Psychiatry and Behavioral Sciences 2020;10(1):18-24

Doi: 10.5455/PBS.20190802122307

ORIGINAL ARTICLE

Depression in Children and Adolescents with Tension Type Headache May Not Be Related with Vitamin D and Vitamin B12 Deficiencies

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Abstract

Objective: Aim of this study was to investigate relation between serum 25 (OH) vitamin D or B12 levels and depressive symptoms in children and adolescents with tension-type headache.

Methods: Electronic records of children and adolescents diagnosed with tension-type headache in Ankara Training and Research Hospital Child Neurology Department between March 2018 and August 2018 were retrospectively reviewed. Among them, subjects with depression diagnosed based on DSM-5 criteria and its symptoms obtained via Children depression inventory (CDI) and Beck depression inventory (BDI) found in records were collected. Vitamin D deficiency is defined if its serum levels are below 20 ng/mL, and Vitamin B12 deficiency as below 203 pg/mL. SPSS 17.0 was used for analyses and $p<.05$ was considered as significant.

Results: Of 74 subjects with tension-type headache were included. Mean age of all was 14.3 years (9-17) and 81.1% of all were girls. Of 16.2% of them had depression based on DSM-5 criteria. The mean CDI scale was 12.9 (2-32) and BDI scale was 19.3 (9-40). Mean serum level of vitamin D was 14.4 ng/mL (range= 3.80-46.6 ng/mL) and 73% of them had Vitamin D deficiency. Mean serum vitamin B12 levels were 291.3 pg/mL (range= 123.5-792) and 20.3% of them had its "deficiency". There was no significant relation between vitamin deficiencies and having depression or being adolescent (for all variables $p>.05$). There was also not any significant correlation between two vitamin levels and depressive symptoms based on CDI and BDI. There was, however, a relation between being girl and vitamin deficiencies, which 88.9% of all vitamin D deficient cases (48/54, $c2(1) = 7.192$, $p = .016$, Fisher's exact test), and 60% of vitamin B12 deficient subjects (9/15, $c2(1) = 5.451$, $p = .030$, Fisher's exact test) were girls. Correlation analyses revealed that age (years) has significant negative correlation with vitamin B12 (Spearman rho=-.352, p= .002), and positive correlation with CDI (Spearman rho=.282, p=.039). There was another negative correlation found between vitamin D and BDI (Spearman rho=-.499, p=.041).

Conclusions: Girls with tension-type headache would be evaluated for vitamin D and B12 levels. Being adolescents might have effect on vitamin B12 intake and on depression symptoms.

Keywords: Tension-Type Headache , Vitamin D, B12, Adolescent, Depression, DSM-5

INTRODUCTION

Primary headaches are one of the deteriorating disorders over childhood and adolescence periods which their etiologies are not clearly known (1). Tension-type headaches are the most frequent type among primary headaches and it has negative effects on affected subjects' family relation, school performance and peer relations (2). Primary headaches are to be shown as associated with anxiety or depression symptoms (3).

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Citation: Gorucu Aydin R, Eraslan AN, Sivri Colak R, Goker Z, Yilmaz A. Depression in Children and Adolescents with Tension Type Headache May Not Be Related with Vitamin D and Vitamin B12 Deficiencies. Psychiatry and Behavioral Sciences 2020;10(1):18-24.
Doi: 10.5455/PBS.20190802122307

Received: Aug 02, 2019
Accepted: Dec 22, 2019

Depressive disorder is an important psychiatric condition seen in especially adolescents causing individual, social and academic deterioration in affected person. Epidemiological and clinical studies showed that there is a relation between lower levels of vitamin D and depressive symptoms (4,5) and nutritional supplements having a positive effect on treatment of depressive disorders (6).

