NÖRO PSİKİYATRİ ARŞİVİ

Research Article

Arch Neuropsychiatr 2016; 53: 33-37 • DOI: 10.5152/npa.2015.8763

Vitamin D Deficiency in Obsessive–Compulsive Disorder Patients with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections: A Case Control Study

Gonca ÇELİK[1], Didem TAŞ[2], Ayşegül TAHİROĞLU[1], Ayşe AVCI[1], Bilgin YÜKSEL[3], Perihan ÇAM[2]

[1]Department of Child and Adolescent Psychiatry, Çukurova University, School of Medicine, Adana, Turkey
[2]Department of Rheumatology Immunology, Çukurova University School of Medicine, Adana, Turkey
[3]Department of Pediatric Endocrinology, Çukurova University School of Medicine, Adana, Turkey

ABSTRACT

Introduction: Previous studies have indicated that vitamin D deficiency is common in psychiatric patients, particularly in those with neuropsychiatric disorders such as autism and schizophrenia. Vitamin D is an important neurosteroid hormone and immunomodulatory agent that also has bone metabolic effects. There has been an increasing interest in immune-related neuropsychiatric symptoms that are triggered by group A beta-hemolytic streptococcal infections. In this study, we aimed to compare the serum levels of vitamin D between obsessive–compulsive disorder (OCD) patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and control subjects

Methods: Thirty-three OCD patients with PANDAS and 20 healthy controls were enrolled in the study. Serum 25-hydroxyvitamin D (25-(OH) D), calcium, phosphorus, alkaline phosphatase, and parathormone levels of the two groups were compared. Serum 25-(OH) D levels of <15 ng/mL were classified as vitamin D deficiency. The children's Yale–Brown Obsessive Compulsive Scale (YBOCS) and Clinical Global Impression (CGI) were used to assess the severity of OCD symptoms.

Results: There was no significant difference in serum 25-(OH) D levels between the patient and control groups. However, vitamin D deficiency was significantly more frequent in the patient group than in the control group (48.5% vs. 20.0%; p=0.038). Moreover, OCD patients with vitamin D deficiency had higher rates of comorbid ADHD than those without vitamin D deficiency (87.5% vs. 52.6%; p=0.027). While serum phosphorus levels were negatively correlated with age as well as alkaline phosphatase and ASO levels, they were positively correlated with the YBOCS total score and global severity score. Serum parathormone levels were positively correlated with the YBOCS total score, compulsion score, obsession score, and global severity score.

Conclusion: This study supports the hypothesis that an association between vitamin D metabolism and PANDAS-related OCD exists. We suggest that biochemical parameters predicting metabolic bone diseases are more common in PANDAS patients. There is a need for prospective studies to show a clear association between PANDAS and bone metabolic turnover based on autoimmune mechanisms.

Keywords: Group A beta hemolytic streptococcal Infection, obsessive–compulsive disorder, vitamin D

INTRODUCTION

Obsessive–compulsive disorder (OCD) is characterized by the presence of obsessions (persistent and intrusive thoughts, ideas, impulses, or images that result in anxiety) and/or compulsions (repetitive or ritualistic behaviors or mental acts that reduce or prevent anxiety in response to the obsessive thought) that cause distress, interfere with age-appropriate functioning, and are time consuming. In addition, it is a severe neuropsychiatric disorder with a strong genetic component and may involve the autoimmune processes. Support for this hypothesis comes from the identification of a subgroup of children, described by the term pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), with the onset of OCD symptoms following streptococcal infections (1).

However, the mechanisms underlying PANDAS and autoimmunity have not been fully understood yet. The most commonly accused factors are recurrent infections, genetic tendency, or possible psychosocial stress, although controversial studies have reported a pathogenic link between neuropsychiatric exacerbation and streptococcal infection (2,3). Other microorganisms may be linked to neuropsychiatric exacerbation; therefore, the description of PANDAS may change to pediatric acute-onset neuropsychiatric syndrome (PANS) (1). Recently, there has been no consensus on the etiology or definition of PANDAS (3).

This study is presented in 15th International Congress of ESCAP European Society of Child and Adolescent Psychiatry, 6-10 July, 2013, Dublin, Ireland.

