demyelinating symptom in MS usually appears during the second or third decades of life, earlier in women than in men. A longitudinal prospective study of vitamin D intake and the incidence of MS in women recently found that vitamin D supplementation reduced the life-time incidence of MS by 40% [10]. In this study, dietary vitamin D was examined directly in relation to the risk of MS in two large cohorts of over 90,000 women. Total daily intake of vitamin D and the intake from supplements (but not from food) were inversely associated with the risk of MS, with a 40% reduction in the risk. This was the first, large prospective study convincingly demonstrating a benefit of dietary vitamin D supplementation and

its role in prevention of MS. Because the recruited subjects in this study were adults, the results seem to suggest that the protective effect of sunlight or vitamin D extended to the age of young adulthood.

Protective role of vitamin D in MS: unanswered questions

Is the protection against MS offered by solar radiation or by vitamin D (a product of solar radiation)?

Those who favour an immunopathogenic hypothesis of MS have proposed that the observed latitudinal variations in MS and the protective effect of solar exposure is related to the direct ''immunosuppressive'' effect of ultraviolet radiation [54,55]. It is difficult to accept this explanation given that protection against the disease is not paralleled by the expected side effects of solar radiation (skin cancer) in healthy population living at an area of high MS prevalence. Also, population based record linkage studies indicate that skin cancer is significantly less common in MS but not in those with other autoimmune diseases [56]. Population based, longitudinal prospective studies are required to establish a definite relationship between solar exposure, serum vitamin D level and life-time risk of MS.

Is the protective role of vitamin D in MS related to an immunological mechanism?

Vitamin D, because of its effect on proliferating T- and B-cells, does have immunoregulatory effects and there are studies showing that EAE can be blocked by vitamin D pre-treatment [57,58]. However, EAE is not an acceptable model for MS [1] and the EAE hypothesis cannot explain the effect of early life events and migration effect in MS.

Does vitamin D play a part in the development of myelin?

Myelinisation in the central nervous system is a process by which oligodendrocytes wrap the axons with closely apposed layers of their own cell membranes. Each oligodendrocyte cell envelops several axons, 15 on average, and maintains over 50 internodal segments. Central nervous system myelinisation is a multi-step process and the first step is axonal adhesion by the differentiating oligodendrocytes that leads to ensheathing of axons and progressive compaction of myelin.

N-cadherin is a calcium-dependent cell adhesion molecule that is considered to play an important role in establishing the first axon-oligodendrocyte contact and myelination [59]. Adhesion via N-cadherin is also involved in the oligodendrocyte—oligodendrocyte adhesion between myelin lamellae. The more differentiated oligodendrocytes are, more likely they are able to make long-lasting axonal contact [60]. There are large numbers of oligodendrocyte precursors in the adult brain that are able to divide slowly without differentiation; however, remyelination after myelin injury is very limited. Although substantial number of oligodendrocyte progenitors can be found in contact with the demyelinating plaques in MS, effective remyelination is not seen [61]. One possible reason for this is that N-cadherin is developmentally downregulated in the adult central nervous system and very little N-cadherin can be detected on axons once the development is completed [62].

During early embryonic development, VDR is expressed in the neuroepithelium and later, in the subventricular zone [12]. In rats, oligodendrocytes expressing VDR are present throughout the white matter of the brain and spinal cord and these cells are sensitive to vitamin D [63]. Microglial cells in culture produce 1,25 dihydroxy vitamin D_3 from its precursor [64]. When MS patients were supplemented with vitamin D, there was a significant increase in transforming growth factor (TGF)-β1 levels paralleling the rise in vitamin D [65]. In experiments using explanted mesenchymal cell lines, expression of N-cadherin in developing chondrocytes was regulated by 1,25 dihydroxyvitamin D_3 and TGF-β1 [66]. Research should be directed to answer if vitamin D may play a role in the regulation of calcium-dependent cell adhesion molecules such as N-cadherin in which case it is possible that relative deficiency of vitamin D may adversely affect VDR-expressing oligodendrocytes in axonal adhesion and differentiation.

Is the protective role of vitamin D in MS genetic rather than environmental?

The protective role of early life solar exposure and cutaneous vitamin D synthesis on the life-time risk of developing MS is probably not without genetic predisposition because the population prevalence of MS does not parallel the prevalence of rickets or osteomalacia and while subclinical vitamin D deficiency is more common in dark-skinned races, MS is more common in fair-skinned races of Euro-

pean origin. However, gene analysis studies have shown no association between MS and vitamin D related genes or VDR gene polymorphisms [67,68]. It is also unlikely that 1,25 dihydroxyvitamin D has regulatory effects on myelin proteins [63], presumed to be the target for autoimmune attack in MS in the EAE model.

