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Review Article

Multiple Sclerosis and Vitamin D: Is there a Link in the Multifactorial Model?

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Abstract

MS is a rare neurodegenerative disease with an immunopathological background. Although, it has a rather low global prevalence, it can be considered among one of the most common youth disabling disorders that are not related to trauma. It is also classified as a complex disease with many susceptibility genes incriminated in its etiology and prognosis. In addition, several well identified and extensively studied environmental factors are implicated as vitamin D metabolism & ultraviolet B (UVB) exposure, Epstein Barr virus (EBV) infection, smoking and morbid obesity. The infamous relationship between Vitamin D and MS has been an area of extensive research in many aspects; pathophysiology, disease course, prognosis and even response to treatment.

Keywords: Autoimmune demyelinating diseases, 1,25 dihydroxy vitamin D3, Autoimmune diseases.

Introduction

Multiple sclerosis (MS, OMIM 126200) is a chronic autoimmune, neurodegenerative, demyelinating disease of the central nervous system with a complex etiology that affects over 2.8 million people worldwide[1]. Full etiology of this disease remains unknown, but genetic and environmental factors play important roles in susceptibility to the disease[2]**.** Thus far, many genes have been identified in predisposing to MS disease. Genome wide association studies (GWAS) suggested more than 200 MS associations in MS susceptibility, most of which were autosomal and included vitamin D receptor gene (VDRG) area[3]. Since the seventies, vitamin D emerged as a crucial factor in the development of MS. A cascade of studies, both observational and experimental, were conducted to unravel the ambiguous link between vitamin D and MS starting from causality and ending with favorability of the disease course and treatment outcomes[4]. A constellation of studies suggested that the role of vitamin D in the pathogenesis of MS is through its robust immune-modulating effect[5]. The activated form of vitamin D has a pivotal role

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in maintaining the immunological homeostasis. It also exerts a direct impact on T-lymphocyte proliferation notably by upregulating T regulatory cells (Treg) and inhibiting the cascade of the adaptive immunity[6]. In the past 20 years, an array of studies with interesting results has investigated the association of VDRG polymorphisms with MS in various ethnic populations. Most of which have shown a significant association between VDRG polymorphisms in terms of genotype and allele distribution and susceptibility of MS[7].

Multiple Sclerosis: Background and epidemiology

MS is a rare neurodegenerative disease with an immunopathological background. Although, it has a rather low global prevalence approximating only 3 million cases worldwide , it can be considered among one of the most common youth disabling disorders that are not related to trauma[1]. It is also classified as a complex disease with many susceptibility genes incriminated in its etiology and prognosis. In addition, several well identified and extensively studied environmental factors are implicated as vitamin D metabolism & ultraviolet B (UVB) exposure, Epstein Barr virus (EBV) infection, smoking and morbid obesity[8].

I. Epidemiology

World-wide

Many studies have investigated the prevalence of MS either on a country or regional level. The atlas of MS assembled by the MS International Federation represents an open-source universal anthology of high-quality MS epidemiological data of 115 countries (87% of world population). It comprises the data (prevalence, incidence, gender, age distribution, disease patterns) gathered through a comprehensive survey between late 2019 and early 2020 with comparative data from the previous edition in 2013[9]. The survey announced that nearly 2.8 million people are currently diagnosed with frank MS with a mean prevalence of 35.9/100,000 and a mean diagnostic age of 32 years old as shown in an informative heat map that illustrates the discrepancy in the disease prevalence worldwide (Figure 1).

Middle East North Africa (MENA) region:

It is a consensus that autoimmune diseases are less prevalent in non-European countries. This is also the case for MS. Studies performed before the new millennium in Arabic countries as Saudi Arabia, Iraq, Libya, Kuwait, Tunisia and Jordan, have all reported a rather low prevalence rates of an approximated mean of 11.5/100,000[1011]. These figures nearly tripled in studies performed after the year 2000 to reach a mean of 34/100000[12,13]. An interesting and quiet informative revision of these valuable epidemiological data was conducted by a research group in Beirut[14].

