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Rapid communication

Low serum vitamin D levels and anti-*N*-methyl-D-aspartate receptor encephalitis: A case-control study

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ABSTRACT

Background: Low vitamin D levels are associated with autoimmunity, but the relationship with anti-*N*-Methyl-D-aspartate receptor (anti-NMDAR) encephalitis is unknown.
Methods: 25(OH) D levels and clinical and cerebrospinal fluid parameters were evaluated in 30 patients with anti-NMDAR encephalitis and compared with 90 age-, sex-, and season-matched healthy controls.
Results: 25(OH)D levels were lower in patients with anti-NMDAR encephalitis compared to controls (43.89 ± 17.91 vs 64.24 ± 24.38 nmol/L, $p < 0.001$), especially for females (vs males, $p = 0.008$), aged $\leq$30 years (vs > 30 years, $p = 0.002$), severe impairment (mRS ≥ 5) (vs mRS < 5, $p = 0.018$), and limited treatment responses (vs favorable treatment, $p = 0.02$). Serum 25(OH)D levels were associated with age ($r = 0.393$, $p = 0.032$), and mRS ($r = -0.417$, $p = 0.022$).
Conclusions: Our data showed that serum 25(OH)D levels were reduced in patients with anti-NMDAR encephalitis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder characterized by immunoglobulin G (IgG) antibodies against the GluN1 subunit of the NMDAR and presents with psychosis, seizures, encephalopathy, and cognitive and movement impairment (Dalmau et al., 2008; Hughes et al., 2010). This disorder can affect patients of all ages, but usually occurs in young women and children (Florance et al., 2009). Some patients have an ovarian teratoma, but the disorder may occur without tumor association. Most patients experience remarkable improvement after immunotherapy (Ishiura et al., 2008).

Vitamin D is synthesized from 7-dehydrocholesterol in the skin by the action of ultra violet light and to a limited extent from diet. Vitamin D is both a modulator of calcium homeostasis and immunity. Recently, the immuno-biological effects of vitamin D have received increasing attention. Vitamin D suppresses B cell proliferation and differentiation causing a decrease in immunoglobulin secretion as well as affecting T cell proliferation and maturation causing a decrease in the numbers of T cells with T helper (Th)1 and Th17 phenotypes (Boonstra et al., 2001). The major circulating form of vitamin D is 25-hydroxyvitamin D (25(OH)D) is measured to assess vitamin D status (Holick, 2007).

Low levels of vitamin D are associated with a variety of autoimmune disorders (AIDs) including multiple sclerosis (MS) (Salzer et al., 2012), recurrent inflammatory spinal cord disease (Mealy et al., 2012), neuromyelitis optica spectrum disorder (NMOSD) (Min et al., 2014), and other systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and insulin-dependent diabetes mellitus (IDDM) (Agmon-Levin et al., 2013). However, the importance of vitamin D in anti-NMDAR

Abbreviations: anti-NMDAR encephalitis, Anti-*N*-Methyl-D-aspartate receptor encephalitis; AIDs, autoimmune disorders; 25(OH)D, 25-hydroxyvitamin D; IgG, immunoglobulin G; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; IDDM, insulin-dependent diabetes mellitus; CTLs, healthy controls; CSF, cerebrospinal fluid; mRS, modified Rankin Scale; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine; MRI, brain magnetic resonance imaging; Gd-DTPA, gadopentetate dimeglumine; BMI, Body mass index.

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encephalitis is unknown. Here, we analyzed 25(OH)D levels in anti-NMDAR encephalitis patients, and determined the association of vitamin D levels with clinical parameters in these patients.

2. Materials and methods

2.1. Patients and controls

This study recruited 30 patients with anti-NMDAR encephalitis (n = 30), and age-, sex-, and season-matched healthy controls (CTLs, n = 90). For each case, three control subjects were randomly selected and matched to the index case on age (±1), sex and season. All patients had been hospitalized from 1 August 2014 to 31 December 2015. All patients' serum and/or cerebrospinal fluid (CSF) were analyzed by indirect immunostaining using a commercially available kit (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany) designed to detect an IgG antibody against NMDAR according to the manufacturer's instructions.

