

HLA-DR as a critical player in Vitamin-D associated Multiple sclerosis pathogenesis.

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ABSTRACT- Multiple Sclerosis (MS) is a chronic inflammation resulting in demyelination and progression loss of brain cells. So far vitamin D has been known as the regulator of calcium homeostasis, but through the course of recent years, it has emerged as a potential immune modulator, especially in autoimmune disorders like MS. Vitamin D acts on Class II MHC region HLA-DRB1, the allelic variants of which serve as strong genetic risk for MS. Hence it can be hypothesized that MS can be the result of interaction between certain genetic and environmental factors. This study includes the effect of these two factors on MS in consideration with MS model.

Keywords- Experimental Autoimmune Encephalomyelitis, Human Leukocyte Antigen class II DR beta 1, Antigen presenting cells, Vitamin D Receptor, **Myelin** Oligodendrocyte Glycoprotein, 25-hydroxy vitamin D, Inflammation.

1 INTRODUCTION:

Multiple sclerosis (MS), first illustrated in 1868 by Jean-Martin Charcot, is a central nervous system inflammatory disorder distinguished by loss of myelin, axonal pathology, and gradual neurological dysfunction (Ramagopalan, Maugeri et al. 2009). It is an autoimmune disease leading to scarring due to the demyelination of myelin protective sheath which is present around the nerve cells and the spinal cord. Signs and symptoms may vary, depending upon the localization of the lesion but some common manifestations include weakness in leg muscles, sensory loss, speech trouble, loss of coordination and

unsteadiness. Multiple sclerosis (MS) affects young adults, with a predominance in females (*Kampman and Steffensen 2010*). The disease progression is normally in the relapsing-remitting pattern for about 10 years which may later on develop into a secondary progressive phase.

The pathogenic processes involved are still unclear; however, the risk factors for MS are becoming evident with advancing scientific tools. Of many factors, genetic and environmental factors tend to be the two major risk factors for MS, their complex interaction and their effects depending upon the case (*Goodin 2009*). The genetic factors are various (*Booth, Heard et al. 2009*) and are still a major issue for debate. The three environmental causative factors recently mentioned in literature (*Ascherio and Munger 2007; Ascherio and Munger 2007*) includes past infection with EBV,

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smoking and Hypovitaminosis D- with exacerbating effects (*Chao, Ramagopalan et al. 2009; Zhang and Wu 2010*). In this study, we shall emphasize on the role of Vitamin D as a major trigger in MS disease cause and progression.

1.1 Role of Vitamin-D in Immune Mechanisms:

It is debated that deficiency of vitamin D is presently one of the most leading causes of many neurological and inflammatory disorders, most importantly Multiple sclerosis, in terms of new clinical implications. (*Pierrot-Deseilligny 2009*). Vitamin D, which is a fat-soluble vitamin of plant origin is involved in the metabolism of phosphorus and calcium, ossification and mineralization, via attaching to a specific receptor in nucleus, known as, vitamin D receptor (VDR) (*Brustad, Alsaker et al. 2004*). Relation between vitamin D metabolism and the incidence of autoimmune diseases have been reported in rheumatoid arthritis (RA), multiple sclerosis (MS) (*Brustad, Alsaker et al. 2004*), Systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), Diabetes mellitus (*Van Belle, Gysemans et al. 2011*).

Cholecalciferol (vitamin D₃) is synthesized under the UV radiation in skin via its precursor 7-dehydrocholesterol which results in the formation of 25-hydroxyvitamin D [25(OH)D₃] and 1, 25-dihydroxyvitamin D [1,25(OH)₂D₃], which are the prime circulatory agents because these are physiologically active isotypes. (*Ramagopalan, Herrera et al. 2008*). It is therefore postulated that the presence of vitamin D exerts a protective effect in individuals,

supported by the fact that people with increased circulating levels of Vitamin D are at a much lower risk of developing MS (*Correale, Ysraelit et al. 2011*). The serum constituent of vitamin D frequently measured is 25-hydroxyvitamin D, a marker that identifies an individual's overall levels of vitamin D.

The daily vitamin D required by a person has been evaluated to be no less than 2,000 IU/d (*Rigby, Waugh et al. 1990*). Vitamin D consumption via (non-enriched) food is generally less than 100 IU/d, depending on the geographical locations, which turns out to be below average, as per daily requirement. Sunshine is a prime contributor of the required dosage i.e about 90%. Increasing the amount of time spent in sun i.e. through sunbathing can deliver about 10,000–20,000 IU in around 15–30 minutes, but this supply is not constant and it disappears within a few weeks' time and except for the tropical countries, this supply cannot readily be regained throughout the year. (*Rigby, Waugh et al. 1990*).

