Serum 25-hyroxyvitamin D levels and tic severity in Chinese children with tic disorders

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ABSTRACT

The aim of this study is to evaluate serum 25-hydroxyvitamin D[25(OH)D] levels in children with tic disorders and to explore the relationship between serum 25(OH)D level and tic severity. Children (n = 179, 31 females, 148 males, mean age at diagnosis: 8.0 ± 2.7 years old, age ranged from 3 to 14.5 years old) who were diagnosed with a tic disorder were enrolled as case group, 189 healthy children were recruited as control group. Serum level of 25(OH)D of each child was measured by high performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS). Yale Global Tic Severity Scale (YGTSS) was used to assess tic severity. Mean serum level of 25(OH)D in the case group was significantly lower than that of the control group. The serum 25(OH)D level was significantly associated with tic severity after adjusting for age and body mass index (BMI). This study identified a high prevalence of vitamin D insufficiency or deficiency in children with tic disorders, and there was a negative correlation between the serum 25(OH)D level and tic severity. In the future, large sample size studies are urgently needed to further clarify this correlation.

1. Introduction

Tic disorders are a group of neurodevelopmental disorders that are characterized by non-rhythmic, stereotyped movements and/or vocalizations due to the sudden and involuntary contractions of one or more muscles (Sanger et al., 2010). Tic disorders have a typical age of onset between 3 and 8 years of age, with maximal tic severity commonly occurring between 8 and 12 years of age (Leckman et al., 1998). According to the Diagnostic and Statistical Manual of mental disorders - fifth edition (DSM-5) of American Psychiatric Association (2013), tic disorders have been divided into the following groups: Tourette's syndrome (TS), chronic motor or vocal tic disorder, provisional tic disorder, other specified and unspecified tic disorders. The prevalence of tic disorders during childhood and adolescence is close to 3%, and that of TS is approximately to 0.52% between the age of 4 and 18 years old (Robertson, 2015; Scharf et al., 2015).

The etiology and pathogenesis of tic disorders have not been fully elucidated. Many studies have shown that the combination of genetic, biological, psychological and environmental factors play a significant role in this disease. It is therefore hypothesized that multiple neurotransmitters are involved in the pathophysiology of tic disorders. Above all, dopaminergic dysfunction of the cerebral basal ganglia and the limbic system are purported to play a primary role in the pathogenesis of TS (Buse et al., 2013; Müller-Vahl et al., 2017; Singer et al., 1982).

Vitamin D could exert protective and neurotropic effects directly at cellular level to protect the dopamine system by regulating gene expression (Liu et al., 2013). Interestingly, vitamin D can directly modulate tyrosine hydroxylase expression, a rate-limiting enzyme necessary for the production of dopamine, epinephrine, and norepinephrine (Cui et al., 2015). Therefore, insufficient serum levels of 25-hydroxyvitamin D[25(OH)D] could inhibit tyrosine hydroxylase, which might lead to imbalance of these neurotransmitters and produce a wide range of emotional and behavioral problems (Sanchez et al., 2009).

Little data is available on the nature of serum 25(OH)D levels in patients with tic disorders. However, Stagi et al. (2017) reported that patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, characterized by obsessive-compulsive symptoms and/or tic exacerbations, showed greater serum 25(OH)D insufficiency of deficiency relative to healthy controls.

Furthermore, our preliminary data show that children with tic disorders have more severe serum 25(OH)D insufficiency or deficiency than healthy controls (Li et al., 2017). However, the relationship between tic severity and serum 25(OH)D level in children with tic disorders is still unknown. The objective of this current study is to evaluate serum 25(OH)D levels in 179 Chinese children with tic disorders and explore the correlation between 25(OH)D level and tic severity.

2. Methods

2.1. Study design

This is a case-control study, approved by the Ethics Committee of the First Hospital of Jilin University. Parents or legal guardians have provided written consent after a thorough explanation of this study.