Season at blood sampling, defined as spring (March to May), summer (June to August), fall (September to November), and winter (December to February) was also acquired and matched to healthy controls.

Symptoms were categorized into the following nine groups: prodromal symptoms such as headache, fever, psychiatric symptoms, memory deficits, speech disturbances, seizures, movement disorders, loss of consciousness, sleep disorder, and central hypoventilation. Brain magnetic resonance imaging (MRI) and CSF examinations were reviewed. Individual or combined use of corticosteroids and intravenous immunoglobulins was defined as first-line immunotherapy, while administration of rituximab or azathioprine was defined as second line immunotherapy. The patients' neurological status was assessed using the modified Rankin Scale (mRS) (van Swieten et al., 1988). This study was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University (No. [2015]2-175). All participants involved in this study provided written informed consent.

2.2. Vitamin D measurements

Serum 25(OH)D levels were measured with a commercially available Enzyme Linked Immunosorbent Assay kit (Immunodiagnostic Systems Limited, Bolton, UK) according to the manufacturer's instructions. Levels of 25(OH) D < 50 nmol/L were determined to be deficient and ≥50 nmol/L but < 75 nmol/L as insufficient (Holick, 2007).

2.3. MRI scanning

Brain MRI scanning was carried out for anti-NMDAR encephalitis patients using a GE 1.5T MR scanner (General Electric, Milwaukee, WI, USA). The slice thickness of axial scans was 5 mm. Conventional MRI protocols were previously described (Zhang et al., 2014). Gadopentetate dimeglumine (Gd-DTPA) was administered intravenously at a dose of 0.1 mmol/kg, and at about 15 min after contrast injection the T1-weighted sequence was repeated. Patients were considered to be active by MRI if there was one or more enhancing lesions in T1-weighted spin echo images after injection of Gd-DTPA.

2.4. Statistical analysis

The data were presented as the mean ± standard deviation (SD) [25(OH)D, age, BMI, CSF total protein (TP), CSF glucose (Glu), CSF chlorine (CL) levels] or median with range (mRS score, CSF white blood cell (WBC)).

As anti-NMDAR patients and CTLs were enrolled with 1:3 matched pair, the linear mixed effect model statistical test accounting for the pair information was used. In detail, "serum 25(OH)D level" as the dependent variable, "groups (anti-NMDAR patients or CTLs)" as the fixed variable, and "pair id" as the random variable were applied. At last, the difference between the model means (least square means) of two groups was estimated and tested.

In anti-NMDAR encephalitis subgroups, student *t* test was used to compare mean values of serum 25(OH)D levels. Correlations between serum 25(OH)D and age, BMI, mRS score, and CSF factors (CSF WBC, TP, Glu and CL) were analyzed by Spearman's rank test. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 software (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Demographic and clinical features of anti-NMDAR encephalitis patients and healthy controls

As shown in Table 1, a total of 30 anti-NMDAR encephalitis patients (mean age, 34.10 ± 16.17 years; mean BMI, 20.60 ± 2.75; female:male = 13:17; spring:summer:fall:winter = 8:9:6:7), and 90 CTLs (mean age, 35.32 ± 9.19 years; mean BMI, 21.99 ± 3.67; female:male = 39:51; spring:summer:fall:winter = 24:27:18:21) were included in our study. The median mRS in anti-NMDAR encephalitis patients was 3.0 (range, 1–5). Of 30 patients with anti-NMDAR encephalitis, 6 patients (20%) had prodromal symptoms (such as headache, fever), 17 patients (56.7%) had psychiatric symptoms, 3 patients (10%) had memory deficits, 4 patients (13.3%) had speech disturbances, 9 patients (30%) had seizures, 6 patients (20%) had movement disorders, 5 patients (16.7%) had loss of consciousness, 2 patients (6.7%) had sleep disorders, and 2 patients (6.7%) had central hypoventilation. Twenty-two patients (73.3%) received first line treatment such as corticosteroids or intravenous immunoglobulin, and 8 patients (26.7%) received second line treatments such as rituximab and azathioprine.

