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Research Article

Association between Level of Vitamin D with Environmental and Bioelement Factors in Children with Attention Deficit Hyperactivity Disorder (ADHD)

Gholamreza Noorazar[1], Gita Mehdizadeh[2], Aida Ghaffari[3], Nadia Dehbokri [2], Mohammad Taghi Khodayari[4], Saba Ghaffary[5]*

[1]*Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2]*Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*
[3]*Student Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.*
[4]*Faculty of Management and Medical Informatics, Tabriz University of Medical Sciences, Tabriz, Iran.*
[5]*Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

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ABSTRACT

Background: Attention deficit hyperactivity disorder (ADHD) is a behavioral disorder. The exact pathophysiology of ADHD is not completely recognized. Previous studies have shown the role of different genetic and environmental factors in it. This study investigates the relationship between vitamin D and environmental factors in ADHD.

Methods: In this study, 182 children from 2 to 18 years with confirmed ADHD were allocated in this cross-sectional study. Patients with a history of any chronic disease, anticonvulsants and corticosteroids consumption were excluded from the study. The ADHD severity was assessed by Conners' parent scale test. The level of serum vitamin D, ferritin, iron, total iron binding capacity, zinc, magnesium, calcium and routine complete blood count (CBC) were measured.

Results: Although the results showed a U shaped pattern between vitamin D levels and ADHD severity, the correlation between vitamin D level did not show any significant relation with ADHD symptoms severity (p=0.786). Our data showed significant relation between level of vitamin D and ferritin in patients with ADHD (p=0.003). The analysis demonstrates significant relation between vitamin D level and duration of daily TV watching in children with ADHD (p=0.002).

Conclusion: The vitamin D supplementation may improve ADHD symptoms in patients with vitamin D deficiency. In addition, due to the proved effect of ferritin level in ADHD and significant relation with vitamin D level in this study, treatment of vitamin D deficiency is necessary in children with ADHD. Replacing TV watching by more outdoor activity may improve ADHD symptoms.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a chronic behavioral disorder accompanied by three main symptoms such as hyperactivity, restlessness and decreased attention.[1,2] ADHD interrupts patient's cognitive and educational function. In addition, behavioral, emotional and other psychiatric problems increased in these patients. [1,2] This disorder affects both children and adults, with the higher incidence in children 2 to 18 years.[1] The diagnostic and statistical manual of mental disorders-V (DSM-V) defines ADHD syndrome with hyperactivity/impulsivity (H/I) and inattention (IA) category. Children categorized into subtypes by presenting six or more criteria of either IA, H/I, or combination of both (C).[3]

Although, the exact pathophysiology of ADHD is not fully understood, several studies have shown the role of genetic and environmental factors in its outbreak.[1,2] Medication is the main management of children with ADHD. However, the preventive and treatment role of environmental and nutritional factors have been attracting the attention of researchers in recent years.[4] There is not any ultimate data to support that nutrient deficiencies may cause ADHD. However, some studies showed reduced levels of ferritin, vitamin D, zinc and magnesium in patients with ADHD.[5] Of these nutritional factors, ferritin level has more significant relation with ADHD. Ferritin is a storage form of iron in body and releases it in a controlled pattern. Iron plays an important role in the regulation of dopaminergic activity, which is associated with the pathogenesis and symptoms of ADHD.[6]

Deficiency of vitamin D is associated with psychiatric diseases such as autism, schizophrenia, and depression.[4] Recent studies have suggested a pathophysiological effect

***Corresponding Author:** Saba Ghaffary, E-mail: ghaffarys@tbzmed.ac.ir

of vitamin D deficiency in ADHD.[7] Vitamin D not only plays a role in bone and calcium hemostasis, but also is distributed across many tissues. The widespread distribution of vitamin D receptors in different tissues prove the non-classical and different potential physiologic actions of Vitamin D in body.[8] Kamal et al showed that vitamin D metabolism depends on iron. Furthermore, iron deficiency might disturb vitamin D activation. There are also several trials evaluating the effect of iron intake on vitamin D concentration and vice versa.[9]

In addition, previous studies showed relation among hours of computer/video games, watching TV and ADHD.[10] Moreover, normal children with long duration of TV/computer usage had deficient level of vitamin D.[11]

In this study the association between vitamin D level and some environmental and bioelement factors in children with ADHD was investigated.

Materials and Methods

Study population

In this cross-sectional study, patients were drawn from the outpatient clinic of the child psychiatry department. Patients who had a history of any chronic disease, received medications such as anticonvulsants and corticosteroids were excluded from the study. Total off 2400 patients from 2 to 18 years old, who had referred to outpatient clinic of the child psychiatry department were screened from May 2016 to February 2017. According to the inclusion and exclusion criteria, 182 patients with confirmed ADHD were involved in this study.