2.2. Participants

Between December 2016 and November 2017, 179 children with tic disorders (31 females, 148 males, mean age at diagnosis: 8.0 ± 2.7 years old, age ranged from 3 to 14.5 years old) were recruited through the developmental and behavioral pediatric clinic of the First Hospital of Jilin University. Among them, 10 children got the diagnosis of TS, 46 children of chronic motor or vocal tic disorder, and 123 children of provisional tic disorder. Healthy Chinese children ($n = 189$, 35 females, 154 males, mean age at diagnosis: 8.1 ± 2.6 years old, age ranged from 3 to 14 years old) were recruited as case controls matched on age, sex, and season of blood collection during the same period and at the same clinic.

All children with tics were evaluated by a trained physician according to DSM-5 diagnostic criteria to determine appropriateness for study inclusion. In addition, the following data were collected including demographics and medical history, height and weight, tic age of onset, duration of symptoms, presence or absence of comorbidities, tic severity, and vitamin D level. The self-made behavioral screening questionnaire was used to exclude possible comorbidities. These will be described in detail in the measurement section. Results of 128 cases and 131 healthy controls of our participants have been previously published (Li et al., 2017).

Exclusion criteria for the case group were previous diagnosis of Neuropathic disease and other neuropsychiatric disorders (including epilepsy, autism, mental retardation and neurodegenerative disease), rheumatic fever and obvious comorbid conditions (including attention deficit hyperactivity disorder, obsessive compulsive disorder, learning disorder, sleep disorders, mood disorders) more severe than the tic disorder. Additional exclusion criteria for both groups were recent history of traveling to warm or sunny areas prior to study enrollment or use of vitamin D supplements within the past 6 months. Children with a history of bone, endocrine, liver, or kidney diseases or taking medication that may interfere with vitamin D metabolism were also excluded.

2.3. Study evaluations and measurements

2.3.1. Baseline questionnaire

Children and their parents were interviewed by physician to obtain sociodemographic information such as sex, age, date of birth and place of residence (urban and rural), outdoor play conditions, medical history, recent diet and vitamin supplements. Also, they were interviewed by a physician to determine whether or not they had attention deficit, hyperactivity, compulsion symptoms, anxiety or depression, reading and math difficulties, etc.

2.3.2. Anthropometric measurements

For both groups, height was assessed with a stadiometer and weight with an electronic scale. All children wore light clothes without shoes for this part of the examination. Body mass index (BMI) was calculated

as the weight in kilograms divided by height in squared meters. BMI < 85th percentile was considered as normal weight, 85–95th percentile as overweight and > 95th percentile as obesity (Li et al., 2010).

2.3.3. Symptom evaluation

The clinical evaluation of tics was performed by using the Yale Global Tic Severity Scale (YGTSS), a semi-structured scale that measures tic severity and impairment. The tic severity scale assesses number, frequency, intensity, complexity of tics and the degree of interference for motor and phonic tics; and ranges from 0 to 50 points. The YGTSS includes also an impairment rating scale focused on tic-related impact on functioning across a wide range of domains (i.e., psychosocial, family, physical etc) that is scored on a 0 to 50 points scale. Total scores of this scale range from 0 to 100 points. The Chinese version of the YGTSS had been validated for clinical practice. YGTSS is a widely used scale with excellent psychometric properties (Leckman et al., 1989).

2.3.4. Vitamin D level

Samples of 3 ml peripheral venous blood were collected from each child. The serum was isolated from these samples by using centrifugal sedimentation method within 6 h. Serum samples were frozen at −20 °C and later shipped to Guangzhou King Medical Center (Clinical Laboratory) to measure serum 25(OH)D levels by using high performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS). This current gold standard measurement had been chosen to investigate serum 25-hydroxyvitamin metabolites, with the purpose of maximally reducing the testing bias (Black et al., 2015; Ferrari et al., 2017; Jukic et al., 2017), in order to minimize problems related to study replication issues (Loken and Gelman, 2017).