Why should we use vitamin D to prevent MS?

There are many examples where simple dietary supplementation has been remarkably effective in preventing neurological diseases and folic acid supplementation in pregnancy to prevent neural tube defects is a particularly good example. In veterinary medicine, copper supplementation in ewes prevented the demyelinating disease of the newborn lambs (swayback). However, in preventing neural tube defects, folic acid does not work by correcting a simple nutritional deficiency in pregnancy but rather it works by influencing one or more metabolic pathways in early brain development that can be corrected by sufficiently large doses [69].

Epidemiological studies point strongly towards a role of vitamin D during development as protective against MS. Vitamin D effect may also explain the age effect on migration studies because adult brain development is completed by the age of 15 years. Oligodendroglial apoptosis [4] and dystrophy [70] are being recognised as important pathological features in the demyelinating lesions of MS. The pathogenesis of MS is not clearly known but it is possible to have a working hypothesis (Fig. 3) where vitamin D is required for oligodendroglial differentiation. Because oligdodendrocytes express VDR, one may speculate that vitamin D maintains a normal balance between oligodendroglial differentiation and axonal adhesion during normal brain development and vitamin D depletion leads to slower rate of oligodendrocyte differentiation with an increased proportion of cells in apopotosis. In an appropriately ''primed'' central nervous system, environmental triggers in adult life may lead to axonal injury

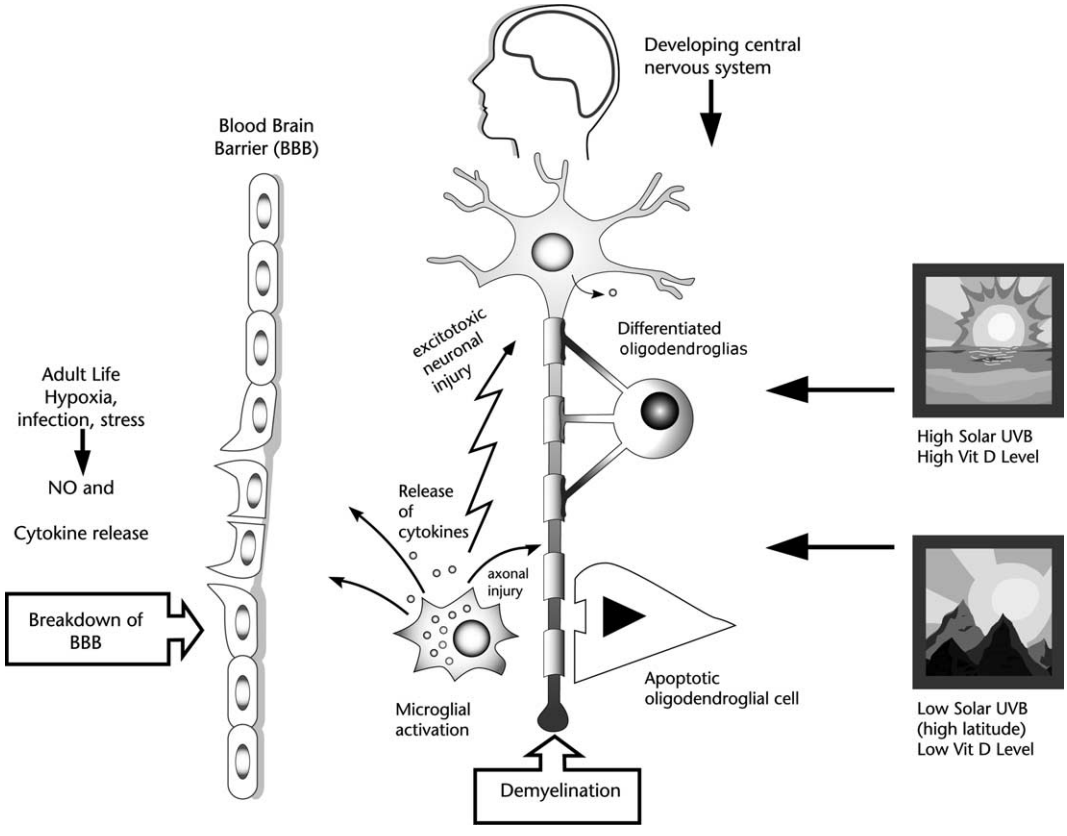

Figure 3 A proposed model of MS pathogenesis. Early life vitamin D insufficiency may interfere with oligodendroglia-axonal adhesion and myelinisation. An appropriate environmental event in adult life may precipitate oligodendroglial apoptosis and microglial activation, leading to the cascade of events associated with demyelination and neuronal injury in MS. NO: nitric oxide; BBB: blood-brain-barrier, UVB: ultraviolet B radiation.