Correspondence Address: Gonca Çelik, Çukurova Üniversitesi Tıp Fakültesi, Çocuk Ergen Ruh Sağlığı ve Hastalıkları Anabilim Dalı, Adana, Türkiye E-mail: goncagulcelik@gmail.com

Received: 22.04.2014 **Accepted:** 03.12.2014

The active form of vitamin D plays a major regulatory role in the immune system, while vitamin D3 enhances macrophage functions (4). The former also regulates tyrosine hydroxylase, which is the rate-limiting enzyme necessary for the production of dopamine, epinephrine, and norepinephrine. Insufficient levels of vitamin D inhibit tyrosine hydroxylase, which may lead to disturbances of these neurotransmitters and a wide range of emotional and behavioral problems (5). Currently, according to pediatricians, vitamin D insufficiency is defined as serum 25-hydroxyvitamin D (25-(OH) D) levels of <10 ng/mL; vitamin D deficiency is defined as 25-(OH) D levels of <30 ng/mL, and sufficient levels of vitamin D are equal to 30 ng/mL (6).

The major role of vitamin D in the immune system is the modulation of innate immunity and autoimmunity. Therefore, insufficient vitamin D levels are thought to be linked to a higher susceptibility for infectious and autoimmune diseases (7).

Considering the immune modulator role of vitamin D, several autoimmune mechanisms may account for the clinical aspects of PANDAS. To date, no clinical study has described an association between pediatric OCD and vitamin D deficiency. The aim of this study is to clarify the possible association between OCDs that are triggered by group A beta-hemolytic streptococci and vitamin D deficiency.

METHODS

Participants

Thirty-three OCD patients with PANDAS and twenty healthy controls were enrolled in the study. All OCD patients were followed-up for 3 years to ensure the reliability of the differential diagnosis of OCD subgroups. The patients were chosen from those treated at University, School of Medicine, Child and Adolescent Psychiatry Outpatient Department. The controls, none of whom had a chronic disorder, were recruited from a primary health care clinic. The diagnostic criteria for PANDAS proposed by Swedo et al. were as follows: 1) presence of a tic disorder or OCD, 2) prepubertal age (usually between 3–12 years) at onset, 3) abrupt symptom onset or episodic course of symptom severity, 4) temporal association between symptom exacerbation and streptococcal infection, and 5) presence of neurologic abnormalities during the periods of symptom exacerbation (1).

Serum 25-(OH) D, calcium, phosphorus, alkaline phosphatase (ALP), and parathormone levels in both groups were compared. Serum 25-(OH) D levels less than 15 ng/mL were classified as indicating deficiency. All blood specimens were collected during the interval between June and September 2012. Informed consent was obtained from all patients and their parents. The study was approved by Medical Ethics Committee of School of Medicine, Cukurova University.

Measurements

A socio-demographic questionnaire recording information on age, gender, and onset age of illness was used. Psychiatric diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (8), and the Turkish version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL) (9,10). The children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) was used to assess the severity of obsessive–compulsive symptoms (11).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 13.0 for Windows (SPSS Inc; Chicago, IL, USA). Pearson's chi-square and Fisher's exact tests were used for comparing categorical variables (patients and control groups, age, and vitamin D status according to serum levels). The Mann–Whitney U test was used to compare the mean values of vitamin D levels between both groups and other continuous variables as well. Correlations between bone metabolic markers (Ca, P, ALP, PTH, and vitamin D) and YBOCS scores were evaluated by Pearson's correlation coefficient.

RESULTS

Of the 33 PANDAS OCD patients, 14 (42.4%) were female and 19 (57.6%) were male. Of the 20 control patients, 4 (20%) were female and 16 (80%) were male. The mean age in the OCD group was 9.5±2.5 years and that in the control group was 11.7±5.2 years.

