Multiple Sclerosis and Related Disorders 43 (2020) 102156

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

The Potential Immunoregulatory Roles of Vitamin D in Neuromyelitis Optica Spectrum Disorder

Yifan Wu[a], Yu Cai[a], Mingyuan Liu[b], Desheng Zhu[a], Yangtai Guan[a,*]

[a] Department of Neurology, Renji Hospital, School of medicine, Shanghai Jiaotong University, No.127, Pujian Road, Shanghai 200127, China
[b] Department of Neurology, Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai University of Traditional Chinese Medicine, 110 Ganhe Road, Shanghai 200437, China

ARTICLE INFO

Keywords:
neuromyelitis optica spectrum disorder
NMOSD
vitamin D
immunoregulation
autoimmunity

ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is an autoantibody-mediated disease affecting the central nervous system (CNS). Its pathogenesis involves both innate and acquired immune reactions; specific antibody (Aquaporin-4 antibody) and inflammatory cells cause direct damage on lesion sites, while B cell-T cell interactions facilitate the demyelination. However, its etiology is still not fully understood.

Vitamin D deficiency is present in numerous autoimmune diseases, including NMOSD. Evidence suggests that low vitamin D levels mayassociate with disease activity and relapse rate in NMOSD, indicating the participation in the pathogenesis of NMOSD. The immunoregulatory roles of vitamin D in both numerous autoimmune diseases and experimental autoimmune encephalomyelitis (EAE) models are increasingly recognized. Recent studies have revealed vitamin D modulation in cytokine production, immune cell development and differentiation, as well as antibody production. By enhancing an anti-inflammatory environment and suppressing the overactivated autoimmune process, vitamin D shows its potential immunoregulatory roles in NMOSD, which could possibly introduce a new therapy for NMOSD patients.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS), characterized by recurrent longitudinally extensive transverse myelitis (LETM) and optic neuritis (ON) (Marignier et al., 2017; Patterson and Goglin, 2017). There are 80-90% patients having a remission-relapse course and developing permanent sequelae in CNS in result (Wingerchuk et al., 2007). Neuromyelitis optica (NMO) is once thought to be a variant of multiple sclerosis. Since the identification of immunoglobulin against aquaporin-4 (AQP4-IgG, also known as NMO-lgG), a water channel mainly located on astrocytes in the brain, in 2004. The term NMOSD was introduced in 2007 to include mainly AQP4-lgG seropositive patients (Wingerchuk et al., 2007) and has an extensive define in 2015 to include seronegative patients (Wingerchuk et al., 2015).Therefore, there are two kinds of NMOSD patients, AQP4-IgG NMOSD and seronegative NMOSD, accounting for 10-25%patients (Lennon et al., 2004). NMOSD now has six core symptoms: optic neuritis (ON); acute myelitis; area postrema syndrome (APS); acute brainstem syndrome; symptomatic narcolepsy or acute diencephalic clinical syndrome and symptomatic cerebral syndrome (Wingerchuk et al., 2015). For AQP4-IgG NMOSD patients, they only need to meet at least one of six core syndromes, but seronegative patients should meet at least two core syndromes and at least one symptom is one of ON, acute optic neuritis and APS (Wingerchuk et al., 2015).These findings not only confirmed NMOSD as a distinct entity, but also led to the concept that NMOSD may be an antibody-mediated inflammatory disorder (Weinshenker and Wingerchuk, 2017; Wu et al., 2019).

The prevalence of NMOSD meeting 2015 diagnostic criteria varies from 0.37/100,000 to 10/100,000, and the age of onset is from 25 to 45.7 (Etemadifar et al., 2015; Mori et al., 2018; Pandit et al., 2015). Recognized differences are seen ethnicity, geography, and sex. NMOSD is more prevalent among non-European populations, such as East Asia and Africa (Hor et al., 2018; Houzen et al., 2017; Mori et al., 2018; Papp et al., 2018). Higher susceptibility and disease severity are observed in nonwhite races compared to the white population (Cabrera-Gomez et al., 2009; Flanagan et al., 2016). Additionally, females show higher disease prevalence compared to males by almost 2-10 times (Etemadifar et al., 2015; Gold et al., 2019; Pandit et al., 2015). According to the latest diagnostic criteria in 2015, more patients have been included. Epidemiological studies showed new criteria made the rate of incidence and prevalence 1.5-2 times higher, compared with the

* Corresponding author: Yang-Tai Guan, MD, Ph.D.
E-mail address: yangtaiguan@sina.com (Y. Guan).

https://doi.org/10.1016/j.msard.2020.102156
Received 8 January 2020; Received in revised form 13 April 2020; Accepted 26 April 2020

criteria published in 2006 (Papp et al., 2018; Sepulveda et al., 2017).