Vitamin D (Calctriol) is one of the substrates that regulate tyrosine hydroxylase and dopamine pathways which both processes operate with serotonin and dopamine-related neurotransmitters (7). It mainly stems from synthesis located on the skin and this inactive form of vitamin D is medicated by liver and renal enzymatic processes and transforms its hormonally active form of 1,25-dihydroxy-vitamin D_3

[1,25(OH)$_2$D$_3$] and this form of vitamin D acts within the whole body after binding with vitamin D receptor/ retinoic X receptor (VDR/RXR) heterodimeric complex (8). Vitamin D deficiency, which is defined by Institute of Medicine (IOM) as serum 25-hydroxyvitamin D [25(OH)D]) as below 20 ng per milliliter (50 nmol per liter)(9), is well-documented issue that its insufficient levels are likely to be responsible for a wide-range disorder spectrum from cancer development, (10) autoimmune disorders, (11) cardiovascular problems, (12) to psychiatric symptoms of depression (13) and anxiety (14). There are also some reports pointing out that there is a relation between the primary headaches of childhood and lower levels of vitamin D (15, 16).

Vitamin B12 (Cyanocobalamin), is also another important substance that plays a crucial role in nucleic acid and cellular energy metabolisms (17). According to the World Health Organization (WHO), vitamin B12 deficiency is when serum levels are under 203 pg/mL (150 pmol/L) (18). Its lower levels were found to be related with neurological dysfunctions (19). There are contradicting results related to serum vitamin B12 levels and its association with psychiatric disorders studies. Kar et al (2018)(20), for instance, reported significantly lower level of serum vitamin B12 levels in a psychiatric admission sample, whereas, Atadag et al (2017)(21) revealed that there was no association with depression or anxiety disorders and vitamin B12 deficiency. In another study, vitamin B12 levels were found to be lower in children with tension-type headache compared to the healthy subjects (22).

Up until now, there was no found any study in the literature examining vitamin D or vitamin B12 levels in children with tension-type headache and its relation with depressive disorder, all aforementioned subjects are to be related with tension-type headache etiology. The aim of this study was to investigate the vitamin D and vitamin B12 deficiencies in patients with tension-type headache and to examine whether age groups (children vs. adolescents) or having depression that might have an effect on tension-type headache .

METHODS

Electronic records of children and adolescents aged 6-18 years who admitted to the Ankara Training and Research Hospital Child Neurology Department between March 2018 and August 2018 for complaint of headache and diagnosed by tension-type headache. based on International Headache Society's International Classification of Headache Disorders (ICHD-3, 2013) criteria (23) were retrospectively reviewed. Among them those who were consulted to the child psychiatry department to evaluate their mental status were selected. It was noticed that 40% of all participants (n = 51/125) did not come for psychiatric examination. Consequently, the study and statistical analyses were carried out by 74 children and adolescents with tension-type headache . Since both tension-type headache and depression are more prevalent in adolescents than that of children, all samples of tension-type headache were divided into two groups as children (aged 9-11 years) and adolescents (aged 12-17 years).

Inclusion criteria for tension-type headache group were the following; Normal neurological findings of cranial MRI or computerized tomography, not having mental retardation and absence of the concomitant chronic medical disorder. The proportion of depression diagnosis determined by DSM-5 criteria (24) by the child psychiatrists were also recorded. Participants' serum vitamin D, vitamin B12 levels were obtained from the records.

Tools Used

The Children's Depression Inventory (CDI): Developed by Kovasc (1983), applied to aged 6-17 years old children and adolescent, is a 27-item three-point (from 0 to 2) self-report scale (25). Total score of it is 54. The higher the scale score, the greater the severity of depression. The scale is filled in by reading it to the child or read by the child. This scale's Turkish validity and reliability was carried out by Öy in 1991 (26).

The Beck Depression Inventory (BDI): A 21-item 4-point (from 0 to 3) scale evaluating depressive symptoms of the 17 aged and above subjects, was developed by Beck (27). Total scores is positively correlated with the severity of depression. Hisli (1989) showed this scale's Turkish reliability and validity (28).

Serum <20 ng/mL vitamin D levels was accepted as "deficient" based on IOM cut-off[9], and serum vitamin B12 levels of <203 pg/mL as "deficient" based on WHO cut-off (18).

Statistical Analyses

Sociodemographic and clinical variables were analyzed using SPSS 17.0 (Chicago Inc., 2008). Continuous variables were expressed in terms of arithmetic mean, standard deviation, minimum-maximum values and categorical ones were defined in terms of frequency

(n) and percentage (%). Conformity of continuous variables to normal distribution was examined with Kolmogorov-Simirnov test. Student-t test was used to compare vitamin D levels, whereas Mann Whitney U test was used to analyze vitamin B12 levels. Categorical variables were analyzed with Chi-square and Fisher's exact tests. Spearman correlation test was used to evaluate association of vitamin D and vitamin B12 levels with CDI and BDI scale scores. $p<.05$ was considered significant.