Gender and MS:

Gender related discrepancies in the prevalence and incidence rates is well-established in most autoimmune disorders. The consensus is that females are more frequently affected than males[22]. MS, as many autoimmune diseases, has gender related incidence approaching 3:1 as a female to male ratio[2]. Also, females are twice as likely to live with MS as males[9]. This has not generally been the situation during the past century according to some case series in which the sex ratio was almost equal. In the eighties, the ratio doubled to be 2:1[23] and steadily increased causing an increased gender bias with a current female to male ratio of 3:1[1]. The exact reason for the increased incidence of MS in women is

unknown, nevertheless the change occurred too fast to be attributable to genetic causes alone, suggesting environmental factors that are sexually dimorphic & are more commonly encountered in one sex than the other could intervene[24].

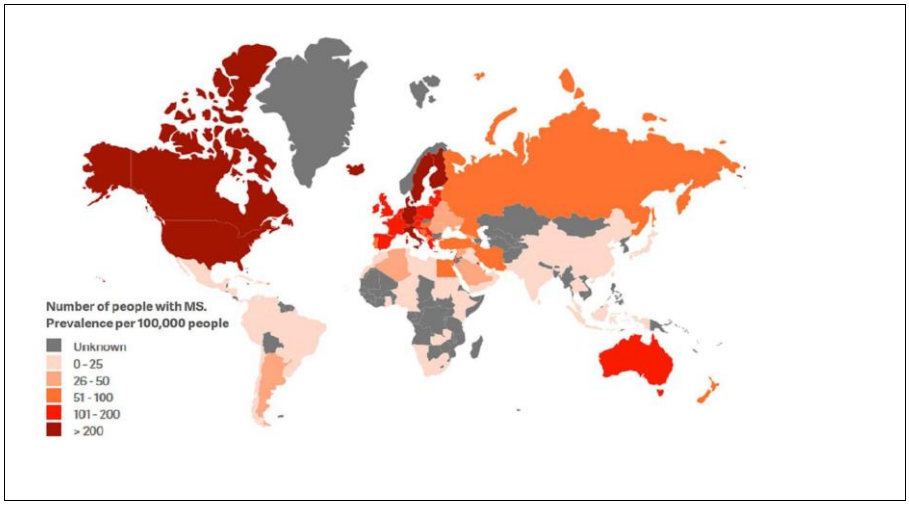

Figure 1: Heat Map showing geographic variation in MS prevalence
MS prevalence per 100,000 population by country shown in shades of orange and red. Countries without prevalence data are shown in grey.[Map adopted from Atlas of MS, 3rd edition[9].

Over the preceding 50 years, lifestyle modifications affected many females across the world, especially in the developed countries. Smoking, utilization of anti-conception medication, parity, dietary habits, obesity, and daylight openness & sun exposure ,all of which can explain the contrasts seen recently[25,26]. Pregnancy has an undeniable and strong effect on MS course and relapse rate. Evidence of the effect comes from studies reporting an astonishing 70% decrease in relapse rates during the 3rd trimester compared with pre-pregnancy levels. The relapse rates 3–6 months after delivery interestingly increase to levels almost 3 times higher than pre-pregnancy ones[27] .The apparent reason is that normal pregnancy induces physiological and drastic immunological changes to promote early immunological tolerance to preserve the growing fetus against rejection. This is achieved through Treg elevation, reduction in T helper cells (Th)1/Th17 activity and increase in Th2 activity with significant reduction in the total number of natural killer (NK) cells[28,26]. During puerperium, a clear increase in relapse rates has been observed. This may be attributed to abrupt drop in estrogen, progesterone, and glucocorticoids levels and rapid normalization of immune function to pre-pregnancy conditions[29] . In fact, after delivery the situation can even be attributed to what has been defined as an immune reconstitution inflammatory syndrome-like phenomenon, secondary to rebound of pro-inflammatory cell types and functions as a consequence of fetal and placental delivery[30]. Concurrently, the rise of hormones involved in breastfeeding mechanisms activated at this time may also play a role in increasing disease activity[31]. It is worth mentioning that MS disability following menopause seems to aggravate. Nevertheless, it should be pointed out that most studies on this issue do not include cohorts of men as a comparison group, which would be necessary to distinguish