Vitamin D, whose function is now established far beyond the regulation of bone metabolism, has been reported to have immune-modulatory properties through inhibiting pro-inflammatory reactions and enhancing anti-inflammatory processes. Vitamin D deficiency is found in various autoimmune diseases, and NMOSD is no exception. Numerous studies have suggested that a low level of vitamin D is likely to correlate with disease activity in experimental autoimmune encephalomyelitis (EAE) mice, an animal model for multiple sclerosis(MS) and NMOSD (Min et al., 2014; Shan et al., 2016; Sintzel et al., 2018), and in MS patients. Additionally, vitamin D supplementation showed therapeutic effectiveness in both animal models and patients. However, although vitamin D deficiency is revealed to associate with higher Expanded Disability Status Score (EDSS) and annual relapse rate (ARR) in both MS and NMOSD (Ascherio et al., 2014; Shan et al., 2016), the efficacy of vitamin D as an immunoregulator for disease development and relapse is not yet understood.

This review focuses on the immunomodulatory effects of vitamin D based on the pathogenesis of NMOSD and discusses its role in the disease course.

2. Vitamin D: its metabolism and physiology

Vitamin D, a lipid-soluble vitamin, can be synthesized by the human body with exposure to sunlight or absorbed from the diet. Endogenous and exogenous vitamin D, also called cholecalciferol (vitamin D_3 synthesized endogenously) or ergocalciferol (vitamin D_2 originating in plants). Both vitamin D_3 and vitamin D_2 undergo a transformation to 25(OH)D (calcidiol) by 25-hydroxylase in the liver. Vitamin D_3 is more potent than vitamin D_2 at increasing the 25(OH)D level (Tripkovic et al., 2012). The transportation of vitamin D and its metabolites needs vitamin D binding protein (DBP) (Gauzzi, 2018; Sintzel et al., 2018). At least four enzymes could accompany this procedure, namely, Cytochrome P450 (CYP450) isoforms CYP2DII, CYP2D25, CYP3A4, and CYP2R1 (Rolf et al., 2014). Next, calcidiol needs a second hydroxylation mainly in the kidney to achieve its active form 1,25(OH)2D (calcitriol) (Sintzel et al., 2018). CYP27B1 seems to be the only 25-OHD-1α-hydroxylase expressed in numerous immune cells (Rolf et al., 2014). On the other hand, the downregulation of these active metabolites needs CYP24A1, the 24-hydroxylase. $1,25(OH)_2D$ from the kidney is then released into blood and transported to target organs (bone and gut) to exert its biological function via its interactions with the intracellular vitamin binding receptor (VDR) and this process is regulated by parathyroid hormone (PTH) (VanAmerongen et al., 2004; Wimalawansa, 2012; Yang et al., 2012). The vitamin D-VDR complex acts as a transcription modulator for the expression of various genes (Yang et al., 2012) .

Vitamin D is traditionally thought to maintain calcium homeostasis, which involves organs such as bone, gut, and kidney (Wimalawansa, 2012). Nowadays, non-canonical effects of vitamin D receive considerable attention. Cells from the immune system, such as macrophages, dendritic cells, and activated T cells and B cells are also found to express VDR (Arnson et al., 2007; Sintzel et al., 2018).Also, Various immune cells, such as CD4+ T cells, CD8+ T cells and B cells expressed CYP27B1 and CYP24A1 (Peelen et al., 2011; Rolf et al., 2014). As a result, immune cells may have the ability to regulate the local vitamin D level, which is not regulated as its production in kidney (VanAmerongen et al., 2004). The interaction may indicate that vitamin D may contribute to the immune homeostasis through interactions with vitamin D.

In MS, also a demyelinating disease in the brain, a low level of vitamin D not only is risk factor of MS (Mokry et al., 2015), but correlates with increasing disease activity and a higher risk of relapse (Ascherio et al., 2014). In SOLAR trial, it is established that orally high-dose vitamin D_3 (14,007 IU/d) was not beneficial as an add-on therapy to IFN-β-1a considering ARR and EDSS progression at week 48 but inhibited development of new MRI lesions (Hupperts et al., 2019). EVIDIMS trial found that the high dose (20,400 IU/d) group and low dose (400IU/d) group did not show difference in exploratory outcomes above (Dörr et al., 2020).Several studies comparing the efficacy of different dosage, such as VIDAMS, are being researched at present (Bhargava et al., 2014). In addition, vitamin D supplementation could also improve the quality of life and cognition performance in MS (Darwish et al., 2017; Sotirchos et al., 2016). However, meta-analyses brought about problems of current studies, like low-quality of evidence and uncertainty to the most appropriate dose (Jagannath et al., 2018; McLaughlin et al., 2018).

3. Vitamin D and immune system

The immunomodulatory effect of vitamin D was confirmed both in acquired immunity and innate immunity. $1,25(OH)_2D_3$ and VDR signaling exert an anti-inflammatory effect to various kinds of immune cells (Pierrot-Deseilligny and Souberbielle, 2017).

