RESEARCH ARTICLE

Erman Esnafoglu[1]

[1] Ordu University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Ordu, Türkiye

Corresponding Author:
Erman Esnafoglu
mail:ermanesnafoglu@yahoo.com.tr

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Investigation of the Relationship Between Vitamin D and Peripheral Inflammatory Parameters in Children with Attention Deficit and Hyperactivity Disorder

ABSTRACT

Objective: We aimed to investigate the effects of vitamin D and some nutritional factors such as vitamin B12, folate, homocysteine, and ferritin, which play a role in the pathogenesis of attention deficit and hyperactivity disorder (ADHD), on inflammation, which is also claimed to play a role in the pathogenesis of ADHD.

Method: 39 ADHD and 39 healthy controls were compared with similar age, gender and BMI. The severity of the disease was evaluated with the Turgay ADHD scale. Inflammatory and nutritional parameters were measured routinely.

Results: In the patient group, Vitamin D was found to be significantly lower ($p<0.001$), while homocysteine was found to be significantly higher ($p=0.003$). CRP and MPV values among inflammatory parameters were found to be significantly higher ($p<0.001$ for both). No significant correlations were found between nutritional factors and inflammatory parameters ($p>0.05$ for all).

Conclusion: It can be suggested that low levels of vitamin D and high levels of homocysteine, which is related to one carbon metabolism, may play a role in the pathogenesis of ADHD. High levels of some inflammatory values may also indicate the role of inflammation in the pathogenesis of ADHD. No significant relationship was found between nutritional and inflammatory parameters. However, considering the limitations of the study, further research is needed on this subject.

Keywords: Vitamin D, Nutrition, Inflammation, Peripheral Inflammatory Markers, Attention Deficit and Hyperactivity Disorder, One-Carbon Metabolism.

Dikkat Eksikliği ve Hiperaktivite Bozukluğu Bulunan Çocuklarda Vitamin D ile Periferal İnflamatuar Parametreler Arasındaki İlişkinin Araştırılması

ÖZET

Amaç: Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) patogenezinde rol oynayan vitamin D ile vitamin B12, folat ve homosistein, ve ferritin gibi bazı nütrisyonel faktörlerin, yine DEHB patogenezinde rol oynadığı ileri sürülen inflamasyon üzerine olan etkileri araştırılmasını hedefledik.

Gereç ve Yöntem: 39 DEHB bulunan ve 39 sağlıklı kontrol grubu yaş, cinsiyet ve BMI benzer olacak şekilde karşılaştırıldı. Turgay DEHB ölçeği ile hastalığın şiddeti değerlendirildi. Rutin olarak inflamatuar ve nütrisyonel parametreler ölçüldü.

Bulgular: Hasta grubunda, Vitamin D anlamlı olarak düşük bulunurken ($p<0.001$), homosistein ise anlamlı olarak yüksek bulunmuştur ($p=0.003$). İnflamatuar parametreler içinde CRP ve MPV değerleri anlamlı olarak yüksek bulunmuştur (ikisi için $p<0.001$). Nütrisyonel faktörler ile inflamatuar parametreler arasında anlamlı korelasyonlar tespit edilmemiştir (hepsi için $p>0.05$).

Sonuç: Vitamin D'nin ve tek karbon metabolizması ile ilgili olan homosistein yüksekliğinin DEHB patogenezinde rol oynayabileceği düşünülebilir. Bazı inflamatuar değerlerin yüksek olarak bulunması da DEHB patogenezinde inflamasyonun rolüne işaret edebiliri. Nütrisyonel ve inflamatuar parametreler arasında anlamlı bir ilişki bulunmamıştır. Fakat çalışmanın kısıtlılıkları göz önüne alındığında bu konuda ileri araştırmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Vitamin D, Nütrisyon, İnflamasyon, Periferal İnflamatuar Belirteçler, Dikkat Eksikliği ve Hiperaktivite Bozukluğu, Tek-Karbon Metabolizması.

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konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood period. ADHD is a disorder characterized by clinical symptoms such as inattention, impulsivity, and hyperactivity that begin before the age of 12 (1). Its incidence is around 5.29% worldwide (2). Despite numerous studies, the pathogenesis of ADHD has not been fully elucidated. Although no specific cause has been identified, ADHD is a multifactorial disorder (3).