the effects of ageing per se from those linked to diminished reproductive function at this stage of the female life[32].

II. Environmental factors and MS

It is widespread for MS etiology to be addressed as unknown or idiopathic. Although there are many well studied and established direct causes or risk factors that individually or together can initiate the diseases in a genetically predisposed person[33] .This postulation is strongly supported by migration studies exploring generations of migrants from low risk to high risk countries and their offspring up to their third generation[34] . Vitamin D is the most famous factor implicated in interaction scheme; Therefore, it will be discussed in more details separatelyin the upcoming sections.

1. EBV

The interchanging causality dilemma between MS and EBV has been going on for years. It was proven that the risk of having MS is significantly low among those who were not infected earlier with EBV, but it increases drastically in the same subjects post infection with the virus[35] . The underlying mechanisms sway between molecular mimicry, bystander T cell activation or retroviral induction and reactivation[36]. The astonishing immortalization effect of the virus to the infected B cells has been strongly introduced in the past decade as a very important pillar in the MS immunopathology[37] .

2. Latitude

There are also multiple pieces of evidence that link the increase in the MS risk to latitude and UVB exposure accordingly. This must also be combined with a reduction in vitamin D intake or diminished periods of sun exposure and more recently genetic polymorphisms affecting vitamin D levels &/or levels that collectively modify the risk for MS[2,4,3].

3.Obesity

Observational studies have reported an association between obesity, as measured by elevated body mass index (BMI), in early adulthood and risk of MS. However, bias potentially introduced by confounding and reverse causation may have influenced these findings. A mendelian randomization study that employed summary statistics from the Genetic Investigation of Anthropobmimetric Traits (GIANT) consortium and the International MS Genetics Consortium (IMSGC), the largest genome-wide association studies for BMI and MS, respectively (GIANT: n = 322,105; IMSGC: n = 14,498 cases and 24,091 controls) concluded that genetically elevated BMI is associated with risk of MS, providing evidence for a causal role for obesity in MS etiology[38].

5. Smoking

Cigarette smoking has been extensively studied in relation to both the development and progression of MS. According to the Bradford Hill criteria, which evaluate potentially causal risk factor-disease outcome relationship; smoking exhibited a statistically significant association with MS risk {Odds Ratio (OR) of 1.54} which provides evidence supporting the causal involvement of smoking in the natural history of MS[39].

III. Immunopathological dysregulation in MS

MS is a complex genetic disease in which individual genetic susceptibility, epigenetic factors and post translational modifications drive the disease clinical progression. Yet, the intense immunopathological findings in the MS plaques suggest an