The diagnosis of ADHD and its subtypes (IA, H/I, or C) was based on children psychiatrist assessment according to DSM-V criteria. The clinical history, ADHD symptoms and school performance were assessed by Conners' Parent Rating Scale. In addition, the questionnaire which contains demographic information and environmental factors such as duration of nap at noon, night sleep, TV watching, computer activity and toy life was filled out for all patients.

Conners' Parent Rating Scale

The Conners' Parent Rating Scale (CPRS) was designed as a comprehensive checklist for making parental reports of the basic problems for children in outpatient psychiatric setting. The CPRS contained sections about problems related to sleep, eating, temper, keeping friends, and school performance.[12] The conners test score shows severity of ADHD symptoms.

After ADHD diagnosis confirmed, all children's parent (mother, father or both) were asked to fill the CPRS. Then, the CPRS was assessed by children psychiatrist and reported by numbers as ADHD conners.

Laboratory analysis

From allocated patients (n=182), 5 mL venous blood sample has been drawn. Serum vitamin D level was determined using enzyme-linked immunosorbent assay (ELISA; DRG Instruments, Marburg, Germany). To probe the vitamin D level, we have used approved standards as follows;[13] Vitamin D sufficiency: (50 nmol/L) 20 ng/ml $\leq$ 25OHD; Vitamin D insufficiency: (37.5-50 nmol/L) 15 ng/ml $<$ 25OHD $<$ 20; Vitamin D deficiency: (37.5 nmol/L) 15 ng/ml $\geq$ 25OHD. In addition, the serum level of ferritin, iron, total iron binding capacity (TIBC), zinc, magnesium (mg), calcium (Ca) and routine complete blood count (CBC) were measured.

Statistical Analysis

Data were analyzed using SPSS version 21 and the results were expressed as means ± SD. Normal distribution was tested with the Kolmogorov-Smirnov test. Data with normal and abnormal distributions were analyzed with T-test and Mann-Whitney U-test, respectively. Chi-Square tests were done to assess the relation between the vitamin D status (sufficient, insufficient, and deficient) and ADHD conners scale. The Pearson correlation was performed to find association between vitamin D level and ADHD conners scale, toy life, laboratory tests, duration of nap at noon, night sleep, TV watching and computer related activity. Kruskal Wallis test was used to see relation between different age group and vitamin D level. Moreover, to see the correlation between vitamin D level and weight Kendall's Tau-b and Spearman's rho were used. P value less than 0.05 was considered significant in all statistical analyses.

Ethics

The study protocol was approved by the Research Ethics Committee at Tabriz University of Medical Sciences. All patients were informed about the study and gave a written informed consent before the study initiation. Children with ADHD and their parents were free to continue allocation during the study period.

Results

Our data showed that the proportion of vitamin D deficiency was 41.8% in children with ADHD. The frequency of gender type, ADHD type and vitamin D status are shown in Table 1. The relation pattern of ADHD conners with vitamin D level is illustrated in Figure 1.

Table 1. The frequency of gender type, ADHD type and vitamin D status.

Parameters		Frequency (%)
Sex	Female	45 (24.7)
	Male	137 (75.3)
ADHD Type	C	124 (68.1)
	IA	8 (4.4)
	H/I	17 (9.3)
Vitamin D status	Sufficient	33 (18.1)
	Insufficient	73 (40.1)
	Deficiency	76 (41.8)

ADHD: attention deficit hyperactivity disorder; H/I: hyperactivity/impulsivity;
IA: inattention; C: both H/I and IA