Regarding single carbon metabolism, vitamin B12, folate and homocysteine may contribute to many childhood and adolescence psychiatric disorders. It has been reported that these factors may have an effect on neuropsychiatric diseases such as depressive disorder, obsessive-compulsive disorder, ADHD, special learning disability and autism spectrum disorder (4-7). One-carbon metabolism (OCM), including these vitamins, plays a role in DNA synthesis as well as in the synthesis of neurotransmitters such as serotonin and dopamine. Besides, the synthesis of S-adenosyl methionine (SAM) which is the universal methyl donor, is formed by these metabolic reaction chains. SAM provides normal functioning of epigenetic mechanisms by taking part in DNA methylation together with methylation of many proteins. Therefore, gene expressions are negatively affected in situations of vitamin B12 and folate deficiency in which SAM production decreases (8). In addition, homocysteine, which increases as a result of vitamin B12 and folate deficiency, is an extremely neurotoxic substance. Besides, it damages the vascular endothelium. Increase in homocysteine is one of the most important parameters indicating vitamin B12 and folate deficiency (9). It has also been reported that the polymorphism of the enzyme methyltetrafolate reductase, which is one of the OCM enzymes, plays a role in the etiology of ADHD (10).

After it was understood that vitamin D has many effects other than bone metabolism, there has been an explosion in the studies that vitamin D may play a role in psychiatric diseases in recent years. There are many publications showing that it has an effect on pathogenesis of neuropsychiatric disorders in childhood and adolescence period(4-7). These effects of vitamin D have been particularly interesting as it has been shown that they are involved in the synthesis of neurotransmitters such as serotonin and dopamine (11,12). Vitamin D takes part in mechanisms necessary for the development of the brain and the continuation of its normal functions, such as neurogenesis, neuroplasticity, myelination, and neuroprotection (13). In addition to all these neurological effects, vitamin D has anti-inflammatory, autoimmunity suppression and protective effects against oxidative stress (14).

In addition to being a good indicator of iron stores, ferritin is known as an acute phase reactant that increases in the inflammatory response (Koorts 2011). It has been shown that low ferritin levels are associated with ADHD symptoms (Oner 2008). Ferritin has a protective effect against microbial proliferation, oxidative damage and inflammation by removing intracellular iron and storing it during inflammation (15).

Irregularities in the immune system and inflammation have been found to be effective in the pathogenesis of ADHD (16). Hemogram values, CRP and sedimentation evaluations, which are simple inflammatory parameters (SIP), are routine measurements that are easily performed and cost-effective. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio and platelet-to-lymphocyte ratios are obtained by dividing the hemogram values. Besides being easy and inexpensive, they are good markers of inflammation (17).

There are evidences that there may be a relationship between inflammation and nutritional parameters such as vitamin B12, folate, vitamin D, homocysteine and ferritin, which are effective in the evaluation of nutritional status (18). It has been shown in an animal study that vitamin B12 may have an anti-inflammatory effect (19). In addition, it has been found that hyperhomocystinemia, which occurs as a result of vitamin B12 and folate deficiency, is associated with inflammatory processes (20,21). Again, in a recent animal study, it was shown that hyperhomocysteinemia cause increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines in brain and retinal cells (22). In addition to these effects of vitamin B12 and folate on inflammation, it has been found that many immune cells carry Vitamin D receptors. Therefore, these findings indicate that vitamin D has effects on the immunological response (23). Vitamin D shows anti-inflammatory properties. Vitamin D reduces the expression of proinflammatory cytokines such as TNF-alpha, IL-1β, IL-6 and IL-8 (24).

In this study, considering the relationship of nutritional parameters such as vitamin B12, folate, homocysteine, vitamin D and ferritin with the inflammation, the hypothesis that there may be an interaction between these vitamins and inflammation in ADHD pathogenesis was investigated.

MATERIAL AND METHODS

Ordu University Medical Faculty Hospital Child and Adolescent Psychiatry Clinic conducted this study. The patients who applied to our clinic and diagnosed ADHD formed patient group. ADHD diagnosis were made according to DSM 5 criteria. A healthy control group was formed from the subjects who came to the healthy child follow-up outpatient clinic in the pediatrics department

without any medical or psychiatric diagnosis. Psychiatric diagnoses were generally investigated by applying K-SADS-PL to all subjects. Subjects were included in the study as a result of detailed psychiatric examination, family interviews and medical record reviews by the child psychiatrist. Subjects with ADHD were administered the Atilla Turgay ADHD scale to assess the severity of the disorder. In addition to these, sociodemographic data form was filled in all subjects. Nutritional and inflammatory parameters were measured routinely in the hospital laboratory. Blood samples were taken between 08:00 and 11:00 in the morning before breakfast. Under steril conditions, samples were taken from antecubital vein. Exclusion criteria were those with a history of systemic diseases, obesity, acute and chronic infections, nutritional support in the last one year, and those with epilepsy and neurological deficits. Ethics Committee of Ordu University Faculty of Medicine approved the study (Decision no: 2021/225).

Sociodemographic Form: With this form, information such as age, height, weight, BMI, medical history, family history, birth history, breastfeeding time, and drug use information were obtained.