According to the internationally accepted standards Vitamin D levels in a range between 75 and 200nmol/l are normal, however, with levels lower than 75nmol/l a person is said to be insufficient, and those below 25nmol/l are characterized as severely deficient. Moreover, the levels of Vitamin D are dependent on gender, age, skin tone, geographical location, personal habits and most importantly the genetic polymorphism.

1.2 Vitamin D Metabolic and Physiologic Basis:

Vitamin D is a steroid hormone which is either acquired directly through diet, or, is formed in the skin by UV exposure. This results in activation of 1,25 dihydroxyvitamin D₃ (calcitriol) by undergoing numerous hydroxylation steps. Apart from its role in maintaining outstanding health of bones, vitamin D receptors have also been categorized to play a distinctive role in many areas of our body including muscles, gonads, gut, skin, central nervous system (CNS), bones, microglia, monocytes, oligodendrocytes and B and T lymphocytes (*Chaudhuri 2005*).

The possibility of developing MS is highest in the areas where the environmental exposure of vitamin D are lowest. As the sun light facilitates the production of vitamin D₃ (D3) in the skin, many epidemiological studies and corresponding data elucidates that higher vitamin D blood levels results in lower risk, less relapses and consequently reduced progression of MS. In order to achieve higher circulating levels of vitamin D, oral intake of D3 is suggested. According to a meta-analysis, it now known that areas of higher latitudes, such as Northern Europe, where the intensity of sun is lower, the incidence of MS is higher as compared to areas of lower latitude. In support of this idea, an evidence suggests that vitamin D – formed in the skin on direct exposure to sunlight – can produce crucial immune chemicals, also known as cytokines, in mice models having EAE, which is the MS-like disease, and hence revert or prevent its manifestation. According to another study, low ultraviolet light (UVL) exposure reduces vitamin D stores, (*Kampman and Steffensen 2010*) which correlates strongly with high MS rates. One of the major function of the CNS is to convert vitamin D (*Kampman and Steffensen 2010*) into a

physiologically active hormone with certain neuro-protective and anti-inflammatory functions that rely on IL-10-producing lymphocytes.

The lack of sunlight exposure may contribute to stimulate a defect in regulatory IL-10 lymphocyte function which will eventually weaken a cascade of self-tolerance processes and generate an autoimmune response which is pathogenic in response to certain neural proteins like Myelin oligodendrocyte glycoprotein (MOG) (*Holick 2008*). Most people use a vitamin D deficient diet, therefore, a negative correlation of vitamin D from food sources is only discovered when the exposure of UVR is low (*Andersson 1998; Van Belle, Gysemans et al. 2011*) In the Nurses' Health cohort study of 187,000 women who were aged 25–55 years, the total vitamin D consumption from use of vitamin D supplements P400 IU/day, and not from dietary source, were correlated with higher serum 25(OH)D levels and thus reduced MS risk (*Chao, Ramagopalan et al. 2009*). Consequently, MS risk is not regulated by the environment alone, but, is also dependent on an individual's gene-environment interaction which proves to be a strong candidate for the disease occurrence.

2 Multiple Sclerosis Risks:

The risks linked to Multiple Sclerosis (MS) are determined by a person's genetics and environmental interactions. Both, epidemiologic and experimental studies have depicted a correlation between lower

environmental supply of vitamin D to an increased vulnerability to MS (*Kampman and Steffensen 2010*). Also the HLA-DRB1*15 allele specifically established MS associated disease susceptibility. Inside the Major Histocompatibility Complex (MHC), class II lies the major locus for MS, i.e., the HLA-DRB1*15, the strongest MS susceptibility factor (*Zhang and Wu 2010*). Sequence analysis was used to determine the presence of a single MHC, vitamin D Response Element (VDRE), in the early promoter region of HLA-DRB1. Further studies identified a specific location of vitamin D receptor to the VDRE, in the HLA-DRB1*15 promoter region. (*Ramagopalan, Maugeri et al. 2009*).

It has been found that, prior to disease onset, patients with MS have considerably low levels of vitamin D [25(OH)D] in their blood serum, as compared to the normal people with reference to age, sex and ethnicity (*Ascherio and Munger 2007*).

Environment has seen to play a crucial role in the increased risk of MS in certain populations. As sunlight is the major source for Vitamin D synthesis in our body, the individuals living at a higher altitude experience low sunlight, thus, are prone to Vitamin D deficiency and so at an elevated risk for MS. However, the risk of developing MS is also dependent upon the haplotype of the individual, not the allele that affects the occurrence of MS.