and demyelination. The inherited risk in MS possibly relates to the rate of neurodegeneration and patients with primary progressive MS may represent the more conserved genetic manifestation of the disease with relatively less environmental influence (vitamin D metabolism). In this hypothetical model, MS is a metabolically influenced developmental disease of myelin and genetic risks are chiefly responsible for the rate of progressive neurodegeneration. It has to be emphasised that it is not known if the oligodendrocyte adhesion to axon for the process of myelination is dependent on vitamin D or calcium-binding proteins regulated by vitamin D.

However, it seems likely that beyond a stage, myelin loss and axonal injury MS may become self-perpetuating, as suggested from a recent epidemiological model [71]. Once damaged, the prospect of axonal regeneration and remyelination is extremely limited, whether spontaneous or induced by neural cell transplants. The failure of the central neurons to regenerate is not due to the inability to sprout new axons but rather due to the changes in the local environment after injury [72]. In other words, the human central nervous system represents an unfavourable molecular environment for regrowth and the best strategy in MS would be to prevent demyelination rather than to attempt repair after myelin injury and axonal transaction have already occurred. Longitudinal and prospective epidemiological studies probably spanning over 25—30 years are required to evaluate the protective role of vitamin D supplementation during pregnancy and early life.

Is the protective effect of vitamin D gender-specific, i.e., seen in women?

MS and its relapsing form are more common in women and women are more likely to have hypovitaminosis D. Epidemiological data are required to answer this question but it is likely that the protective effect of vitamin D would be more obvious in women because their vitamin D levels are influenced by seasonal and reproductive changes. Present studies indicate that vitamin D supplementation is likely to reduce the incidence of MS and may continue to offer additional protection in all adult women who, unlike adult men, are more likely to have wider seasonal fluctuations in vitamin D levels.

What is the recommended vitamin D supplement for MS prevention?

Vitamin D insufficiency is widespread in northern latitudes. The assumption that vitamin D nutrition is adequate in the absence of clinical or radiographic signs of rickets is probably flawed and the existing recommendations for vitamin D have been criticised for being inadequate [73]. A daily supplement of 1000 units of vitamin D is considered advisable for all adults [73] and this dose should be routinely recommended to all women during pregnancy and lactation, and particularly to those who have recently migrated to higher prevalence areas for MS. All children in temperate climate should be encouraged to have sports or other outdoor activities and to take vitamin D-rich food. Children born to a family with parental history of MS should have vitamin D supplementation of 200—400 units/day. Prospective, longitudinal epidemiological studies should be able to detect whether the intervention reduces the incidence of MS in areas of high prevalence in the northern latitudes of 34° N and above.

Conclusions

Early life sunlight exposure and dietary vitamin D supplementation diminish the risk of MS. Despite the convincing epidemiological data on the protective effect of sunlight exposure during pregnancy and childhood and the effect of vitamin D supplementation in adults, we do not clearly know how vitamin D may prevent MS because there has not been enough research in this area. However, low vitamin D appears to be an important modifiable external risk factor for MS. Reduced maternal vitamin D levels may increase the risk of MS in the offspring independent of the inherited genetic predisposition. It is unclear how the protective effect of vitamin D operates for MS but it may do so by maintaining a balance between oligodendroglial differentiation and apoptosis in the developing brain before growth is completed.

Traditionally, preventive measures in medicine have seldom found contemporary favour although history has shown that preventive medicine has always offered the greatest benefit. Men and women who develop MS do not have skeletal features of vitamin D deficiency (rickets or osteomalacia). However, relative hypovitaminosis D in early life may increase the risk of MS by influencing metabolic pathways in the myelinating central nervous system that we do not understand at present. The

potential health and economic benefits of vitamin D supplementation in areas of high MS prevalence are huge. Routine vitamin D supplementation in pregnancy and childhood is a simple yet cost-effective strategy to try and reduce the burden of a devastating disease that has destroyed, and continues to destroy, many young lives.

Conflict of interest. I have no conflict of interest to declare.

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