In NMOSD (85% AQP4-IgG NMOSD), neutrophils show an activated phenotype and dysfunction (Hertwig et al., 2016). Intracerebral administration of the neutrophil protease inhibitors could reduce the lesion in NMOSD mice, a model of NMOSD in mice, analogous to that of EAE for MS (Saadoun et al., 2012).$1,25(OH)_2D_3$ causes less neutrophil recruitment and decreased the neutrophil extracellular traps, thus causing less tissue damage and increasing apoptosis rate of neutrophils (Handono et al., 2014; Takano et al., 2011; Yang et al., 2015). DBP bound to neutrophils is essential for chemotaxis enhancement of C5a (DiMartino et al., 2001), which could be inhibited by $1,25(OH)_2D_3$ (Shah et al., 2006). Additionally, $1,25(OH)_2D_3$ induces C2 production together with IFN-γ stimulation (Littman and Sanders, 1988) and C3 production (Hong et al., 1991), and AQP4-IgG is thought to exert direct damage through complete complement dependent cytotoxicity (Jasiak-Zatonska et al., 2016).

Regarding acquired immunity, Jurgen *et al* found B cells from MS patients with hypovitaminosis D exhibited increased immunoreactivity, and this could be reversed after cocultured with vitamin D. Another finding is that vitamin D deficiency was correlated with intrathecal accumulation of plasma cells (Fyfe, 2016). Chen *et al f*ound that $1,25(OH)_2D_3$ inhibited the proliferation of activated peripheral B cells, induced their apoptosis, and prevented plasma cell differentiation in systematic lupus erythematosus (SLE), but only in the first five days. Additionally, the generation of post-switched (IgD^-CD27^+) memory B cells, cells with the propensity to differentiate to plasma cells (Kurosaki et al., 2015), are also decreased by $1,25(OH)_2D_3$ (Chen et al., 2007).

$1,25(OH)_2D_3$ is proven to suppress the activation of both $CD8^+$ and $CD4^+$ T cells and enhance the immunosuppressive function of regulatory T cells (Tregs) and invariant Natural killer T cells (Alhassan Mohammed et al., 2017; Dankers et al., 2016). André *et al* found that $vitD_3$ affected T helper (Th) cell polarization, in which vitamin D inhibited T helper1 (Th1) cells development and enhances T helper 2 (Th2) cells differentiation via an interleukin-4 (IL-4) dependent manner (Boonstra et al., 2001). Additionally, $1,25(OH)_2D_3$ is found to upregulate Th2 to Th1 and T helper 17 (Th17) cells about 2-4 times (Sloka et al., 2011) and inhibit $CD4^+$ interleukin-17 (IL-17) secreting T cells while inducing the differentiation of regulatory T cells (Zhou et al., 2017).

4. Immunomodulatory effects of Vitamin D supplementation in clinical applications

Vitamin D has already been applied in clinical studies in many other autoimmune diseases, such as MS (Dörr et al., 2012; Muris et al., 2016). Vitamin D therapy at various dosages shows immunomodulatory effects, and both cellular and humoral immunity are involved (Ashtari et al., 2015; Haas et al., 2016; Mosayebi et al., 2011). More

importantly, these findings indicate that the effect might be dose-dependent.

After the supplementation of vitamin D_3 for 12 weeks (20,000 IU/day), no difference was seen in the absolute count of B lymphocytes or the proportions of naïve and memory B cells in MS patients (Knippenberg et al., 2011b). Another study in 2016 showed reduction of the proliferative response and release of interleukin-6 (IL-6) to stimulate B cells upon exposure to $1,25(OH)_2D_3$ and exhibited a dose-dependent manner at 10 and 50 ng/ml, respectively (Haas et al., 2016). In other autoimmune diseases, vitamin D supplementation caused a reduction of memory B cells and anti-dsDNA antibody in SLE patients, indicating the effect of vitamin D_3 in preventing the production of immunoglobulin, which may become a therapeutic mechanism for NMOSD (Terrier et al., 2012). Ashtari *et al* and Mosayebi et *al* showed interleukin-10 (IL-10) levels increased significantly after receiving high-dose vitamin D_3 (50,000 IU every 5 days for 3 months and 300,000 IU monthly for 6 months)(Ashtari et al., 2015; Mosayebi et al., 2011).

The effects of vitamin D on IL-17 or IL-17 T cells remain controversial. The possible explanation might lie in that there is not a commonly accepted optimal treatment for vitamin D. Bahar *et al* found that vitamin D (50,000 IU/week for 2 months) upregulates IL-6 and IL-17A gene expression, especially in the vitamin D responsive group (Naghavi Gargari et al., 2015). Elias *et al* demonstrated that high dose vitamin D_3 (10,400 IU/d for 6 months) supplementation reduced Th17 cells via a dose-dependent manner in MS patients. When serum 25(OH)D_3 was greater than 18 ng/mL, every 5 ng/mL increase caused a 1.0% decrease in the percentage of IL-17 $CD4^+$T cells (Sotirchos et al., 2016). However, Toghianifar *et al* found that patients receiving 50,000 IU vitamin D_3 every five days for 12 weeks showed a significant increase of IL-17 (Toghianifar et al., 2015). The SOLARIUM study argued that supplementation with vitamin D_3 (7,000 IU/d for 4 weeks) did not have an impact on frequency of Th17 cells and IL-17 production (Muris et al., 2016).