Studies of MS and its linkage with HLA-DRB1*15 locus and vitamin D shows that HLA-DRB1*15 is only a region of a susceptibility haplotype and itself is not the susceptibility allele. The HLADRB1* 15 haplotype is maternally transmitted three times more often as

compared to the paternal transmission (*Ramagopalan, Herrera et al. 2008*). This type of transmission and expression of HLA-DR1*15 requires either epistatic interactions i.e the effect of another gene on it, epigenetic modifications on some haplotypes i.e modifications caused by factors other than DNA, or nearby structural variation (*Kampman and Steffensen 2010*). So the active form of vitamin D (1,25 dihydroxyvitamin D3), interacts directly with the promoter of HLA-DRB1*15 gene, hence, increasing the expression of this gene (*Kampman and Steffensen 2010*)

2.1 The crosstalk between Vitamin D and HLA-DRB1*15:

The active type of vitamin D (1,25-dihydroxyvitamin D3) performs the biological effects via the receptor (VDR), a component of the Steroid Receptor Superfamily. VDR acts by binding to response elements known as, vitamin D response elements (VDREs) in the genome, thus, influencing the rate of transcription of vitamin D-responsive genes (*Ascherio and Munger 2007*). A separate VDRE in the HLA-DRB1*15 promoter region is categorized. In an experiment, where B cells were transiently transfected with the gene promoter (HLA-DRB1*15), an enhanced expression upon its activation with 1,25-dihydroxyvitamin D3 was observed. The enhanced expression depleted either by, the deletion of the specific region, VDRE or, with the homologous "VDRE" area in the non-MS-linked HLADRB1 haplotypes; confirming, that it is the haplotype which is susceptible to MS not the allele (*Kampman and Steffensen 2010*).

The VDRE shows differences that are haplotype specific. It is highly conserved, that is, in about 600 chromosomes the mutations are lacking. The main MS-linked haplotype having the HLA-DRB1*15 allele is conserved, but among non-MS-associated haplotype it was generally not conserved and are also not receptive to 1,25-dihydroxyvitamin D3 (*Ascherio and Munger 2008*). It has been found that during early life, a decreased incidence of expression of the disease-associated class II alleles, which includes HLA-DRB1*15 in the thymus, might result in a loss of central tolerance, which, in later life may increase the risk of

autoimmunity (*Pierrot-Deseilligny 2009*). Further studies are being carried out in this respect using various models, the most common among them being EAE for MS study.

2.2 Regulation of Vitamin D in Autoimmune Encephalomyelitis:

Autoimmune encephalomyelitis is an inflammatory demyelinating disease of the central nervous system (CNS), used as an experimental animal model of brain inflammation. It's mostly used as an animal prototype of the human CNS demyelinating diseases. EAE is a model for T-cell-mediated autoimmune diseases. Several experiments are being conducted to validate the distinctive role of Vitamin D in experimental autoimmune encephalitis (EAE). Additionally, many up-to-date findings of various immunological studies, propose that this function could be anti-inflammatory as well as immunomodulatory. Vitamin D evidently inhibits stimulation of EAE, if introduced before the onset of the disease. It categorically improves and alleviates the clinical signs in affected mice, notably, however, if administered afterwards, thus having a noteworthy effect that is protective and therapeutic (*Branisteanu, Waer et al. 1995; Becklund, Hansen et al. 2009*). Vitamin D could induce an anti-inflammatory response in EAE, (*Spach, Pedersen et al. 2004*) by various methods, such as:

1. By reducing the amount of macrophages and/or by the regulation of certain important cytokines (*Cantorna, Woodward et al. 1998*) or,

2. The activation of oligodendrocytes which produces a defensive effect on myelin (*Chaudhuri 2005*) and/or,
3. Inhibition of the development of Th1 cells and an increased Th2 and Tr (regulatory T) lymphocyte restoration, in order to produce an immunomodulatory effect on T lymphocytes (*Cantorna 2006*).

The latter effect seems to be in close association with vitamin D thus, having a possibly, similar mechanism, to that of interferon beta, the protective effect of which is mediated by vitamin D in EAE mouse models. (*van Etten, Gysemans et al. 2007*)

The presumption that vitamin D3 may decrease the severity and occurrence of MS, is supported by the findings that EAE was inhibited by initiation of vitamin D3 and 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3). To explore that how 1,25-(OH)2D3 could carry out anti-inflammatory functions, 1,25-(OH)2D3 was administered to mice having EAE, and the clinical pattern of disease was consequently observed, with reference to the concentration levels of chemokines, inducible nitric oxide synthase (iNOS), and employment of specific dye-labeled monocytes. The clinical severity of the disease was significantly reduced within 3 days, after the administration of 1,25-(OH)2D3 treatment. After the treatment with 1,25-(OH)2D3, sharp declines in the levels of chemokines, inducible iNOS, and CD11b+ monocyte recruitment into the central nervous system (CNS) were observed. The inhibition of cytokine synthesis did not occur, neither directly nor rapidly by the administration of 1,25-(OH)2D3, instead, it swiftly stimulated the

activation of CD4+ T cell apoptosis in the spleen and CNS. Combining the data from previous studies, these results indicate that 1,25-(OH)2D3 induces anti-inflammatory response. Like this, the sunlight-derived hormone could decrease the incidence of producing severe CNS inflammation and autoimmune mediated neurodegenerative disease (*Pedersen, Nashold et al. 2007*)

3 DISCUSSION:

In anticipation of advancements in extensive medicinal research using vitamin D, which would complete in its own time, we however, could offer at least some studies on use of Vitamin D that are rare and have a limited scope. Treatment with vitamin D for two years (5,000 IU/d as cod liver oil supplement), there were around 10 MS patients, exhibiting a 60 percent decrease in the predicted number of relapses; however, no control group was present. (*Munger, Levin et al. 2006*).