underlying war between the body and the autoreactive cells[40]. The immunopathological events underlying MS intermingle in a web like network and involves not only the adaptive immune system but the innate immune cells are also active participants[41]. The Dendritic cells (DCs) of the innate immunity shape the adaptive immune response of the naïve T cells. They acquire an activated phenotype in MS patients ($CD83^+$) and direct the Th polarization and differentiation in the CNS[42]. Upon Ag presentation, Antigen-presenting cells (APCs) produce cytokines of differentiating nature and directed mainly to the naïve T cells. According to the milieu, these CD4+ cells evolve to Th1 or Th17. If interleukin12 (IL-12) has the upper hand, then they differentiate into interferon γ (IFN γ) secreting T cells. But if IL-23 predominates, the cells differentiate into Th17 cells that secrete IL-17. In a normal physiological setting, Th1 targets intracellular microbes while Th17 mediates the defense against extracellular bacterial and fungal infection[43]. The same normal scenario of the differentiation cascade following antigen presentation to naïve T cells occur in MS except for being exaggerated, targeted against myelin self Ag and with detrimental consequences[41]**.** Recently, novel candidates that participate in this immunopathology have been introduced as potential players in the neurodegenerative insults. The most famous are Th1-like Th17 and Th22. Additionally, the interesting role of Treg cells was also revised[44]**.** The role of these cells was proposed due to extensive post-mortem examination of MS plaques and brain biopsies together with experimental evidence from animal model i.e., Experimental Allergic Encephalomyelitis (EAE) mouse model. Moreover, modulation of disease course in response to immunomodulatory drugs[5,45,46].

Vitamin D and Multiple Sclerosis

Vitamin D or in other words, "the sunshine vitamin", and sunlight have been implicated among several other environmental factors thought to contribute to an individual's risk of developing MS.

Source and Physiology of Vitamin D

Biochemically speaking vitamin D is a prohormone that is synthesized in the skin from 7-dehydrocholesterol upon exposure to solar UVB or obtained through dietary ingestion (e.g., salmon, tuna, egg yolk, mushrooms, fortified milk, and yeast). UVB radiation cause photolysis of 7-dehydrocholesterol to pre-vitamin D3 which is subsequently isomerized by a nonenzymatic membrane enhanced catalysis to vitamin D3[47]. The above process is affected by a number of individual factors (e.g. age, increased skin pigmentation, use of sunscreen, time spent indoors) and environmental factors (e.g. season, time of day, latitude, pollution, climate changes), all of which represent a factor that affects sunlight as a source of vitamin D[48].

Metabolism and Function of Vitamin D

Upon its formation, vitamin D weakly binds to the vitamin D-binding protein and is transported via blood to the liver for enzymatic conversion to 25-hydroxyvitamin D (25(OH)D). This is subsequently hydroxylated to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in the kidneys for regulating calcium, phosphate, and bone metabolism [49]. $1,25(OH)_2D$ then interacts with its nuclear VDR in the small intestine resulting in the enhancement of dietary calcium and phosphate absorption. In the bone, this hormone interacts with its receptor in osteoblasts resulting in the increased expression of Receptor Activator Of Nuclear Factor Kappa-B ligand (RANKL), which in turn interacts with monocytes to metamorphize into mature osteoclasts which

trigger Calcium immobilization from the skeleton to maintain its homeostasis[50]. An array of tissues and cells also have the capacity to convert 25(OH)D to $1,25(OH)_2D$ as macrophages, monocytes, breast, colon, brain, and prostate among other tissues. The vitamin D endocrine system is also involved in a number of other important physiological processes including blood pressure regulation, immune function, mammary gland development, hair follicle cycling, and protection against chemical and ultraviolet light-induced skin tumorigenesis[51]. It is believed that the local production of $1,25(OH)_2D$ acts in an autocrine or paracrine fashion to regulate a wide variety of genes controlling DNA synthesis, apoptosis, and cellular maturation among many other activities [52].

Immunomodulatory Effects of Vitamin D

The immunodysregualtory nature of MS as an autoimmune disease requires a brief review of the potential effects of vitamin D related to immune function. Vitamin D does not appear to be immunosuppressive, but rather immunomodulatory, with pleotropic effects on immune function. When healthy adults ingested 2000 IUs/day of vitamin D for 12 weeks, 291 genes responsible for regulating more than 100 different metabolic processes were altered in their peripheral white blood cells [49]. These non-calcemic genomic activities may be responsible for the importance of vitamin D in such diverse roles as cancer prevention as well as immune disease[53]. The role of vitamin D in immune function has been the subject of extensive investigation since the discovery of VDRs in activated human T and B lymphocytes in the eighties. VDRs have been identified on virtually all immune cells, many of which are also capable of converting 25(OH)D into $1,25(OH)_2D$, allowing $1,25(OH)_2D$ to modulate both innate and adaptive immune function at sites of inflammation[54]. The active form of vitamin D plays an essential role in lymphocyte activation and proliferation, Th cell differentiation, tissue-specific lymphocyte homing, the production of specific antibody isotypes, and regulation of the immune response[55]. All these targeted cells have VDR which is unequally expressed among them. Macrophages and DCs constantly and constitutively express VDR whereas VDR expression in T cells are only upregulated upon their activation. The upcoming bullet points summarize its role among different immunological cells:

