

Editorial

Vitamin D and Neuromyelitis Optica Spectrum Disorders

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Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a Central Nervous System (CNS) inflammatory demyelinating disease which distinct from Multiple Sclerosis (MS) in its pathogenesis and treatment responses. The pathogenesis of MS has not been clearly elucidated but mainly involved in T-cell mediated immune responses and partly imparted by B-cell via antigen presenting cell processes. In contrast, humoral immunity namely Aquaporin 4-IgG antibody (AQP4-Ab) in NMOSD effects on aquaporin channel located at foot process of the astrocytes, caused complement deposition and granulocyte infiltration or astrocytic alterations associated with AQP4 internalization, leading to demyelination and astrocyte necrosis [1,2]. Recently study demonstrated that a cellular response, CD4 T cell reactivity against AQP4, is likely to play a role in seronegative NMOSD [3]. An immune response is hypothesized that either related with a direct pathogenic effect of TH1/TH17 lymphocytes or tissue destruction mediated by CD8 T cell [1,2].

Vitamin D is essential in bone homeostasis and calcium metabolism and play an important role in human immune system both in activating immune defense mechanism and suppressing immune disease [4-6]. Vitamin D is obtained either from dermal synthesis or diet. The major source of vitamin D is from sunlight specifically UVB radiation in latitude with less ozone. After exposure to sunlight, 7-dehydrocholesterol in the skin converted to an inactive form, provitamin D₃, and passed enzymatic hydroxylation in the liver and kidney to form vitamin D₃ or cholecalciferol [7] and finally to its active metabolite “1,25 hydroxy vitamin D” [8,9]. Average serum concentrations of 25(OH)D are between 30 and 150nmol/L and is considered a good measurement of vitamin D availability as its formation has a relatively long half-life of 20–60 days and shows little variation compared to 1,25(OH)D. Alternative route of vitamin D is from foods rich of vitamin D₂ or Ergocalciferol such as milk, fatty fish or liver.

Vitamin D has been documented its role associated with in many autoimmune diseases i.e. Rheumatoid Arthritis, Systemic Lupus Erythematosus, Crohn’s disease, Type 1 diabetes mellitus, Multiple sclerosis etc. and colon cancer.

The association between vitamin D and MS has been continuously

documented. In animal model, calcitriol (1,25(OH)D) has been shown to protect against the development and progression of Experimental Autoimmune Encephalomyelitis (EAE). This effect is mediated through promotion of regulatory T-cell function as opposed to direct effects on Th1 or Th2 cells [10]. In clinical trials, vitamin D shows the association with MS in many aspects; 1) having low vitamin D level is one of the risk factors for developing MS, supported by many studies revealed low level of vitamin D in patients with MS and also those with Clinically Isolated Syndrome (CIS) [11-13]; 2) having enough or high vitamin D level may be a protective effect to prevent MS, woman who had high 25(OH)D level decreased the risk to develop MS and intake of multivitamin including vitamin D in woman had protective effect for MS [14]; 3) Replacement of vitamin D in MS patients to optimal level associated with a decrease in relapse rates [15]; 4) High 25(OH)D levels reduced MS activity measured by MRI [16].

In contrast to MS, there are a few studies reported the relationship between vitamin D and NMOSD. Although they differ in pathogenesis and clinical characteristics, they both seem to have both cell and humoral mediated immune responses played their role in the pathophysiology of the diseases [17,18].

There are several cytokines and humeral immune response mechanism involving during the acute attack [19]. Vitamin D may also be part of immune mechanism in NMOSD. First study in NMOSD and vitamin D from South Korea revealed almost all NMOSD patients; 47/51 patients (92.1%), had vitamin D insufficiency compared with 135 (66.2%) of 204 healthy controls in cross sectional study [20]. This study found disease severity determined by Expanded Disability Status Scale (EDSS) inversely associated with vitamin D level. However, no correlation between disease activities measured by Annualized Relapse Rates (ARR) was found.

It is well-known that the prevalence of MS is higher in high-latitude regions. In contrast, geographic distribution is not observed in the prevalence of NMO [21]. To date, there is no study investigated the association between vitamin D among each demyelinating disease including NMOSD, MS and CIS from the same base population.