Ethical approval for this study was obtained from Ankara Training and Research Hospital Medical Education Board (issue numbered with 14.11.2018-60 / 621)

RESULTS

Of the 125 cases referred to the Pediatric neurology outpatient clinic within the specified period aforementioned, only 74 were evaluated by our polyclinic. Consequently, this study was carried out with 74 children and adolescents with tension-type headache . Mean age of the cases was 14.3 ± 2.3 years (range: 9-17 years). Of 81.1% (n=60) subjects were girls and 18.9% (n=14) were boys.

As regards age groups, 13.5% (n=10) subjects with tension-type headache were children (9-11 years old) whereas 86.5% (n=64) were adolescents (aged 12-17 years). Academic achievements of them, 62.1% (n = 41) had normal, 37.9% (n = 25) had poor academic levels. Among the subjects, 91.9% (n = 68) of the patients were previously admitted to the psychiatry very first time, whereas 8.1% (n = 6) were already in psychiatric follow-up. It was determined that 93.2% (n = 69) of the cases did not use any psychiatric medication and the other 6.8% (n = 5) were still using psychotropic drugs except from antidepressants. According to the DSM-5 diagnostic criteria, 16.2% (n = 12) of the patients were diagnosed with depression. The mean CDI scale (n = 54) was 12.9 points (range: 2-32) and the mean BDI scale (n = 17) was 19.3 (range: 9-40) (see Table 1).

Table 1. Demographics and clinical features of the subjects with tension-type headache (n=74)

	Outcome of 74 cases with tension-type headache
Variables	
Age (years), Mean (standard deviation)	14.3 (2.3)
Age groups, n (%)	
Children (9-11 years old)	10 (13.5)
Adolescents (aged 12-17 years)	64 (86.5)
Gender, n (%)	
Girls	60 (81.1)
Boys	14 (18.9)
Academic achievement scores, n (%)	
Poor	25 (37.9)
Normal	41 (62.1)
Psychiatric admission, n (%)	
First admission	68 (91.9)
Followed-up	6 (8.1)
Psychotropic usage history, n (%)	
No	69 (93.2)
Yes	5 (6.8)
Depression diagnosis (Based on DSM-5), n (%)	
No	62 (83.8)
Yes	12 (16.2)
Scales scores, Mean (standard deviation)	
Child Depression Inventory scores (n=54)	12.9 (6.9)
Beck Depression Inventory scores (n=17)	19.3 (11.0)

The mean level of serum vitamin D was 14.4 ± 7.9 ng/mL (range:3.80-46.6 ng/mL). Serum <20 ng/mL levels of vitamin D was defined as "deficient" and ≥20 ng/mL as "sufficient" level of adequacy. Accordingly, 73% (n = 54) of the cases had vitamin D deficiency and 27% (n=20) of the subjects had sufficient vitamin D levels.

Firstly, analyses was carried out based on Vitamin D levels deficient (n=54) vs. sufficient (n=20) in terms of their demographics and clinical variables. Age, academic achievement, psychiatric admission, history of psychotropic usage, depression (based on DSM-5), and CDI or BDI depression scales were similar in vitamin D deficient subject (n=54) with tension-type headache compared to the vitamin D sufficient (n=20) counterparts (for all variables, $p>.05$, not seen in the Table). There

was, however, a significance for being girls in vitamin D deficient group, which 88.9% (n=48/54) of all vitamin D deficient cases were girls ($c^2(1) = 7.192$, p = .016, Fisher's exact test).