- In macrophages and monocytes, $1,25(OH)_2D$ positively impacts its own effects by increasing the expression of VDR and the cytochrome P450 protein; CYP27B1. It also induces their proliferation and the expression of IL-1 and cathelicidin (an antimicrobial peptide) by macrophages, contributing to innate immune responses to some bacteria.
- Activated Vitamin D decreases DC maturation, inhibiting upregulation of the expression of major histocompatibility complex (MHC) class II, CD40, CD80, and CD86. In addition, it decreases IL-12 production by DCs while inducing the production of IL-10.
- In T cells, vitamin D reduces the production of IL-2, IL-17, and IFNγ and attenuates the cytotoxic activity and proliferation of CD4+ and CD8+ T cells.
- The active metabolite of vitamin D might also promote the development of FOXP3+ T reg cells and IL-10-producing T regulatory type 1 (TR1) cells.
- $1,25(OH)_2D$ blocks B cell proliferation, plasma cell differentiation, and immunoglobulin production[56].

Vitamin D Deficiency and Insufficiency

In 2011, recommended guidelines for the general population dietary vitamin D intake were released by the Institute of Medicine which recommended the intake of

600 IU/day for those aged 1–70 years , and 800IU/day for those >70 years old, corresponding to serum levels of 25(OH)D of 16ng/mL it emphasized that most (97.5%) individuals' nutritional needs would be met at serum levels of 25(OH)D <20ng/mL[57]. However, the Endocrine Society whose guidelines were for the treatment and prevention of vitamin D deficiency in children and adults defined deficiency as <20ng/mL, insufficiency as 21–29ng/mL, and sufficiency as ≥30ng/mL for maximum musculoskeletal health[58]. The definitions proposed by these two groups have been extensively debated in the literature. So, it is important to declare the methodology and cut off levels recommended by the manufacturer in any study that involves measurement of vitamin D so as not to cause confusion to the reader.

Vitamin D Status and Risk of MS

Several key observations form the foundation for the hypothesis that hypovitaminosis D, marked by low serum levels of 25(OH)D, is a risk factor of MS in adulthood[59]. First, regional UVB radiation is predictive of corresponding MS prevalence rates and supports the hypothesis that sunlight exposure and the corresponding vitamin D levels influences MS risk[60,61]. Second, MS risk varies by latitude; the risk appears to decrease with early migration from higher to lower latitudes. Moreover, Vitamin D status is inversely related to latitude[33]. Third, populations at high latitudes but with higher consumption of vitamin D-rich fatty fish exhibit a lower than expected prevalence of MS[62]. These observations have been modified in recent decades, possibly related to increasing tendency to avoid sun exposure, and stay indoors for greater portions of the day even in warmer climates[48]. One of the strongest evidence is a prospective, nested case-control study of United States military personnel found that high levels of serum vitamin D were associated with a decreased risk of MS[63] .This results were also supported by a similar nested case-control study in northern Sweden who declared similar significantly decreased risk of MS with higher vitamin D levels[64]. *Munger et al.,(2017)*[65] recently reported the results of a nested case-control study of 1092 women diagnosed with MS in the Finnish maternity cohort. 25(OH)D was quantified in serum obtained prior to MS diagnosis, and subjects were matched with up to three controls on date of birth and area of residence. Conditional logistic regression adjusted for year of sample collection, gravidity, and parity were used to estimate relative risks and 95% confidence intervals. They found that women with 25(OH)D levels <12ng/mL had a 43% higher risk of MS compared to those with levels ≥20ng/mL.