An unpublished data from Thailand revealed that each group of the patients with CIS, MS, and NMO/NMOSD had high frequency of vitamin D insufficiency (16/20 (80% in CIS, 73.52% in MS and 73.28% in NMOSD group). No correlation between vitamin D level and either with disease activity measured by ARR or severity determined by EDSS were found in our study [22].

Since Thailand is located in equator line and has sunrise for the whole year whereas Korea is not. The concordance of the results for high frequency of vitamin D insufficiency in patients with NMO from the two studies may be explained by two possible hypotheses. Firstly, it could be from lacking of sun exposure caused by limitation of outdoor activities related to disability in patients with NMO. Secondly vitamin D deficiency may take part in immunopathogenesis in patients with NMOSD.

MS and NMOSD differ in geographic distribution, pathogenesis, clinical characteristics, cerebrospinal fluid analysis and radiological findings. Nevertheless they both seem to have both cell and humoral mediated immune responses played their role in the pathophysiology of the diseases [17,18]. Further studies are needed to be sought out the mechanism of vitamin D in NMOSD.

Plausible mechanism of vitamin D in NMOSD

After the active form of vitamin D binds to intracellular Vitamin D Receptor (VDR) to form Vitamin D Response Elements (VDREs), it influences in the process of protein transcription in DNA and in the regulation of innate and adaptive immunity [23]. As mentioned above, AQP4-IgG, one of the humoral immunities, is the key factor in the pathogenesis of NMOSD. In addition cell mediated immune response seems to play an important adjunct. Recently study demonstrated that a cellular response, CD4 T cell reactivity against AQP4, is likely to play a role in seronegative NMOSD [3]. A cellular immune response is hypothesized that it is related with a direct pathogenic effect of TH1/TH17 lymphocytes or may be caused tissue destruction mediated by CD8 T cell [1,2].

In central nervous system, VDRs and 1 alpha hydroxylase are localized both in neurons and glial cells [24]. VDREs can be found on several immune cells i.e. lymphocytes, macrophages and dendritic cells. It involved in suppression of T-cell response by inducing T regulatory cell which has an anti-inflammatory effect [25].

Vitamin D induces apoptosis in B cells which lead to decrease in immunoglobulin production [26]. Moreover, vitamin D induces interleukin (IL)-10 synthesis [27] and suppresses IFN- γ and IL-2 [28].

There is an evidence that IL-10-producing regulatory CD4(+) T Cells is inhibited by T helper Type 1 (Th1)- and Th2-inducing cytokines [25].

1,25-(OH) $_2$ D $_3$ enhances an anti-inflammatory cell-produced IL-10 acting on brain parenchymal cells and in turn IL-10 signaling is essential for 1,25-(OH) $_2$ D $_3$ as documented in Experimental Autoimmune Encephalomyelitis [29].

In vitro study, 1, 25-(OH) $_2$ D $_3$ can inhibit TNF and IL-6 producing from microglial. Study in Irish adults reported an increase correlation between IL-6 level (1.45, 1.71, and 2.29pg/mL) and the level of 25(OH) D (>75nmol/L, 50-75nmol/L and <50nmol/L, respectively; p<0.001) [30]. In addition, this study found the association of high CRP in patient who had low vitamin D level [30]. As shown in the clinical trial, anti-IL-6 inhibitor is one of the targeting therapies in NMOSD. Therefore having adequate vitamin D level may reduce inflammatory response related to high level of IL-6 in NMOSD.

Anti-CD 20 therapy like Rituximab showed the efficacy in preventing relapses in the patients with NMOSD [31]. Also anti-CD-19 is another promising B-cell depleting treatment [32]. These targeting therapies on B-cell, which produces AQP4-IgG, are proven the important role of B cell in the pathogenesis in NMOSD. High level of CD56+ NK cell and CD19+ B cell levels were found in the context of low level of vitamin D [33].

The meta-analysis of vitamin D supplement in patients with MS showed no significant difference in its benefit compared to

those without supplement [34]. Until now, there is no international consensus about the treatment of vitamin D in patients with MS who has vitamin D deficiency. Up to date, there has no study about vitamin D treatment in NMOSD patients. Future research about vitamin D in NMOSD should be investigated regarding as a risk factor, the association with disease activity/ severity and benefit of the treatment.

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