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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.

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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 needs 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].

$1,25\text{-}(OH)_2D_3$ enhances an anti-inflammatory cell-produced IL-10 acting on brain parenchymal cells and in turn IL-10 signaling is essential for $1,25\text{-}(OH)_2D_3$ as documented in Experimental Autoimmune Encephalomyelitis [29].

In vitro study, $1, 25\text{-}(OH)_2D_3$ 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.

References

1. Hinson SR, Romero MF, Popescu BF, Lucchinetti CF, Fryer JP, Wolburg H, et al. Molecular outcomes of neuromyelitis optica (NMO)-IgG binding to aquaporin-4 in astrocytes. Proc Natl Acad Sci USA. 2012; 109: 1245-1250.
2. Misu T, Höftberger R, Fujihara K, Wimmer I, Takai Y, Nishiyama S, et al. Presence of six different lesion types suggests diverse mechanisms of tissue injury in neuromyelitis optica. Acta Neuropathologica. 2013; 125: 815-827.
3. Zeka B, Hastermann M, Hochmeister S, Kögl N, Kaufmann N, Schanda K, et al. Highly encephalitogenic aquaporin 4-specific T cells and NMO-IgG jointly orchestrate lesion location and tissue damage in the CNS. Acta Neuropathologica. 2015: 1-16.
4. Smolders J, Moen SM, Damoiseaux J, Huitinga I, Holmøy T. Vitamin D in the healthy and inflamed central nervous system: access and function. Journal of the Neurological Sciences. 2011; 311: 37-43.
5. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinal Metab Clin North Am. 2010; 39: 365-379, table of contents.
6. Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med. 2011; 364: 248-254.
7. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and Skin Physiology: A D-Lightful Story. Journal of Bone and Mineral Research. 2007; 22: 28-33.
8. Holick MF. Vitamin D Deficiency. New England Journal of Medicine. 2007; 357: 266-281.
9. Rosen CJ. Vitamin D Insufficiency. New England Journal of Medicine. 2011; 364: 248-254.
10. Chang J-H, Cha H-R, Lee D-S, Seo KY, Kweon M-N. 1,25-Dihydroxyvitamin D(3) Inhibits the Differentiation and Migration of T(H)17 Cells to Protect against Experimental Autoimmune Encephalomyelitis. PLoS ONE. 2010; 5: 12925.
11. Behrens JR, Rasche L, Gieß RM, Pfuhl C, Wakonig K, Freitag E, et al. Low 25-hydroxyvitamin D, but not the bioavailable fraction of 25-hydroxyvitamin D, is a risk factor for multiple sclerosis. European Journal of Neurology. 2015.
12. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006; 296: 2832-2838.
13. Duan S, Lv Z, Fan X, Wang L, Han F, Wang H, et al. Vitamin D status and the risk of multiple sclerosis: A systematic review and meta-analysis. Neuroscience Letters. 2014; 570: 108-113.
14. Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004; 62: 60-65.
15. Simpson S, Jr., Taylor B, Blizzard L, Ponsonby AL, Pittas F, Tremlett H, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. Ann Neurol. 2010; 68: 193-203.
16. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA neurology. 2014; 71: 306-314.
17. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. The Lancet Neurology. 6: 805-815.
18. Vaknin-Dembinsky A, Karussis D, Avichzer J, Abramsky O. NMO spectrum of disorders: a paradigm for astrocyte-targeting autoimmunity and its implications for MS and other CNS inflammatory diseases. J Autoimmun. 2014; 54: 93-99.
19. de Andres C, Teijeiro R, Saiz A, Fernandez P, Sanchez-Ramon S. Changes in B and T-cell subsets and NMO-IgG levels after immunoglobulins and

rituximab treatment for an acute attack of neuromyelitis optica. Neurologia. 2015; 30: 276-282.

20. Min J-H, Waters P, Vincent A, Cho H-J, Joo B-E, Woo S-Y, et al. Low Levels of Vitamin D in Neuromyelitis Optica Spectrum Disorder: Association with Disease Disability. PLoS ONE. 2014; 9: 107274.

21. Marrie RA, Gryba C. The Incidence and Prevalence of Neuromyelitis Optica: A Systematic Review. International Journal of MS Care. 2013; 15: 113-118.

22. Jitprapaikulsan J, Siritho S, Prayoonwiwat N. Vitamin D level and its clinical correlation in Thai patients with central nervous system demyelinating diseases. Poster session presented at the Joint ACTRIMS-ECTRIMS Meeting USA. 2014.

23. Pike JW, Meyer MB. The Vitamin D Receptor: New Paradigms for the Regulation of Gene Expression by 1,25-Dihydroxyvitamin D(3). Endocrinology and metabolism clinics of North America. 2010; 39: 255-269.

24. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the Vitamin D receptor and 1α-hydroxylase in human brain. Journal of Chemical Neuroanatomy. 2005; 29: 21-30.

25. Barrat FJ, Cua DJ, Boonstra A, Richards DF, Crain C, Savelkoul HF, et al. *In Vitro* Generation of Interleukin 10–producing Regulatory CD4(+) T Cells Is Induced by Immunosuppressive Drugs and Inhibited by T Helper Type 1 (Th1)– and Th2-inducing Cytokines. The Journal of Experimental Medicine. 2002; 195: 603-616.

26. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol. 2007; 179: 1634-1647.

27. Allen AC, Kelly S, Basdeo SA, Kinsella K, Mulready KJ, Mills KH, et al. A pilot study of the immunological effects of high-dose vitamin D in healthy volunteers. Multiple Sclerosis Journal. 2012; 18: 1797-1800.

28. Müller K, Ødum N, Bendtzen K. 1, 25-Dihydroxyvitamin D3 selectively reduces interleukin-2 levels and proliferation of human T cell lines in vitro. Immunology Letters. 1993; 35: 177-182.

29. Spach KM, Nashold FE, Dittel BN, Hayes CE. IL-10 Signaling Is Essential for 1, 25-Dihydroxyvitamin D3-Mediated Inhibition of Experimental Autoimmune Encephalomyelitis. The Journal of Immunology. 2006; 177: 6030-6037.

30. Laird E, McNulty H, Ward M, Hoey L, McSorley E, Wallace JMW, et al. Vitamin D Deficiency Is Associated With Inflammation in Older Irish Adults. The Journal of Clinical Endocrinology & Metabolism. 2014; 99: 1807-1815.

31. Kim S, Huh S, Lee S, Joung A, Kim H. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurology. 2013; 70: 1110-1117.

32. Herbst R, Wang Y, Gallagher S, Mittereder N, Kuta E, Damschroder M, et al. B-Cell Depletion In Vitro and In Vivo with an Afucosylated Anti-CD19 Antibody. Journal of Pharmacology and Experimental Therapeutics. 2010; 335: 213-222.

33. Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Hum Reprod. 2014; 29: 208-219.

34. James E, Dobson R, Kuhle J, Baker D, Giovannoni G, Ramagopalan SV. The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis. Multiple Sclerosis Journal. 2013; 19: 1571-1579.

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