There was no significant difference between the patient and control groups for serum 25-(OH) D levels although the controls had higher levels of 25-(OH) D than patients (21.54±10.23 vs. 17.39±9.48; p>0.05). Vitamin D deficiency (levels<15 ng/mL) was significantly more frequent in the patient group than in the control group (48.5% vs. 20.0%; p=0.038; Table 1). The patients had higher serum levels of ALP and lower serum levels of phosphorus than controls (Table 2). The most common comorbid condition in the patient group was ADHD. Moreover, OCD patients with vitamin D deficiency had higher rates of comorbid ADHD than those without vitamin D deficiency (87.5% vs. 52.6%; p=0.027). The serum levels of vitamin D, PTH, ALP, calcium, calcitonin, and parathormone were compared between the ADHD comorbid OCD group and pure OCD group. There was no relationship between two groups for bone metabolic markers (vitamin D, PTH, ALP, calcium, calcitonin, and parathormone) and YBOCS sub scores (p=0.160, 0.062, 0.219, 0.378, 0.548, and 0.161, respectively).

Although there was no significance, the levels of vitamin D and PTH were lower in the ADHD comorbid OCD group than in the control group (p=0.073 and 0.061, respectively).
The serum levels of ALP and phosphorus were lower in the ADHD comorbid OCD group when than in the control group. (p=0.002 and 0.013, respectively).

No correlation was found between the serum vitamin D level and other variables. However, serum phosphorus levels were negatively correlated with age, ALP, and ASO levels and were positively correlated with the YBOCS total score, sub-scores, and global severity score. Similarly, serum PTH levels were positively correlated with the YBOCS total score,

Table 1. Comparison of the vitamin D status between patients and controls

Vitamin D status	OCD with PANDAS	Control patients	p
Sufficient (>20 ng/mL)	15 (45.5%)	8 (40%)	0.003
Insufficient (15-20 ng/mL)	7 (21.2%)	12 (60%)	
Deficiency (<15 ng/mL)	11 (33.3)	0	

OCD: Obsessive-Compulsive Disorder; PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

sub-scores, and global severity score, while they were negatively correlated with ASO titers. In addition, serum PTH levels were positively correlated with the YBOCS total score, compulsion score, obsession score, and global severity score and were negatively correlated with ASO titers (Table 3).

The comparison of vitamin D levels for ADHD comorbidity has been presented in Table 4.

There was no association between the levels of calcium and calcitonin between the two groups (p>0.05; Table 5).

DISCUSSION

Vitamin D deficiency does not only result in low bone mass, but it may also lead to neuropsychiatric disorders (12,13). Recently, the possible etiological role of vitamin D has become increasingly defined among patients with sleep disorders and seasonal affective disorders (14,15). To our knowledge, this is the first study investigating the association between immune-related pediatric OCD and vitamin D metabolism. Based on the present findings, we conclude that the serum levels of bone metabolic turnover markers, including 25-(OH) D3, phosphorus, calcium, and PTH, may be associated with serum ASO titers, age of onset, and clinical severity in PANDAS-related OCD cases. The vitamin D status may be associated with increasing oxidative stress due to recurrent infectious attacks in PANDAS patients.

In particular, the serum levels of phosphorus and PTH may be useful in predicting the autoimmune process in PANDAS-related OCD by identifying the increased osteoclastic activity. PTH and phosphorus levels that have been found to be positively correlated with OCD severity and obsession–compulsion sub-scores in the patient group reveal a relationship with the osteoclastic activity in PANDAS-related OCD. Similarly, increased osteoclastic bone activity is correlated with depression severity in adults (16). In addition, elevated PTH levels and increased osteoclastic activity may be related to increased levels of pro-inflammatory cytokines in psychiatric patients (17). The results showing no difference between serum levels of vitamin D among patients the controls may be explained by endemic vitamin D deficiency. To mention a certain deficiency of vitamin D, there is also a need for other bone metabolism parameters. However, the cutaneous production of vitamin D is known to be influenced by season and latitude (18). Therefore, the seasonal effect should be considered when screening the serum levels of vitamin D in patients.