3.2. Comparison of serum vitamin D levels between patients with anti-NMDAR encephalitis and healthy controls

The mean concentration of serum 25(OH)D in patients with anti-NMDAR encephalitis was 43.89 ± 17.91 nmol/L compared with 64.24 ± 24.38 nmol/L in CTLs, (p < 0.001, Table 1). Among the 30 patients with anti-NMDAR encephalitis, 20 (66.7%) showed vitamin D deficiency (<50 nmol/L), 8 patients (26.7%) had vitamin D insufficiency (50–75 nmol/L), and only 2 patients (6.7%) had a sufficient vitamin D level (≥75 nmol/L). By contrast, 30 (33.3%) of 90 CTLs were considered vitamin D deficient, 39 (43.3%) had insufficient levels, and 21 (23.3%) having sufficient levels (Table 1).

Analysis according to gender demonstrated that 25(OH)D levels in females and male were significantly lower in patients with anti-NMDAR encephalitis than in CTLs (p < 0.001, p = 0.039, respectively) (Fig. 1A). According to season, 25(OH)D levels in the summer, fall, and winter were all significantly lower in patients with anti-NMDAR encephalitis than in CTLs (p < 0.001, p = 0.045, p = 0.048, respectively). Although serum 25(OH)D levels in the spring were also lower in patients with anti-NMDAR encephalitis than in CTLs, the difference was not significant (Fig. 1B). According to age, 25(OH)D levels in patients aged ≤ 30 years were significantly lower than that in CTLs aged ≤ 30 years (p = 0.001), while the difference between subgroup with age > 30 years was not statistical significance (Fig. 2A). According to BMI, patients with BMI ≤ 20 and BMI >20 both have significantly lower 25(OH)D levels

Table 1
Demographic features of patients with anti-NMDAR encephalitis and healthy controls.

	Anti-NMDAR encephalitis (n = 30)	CTLs (n = 90)	p-value
Age (y)	34.10 ± 16.17	35.32 ± 9.19	ns
BMI	20.60 ± 2.75	21.99 ± 3.67	ns
Sex (male:female)	13:17	39:51	ns
Season			
Spring:Summer:Fall:Winter	8:9:6:7	24:27:18:21	ns
25(OH)D level (nmol/L, mean ± SD)	43.89 ± 17.91	64.24 ± 24.38	**p < 0.001**
25(OH)D level < 50 nmol/L (n, %)	20 (66.7)	30 (33.3)	–
25(OH)D level ≥50, <75 nmol/L (n, %)	8 (26.7)	39 (43.3)	–
25(OH)D level ≥ 75 nmol/L (n, %)	2 (6.7)	21 (23.3)	–
mRS (median, range)	3.0 (1–5)	–	–
CSF routine			
CSF WBC (× 10^6, median, range)	6.5 (0–240)	–	–
CSF TP (g/L, mean ± SD)	0.39 ± 0.41	–	–
CSF Glu (mmol/L, mean ± SD)	3.9 ± 1.53	–	–
CSF CL (mmol/L, mean ± SD)	123.2 ± 3.82	–	–
Symptoms (n, %)			
prodromal symptoms	6 (20.0)	–	–
psychiatric symptoms	17 (56.7)	–	–
memory deficits	3 (10.0)	–	–
speech disturbances	4 (13.3)	–	–
seizures	9 (30.0)	–	–
movement disorders	6 (20)	–	–
loss of consciousness	5 (16.7)	–	–
sleep disorder	2 (6.7)	–	–
central hypoventilation	2 (6.7)	–	–
Treatment			
First line treatment	22 (73.3)	–	–
Second line treatment	8 (26.7)	–	–

Anti-NMDAR encephalitis, anti-*N*-Methyl-D-aspartate receptor encephalitis; CTLs, healthy controls; 25(OH)D, 25-hydroxyvitamin D; mRS, modified Rankin Scale; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine; SD, standard deviation.
The bold values showed that there were statistical significance (p < 0.05 or <0.01).

than CTLs with BMI ≤ 20 and BMI > 20 (p = 0.023, p = 0.017 respectively) (Fig. 2B).