Consequently, Vitamin B12 levels were evaluated and its mean levels were 291.3 ± 112.3 pg/mL (range: 123.5-792 pg/mL). Serum vitamin B12 levels of <203 pg/mL was defined as its deficiency. Thus, 20.3% (n = 15/74) of the cases had vitamin B12 deficiency whereas 79.7% (n=59/74) of children and adolescents with tension-type headache had sufficient vitamin b12 levels. Second analyses was carried out in tension-type headache group (n=74) based on vitamin B12 deficiency (n=15) vs. normal vitamin B12 levels (n=59). Between two groups, there was no difference in terms of demographics and aforementioned clinical features (for all variables, p>.05, not shown in Table), apart from gender variable. Of 60% (n=9/15) of all vitamin B12 deficient subjects were girls which it means that being girls was found a significant factor for vitamin B deficiency in the tension-type headache ($c^2(1) = 5.451$, p = .030, Fisher's exact test).

Third analyses were carried out by dividing the sample (n=74) into two groups as depression found (n=12) and no depression (n=62). Comparisons, however, revealed that there was no significant difference between having depression and vitamin D levels (t(72)=1.002, p=.320) or vitamin B12 levels (z=-1.408, p=.159, see Table 2).

Table 2. Comparison of vitamin D or B12 levels and having depression (n=12) or not (n=62) in subjects with TENSION-TYPE HEADACHE

	Total	Depression	No depression	Statistics	
	n=74	**n=12**	**n=62**	**t, z, orc²**	**P value**
Vitamin D (ng/mL)[a]	14.8 (7.9)	12.7 (5.9)	15.3 (8.2)	1.002	.320
Vit-D categories, n (%)				.779*	.494
Deficient (<20)	54 (73.0)	10 (83.3)	44 (71.0)		
Sufficient (≥20)	20 (27.0)	2 (16.7)	18 (29.0)		
Vitamin B12 (pg/mL)[b]	267.4 (123-792)	250.7 (141-430)	274 (123-792)	-1.408	.159
Vit-B12 category, n (%)				1.512*	.248
Deficiency (<200)	15 (20.3)	4 (33.3)	11 (17.7)		
Normal (≥200)	59 (79.2)	8 (66.7)	51 (82.3)		

a: Mean (Standard deviation), *: Fisher's exact test
b: Median (minimum-maximum)

As regards being children or adolescents with tension-type headache , comparisons of gender, academic achievement, psychiatric admission, history of psychotropic usage, having depression (based on DSM-5), and CDI or BDI depression scales were similar adolescents (n=64) with tension-type headache than that of children (n=10) with tension-type headache (for all variables, p>.05, not shown in Table). Children and adolescents with tension-type headache were similar vitamin D and vitamin B12 levels (p>.05, see Table 3).

Table 3. Comparisons serum vitamin D and B12 levels in children (n=10) vs. adolescents (n=64) with TENSION-TYPE HEADACHE

	n=74	n=10	n=64	t, z, orc²	P value
	Total	**Children**	**Adolescents**	**Statistics**	
Vitamin D (ng/mL)[a]	14.8 (7.9)	16.3 (6.3)	14.6 (8.1)	.635	.527
Vit-D categories, n (%)				.289*	.719
Deficient (<20)	54 (73.0)	8 (80.0)	46 (71.9)		
Sufficient (≥20)	20 (27.0)	2 (20.0)	18 (28.1)		
Vitamin B12 (pg/mL)[b]	267.4 (123-792)	339.4 (141-792)	264.4 (123-611)	-1.249	.212
Vit-B12 category, n (%)				1.512*	.248
Deficiency (<200)	15 (20.3)	4 (33.3)	11 (17.7)		
Normal (≥200)	59 (79.2)	8 (66.7)	51 (82.3)		

Correlation analyses of serum vitamin D and B12 levels revealed that age (years) has significant negative correlation with vitamin B12 (Spearman rho=-.352, p= .002), and positive correlation with CDI (Spearman rho=.282, p=.039). There was another negative correlation found between vitamin D and BDI (Spearman rho=-.499, p=.041).

Table 4. The correlations of serum vitamin D or B12 levels with age and depression scale scores

		Vit-D (ng/mL)	Vit-B12 (pg/mL)	CDI total	BDI total
Age (year)	rho	-.011	**-.352****	**.282***	-
	p	.928	**.002**	**.039**	-
Vit-D (ng/mL)	rho	1	.231*	-.071	**-.499***
	p		.048*	.609	**.041**
Vit-B12 (pg/mL)	rho		1	-.243	-.284
	p			.076	.269
CDI total	rho			1	-.011
	p				.976

CDI: Children depression inventory, BDI: Beck depression inventory
**: significance at 0.01, *: significance at 0.05

DISCUSSION

Tension-type headache is one of the most debilitating issues for childhood and according to the literature related to this is closely related to vitamin D and vitamin B12 levels. Recent study aimed to evaluate depression frequency in children and adolescent with tension-type headache and should there is a difference between vitamin D or vitamin B12 levels and depression.