The chromatographic column was Agilent Poroshell 120 EC-C18 (Agilent, 2.1 × 100 mm, 2.7 μm particle size) purchased from United State of America. The liquid chromatograph system includes Shimadzu LC-20AD XR HPLC pump, Shimadzu SIL-20A XR auto sampler, and Shimadzu CTO-20AC column oven. The model of mass spectrograph was API4000 Mass spectrometry (AB, USA). This laboratory owns quality certification from the Chinese National Accreditation Service for Conformity Assessment (CNAS).

Vitamin D level is regarded to be optimal if serum 25(OH)D concentration ranges from 30 to 90 ng/ml. Serum 25(OH)D level between 10 ng/ml and 30 ng/ml is defined as vitamin D insufficiency and serum 25(OH)D level < 10 ng/ml is defined as vitamin D deficiency, according to the clinical practice guidelines of the Canadian Paediatric Society (2007).

Considering seasonal variations, two periods of the year had been chosen in our study - one from November to May (winter) and one from June to October (summer). This strategy is preferable because the exposure to sun and ultraviolet B radiation is negligible between November and April, according to Boston study of Webb et al. (1990) and both Changchun and Boston lie between 40 and 45 ° of North Latitude.

2.4. Statistical analysis

Data were analyzed by using SPSS Statistics 22.0 (IBM Corp., Armonk, NY). Depending on the distribution of the analyzed variable, student's t test, nonparametric Mann–Whitney test and univariate ANOVA were used for the significance of differences between mean values of two or more continuous variables. Chi-square test and non-parametric Mann–Whitney test were performed to test for differences in proportions of categorical variables between two or more groups. Spearman's correlation coefficient was used to evaluate the significance of correlation factors with the serum 25(OH)D levels. Multivariate logistic regression was used to detect the association between serum 25(OH)D levels, presence or absence of tic disorder, and tic severity. All comparisons used 2-sided tests at a 0.05 level of significance. The null

Table 1
Demographic data and serum 25(OH)D levels of study population.

Characteristics	Tics(n = 179)	Controls (n = 189)	Z/t (χ^2)	p
Sex			(0.09)	0.76
Male	148(82.7%)	154(81.5%)		
Female	31(17.3%)	35(18.5%)		
Age.y	8(6–9.5)	8(6–10)	0.22	0.83
Date of birth			(0.02)	0.89
Winter	101(56.4%)	108(57.1%)		
Summer	78(43.6%)	81(42.9%)		
Season of blood collection			(0.21)	0.65
Winter	128(71.5%)	131(69.3%)		
Summer	51(28.5%)	58(30.7%)		
BMI			0.009	0.99
<85th	139(77.7%)	146(77.2%)		
85–95th	27(15.1%)	29(15.3%)		
>95th	13(7.2%)	14(7.4%)		
25(OH)D, (ng/ml)	22.9 ± 7.5 [a]	28.9 ± 8.3	7.2	<0.001
Vitamin D status			(28.7)	<0.001
optimal	33(18.4%) [a]	84(44.4%)		
insufficient or deficient	146(81.6%) [a]	105(55.6%)		
YGTSS total scores	30.7 ± 12.7	–	–	–
Motor tics	10.3 ± 5.1			
Phonic tics	5.6 ± 5.4			
Total tics	15.8 ± 6.8			
Impairment	15.0 ± 7.3			

Abbreviations: Tics: case group; Controls: healthy control group.
Data are presented as percentage of children, mean ± SD or median (P25–P75). Student's t test, nonparametric Mann–Whitney test and χ^2 test were applied to compare children with tic disorders versus healthy controls.
[a] Significantly different from the control group ($p < 0.05$).

hypothesis for all analyses was that there is no difference between the study groups.