Table 2. Comparison of bone metabolism markers for both groups

Bone metabolism markers	PANDAS OCD	Control group	p
25-hydroxyvitamin D	17.39±9.48	21.54±10.23	0.180
PTH	34.77±17.50	32.03±21.73	0.667
ALP	179.35±67.50	114.33±60.08	0.004
Calcitonin	0.42±0.11	0.53±0.21	0.161
Calcium	9.58±0.40	9.61±0.42	0.542
Phosphorus	4.2±0.85	4.8±0.66	0.018

PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; OCD: Obsessive–Compulsive Disorder; PTH: Parathormone; ALP: Alkaline Phosphatase

Table 4. Comparison of vitamin D levels for ADHD comorbidity

Serum vitamin D levels	OCD n (%)	OCD comorbid ADHD n (%)	p
Sufficient	7 (29.2)	10 (90.9)	0.003
Insufficient	6 (25)	1 (9.1)	
Deficient	11 (45.8)	-	
<25	15 (62.5)	2 (18.2)	0.015
>25	9 (37.5)	9 (81.8)	

ADHD: Attention Deficit Hyperactivity Disorder and OCD: Obsessive–Compulsive Disorder

Table 3. Correlations between bone metabolic markers and YBOCS

	25-(OH) D	Age	Onset	PTH	Calcium	Calcitonin	Phosphorus	ALP
CS	−0.18	0.25	0.34	0.64	0.17	−0.19	0.21	0.01
OS	−0.06	0.18	0.05	0.54	0.18	−0.33	0.34	0.31
TS	−0.16	0.14	0.13	0.63	0.18	−0.27	0.28	0.16
Insight	−0.05	−0.37	0.04	0.43	0.15	−0.00	0.67	−0.37
Avoidance	−0.37	−0.27	0.03	0.58	0.36	−0.36	0.37	0.05
Indecision	−0.28	−0.18	0.11	0.69	0.18	−0.41	0.42	0.16
Responsibility	0.03	−0.13	−0.11	0.28	0.29	−0.24	0.27	−0.05
Slowing	−0.28	−0.14	−0.12	0.54	0.14	−0.22	0.20	−0.02
Skepticism	−0.17	−0.17	−0.24	0.12	0.27	−0.22	0.01	0.04
Severity	−0.12	−0.04	0.24	0.63	0.23	−0.23	0.31	0.15
ASO	0.01	0.01	0.12	−0.45	−0.58	0.53	−0.43	0.00
CRP	0.03	0.05	0.28	0.03	−0.53	0.75	−0.02	0.00

Spearman Correlation test. CS: YBOCS-Compulsion Sub-score; OS: YBOCS-Obsession Sub-score; TS: YBOCS-Total Score; ASO: Antistreptolysin Serum Titers; CRP: C-reactive protein; 25-(OH) D: 25-hydroxyvitamin D; PTH: parathormone; ALP: alkaline phosphatase

Table 5. Comparison between OCD patients with PANDAS based on ADHD comorbidity

	OCD comorbid ADHD	OCD	Control	P[1]	P[2]	P[3]
Vitamin D	16.6±9.9	19.3±8.2	21.5±10.2	0.160	0.073	0.887
PTH	37.1±18.6	28.0±12.5	32.0±21.7	0.062	0.061	0.941
ALP	197.1±69.4	137.8±42.7	114.3±60.0	0.219	0.002	0.285
Calcium	9.5±0.4	9.6±0.1	9.6±0.4	0.378	0.550	0.735
Calcitonin	0.4±0.1	0.4±0.1	0.5±0.2	0.548	0.148	0.613
Phosphorus	4.9±0.6	4.5±0.7	4.2±0.8	0.161	0.013	0.316

P[1] (ADHD comorbid OCD and OCD), P[2] (ADHD comorbid OCD and control), and P[3] (OCD and control). PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; OCD: Obsessive–Compulsive Disorder; PTH: parathormone; and ALP: alkaline phosphatase

Vitamin D deficiency due to demographic characteristics is very common in our society.

The finding that OCD patients with vitamin D deficiency had higher rates of comorbid ADHD than those without vitamin D deficiency was consistent with the findings of Goksugur et al. (19). All bone metabolic markers were compared between the ADHD comorbid OCD group and OCD group to eliminate any association between vitamin D deficiency and ADHD. However, compared with the pure OCD group, there was no significant relationship between metabolic markers and YBOCS sub-scores in the ADHD comorbid OCD group.