5. Potential immunoregulatory roles of vitamin D in NMOSD

5.1. Vitamin D deficiency in NMOSD patients

Few studies have been done on vitamin D levels in patients with NMOSD (Table 1). According to current studies, unlike in MS, the role of vitamin D in NMOSD is not well understood. It is commonly accepted that higher MS risk correlates with higher latitude (Olsson et al., 2017). Vitamin D insufficiency, which may be a result of lack of solar radiation due to a high latitude, is reported to contributed to MS susceptibility (Kočovská et al., 2017; Pierrot-Deseilligny and Souberbielle, 2017). Although the correlation with latitude was not seen in NMOSD yet (Mori et al., 2018), researchers did not ignore the role of vitamin D in NMOSD.

A lower vitamin D level was correlated with recurrent inflammatory spinal cord diseases, including AQP4-IgG NMOSD (Mealy et al., 2012). Additionally, Kimbrough *et al* found vitamin D insufficiency ($25(OH)D_3 < 30$ ng/mL) at the initial attack was associated with the eventual diagnosis of AQP4-IgG or seronegative NMOSD for those with recurrent myelitis (Kimbrough et al., 2014), suggesting that vitamin D might be involved in the pathogenesis of NMOSD.

A relatively lower vitamin D level ($25(OH)D_3 < 20$ ng/mL) in NMOSD patients is widely accepted. Min *et al* showed that $25(OH)D_3$ levels were significantly lower in AQP4-IgG NMOSD patients in South Korea when compared to healthy controls (Min et al., 2014). This finding was replicated in studies in south China and Turkey of NMOSD (54.4% AQP4-IgG NMOSD) and AQP4-IgG NMOSD patients, respectively (Shan et al., 2016; Tuzun et al., 2015). In our previous study, we found low levels of 25(OH)D and $25(OH)D_3$ in patients with NMOSD (70.2% AQP4-IgG NMOSD) except 25(OH)D2 (Gao et al., 2019).

The correlation between vitamin D levels and disease activity remains controversial. Shan *et al* indicated that vitamin D levels were lower in relapse patients (94.5% AQP4-IgG NMOSD) in South China (Shan et al., 2016), while Min *et al* found no difference of vitamin D levels between AQP4-IgG NMOSD patients in acute phase and remission (Min et al., 2014). As for EDSS, ARR and vitamin D levels, both Shan *et al* and Min *et al* found an inverse correlation (Min et al., 2014; Shan et al., 2016). However, in the study of Jitprapaikulsan *et al*, Tuzun *et al* and our team, neither ARR nor EDSS was correlated with vitamin D levels (Gao et al., 2019; Jitprapaikulsan et al., 2016; Tuzun et al., 2015) in NMOSD (73.7% AQP4-IgG NMOSD) and AQP4-IgG NMOSD patients, respectively. However, different latitudes of these regions might result in different average vitamin D levels. So far, no studies focus on new onset NMOSD.

It is worth mentioning that studies only involved AQP4-IgG NMOSD patients found the inverse correlation while studies included both AQP4-IgG NMOSD and seronegative patients did not find such correlation (Subjects of studies are listed in Table 1). Shaygannejad *et al* found that sunshine exposure and 25(OH) D_3 in AQP4-IgG seronegative patients were significantly higher than patients with AQP4-IgG seropositive (Shaygannejad et al., 2018). These results may indicate the role of vitamin D in AQP4-IgG synthesis in AQP4-IgG NMOSD. More studies should be conducted focusing on vitamin D levels between different antibody status.

Further analysis of vitamin D levels in NMOSD showed other possible associations with prognosis. Greater improvement of symptoms was seen in patients with higher level of serum $25(OH)D_3$ during corticosteroid therapy in acute phase and people with low serum 25(OH)D_3 who received vitamin D supplementation (100–2000 IU) had lower ARR than before (Shan et al., 2016). Additionally, a modestly positive correlation was seen between serum $25(OH)D_3$ levels and disease duration (from the appearance of symptoms to the test of $25(OH)D_3$) in NMO. Patients with cerebrospinal fluid oligoclonal bands (OCB) showed significantly lower $25(OH)D_3$ levels (Tuzun et al., 2015). However, further clinical studies on the therapeutic effects of vitamin D supplementation in NMOSD are required. The following discussion will introduce several possible mechanisms of the therapy.

5.2. Potential role of Vitamin D in NMOSD

The pathogenesis of NMOSD involves both innate immunity and acquired immunity. Recognition of AQP4 as self-antigen by antigen presenting cells activated B cells to differentiate to plasma cells which can secret AQP4-IgG, with the help of various kinds of T cells, such as Th17(Flanagan and Weinshenker, 2014; Weinshenker and Wingerchuk, 2017). AQP4-IgG then exerts direct damage to astrocyte through antibody-dependent cell-mediated cytotoxicity and complement dependent cytotoxicity (Ratelade et al., 2012; Waters et al., 2008) across the leaky blood-brain barrier (BBB) into CNS. AQP4-IgG NMOSD also found to associate with different types of autoimmune disease such as SLE and Sjögren's syndrome (Asgari et al., 2018; Martín-Nares et al., 2019), suggesting the overlapping of pathogenesis of these diseases. However, the pathogenesis of seronegative NMOSD still need further research.