3.3. Comparison of serum vitamin D levels between subgroups of patients with anti-NMDAR encephalitis

In the present study, anti-NMDAR encephalitis patients were further subdivided into two subgroups by gender, age, mRS, normal or abnormal brain MRI, with or without prodromal symptoms, and response to therapy (Table 2). The serum 25(OH)D level in male patients was significantly higher than in female patients (p = 0.008). Older patients (age > 30 years) had significantly higher serum 25(OH)D levels than those aged ≤ 30 years (p = 0.002). Patients with mRS <5 had significantly higher serum 25(OH)D levels than those with mRS ≥ 5 (p = 0.018). Serum 25(OH)D levels in patients favorable to treatment were significantly higher than in patients with limited responses to treatment (p = 0.02). Although patients with abnormal brain MRI had higher serum 25(OH)D levels than those with normal brain MRI (p = 0.345), and patients without prodromal symptoms had higher serum 25(OH)D levels than those with prodromal symptoms (p = 0.076), these differences were not significant (Table 2).

3.4. Association between serum vitamin D levels, clinical characteristics and CSF parameters in anti-NMDAR encephalitis patients

The relationship between serum 25(OH)D, clinical characteristics and CSF parameters in anti-NMDAR encephalitis patients were evaluated (Table 3). There was a positive correlation between serum 25(OH)D and age (r = 0.393, p = 0.032), and a negative correlation between serum 25(OH)D and mRS (r = −0.417, p = 0.022). However, correlations between serum 25(OH)D and BMI, CSF parameters (CSF WBC, CSF TP, CSF GLU, CSF CL) were not significant (Table 3).

4. Discussion

This is the first study, to the best of our knowledge, to analyze vitamin D levels in patients with anti-NMDAR encephalitis. We found that patients with anti-NMDAR encephalitis had significantly lower levels of 25(OH)D than age-, season- and sex-matched control subjects. Furthermore, low levels of 25(OH)D were associated with female sex, younger age and a worse prognosis of the disease.

The role of vitamin D in the pathogenesis of anti-NMDAR encephalitis is poorly understood, but is probably associated with its anti-inflammatory and immunomodulatory functions. Vitamin D has a physiological role in the endocrine, intracrine and paracrine regulation of innate and adaptive immunity. This effect is mediated by signaling through the vitamin D receptor expressed on cells of the innate immune system (macrophages and dendritic cells), and cells of the adaptive immune system ($CD4^+$ T, $CD8^+$ T, B, and natural killer lymphocytes) (Delvin et al., 2014). Vitamin D suppresses *in vitro* T cell proliferation and the secretion of interleukin-2 (IL-2) and interferon (IFN) by $CD4^+$ T cells and the cytotoxicity of $CD8^+$ T cells. Vitamin D also affects Th cell polarization by inhibiting Th1 cytokine production (IFN-γ) and augmenting Th2 cytokine production (IL-4, IL-5, and IL-10) (Boonstra et al., 2001; Delvin et al., 2014; van der Aar et al., 2011). The same modulating action of vitamin D was observed for B cells as it inhibited the proliferation of activated B cells and induced their apoptosis (Chen et al., 2007). Thus, it has been hypothesized that vitamin D deficiency can act as an environmental trigger that increases the prevalence of AIDs (Delvin et al., 2014). Many studies have reported that vitamin D deficiency is associated with AIDs such as SLE, RA, MS, NMOSD, autoimmune thyroid diseases and autoimmune cytopenias