Schedule for Affective Disorders and Schizophrenia for School-Age Children– Present and Lifetime Version DSM 5 (K-SADS-PL DSM 5): This scale is arranged according to DSM 5. Determines whether diagnoses found according to DSM 5 in children and adolescents are present now and throughout life. In this scale, psychiatric symptoms are determined. There is also a further list of symptoms. Here, a psychopathological evaluation is made. This assessment scale has Turkish validity and reliability (25).

Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale: Turgay developed this scale according to DSM-IV criteria. 9 items determines attention deficit. 6 items questions the symptoms of hyperactivity. While 3 items evaluate impulsivity, 8 items determine oppositional defiant disorder. Conduct disorder is evaluated in 15 items. In each item, the degree of symptom is determined as 0-1-2-3. This scale has validity and reliability in Turkish (27).

Blood Tests: Hemogram parameters were determined with the Abbott CELL-DYN 2700 device (Abbott Laboratories, Illinois, USA). CRP levels were measured with the immunoturbidimetry method (Archem Diagnostic Industry, Istanbul, Turkey). The Architect i1000 analyzer measured 25-OH-Vitamin D levels (Abbott Laboratories, Abbot Park, Illinois, USA). This measurement was made using the chemiluminescent microparticle immune study method. Homocysteine levels were measured in accordance with Abbott Laboratory commercial kits. The chemiluminescent immunoassay method was used. Again, vitamin b12 was measured with the same commercial company kits. Chemiluminescent micro particle Intrinsic Factor ARCHI-TECT B12 method was used. In addition, folate was determined with the same method and kits.

Statistics: SPSS 22.0 software program was used for data analysis. Whether the numerical variables were normally distributed or not was evaluated with the Shapiro-Wilk test. Normally distributed numerical variables are shown as mean±SD, while non-normally distributed variables are shown as median (IQR). Chi-square test was used to compare categorical variables. Student-t test was used to compare normally distributed variables. Mann Whitney-U test was used to compare variables that show non-normally distribution. We accepted P values below 0.05 as significant.

RESULTS

The groups are almost completely similar to each other in terms of gender and age. BMI comparisons between two groups showed no significant differences (Table 1). Vitamin B12 and folate were found to be insignificantly similar between the two groups. On the other hand, while vitamin D was found to be low in the patient group, homocysteine was found to be high in the patient group. These differences found to be significant. Ferritin values also did not differ between the two groups (Table 1).

Table 1. Characteristics of groups and values of nutritional factors

	Patients Group (n=39)	Healthy control group (n=39)	P value
Gender (Female/Male)	6/33	6/33	1[a]
Turgay ADHD scale (median) (IQR)	54 (18)	-	-
Age (median) (IQR)	8 (3)	7 (4)	0.916[b]
BMI (kg/m2) (median) (IQR)	17.08 (1.77)	16.82 (2.47)	0.168[b]
Vitamin B12 (pg/ml)(mean±SD)	402.74±141.67	438.07±190.72	0.356[c]
Folate (ng/ml) (mean±SD)	8.87±3.43	8.23±2.87	0.378[c]
Vitamin D(ng/ml) (median) (IQR)	20.8 (8.1)	28.5 (9.6)	<0.001[b]
Homocysteine (umol/L) (median) (IQR)	10.10 (4)	8.60 (1)	0.003[b]
Ferritin (ug/L)(mean±SD)	35.67±12.10	28.91±19.48	0.189[c]

Footnot: a.Chi-square test b.Mann Whitney-U test c.Student t test

Hemogram parameters such as neutrophil, lymphocyte, monocytes and platelet counts were similar between the two groups. MPV values were found to be significantly higher in the patient group. Although NLR values were found to be high in the patient group, this difference was found to be statistically insignificant. However, this value was found close to the significance limit (p=0.092). MLR and PLR values did not differ. Likewise, sedimentation values did not differ. CRP levels were determined higher in the patients group and this was statistically significant (p<0.001) (Table 2). Demographic data is 2 (age, BMI), nutritional values are 5 (vitamin B12, folate, vitamin D, homocysteine and ferritin), and inflammatory and hemogram parameters are 10 (neutrophil, lymphocyte, monocytes, platelet, MPV, NLR, MLR, PLR, CRP and sedimentation), their correlation analysis results have been obtained in large numbers. Since presenting all of them would take up a lot of space for an article, a general evaluation was made. As a result, when these reciprocal correlation analyzes were evaluated, no significant result was obtained between demographic and nutritional factors, inflammatory and hemogram parameters (p>0.05 for all). Only as expected, significant correlations were found between homocysteine and vitamin B12 (r=-0.386 and p=0.01) and between ferritin and sedimentation (r=0.458 and p=0.003). No correlation was found between T-DSM-IV-S, which shows ADHD severity, and both nutritional and inflammatory parameters (p>0.05 for all).