Based on the total scores of the YGTSS, case group was divided into two subgroups. Patients who received a YGTSS total score of less than 30 points by the YGTSS evaluation were classified as less severe group (n = 97, median YGTSS score: 21), whereas children who scored higher than 30 points were classified as more severe group (n = 82, median YGTSS score: 40). Score of 30 points had been chosen to divide the group because it was close to the mean point of the YGTSS total score, measured in the whole case group (30.7).

3. Results

Demographic data of the study population are shown in Table 1. Children with tic disorders and healthy controls showed no significant differences, with respect to sex, age, date of birth, season of blood collection and BMI. Other factors such as place of residence, medical history, and vitamin supplements were also similar between the two groups (these data were not listed in Table 1). Mean serum level of 25(OH)D in children with tic disorders was significantly lower than that of the control group. The percentage of 25(OH)D insufficiency or deficiency in the case group was significantly higher than that of the control group.

Serum 25(OH)D levels in children with different subtypes of tic disorders are outlined in Table 2. There were statistically significant differences in serum 25(OH)D levels among different subtypes of tic disorders. The average amount of serum 25(OH)D in the provisional tic disorder group was higher than that of TS and chronic motor or vocal tic disorder group, and significantly lower than the healthy control group (t = 4.74, $p < 0.001$). Percentage of optimal 25(OH)D level, 25(OH)D insufficiency or 25(OH)D deficiency from each subgroup was statistically significant different. The percentage of 25(OH)D insufficiency or deficiency in the provisional tic disorder group was significantly lower than that from other subtypes.

Table 2
Serum 25(OH)D levels in children with different subtypes of tic disorders.

Status	TS(n = 10)	CTD(n = 46)	PTD(n = 123)	F(Z)	p
25(OH)D, (ng/ml)	16.8 ± 4.6	19.9 ± 7.2	24.6 ± 7.3 [a]	11.0	<0.001
Vitamin D status				(2.69)	0.007
optimal	0(0%)	4(8.7%)	29(23.6%)		
insufficient or deficient	10(100%)	42(91.3%)	94(76.4%) [a]		

Abbreviations: TS: Tourette syndrome; CTD: chronic motor or vocal tic disorder; PTD: provisional tic disorder.
Data are presented as percentage of children or mean ± SD. Univariate ANOVA and nonparametric Mann–Whitney test were applied to compare children with different subtypes of tic disorders.
[a] Significantly different from the subtypes($p < 0.05$).

There was significant negative correlation between 25(OH)D levels and YGTSS total scores ($r_s = -0.32$, $p < 0.001$), motor tics scores ($r_s = -0.18$, $p = 0.01$), phonic tics scores ($r_s = -0.15$, $p = 0.045$), YGTSS total tic scores ($r_s = -0.27$, $p < 0.001$), impairment scores ($r_s = -0.31$, $p < 0.001$) and BMI ($r_s = -0.41$, $p < 0.001$) in children with tic disorders. Multivariate logistic regression analysis showed that serum 25(OH)D level was significantly associated with presence or absence of tic disorder, after adjusting for sex, age, date of birth, season of blood collection and BMI (adj. OR = 0.89; 95 % CI 0.863–0.921; $p < 0.001$).

Features of children with more severe and less severe tics are shown in Table 3. Children of these two groups were comparable in terms of sex, date of birth and season of blood collection. Median YGTSS total scores, total tic scores and age of the more severe group were significantly higher than that of the less severe group. Median 25(OH)D serum level in the more severe group was significantly lower than that of the less severe subjects. The rate of obesity and overweight in the more severe group was significantly higher than that of the less severe group.

Multivariate logistic regression analysis showed that serum 25(OH)D level was significantly associated with tic severity, after adjusting for age and BMI (adj. OR = 0.94; 95 % CI 0.897–0.989; $p = 0.02$). Result is

Table 3
Features of children with more severe and less severe tics.