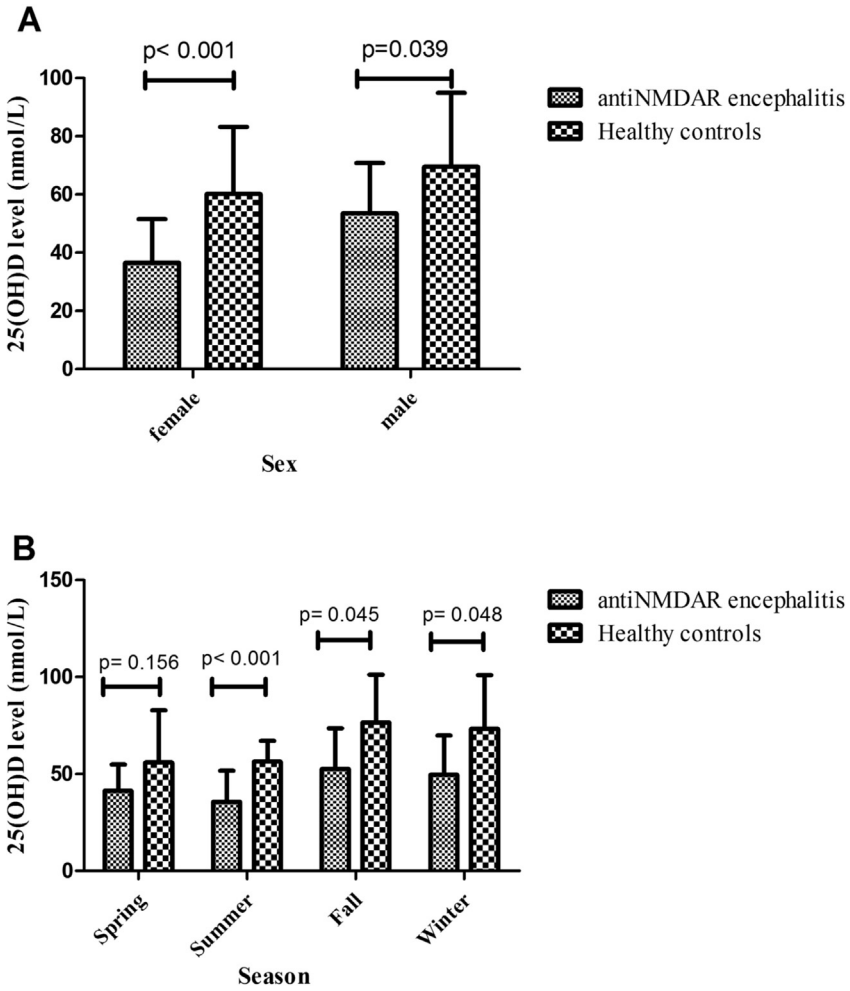

Fig. 1. A) 25(OH)D levels are significantly lower in females and males with anti-NMDAR encephalitis compared with healthy controls ($p < 0.001$, $p = 0.039$, respectively). **B)** 25(OH)D levels are significantly lower in the summer, fall, and winter in patients with anti-NMDAR encephalitis compared with healthy controls ($p < 0.001$, $p = 0.045$, $p = 0.048$ respectively).

(D'Aurizio et al., 2015; Delvin et al., 2014; Fattizzo et al., 2016; Min et al., 2014). However, the administration of vitamin D might have a preventive action in AIDs because animal experiments demonstrated it blocked the progression of disease (Cantorna et al., 1996; Zella and DeLuca, 2003). In our study, we found that serum vitamin D levels were significantly reduced in anti-NMDAR encephalitis patients, which was in line with that reported for other AIDs. Additionally, we also found that serum 25(OH)D levels were significantly higher in patients with favorable responses to therapy compared with those with limited responses. This suggests that higher serum vitamin D levels might contribute to the treatment of the anti-NMDAR encephalitis.

Increasing evidence has suggested that immune cells, especially B cells, are important effectors and regulators of inflammation and autoimmunity in anti-NMDAR encephalitis (Camdessanche et al., 2011; Hachiya et al., 2013; Martinez-Hernandez et al., 2011; Simma et al., 2014). Analysis of the inflammatory infiltrates in brain samples from anti-NMDAR encephalitis patients demonstrated numerous antibody-secreting cells in perivascular, interstitial, and Virchow-Robin spaces, and B and T cells predominantly located in perivascular regions (Martinez-Hernandez et al., 2011). Furthermore, prominent B cell cuffing was present around brain vessels accompanied by plasma cells in anti-NMDAR encephalitis patients (Camdessanche et al., 2011). Therefore, we speculate that low serum vitamin D may be a risk factor for developing anti-NMDAR encephalitis, as it might affect immune cells, especially B cells. More extensive epidemiological studies regarding the role of vitamin D in the pathogenesis of anti-NMDAR encephalitis is required.