Depression is an important disorder that causes deteriorate in children and adolescent's daily basis functioning including school, family and peer relations and might be related vitamin D or vitamin B12 insufficiency. In our sample, 73% (n = 54) of the tension-type headache cases had vitamin D insufficiency and the proportion of depressive disorder was 16.2%. Previous studies evaluated the vitamin D levels in tension-type headache subjects without their vitamin D levels. Donmez et al (2017), for instance, reported their samples of tension-type headache aged 5 to 16 years, pointing that 67.2% of all children with tension-type headache had vitamin D deficiency (14). Our study did not contain control group and it was not possible to compare these results. What our study points out that being girl with tension-type headache had a significance for having vitamin D insufficiency. Vitamin D levels were reported to be important for school functioning. Kaczynski et al., (2013) reported that tension-type headache affects children's school performance negatively(2). In our sample, academic achievements, obtained from participants subjectively, did not differ in terms of vitamin D insufficiency. What we evaluated that there was not statistically significant between having depression and vitamin D insufficiency or not.

There was a few studies pointing out that the lower vitamin D, the higher rate of depression symptoms. Föcker et al (2017), for instance, reported that depression symptoms obtained by BDI scale was found at a higher proportions in children with lower vitamin D levels.[5] In another study, conducted by Jorde et al (2008) showed vitamin D treatment is to be effective on depression compared to the placebo (29). Thabrew et al. (2018) evaluated the children and adolescents with long-term physical conditions aged up to 18 years (16). They revealed that long-term chronic conditions including tension-type headache result in higher depression symptoms.

As regards vitamin B12 levels, our tension-type headache samples' vitamin B12 deficiencies were not different from optimal vitamin B12 levels in terms of demographics and clinical findings, apart from being girl. Majority of girls with tension-type headache had vitamin B12 deficiency. Lastly, we found that vitamin B12 deficiency had no significant differences of having depression or not. A study, conducted by Calik et al (2018) reported that vitamin B12 deficiency were associated with tension-type headache (22). These controversies might stem from the fact that our sample was not be able to compared to control.

Final highlighting is that there was a negative correlation between age and vitamin B-12 levels and positive correlation with depressive symptoms based on CDI. During adolescence, vitamin B12 intake could relate tension type headache and adolescence itself is more vulnerable for developing depression. This, because we found another negative correlation between vitamin D levels and BDI depression scores which fulfilled by adolescent group.

Further studies would enlighten the relation between vitamin B12 or vitamin D deficiency during adolescence.

Limitations of This Study

Vitamin D levels of the subjects were evaluated in which spring and summer season. This could intervene our results. Deficiency and insufficiency samples were relatively limited. Number and cross-sectional nature of our sample may have affected the results. Another limitation was the attrition of the samples which 40%

of all first sample (n = 51/125) could not be evaluated for psychiatric examination. This situation would have affected the proportion of depression diagnosis. And finally, there was no control group to compare two levels of vitamin D or vitamin B12 and tension-type headache subjects. These limitations could not allow the findings to be generalized.

In Conclusion

Our findings have different result from aforementioned studies pointing out that there was no difference between vitamin D or B12 levels deficiency and depression. Our research contributes to the literature in terms of both the presence of depression and the evaluation of vitamin D levels in the tension-type headache . Depression diagnosis and symptoms in children and adolescents apparently independent with tension type headache from serum vitamin D or vitamin B12 levels. Being adolescents and girl might have effect on vitamin B12 intake and on depression symptoms and being girls has risk for developing these two vitamin deficiencies. Studies to be performed longitudinally with larger samples will contribute to the relationship between vitamin D and depression symptoms and diagnosis in tension-type headache .

Funding: There was no funding or any type of support for this study.

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