Characteristics	more severe (n = 82)	less severe (n = 97)	Z (χ^2)	p
YGTSS total scores	40(34–47) [a]	21(19–25)	11.52	<0.001
YGTSS total tic scores	20(16–25) [a]	11(9–15)	8.98	<0.001
25(OH)D, (ng/mL)	19(15–26) [a]	24(20–29)	4.11	<0.001
Age. y	9(7–11) [a]	7(6–9)	4.64	<0.001
Sex			(0.1)	0.75
Male	67(81.7%)	81(83.5%)		
Female	15(18.3%)	16(16.5%)		
BMI			6.13	0.047
<85th	57(69.5%) [a]	82(84.5%)		
85–95th	16(19.5%) [a]	11(11.3%)		
>95th	9(11.0%) [a]	4(4.1%)		
Date of birth			(0.28)	0.60
Winter	48(58.5%)	53(54.6%)		
Summer	34(41.5%)	44(45.4%)		
Season of blood collection			(1.25)	0.26
Winter	62(75.6%)	66(68.0%)		
Summer	20(24.4%)	31(32.0%)		

Abbreviations: more severe: more severe group, YGTSS total scores ≥30; less severe: less severe group, YGTSS total scores <30.
Data are presented as percentage of children or median (P$_{25}$–P$_{75}$). Nonparametric Mann–Whitney test and χ^2 tests were applied to compare children with tic disorders of different severity.
[a] Significantly different from the less severe group ($p < 0.05$).

Table 4

Result of multivariate logistic regression concerning association between serum 25(OH)D level and tic severity.

Variables	Adj. OR (95 % CI)	*p* value
25(OH)D, (ng/mL)	0.94 (0.897–0.989)	0.02
Age, y	1.34 (1.168–1.535)	<0.001
BMI		0.10
<85th		
85–95th	0.52 (0.115–2.335)	0.39
>95th	0.27 (0.071–1.047)	0.06

Adj. OR = adjusted odds ratios, outcome variable = with more severe tics (YGTSS total scores ≥30) (1 = yes, 0 = no) ($p < 0.05$).

shown in Table 4.

4. Discussion

In our study, the serum 25(OH)D levels were significantly lower in children with tic disorders compared to the healthy controls. The rate of vitamin D insufficiency or deficiency in youth with tic disorders was significantly higher than that in the control group. These findings suggest that vitamin D insufficiency or deficiency may be associated with tic disorders in youth. Additionally, the serum 25(OH)D level in the provisional tic disorder group was higher than that of TS and chronic motor or vocal tic disorder group, and significantly lower than the healthy control group, indicating possible varied 25(OH)D levels among different subtypes of tic disorders.

This suggests that 25(OH)D levels may serve as a marker of tic course, with provisional tic disorder transitioning to a chronic tic disorder with further decreasing 25(OHD) levels. Furthermore, serum 25(OH)D level was significantly and negatively associated with presence or absence of tic disorder and tic severity. To the best of our knowledge, this is the first report to investigate the association between serum 25(OH)D level and tic severity. The exact pathophysiological mechanisms underlying tic disorders are not well defined yet. The effects of vitamin D on brain development and functioning, including alterations in neurotransmission, neuro-immunomodulation, antioxidation and its role in behavioral and neuropsychiatric disorders have recently been reviewed (Eyles et al., 2009; Eyles et al., 2013; Groves and Burne, 2017).

The 1,25-dihydroxyvitamin D3 receptor and 1alpha-hydroxylase, the enzyme responsible for the formation of the active vitamin D, are widely distributed in the human brain. Both the receptor and enzyme had been shown in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra by immunohistochemical staining (Eyles et al., 2005). The substantia nigra contains a large amount of dopamine. Interestingly, vitamin D can directly modulate tyrosine hydroxylase expression, a rate-limiting enzyme necessary for the production of dopamine, epinephrine, and norepinephrine (Cui et al., 2015). Vitamin D may exert neurotropic effects directly at cellular level to protect the dopamine system by regulating gene expression (Liu et al., 2013). In addition, Vitamin D regulates the synthesis of neurotrophic factors such as neurotrophin 3, neurotrophin 4, nerve growth factor and glial cell line-derived neurotrophic factor (GDNF), which are important for cell differentiation and survival (Brown et al., 2003; Kalueff et al., 2004). Vitamin D may also exert protective effect on the dopamine system through GDNF (Kočovská et al., 2012).