Certainly, low vitamin D levels patients with anti-NMDAR encephalitis were likely caused by the disease attack. As sun exposure is the most important source of vitamin D, the patients may reduce their outdoor activity and sun exposure after disease onset. Besides, it is possibly difficult to take food into the body and absorb the enough nutrients for the patients after the disease onset, resulting in decreased vitamin D.

In the present paper, lower concentrations of serum 25(OH)D were associated with high mRS scores in anti-NMDAR encephalitis. In other AIDs, vitamin D deficiency was also shown to accelerate the development and increase the incidence of disease (Min et al., 2014; Salzer et al., 2012; Zella and DeLuca, 2003). Our data also showed that anti-NMDAR encephalitis patients with a worse prognosis conversely increase the risk of vitamin D insufficiency.

We also found that female patients with anti-NMDAR encephalitis had significantly lower vitamin D levels compared with male patients, in accord with a previous study (Omdahl et al., 1982). Similarly, Wei et al (2015) investigated serum 25(OH)D levels in community-dwelling Guangzhou residents and found serum

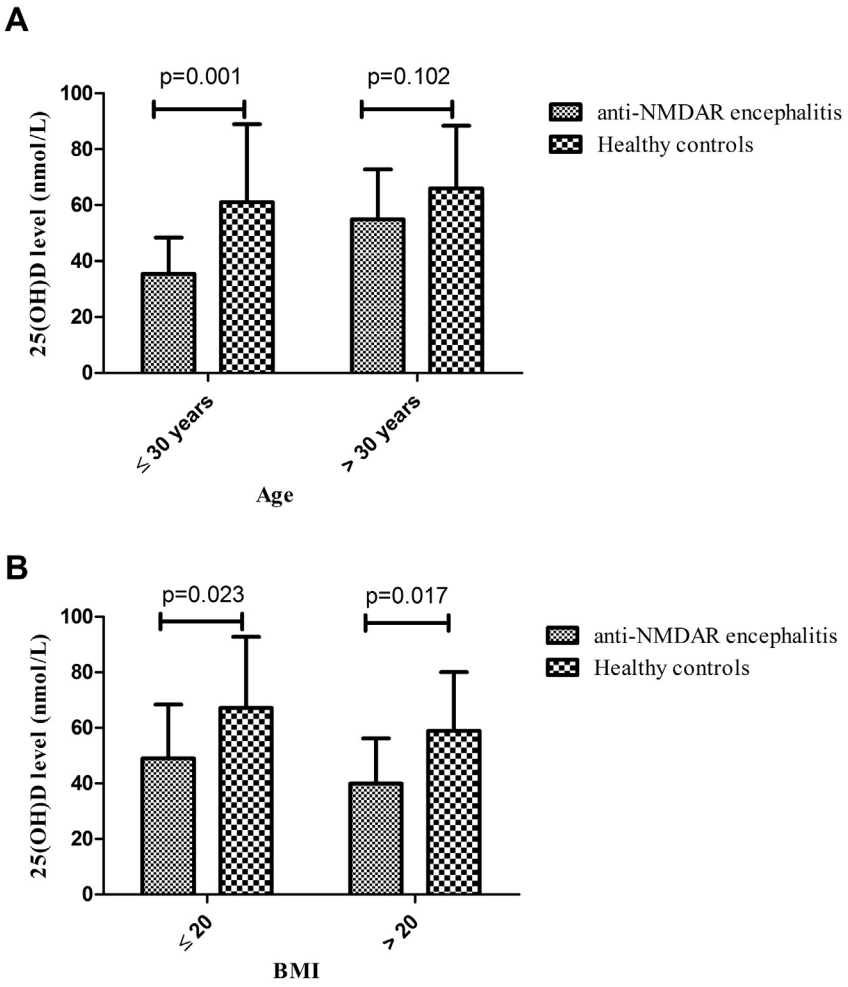

Fig. 2. A) 25(OH)D levels were significantly lower in patients aged ≤ 30 years compared with CTLs aged ≤ 30 years (p = 0.001), while the difference between subgroup with age > 30 years was not statistical significance (p = 0.102). **B)** 25(OH)D levels were both significantly lower in anti-NMDAR encephalitis patients with BMI ≤ 20 and BMI >20 compared with CTLs (p = 0.023, p = 0.017 respectively).