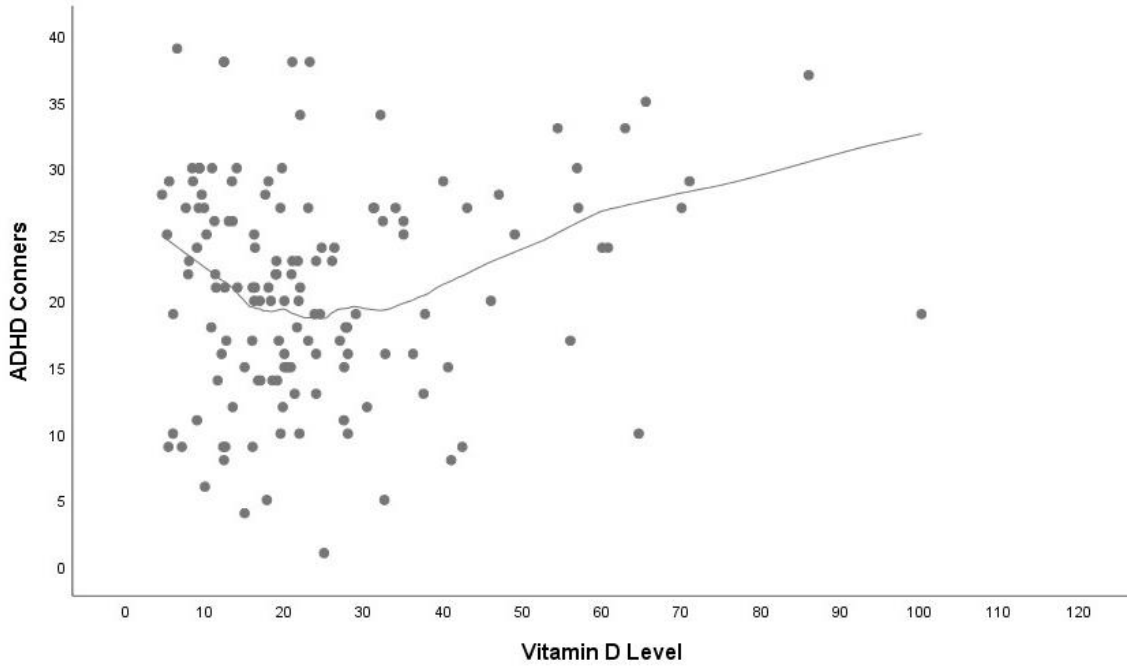

Figure 1. The relation pattern of ADHD conners with vitamin D level.

As shown in Figure 1, there is an inverse relation between vitamin D level and ADHD conners in vitamin D deficient patients. The severity of ADHD symptoms was stable when vitamin D level increased from 20 to 40 ng/ml. ADHD symptoms increased in the vitamin D level of 40 ng/ml. Totally, the correlation between ADHD conners and vitamin D level did not show any significant relation (p= 0.786). The distribution of different vitamin D status in three ADHD subtypes is shown in Table 2. In addition, there is not any significant relation between gender and weight with vitamin D level (p=0.174 and p=0.127, respectively). Our analysis shows significant positive relation between level of vitamin D and Ferritin in patients with ADHD (p=0.003) (Table 3).

Table 2. The distribution of different vitamin D status in ADHD type.

Vitamin D satus	ADHD Type			Total
	C	IA	H/I	
Sufficient	28	3	1	32
Insufficient	46	3	10	59
Deficiency	50	2	6	58
Total	124	8	17	149

ADHD: attention deficit hyperactivity disorder; H/I: hyperactivity/impulsivity; IA: inattention; C: both H/I and IA

Our analysis did not show any significant relation between serum level of iron, TIBC, mg, Ca and CBC parameters with vitamin D level and ADHD conners. From environmental factors, daily TV watching duration of children showed statistically significant inverse relation with vitamin D level (p=0.002) (Table 3).

Table 3. The correlation of environmental and bio elemental factors with Vitamin D level.

Parameters		(P value)
Duration (hour)	Noon sleep	0.144
	Night sleep	0.529
	TV watching	0.002*
	Computer activity	0.768
	Toy life	0.238
Laboratory Data	Magnesium	0.425
	Calcium	0.914
	Phosphorus	0.651
	ALP	0.399
	Ferritin	0.003*
	Fe/TIBC	0.833
	Zinc	0.824

ALP: alkaline phosphatase; Fe: iron; TIBC: total iron binding capacity
* Significant at P< 0.05.

Discussion

Children with ADHD may prone to a variety of nutrient deficiencies.[14] Previous studies suggested that ADHD may be associated with low levels of vitamin D, zinc and iron.[5,14] The prevalence of vitamin D deficiency in normal children is 12.1% in USA.[15] Whereas, the prevalence of vitamin D deficiency is 25% in Iranian children.[16] The results of this study indicate that the proportion of children with vitamin D deficiency in ADHD was 41.8%. Furthermore, the U shaped pattern was demonstrated between vitamin D levels and ADHD severity. There was an inverse association between vitamin D level and ADHD in children with vitamin D deficiency. However, the high levels of vitamin D were positively correlated with ADHD severity in patients with sufficient level. In accordance with our results, Goksugur et al, indicated a significant difference in mean serum vitamin D level between 7 to 18 years old ADHD children (20.9±19.4

ng/ml) and control groups (34.9±15.4 ng/ml).[17] Kamal et al, reported that the mean range of serum vitamin D level of children with ADHD (16.6±7.8 ng/ml) was lower than control group (23.5±9.9 ng/ml).[9] Rucklidge et al, reported that the prevalence of vitamin D deficiency in ADHD patients was 27%. In this study supplementation with vitamin D for eight weeks was found to be helpful in alleviating the signs of the disease.[18] Mossin et al, found an inverse association between cord blood level of 25 (OH) D and ADHD symptoms in toddlers.[19] However, Tolppanen et al, indicated no significant association between some behavioral problems including ADHD and vitamin D level.[20]