In another study of 39 patients with MS for 6 months and 22 control subjects, 17 were given 1,000 IU/d of Vitamin D3 (cholecalciferol) and they showed a significant increase in level of TGF-b1, which is the anti-inflammatory cytokine, affected by vitamin D in EAE (*Hayes and Acheson 2008*). The full scientific context of these studies is fruitful and provides credible amount of justification for much more far-reaching medicinal trials (phase II or phase III). However, there is need to optimize the appropriate Vitamin D doses, since the daily dosage in above-mentioned two studies 1000 and 5,000 IU/d, situation that raises the

bewildering question of the effective therapeutic dosage.

In various studies a convincing relation between the *HLA-DRB1*15* and MS has been shown. It has found through various experiments that MS susceptibility has been attributed to the *HLA-DR1*15* region and it is the haplotype not the allele susceptible to MS, along with epistatic and epigenetic interactions play a major role (*Dyment DA, et al. 2005; Spurkland A, et al. 1997*). Epidemiological data depicts the influence of environmental factors, on the geographical distribution of the disease. Sunlight is the major environmental factor that influences the susceptible haplotypes in one's genome, as sunlight is the vital source of vitamin D. It has been hypothesized that vitamin D interacts with the regulatory elements of class 2 MHC region known as *HLA-DR1* and more appropriately its haplotype *HLA-DR1*15* (*Kampman and Steffensen 2010*).

The role of VDR gene polymorphisms to the immune regulation in MS is not, as yet comprehended. Vitamin D response element differs in MS and non-MS associated individuals and therefore there is a difference in the regulation of *HLA-DR* haplotypes as it is present in the promoter region of *HLA-DR*.

Active Vitamin D is also concerned with inhibiting different transcription factors involved in cytokine gene regulation (*Spach, Nashold et al. 2006*). In the present study, we spoke about how CD4⁺T cells from MS patients, which were cultured in the presence of 1,25 (OH)₂VitaminD gave rise to an enhanced

number of IL-10 producing cells. IL-10, is primarily, a positive autocrine factor, acting precisely on the T cells with an interactive action on the signaling pathways induced by 1,25 (OH)₂ Vitamin D (*Spach, Nashold et al. 2006*).

Overall, these findings suggest that 1,25 (OH)₂ Vitamin D plays an imperative role towards T cell response development, allocating T cells with immunosuppressive characteristics, for instance direct targeting of T cells, however modulation of DCs functions also has a vital involvement in directing T cell response.

Even though the mechanism of its action is still unidentified, vitamin D₃, in its hormonal form may be an immune system regulator also inhibiting MS, and VDRG polymorphism could bear some influence on vulnerability to MS.

All the findings in this research correspond to the experimental evidence, indicating a defensive effect of Vitamin D in animal model (EAE) of MS, prevention of which can be done by administration of the active metabolite 1,25 (OH)₂ of Vitamin D prior to immunization, which could be further enhanced when given after disease onset. Conversely, Vitamin D deficiency reduced the time to onset of EAE and increased severity. This evidence validates the role of Vitamin D as an immunomodulatory molecule.

CONCLUSION:

The findings regarding Vitamin D and its interaction with *HLA-DRB1*15*, for MS susceptibility

discussed here, are still premature. This is mainly because the data reported is by far, scanty and insufficient, also sometimes conflicting. However this data also seemingly maintains the fact that the potential administration of vitamin D supplementation is strongest and multi-purpose for MS, that being said, more and more work and progress, although, is still to be performed in this area of risk for MS. As mentioned previously, vitamin D activates certain proteins that bind to the promoter region of HLA_DRB1*15 in MS patients and which is not the case in the normal persons. Such proteins are still not identified. In addition to this, vitamin D level is low in MS patients so there must be a strategy to bring the level to normal in MS suspects. All Inclusive, 1,25 (OH)₂ Vitamin D affects the immune system at different stages, through different mechanisms, and at different intensities, leading to immunosuppression. Modification of 1,25 (OH)₂ Vitamin D deficiency may be useful to suppress MS like autoimmune disorders. This review open new horizons for research related to treatment of MS by identifying proteins that bind to predisposed gene as well as level regulation of vitamin D.

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