Poststreptococica ADHD cases were reported in the PANDAS subgroup (20). In OCD patients with PANDAS, the symptoms of ADHD may differ from those in pure ADHD patients. Vitamin D deficiency may be related to the heterogeneous nature of pediatric OCD with PANDAS.

Consequently, these bone markers seem to be partially related to the symptom profile for PANDAS-related OCD, probably by underlying autoimmune inflammatory processes. Supplements or vitamin D monotherapy may be useful for reducing psychiatric symptoms in patients with PANDAS OCDs. Further prospective, randomized, and controlled longitudinal studies are needed to define a clear association between vitamin D-related bone metabolism and pediatric OCD.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut 2012; 2:1-8. [CrossRef]
2. Leckman JF, King RA, Gilbert DL, Coffey BJ, Singer HS, Dure LS, Grantz H, Katsovich L, Lin H, Lombroso PJ, Kawikova I, Johnson DR, Kurlan RM, Kaplan EL. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: a prospective longitudinal study. J Am Acad Child Adolesc Psychiatry 2011; 50:108-118. [CrossRef]
3. Murphy TK, Kurlan R, Leckman J. The immunobiology of tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, and related disorders: a way forward. J Child Adolesc Psychopharmacol 2010; 20:317-331. [CrossRef]
4. Canning MO, Grotenhuis K, de Wit H, Ruwhof C, Drexhage HA. 1-alpha, 25-Dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes. Eur J Endocrinol 2001; 145:351-357. [CrossRef]
5. Sanchez B, JL Relova, R Gallego, Ben Batalla I, Perez Fernandez R. 1,25-Dihydroxyvitamin D3 administration to 6-hydroxydopamine-lesioned rats increases glial cell line-derived neurotrophic factor and partially restores tyrosine hydroxylase expression in substantia nigra and striatum. J Neurosci Res 2009; 87:723-732. [CrossRef]
6. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122:398-417. [CrossRef]
7. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002; 347:911-920. [CrossRef]
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders text revision (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Association; 2000.
9. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for affective disorders and schizophrenia for school-age Children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36:980-988. [CrossRef]
10. Gokler B, Unal F, Pehlivanturk B, Kültür EÇ, Akdemir D, Taner Y. Reliability and Validity of Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T). Turkish J Child Adolesc Psychiatry 2004; 11:109-117.
11. Scahill L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, Cicchetti D, Leckman JF. Children`s Yale- Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 1997; 36:844-852. [CrossRef]
12. McGrath JJ, Burne TH, Féron F, Mackay Sim A, Eyles DW. Developmental vitamin D Deficiency and risk of schizophrenia: A 10-year update. Schizophr Bull 2010; 36:1073-1078. [CrossRef]
13. Cannell JJ. Autism and vitamin D. Med Hypotheses 2008; 70:750-759. [CrossRef]
14. Stumpf WE, Privette TH. Light, vitamin D and psychiatry: role of 1,25-dihydroxyvitamin D3 (soltiol) in etiology and therapy of seasonal affective disorder and other mental processes. Psychopharmacology 1989; 97:285-294. [CrossRef]
15. McCarty DE. Resolution of hypersomnia following identification and treatment of vitamin d deficiency. J Clin Sleep Med 2010; 6:605-608.
16. Petronijević M, Petronijević N, Ivković Mc, Stefanović D, Radonjić N, Glišić B, Ristić G,Damjanović A , Paunović V. Low bone mineral density and high bone metabolism turnover in premenopausal women with unipolar depression. Bone 2008; 42:582-590. [CrossRef]

17. Van West D, Maes M. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. Neuroendocrinol Lett 1999; 20:11-17.
18. Holick MF. Vitamin D: a millennium perspective. J Cell Biochem 2003; 88:296-307. [CrossRef]
19. Goksugur SB, Tufan AE, Semiz M, Gunes C, Bekdas M, Tosun M, Demircioglu F. Vitamin D status in children with attention-deficit-hyperactivity disorder. Pediatr Int 2014; 56:515-519. [CrossRef]
20. Waldrep DA. Two cases of ADHD following GABHS infection: a PANDAS subgroup? J Am Acad Child Adolesc Psychiatry 2002; 41:1273-1274. [CrossRef]