B cells are now thought to play dual roles in the pathogenesis of AQP4-IgG NMOSD (Levy et al., 2014). In addition to producing pathogenic antibodies, B cells may act as antigen-presenting cells with expression of MHC II (Häusser-Kinzel and Weber, 2019; Levy et al., 2014; Molnarfi et al., 2013). Naïve B cells continuously express a small amount of VDR and CYP27B1(Chen et al., 2007), both of which are enhanced in activated B cells. In addition, VDR expression is also increased by adding $1,25(OH)_2D_3$(Chen et al., 2007). On one hand, increased local $1,25(OH)_2D_3$ due to CYP27B1 expression further increases the negative feedback loop by inducing CYP24A1 expression. On the other hand, $1,25(OH)2D_3$ enhances the interaction with B cells by upregulating the VDR expression (Rolf et al., 2014). It has been shown that only in the presence of $1,25(OH)2D_3$ is CYP24A1 mRNA expression

Table 1
Recent studies of vitamin D levels in NMOSD patients.

Author & Year	Location	Subjects	Results	Reference
Tuzun et al. (2015)	Turkey	24 NMOSD patients (NMO-IgG seropositive) 19 RRMS patients 22 Heathy people	1 25(OH) was lower in NMOSD and MS patients; 2 NMOSD patients with lower disease duration tended to have a lower 25(OH)D; 3 No correlation was found between 25(OH)D and EDSS in NMOSD patients	(Tuzun et al., 2015)
Min et al. (2014)	South Korea	51 NMOSD (NMO-IgG seropositive) 204 Healthy people	1 $25(OH)D_3$ was lower in NMOSD patients; 2 No association was found between $25(OH)_3$ and ARR but an inverse correlation was found between $25(OH)_3$ and EDSS; 3 Disease duration was positively correlated with 25(OH) D_3	(Min et al., 2014)
Shan *et al.* (2016)	China	40 NMOSD in acute phase (93% NMO-IgG seropositive); 15 NMOSD in remission (NMO-IgG seropositive); 116 Healthy people	1 $25(OH)_3$ was lower in NMOSD patients; $25(OH)_3$ was lower in acute phase than in remission; 2 EDSS was negatively associated with $25(OH)_3$ during attacks; 3 Higher $25(OH)D_3$ was associated with better improvement during corticosteroid therapy; 4 Patients with low $25(OH)D_3$ had a lower ARR after vitamin D supplementation (100–2000 IU).	(Shan et al., 2016).
Gao *et al* (2019)	China	43 NMOSD in acute phase (72.1% NMO-IgG seropositive); 41 NMOSD in remission (68.3% NMO-IgG seropositive)); 84 Healthy people	1 25(OH)D and $25(OH)D_3$ were lower in NMOSD both in acute phase and remission; 2 No correlation was found between 25(OH)D/$25(OH)D_3$ and EDSS/ARR 3 No correlation was found between 25(OH)D/$25(OH)D_3$ and IL-25 /IL-31/IL-33;	(Gao et al., 2019)
Jitprapaikulsan et al. (2016)	Thailand	76 NMOSD (73.7% NMO-IgG seropositive) 34 MS 20 CIS	1 25(OH)D insufficiency was found in 43.4% NMOSD patients; 2 25(OH)D was not associated with EDSS or ARR.	(Jitprapaikulsan et al., 2016)
Kusumadewi et al. (2018)	Indonesia	19 NMOSD patients (73.7% NMO-IgG seropositive) 29 RRMS patients 33 Heathy people	1 25(OH)D was not significant different in NMOSD patients compared to healthy people; 56.2% NMOSD patients have vitamin D deficiency; 2 25(OH)D level was not associated with EDSS and ARR.	(Kusumadewi et al., 2018)
Shaygannejad et al. (2018)	Iran	9 NMO-IgG seropositive NMOSD; 20 NMO-IgG seronegative NMOSD	Sunlight exposure scale and 25(OH) D3 in NMO-IgG seronegative patients were significantly higher than patients with NMO-IgG seropositive.	(Shaygannejad et al., 2018)

NMOSD: neuromyelitis optica spectrum disorder; MS: relapse relapsing remitting multiple sclerosis; CIS: clinical isolated syndrome; EDSS: expanded disability status scale; CSF: cerebrospinal fluid; ARR: annual relapse rate

in B cells detectable (Chen et al., 2007). The interaction between B cells and vitamin D indicates that vitamin D plays a significant role in immune homeostasis, suggesting vitamin D may modulate B cells function in AQP4-IgG NMOSD pathogenesis.

In vitro, $1,25(OH)_2D_3$ has been found to reduce the production of antibodies, such as IgG and IgM (Provvedini et al., 1986). Chen *et al* found that $1,25(OH)_2D_3$ significantly reduced the count of IgG and IgM-producing plasma cells of culture when applied at the beginning of the stimuli. However, this action could not be seen when vitamin D was given after 5 days (Chen et al., 2007). In vivo, the same effects could not be confirmed. No difference was seen in IgM, IgG, or IgA between with and without vitamin D_3 supplementation, and no significant changes were seen in IgG subclasses (Knippenberg et al., 2011b). The probable explanation is that antigen stimulation causes the differentiation of plasma cell precursor-plasmablasts, some of which are competent to become long-life plasma cells induced by survival signals in vivo, accounting for the serum antibody production (Radbruch et al., 2006). The other cells are called short-life plasma cells with a shorter half-life, and vitamin D is supposed to exert effects on short-life plasma cells. However, in the cerebrospinal fluid (CSF), antibodies depend on short-life plasma cells (Cepok et al., 2005). The reduction of IgG levels in CSF during vitamin D supplementation needs further investigation.