Vitamin D Status and MS Activity

Several studies have shown a correlation between relapse rates and vitamin D status. Although these are confounded by the possibility of reverse causation, they lend support to the possible role of vitamin D supplementation in MS. A retrospective study of pediatric patients with MS, after adjusting for several factors including age, race, ethnicity, disease duration, and treatment, found that every 10 ng/mL increase in 25(OH)D levels was associated with a 34% decrease in relapse rate[66]. Similar results were seen in adult-onset MS, where one well-constructed study observed relapse rate to decrease by 27% for every doubling of 25(OH)D levels[67], and another noted that every increase in 25(OH)D by 4ng/mL was associated with up to 12% reduction in relapse rate[68].

Genetic Studies and Vitamin D

Vitamin D deficiency is a candidate risk factor for a range of adverse health outcomes

and MS is one of them. The most recent GWAS of 25(OH)D concentration included 417,580 Europeans and identified 143 independent loci in 112 genetic regions. The mega study provided insights into the physiology of vitamin D and implicated genes involved in lipid and lipoprotein metabolism, dermal tissue properties, & the sulphonation and glucuronidation of 25(OH)D. Mendelian randomization models find no robust evidence that the vitamin has causal effects on candidate phenotypes (e.g. BMI, psychiatric disorders), but many phenotypes have (direct or indirect) causal effects on 25(OH)D concentration, clarifying the epidemiological relationship between 25(OH)D status and the health outcomes examined in the study[3]. Several recent studies have utilized Mendelian randomization to estimate the effect of vitamin D on the risk of MS. This is a method that uses measured variation in genes with known function to estimate the association of modifiable exposures in the risk of disease. Studies using this approach reduce the chance of reverse causation because inherited alleles are not affected by most confounding variables or disease status[69]. Genome-wide data of genetic variants shown to predict levels of serum 25(OH)D were applied to the IMSGC. *Mokry et al., (2015)* found that alleles known to decrease levels of serum 25(OH)D predicted an increased susceptibility to MS. Another study found similar results in two separate populations, including white, non-Hispanic Americans and members of a Swedish population study[69]. These data further support the hypothesis that low levels of vitam D exert independent causal effects on MS.

Summary and Conclusion

MS is a deteriorating neurodegenerative disease that affects adults in their reproductive age. Despite its low prevalence, it has a dreadful impact on the patients' quality of life. Therefore, extensive research has increased dramatically in the past decade to address the possibility of altering the course of the disease to increase disease free years and improve the quality of life of the patients. Different studies agree on some findings and disagree on others. This is due the complexity and heterogeneity of this disease in which multifactors participate collectively or independently to affect the clinical course of the disease and extend also to affect the treatment outcomes. These factors include, but are not limited to, variable ethnicity and migration patterns, latitude and sun exposure, vitamin D metabolism and dermal physiology and access to medical care and supplementation. Investigation of intimate relationship between vitamin D metabolism and receptors, and MS has been a fertile area of research in the past decade. Surprisingly, after years of scientific efforts and acrimonious debate, a causal relation has not been established, not even its direction was yet determined i.e., which causes what? The advance in the molecular techniques and the hugely loaded bioinformatic databases has opened new horizons in the investigation of the multifactorial nature of MS. The degree of incrimination of Vitamin D in the pathophysiology of the disease became more established yet still need more experimental verification. Moreover, large scale studies have been conducted to investigate in depth the effect of Vitamin D in the initiation, course, prognosis and even response to treatment. All the scientific community interested in this intriguing link await impatiently for the results hoping to unveil the interlinking pathways and hopefully help those misfortunate patients.

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