In Iran, several authors have demonstrated the relation of vitamin D and ADHD. Sharif et al, showed that children with ADHD had significantly lower level of vitamin D in comparison with healthy children in trial which performed in Kashan, Iran.[4] In a study by Mohammadpour et al, addition of vitamin D supplement to methylphenidate therapy improved evening symptoms of ADHD in children aged 5 to 12 years in Tehran, Iran.[21]

It was suggested that vitamin D stimulates neurogenesis and regulates the synthesis of neurotrophic factors such as nerve growth factor, glial cell line-derived neurotrophic factor, neurotrophin 3 and 4, which are important for cell differentiation and survival of neurons.[17]

Increased oxidative stress might be associated with the pathophysiology of ADHD. Vitamin D enhances the formation of glutathione, which has the antioxidant effect on brain.[22] Experimental studies showed that vitamin D deficiency facilitates oxidative stress response and changes multiple neuroendocrine transmitters.[17]

Evidence showed that variation in a polymorphism in the promoter of the serotonin transporter influences susceptibility to ADHD.[23] Vitamin D regulates serotonin production through tryptophan hydroxylase 2 (TRH2) and tryptophan hydroxylase 1 (TRH1). These two genes are responsible for the conversion of tryptophan into serotonin in the brain and other tissues. Vitamin D response element (VDREs) is presented in the regulatory regions of both TPH2 and TPH1. It was suggested that VDREs would respond to vitamin D hormone in an inverse mode, with TPH2 being transcriptionally activated in the brain and TPH1 repressed in tissues outside of the blood-brain barrier.[24]

In addition, irregular dopamine concentration in definite areas of the central nervous system might have a role in ADHD. Study in[25] indicated that vitamin D may also have a neuroprotective effect on dopaminergic pathways by preserving dopamine content in the brain. Moreover, insufficiency of this vitamin has unfavorable effects on the dopamine pathways related to brain development.[24]

The present study revealed the negative relation between vitamin D level and daily TV watching duration of children with ADHD. There were inconsistent finding about association between ADHD and increased use of computer/video games and watching television (TV).[10] However, none of these studies evaluated status of vitamin D associated with TV watching duration in children with ADHD. In normal children previous studies showed that the prevalence of vitamin D deficiency is significantly higher in children with long duration of TV/computer use.[11] However, limiting the duration of TV/computer usage and replacing more outdoor activity may protect against vitamin D deficiency and have beneficial effect on vitamin D status.[11]

Previous findings revealed a positive and significant relation between level of vitamin D and ferritin in children with ADHD. Previous findings have shown that children with ADHD have lower mean ferritin levels when compared with normal controls. In addition, low serum ferritin levels are related with more severe ADHD cases.[26] Our data showed remarkable relation between vitamin D and ferritin serum level in patients. In line with our results, Blanco et al, found that 92 % of iron-deficient Spanish women also had vitamin D deficiency or insufficiency.[27] In addition, Wright et al, reported an inverse association between iron status and bone resorption in young menstruating women.[28] Sim et al, demonstrated an association between vitamin D deficiency with anemia, low hemoglobin levels, and a high concentration of the erythropoiesis-stimulating agent.[29]

It was suggested that erythrocyte precursor cells express 1,25-hydroxyvitamin D receptors, which induces the proliferation and maturation of erythroid progenitor cells.[30] Vitamin D receptor activation inhibits the expression of inflammatory cytokines in stromal and accessory cells and upregulates the release of interleukin-10, which exerting both anti-inflammatory activity and proliferative effects on erythroid progenitors.[31] Therefore, deficiency of 1,25-hydroxyvitamin D may affect erythropoiesis.[30]

In addition, it was suggested that vitamin D is a potent regulator of the hepcidin-ferroportin axis. Hepcidin regulates the absorption, tissue distribution and extracellular concentration of iron by suppressing the ferroportin mediated cellular iron export. Vitamin D deficiency may affect the regulation of hepcidin, which decreases iron absorption.[30] However, some studies reported no significant changes in hemoglobin levels by daily supplementation of vitamin D.[30] Due to lack of evidence in children with ADHD, additional research is needed to assess the association of vitamin D deficiency with iron status in children with ADHD.

This study is limited by the small sample size. In addition, to know the incidence of vitamin D deficiency, we should conduct a control group by normal population. Further trials are needed to identify the effect of vitamin D on ADHD.

Conclusion

The low levels of serum vitamin D among the ADHD children and U shaped relationship between them suggest the need for regularly monitoring of serum vitamin D levels. Due to the relation of vitamin D and ferritin level, treatment of vitamin D deficiency is necessary in children with ADHD. Life style modification such as restricting TV use and replacing more outdoor activity by protect

against vitamin D deficiency may help to prevent the ADHD development.

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Conflict of Interests

The authors claim that there is no conflict of interest.

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