Clinical research has brought about the question of whether the reduction of antibody production is beneficial. Hinson *et al* argued that AQP4-IgG titer may not correlate with disease activity (Hinson et al., 2009). In addition, other studies demonstrated that AQP4-IgG titer may not predict the disease course and visual prognosis (Akaishi et al., 2020; Kessler et al., 2017). In this case, the role of AQP4-IgG still needs further study.

Vitamin D might also interact with the IL-10-IL-10R pathway. Higher frequencies of IL-10 secreting B cells, defined as B regulatory cells (Bregs), were found in AQP4-IgG NMOSD and were correlated with higher intensity of AQP4-IgG, suggesting an important role in AQP4-IgG NMOSD (Cho et al., 2018). Another study showed the complicated role of Bregs. $CD19^+CD24^{hi}CD38^{hi}$ and $CD19^+CD5^+CD1d^{hi}$ Bregs, which have a negative regulatory function, were lower in NMOSD patients and were even lower in AQP4-IgG NMOSD than seronegative NMOSD. However, $CD19^+CD24^{hi}CD27^+$ Bregs, leading to excessive inflammatory reaction, were significantly greater than healthy individuals (Han et al., 2017), suggesting that imbalance of pro- and anti-inflammatory Bregs contributes to NMOSD. In an animal model, $1,25(OH)_2D_3$ failed to inhibit EAE in mice with IL-10 or IL-10 gene deficiency (Spach et al., 2006). In another study of human B cells, vitamin D was found to promote the production of IL-10 (Heine et al., 2008), giving the prospect for beneficial interactions between vitamin D and Bregs. Currently, the limited studies that have been performed do not give an explicit conclusion. Although several studies show that $1,25(OH)_2D_3$ supplementation increases IL-10 level both in EAE (Farias et al., 2013) and MS patients (Correale et al., 2011; Smolders et al., 2010), no correlation was found between IL-10-producing B cells and $1,25(OH)_2D_3$ levels in MS patients (Knippenberg et al., 2011a). Therefore, $1,25(OH)_2D_3$ probably upregulated the IL-10 level by enhancing the secretion rather than increasing IL-10-producing B cells. Since there are multiple subsets of Bregs, the modulatory effects of vitamin D needs to be applied to different kinds of Bregs in further research.

Another promising aspect of vitamin D treatment lies in the activation of T cells. The antigen-presenting function is also affected by vitamin D. A reduced expansion of naïve T cells was observed upon co-culture with naïve B cells activated in the presence of $1,25(OH)_2D_3$(Drozdenko et al., 2014). However, this effect was not seen in $1,25(OH)_2D_3$ activated memory B cells (Drozdenko et al., 2014).

Waters *et al* demonstrated that AQP-4 antibody was predominantly IgG1, a T cell dependent subclass (Waters et al., 2008). Vaknin-Dembinsky *et al* showed T-cells with characteristics of both Th1 and Th 17 cells interacted with specific immunodominan AQP4 peptide (Vaknin-Dembinsky et al., 2016) and Zeka *et al* also revealed that AQP4-specific T Cells could cause retinal damage at the initial of NMOSD in animal models (Zeka et al., 2016).Research subsequently focused on the properties of AQP-4 specific T cells and found they demonstrated Th17 polarization (Varrin-Doyer et al., 2012). Furthermore, Th17 cells, Th17-related cytokines such as IL-17 and IL-21 (Li et al., 2015), as well as cytokines that induce Th17, such as IL-6, interleukin-21 (IL-21), interleukin-23 (IL-23) and transforming growth factor-β (TGF-β) (Kebir et al., 2007; Uzawa et al., 2009; Wang et al., 2011), were proven to increase in NMOSD patients (71.4%-100% AQP4-IgG NMOSD). However, IL-21 and IL-17 increased in relapsing NMOSD (78.6% AQP4-IgG NMOSD)(Wang et al., 2011) and could damage BBB through their receptors on endothelial cells (Kebir et al., 2007), causing accumulation of antibody and neutrophils in CNS.