Table 2. Distribution of simple inflammatory parameters by groups

	Patients Group (n=39)	Healthy control group (n=39)	P value
Neutrophil	3010 (1480)	2800 (1370)	0.303[a]
Lymphocyte	2740 (940)	2730 (1350)	0.566[a]
Monocyte	470 (160)	490 (220)	0.853[a]
Platelet	320.28±72.50	316.97±72.15	0.841[b]
MPV	9.4 (1)	7.42 (1.25)	<0.001[a]
NLR	1.08 (0.4)	0.907 (0.372)	0.092[a]
MLR	0.181±0.551	0.173±0.057	0.529[b]
PLR	113.29 (42.49)	108.02 (52.49)	0.382[a]
CRP (mg/dL)	0.06 (0.14)	0.02 (0.04)	<0.001[a]
Sedimentation (1 hour)	8 (6)	8 (11)	0.093[a]

Footnote: MPV: mean platelet volüme; NLR:Neutrophil-Lymphocyte Ratio; MLR:Monocyte- Lymphocyte Ratio; PLR:Platelet-Lymphocyte Ratio; CRP:C-Reactive protein
a.Mann-Whitney U test b.Student t test

DISCUSSION

This study is the first study in the literature investigating the effects of nutritional factors such as vitamin D, vitamin B12, folate, ferritin and homocysteine on simple inflammatory parameters in ADHD patients. Since ADHD is the most common psychiatric disorder in childhood and has many negative consequences, understanding its etiopathogenesis may contribute to the discovery of new treatment options. According to the results obtained, vitamin D among nutritional factors was found to be significantly lower in the patient group. However, homocysteine levels, which are one of the parameters that best show vitamin B12 and folate deficiency, were found to be high in the patient group. When evaluated in terms of inflammatory parameters, NLR was found to be high in the patient group, which was close to statistical significance. In addition, CRP values were found to be high in the patient group. However, no significant effect of all these nutritional factors on SIPs was detected.

It has been reported that decreased vitamin B12 and folate and related increase in homocysteine are effective in many childhood psychiatric disorders (6,28). Indeed, these vitamins are essential for maintaining healthy brain functions. The OCM, of which they are a part, plays a fundamental role in DNA synthesis, neurotransmitter maintenance, and methylation reactions. Although these vitamins were not found to be low in this study, homocysteine was found to be increased. In fact, the increase in homocysteine is one of the best parameters for these vitamin deficiencies. In the results of this study, an inverse correlation was found between vitamin B12 and homocysteine. However, while these vitamins are normally measured in the blood, they can be found in lower levels in the brain tissue (29). Accordingly, brain tissue may have relatively lower vitamin levels. Increased homocysteine may contribute to the pathogenesis of ADHD. Normal vitamin B12 and folate levels were found to be compatible with some previous studies (30).

Vitamin D is necessary for healthy brain functions and is considered as a risk factor in the etiology of many psychiatric disorders. In the last meta-analysis study, it was shown that vitamin D levels were found to be low in children with ADHD (31). In our study, vitamin D levels were found to be low, in line with these results. Vitamin D has

also been reported to play a role in healthy immune system functioning. It has been shown recently that vitamin D deficiency may also play a role in ASD patients and that vitamin D is associated with inflammatory parameters (32). However, no relationship was found between vitamin D and SIP in this study.

There are studies showing that ferritin is associated with ADHD symptoms (33). Ferritin and thus iron metabolism are essential for monoaminergic neurotransmission (34). There are studies reporting that ferritin levels do not differ in adhd patients (30). These reports are consistent with our results.

There are many studies pointing to the association of inflammation and ADHD (35). SIP are parameters that show inflammation, are easily and inexpensively obtained and easily calculated. These parameters have been studied in ADHD patients so far, and some of them have been found to have high indicators such as NLR (36). No significant elevations of SIP were found in this study. However, NLR was found to be high in the ADHD group, close to significance. However, MPV, which is also an indicator of inflammation, and CRP, which is considered an acute phase reactant, were found to be high in the ADHD group. These results are consistent with studies indicating that inflammation plays a role in the pathogenesis of ADHD. However, no effect of nutritional values on these parameters was detected.

Some limitations in this study restrict making a more accurate interpretation. The number of subjects is too small. So, this constitutes serious limitation. The model of the study is cross-sectional. This study models are insufficient to explain the cause-effect relationship. In order to make a better assessment of the relationship between inflammation and nutritional factors, inflammatory mediators such as TNF alpha, IL-6, and IL-1 must be measured and evaluated. And this provides us to make a more accurate explanation.

CONCLUSION

It can be suggested that low vitamin D and high homocysteine levels may contribute to the pathogenesis of ADHD. However, high inflammation parameters such as CRP and MPV support the association of inflammation-ADHD. However, no relationship was found between nutritional values and inflammation. It seems clear that further research is needed on this subject.

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