Table 2
25(OH)D levels in patients with anti-NMDAR encephalitis.

Variables	Mean ± SD (nmol/L)	Range (nmol/L)	*p*
Sex			
Male (n = 13)	53.50 ± 17.30	25.0–80.0	
Female (n = 17)	36.54 ± 14.97	18.9–65.6	**p = 0.008**
Age			
≤30 years (n = 17)	35.47 ± 12.90	18.90–63.50	
>30 years (n = 13)	54.89 ± 17.93	23.00–80.00	**p = 0.002**
mRS			
<5 (n = 22)	48.44 ± 18.12	22.0–80.0	
≥5 (n = 8)	31.36 ± 9.92	18.9–48.0	**p = 0.018**
Brain MRI			
normal (n = 12)	39.95 ± 17.58	18.9–68.0	
abnormal (n = 18)	46.29 ± 17.73	25.0–80.0	**p = 0.345**
Prodromal symptoms			
With (n = 6)	32.32 ± 18.01	18.9–68.0	
Without (n = 24)	46.78 ± 17.03	22.0–80.0	**p = 0.076**
Response to Therapy			
Favorable (n = 20)	49.23 ± 18.98	22.0–80.0	
Limited (n = 10)	33.21 ± 9.11	18.9–48.0	**p = 0.020**

Anti-NMDAR encephalitis, anti-*N*-Methyl-D-aspartate receptor encephalitis; 25(OH)D, 25-hydroxyvitamin D; mRS, modified Rankin Scale; MRI, magnetic resonance imaging; SD, standard deviation.
The bold values showed that there were statistical significance (p < 0.05 or <0.01).

Table 3
Correlation coefficients generated between serum 25(OH)D levels and clinical characteristics, CSF parameters in anti-NMDAR encephalitis patients.

Variable	r_s	*p*
Age	0.393	**0.032**
BMI	0.007	0.972
mRS	−0.417	**0.022**
CSF WBC	−0.275	0.141
CSF TP	−0.016	0.932
CSF GLU	0.359	0.052
CSF CL	−0.296	0.112

BMI, body max index; mRS, modified Rankin Scale; CSF, cerebrospinal fluid; WBC, white blood cells; TP, total protein; Glu, glucose; CL, chlorine, r_s Spearman correlation coefficients.
The bold values showed that there were statistical significance (p < 0.05 or <0.01).

25(OH)D levels were significantly lower in women than men (Wei et al., 2015). We speculate these findings might be related to increased outdoor activity and sun exposure, as well as less calcium loss in men compared with women. A previous study that reported a relationship between age and vitamin D levels was controversial. Some studies correlated age with vitamin D in a direct or indirect manner (Moan et al., 2009; Rucker et al., 2002), whereas others

found no correlation (Kudlacek et al., 2003; Orgaz-Molina et al., 2012). Wei et al. observed an inverse relationship between serum 25(OH)D levels and age in men, but no correlation was found in women (Wei et al., 2015). While our data showed that 25(OH)D levels were positively associated with age in anti-NMDAR encephalitis patients.

This study had several limitations. First, NMDAR antibody titers were not detected in our paper. Second, the sample size of anti-NMDAR encephalitis patients was small. Third, we did not investigate the role of immune cells such as T or B cells and vitamin D receptor expression in relation to the mechanisms underlying disease pathogenesis of anti-NMDAR encephalitis. Forth, the effect of the age gap between anti-NMDAR encephalitis patients and healthy controls might also partly influence the differences of 25(OH)D levels, as the standard deviation for the age of the patients enrolled is much larger than that of the healthy controls in our study.

In conclusion, we report that serum 25-(OH)D levels are reduced in anti-NMDAR encephalitis patients and are associated with disease disability. Our data support its possible protective role against the development of anti-NMDAR encephalitis. Further randomized, controlled, prospective trials are needed to demonstrate the causality of vitamin D in anti-NMDAR encephalitis patients, although it is difficult to design these trials because of the low prevalence of this disease.

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Declaration of conflict of interest

None.

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