In experimental studies, vitamin D inhibits EAE induction and ameliorates disease severity. Mice with inactivated VDR gene had Th17 cells that overproduced IL-17(Bruce et al., 2011), indicating the modulatory impact of vitamin D on IL-17 levels. Vitamin D is confirmed to reduce Th17 in CNS through suppressing IL-17 gene transcription (Joshi et al., 2011) and inhibiting of secretion of IL-17 by Th17. In human studies, adding calcitriol to activated $CD4^+$ T cell reduced the frequency of IL-17 producing cells (Correale et al., 2010; Jeffery et al., 2009), which is more powerful in females, who have fewer CYP24A1 transcripts as well as more effective DBP (Correale et al., 2010). Additionally, IL-6 was observed to decrease in the CNS after treatment with vitamin D (Chiuso-Minicucci et al., 2015; Subramanian et al., 2012), weakening BBB function and increasing leukocyte transmigration in vitro (Takeshita et al., 2016). In addition, in $1,25(OH)_2D_3$-treated EAE mice, no T cells infiltrated in to the CNS. Further findings may explain this result; $1,25(OH)_2D_3$-treated EAE mice had intact BBB (Grishkan et al., 2013), which may, to some extent, result from decreased IL-17 levels. The results above indicate a higher level of vitamin D means less damage to BBB and less neutrophil chemotaxis.

The regulation of other subclasses of T cells, which probably participates in the immunopathology of AQP4-IgG NMOSD, may also suggest the possible treatment prospects of vitamin D. $1,25(OH)_2D_3$ exhibits the ability to inhibit $CD8^+$ T cell proliferation, IL-17 $CD8^+$T cell in particular, and on the other hand, increase IL-10 and IL-17-regulatory T cells, creating an anti-inflammatory environment. Additionally, $1,25(OH)_2D_3$ decreased the proliferation of pathogenic $IL-17^+CD8^+$ T cells (da Costa et al., 2016). Clinically, the frequency of IL-17 secreting regulatory T cells increased in remission and IL-17 $CD8^+$T cells were also found at higher levels in NMOSD patients (78.6%-100% AQP4-IgG NMOSD), indicating their participation in the pathogenesis in NMOSD (Cho et al., 2018; Wang et al., 2011). However, Grishkan *et al* concluded that vitamin D did not show an effect on activation of pathogenetic T cells. They observed equivalent increase in IFN-γ^+ or $IL-17^+$Th cells with or without $1,25(OH)_2D_3$. After treatment, proportions of splenic Th cells in the spleen were equivalent and produced IFN-γ and IL-17. Although the vitamin D-treated mice were disease free when maintained on $1,25(OH)_2D_3$, EAE developed in $1,25(OH)_2D_3$ withdrawal mice (Grishkan et al., 2013). The interaction between vitamin D and various kinds of T cells is gradually being understood. It is likely that the potential of vitamin D therapy will be further confirmed as more subsets of T cells, such as Tregs and $CD4^+$ T cells are shown to be involved in the pathogenesis of NMOSD (including both AQP4-IgG and seronegative NMOSD) (Brill et al., 2019; Fan et al., 2015; Liu et al., 2018).

In addition to Th17 cells, several studies also observed that Th2 cells related cytokines, such as IL-13, IL-5, and IL-4 were upregulated in NMOSD patients (including both AQP4-IgG and seronegative NMOSD) (Uzawa et al., 2014; Zhang et al., 2018). Recent studies present controversial results. Wang *et al* did not find the previously observed increase in Th2 related cytokines, while our team found higher serum levels of IL-25, IL-31, and IL-33 in NMOSD (56.3% AQP4-IgG NMOSD) as compared to healthy controls and the IL-33 level was associated with

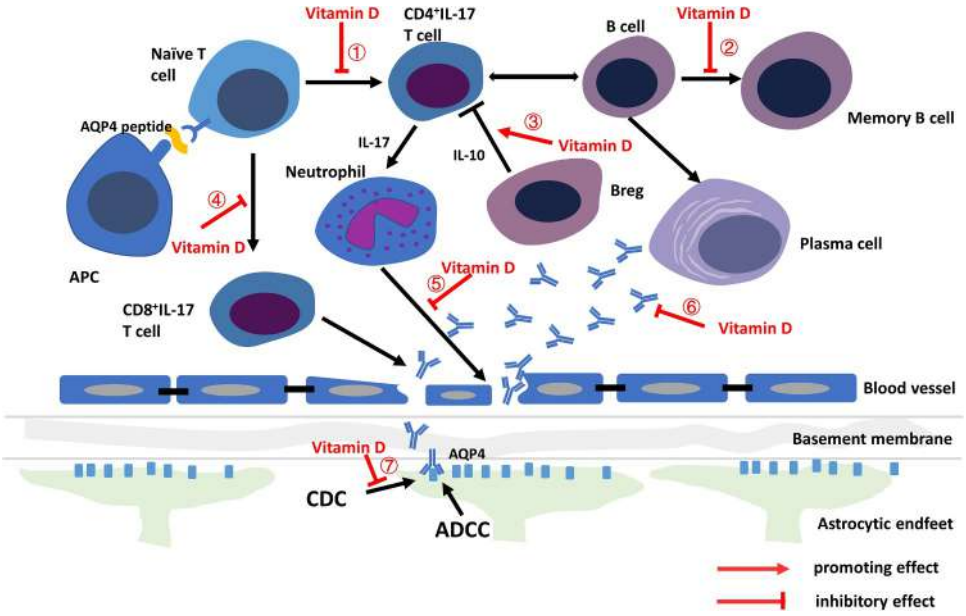

Figure 1. The potential immunoregulatory roles of vitamin D in NMOSD ① inhibit Th17 differentiation; ② reduce memory B cell production; ③ increase IL-10 level;④ reduce $CD8^+$IL-17T cell; ⑤ cause less neutrophil recruitment; ⑥ suppress antibody production; ⑦ decrease completement level.

more past attacks but no correlations were found between these cytokines and vitamin D (Gao et al., 2019; Wang et al., 2016; Zhang et al., 2018). 1,25-$(OH)_2D_3$ was less effective in the absence of IL-4 and vitamin D treatment caused an increase of IL-4 (Cantorna et al., 2000; Shirazi et al., 2017). Additionally, Sloka *et al* found vitamin D could enhance the Th2 shift (Sloka et al., 2011). The role of Th2 in NMOSD is still unclear, and more studies are needed to find the interaction between Th2 and vitamin D.