Studies on animal models revealed that prenatal vitamin D deficiency lead to alterations in the brain morphology of fetal mouse and brain tyrosine hydroxylase gene expression was reduced in vitamin D-deficient female fetuses of the BALB/c mouse (Hawes et al., 2015). In addition, prenatal vitamin D deficiency alters the development of dopaminergic pathways and this disruption is associated with altered behavior and neurochemistry in the adult brain (Cui et al., 2013).

Developmental vitamin D deficiency leads to changes in multiple neurotransmitter systems in the neonate rat brain, such as dopamine system, noradrenaline, serotonin, glutamine, etc (Kesby et al., 2017).

Although the etiology and pathogenesis of tic disorders remains unclear, several researchers have elucidated functional imbalance in the cortical limbic system in children with tics. This theory is further strengthened by dysregulations of dopamine, γ-amino-butyric acid (GABA) and other neurotransmitters (Godar et al., 2014). The most effective treatment for tic disorders is dopamine blocking drugs, implicating the role of nigrostriatal dopamine in their pathogenesis (Cavanna and Seri, 2013). Molecular imaging studies report abnormalities in the striatal dopaminergic system in patients with tic disorders (Denys et al., 2013; Albin et al., 2003). In addition, dysfunction of the GABAergic system in Tourette patients was also found, and the abnormalities in GABA-A receptor binding in the insula and cerebellum may be associated with tic generation (Lerner et al., 2012). Animal models revealed that inactivation of GABA-A receptors in the basal ganglia or selective inactivation of specific population of GABAergic striatal interneurons in mice had been shown to produce abnormal movements (Bronfeld et al., 2013; Gittis et al., 2011). Patients with bipolar spectrum disorders exhibited improvement in their mood symptoms after taking a daily dose of 2000 IU of Vitamin D₃ for 8 weeks, and GABA levels of the anterior cingulate cortex were significantly increased as detected by Magnetic resonance spectroscopy (MRS). This may suggest that vitamin D could improve the functioning and concentration of GABA (Sikoglu et al., 2015).

4.1. Limitations

Although our study is case-controlled in design, it does have some limitations. The children with tic disorders and the control group were matched in terms of age, sex and season of blood collection. Besides that, more factors could be considered concerning influence of vitamin D levels, such as sunlight exposure, nutrition status and diet. Also, we did not include data on recent diet in this study. Additionally, most of the children with tic disorders in this study were school-aged. In conjunction with the psychological pressure caused by tics, the outdoor physical activity of these children might be restricted or limited in duration. As a result, these children theoretically may be more likely to be deprived from getting enough exposure to ultraviolet B and vitamin D biosynthesis. Thus, lack of data on outdoor physical activity is also a limitation. Inclusion of a provisional tic disorder subgroup may be viewed as a limitation, as researchers examining tic disorders often exclude those with provisional tic disorders because it is unclear whether their tics will subside or become persistent (Fourneret et al., 2014). However, in the present study inclusion of children with provisional tic disorder facilitated our understanding of the role of serum 25(OH)D level in tic emergence and course. Further, the provisional tic disorder group will be followed up in the future, helping to clarify the above questions.

4.2. Conclusion

In our study, Serum 25(OH)D level in children with tic disorders was lower than that of the healthy control group and lower 25(OH)D level was associated with increased tic severity. In the future, large sample size and longitudinal follow-up studies are urgently needed to further clarify the correlation between serum 25(OH)D level and tic severity. However, whether vitamin D supplementation should be considered as a potential treatment in children with tic disorders, especially those with vitamin D insufficiency or deficiency, needs further investigation.

disclose.

Conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.05.066.

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