A controversial question should be considered in the potential immunoregulatory roles of vitamin D in NMOSD. Pathologically, NMOSD is regarded as an AQP4-IgG mediated autoimmune astrocytopathy (Fujihara, 2019). However, the pathogenesis of seronegative NMOSD is still unclear. Therefore, the role might not be examined in the seronegative NMOSD patients as this group represents a heterogenous group of patients with a variety of immunological and inflammatory disorders with likely diverse immunopathogenesis, such as myelin oligodendrocyte glycoprotein (MOG) antibodies disease (Fujihara, 2019; Narayan et al., 2018). Clinically, compared with AQP4-IgG NMOSD, seronegative patients are less likely to relapse and develop visual injury but have no difference in treatment response (Matiello et al., 2008; Mealy et al., 2018; Weinshenker et al., 2006). The vitamin D level in seronegative patients is higher than that in seropositive patients (Shaygannejad et al., 2018), indicating the different vitamin D metabolism in seronegative patients.

In addition, the AQP4-IgG status is closely related to disease process, time at detection and methods (Fryer et al., 2014; Liu et al., 2019; Valentino et al., 2017). Furthermore, there are false negative patients due to the limitations of detection reagents and methods (Fryer et al., 2014). Moreover, clinical studies have showed that seropositive and seronegative patients have similar onset age, disease course, lesion distribution (Jarius et al., 2012; Wang et al., 2018). Therefore, the heterogeneity between AQP4-IgG NMOSD and seronegative NMOSD remains to be further studied and the roles of vitamin D in seronegative NMOSD patients has not been satisfactorily answered so far.

6. Conclusion

NMOSD is thought to develop by an antibody-mediated immune response, and the discovery of its immunopathogenesis has facilitated treatment strategies for NMOSD attacks. Abundant evidence shows numerous immune cells participate in this process including myeloid cells, T cell, and B cells (Michael et al., 2013; Mitsdoerffer et al., 2013). Therapeutic targets focus on these pathogenic cells and their interactions. As the pathological mechanism of NMOSD is not fully understood, vitamin D is showing promise to become part of NMOSD treatment, especially in AQP4-IgG NMOSD, with future results of more immune cell involvement in its development. Currently, immune disregulation of vitamin D has been proven in many autoimmune diseases, such as SLE and MS (Dall'Ara et al., 2018; Sintzel et al., 2018). In NMOSD, as summarized in Table 1, vitamin D deficiency is confirmed and is observed to correlate with disease activity (Min et al., 2014; Shan et al., 2016; Tuzun et al., 2015).

Current studies show the possible immunomodulatory effects of vitamin D in NMOSD (Figure 1), especially AQP4-IgG NMOSD, and the efficacy of vitamin D supplementation in other autoimmune diseases. Therefore, management of vitamin D levels in NMOSD patients and clinical application of vitamin D are needed to confirm the role of vitamin D. It remains to be explored whether there is an effective dose and administration course of vitamin D in NMOSD, since the high dose vitamin D supplementation tended to have a more favorable result (Muris et al., 2016; Toghianifar et al., 2015) but sometimes high doses may potentially have worse outcomes (McLaughlin et al., 2018). So far, most studies focus on AQP4-IgG NMOSD; however, there are additional patients who are antibody seronegative. Additionally, a substantial proportion of those seronegative patients have MOG-IgG and nothing is known about vitamin D in this probably distinct condition. (Borisow et al., 2018; Zamvil and Slavin, 2015) Whether vitamin D demonstrates regulatory effects and whether the therapeutic role of vitamin D is greater in seropositive patients compared with seronegative ones or MOG-IgG positive ones remain to be studied.

Authors' contributions

This work was primarily written by YW and YW also contributed to the production of the figure. YC, ML and DZ contributed to the review revision. YG supervised the work and contributed to editing the review. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to disclose in the submission. This manuscript has not been published and is not under consideration for publication elsewhere.

Funding

This study was supported by the Natural Science Foundation of China (Grant No. 81771295), the Municipal Commission of Health and Family Planning Foundation of Shanghai Pudong New Area (No. PW2018D-02), the Translational Medicine Collaborative Innovation Cooperation Research Project (No. TM201706), the Shanghai Municipal Education Commission (YS2017ZY050083) and 2017 Special Clinical Project of Integrated Traditional Chinese and Western Medicine (No. ZHXY-ZXJHZX-1-201701).

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