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Serum Vitamin B12, Folate, and Ferritin levels in Children and Adolescents with Anxiety Disorders; Controlled Study

Anksiyete Bozukluğu olan Çocuk ve Ergenlerde Serum Vitamin B12, Folat ve Ferritin Düzeyleri; Kontrollü Çalışma

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Abstract

Introduction: Vitamin B12, folate, and iron deficiencies both in early life and later can affect brain development and maintenance via potential mechanisms causing impaired synaptogenesis, myelination and neurotransmission, and increased neurotoxicity and oxidative stress, resulting in neuropsychiatric disorders like cognitive impairment, depression and anxiety. This study aimed to compare serum vitamin B12, folate, and ferritin levels between children and adolescents with anxiety disorders and healthy controls.

Materials and Methods: The patient group consisted of 40 children aged 8-17 years who were newly diagnosed with anxiety disorders, had no physical or mental illness other than anxiety disorders, and whose serum vitamin B12, folate, and ferritin levels were measured in the last six months for any reason. As the control group, 40 subjects matched to the patient group for age and sex were selected from mentally and physically healthy children and adolescents. A semi-structured psychiatric interview was used for the diagnosis. Serum vitamin B12, folate, and ferritin levels were obtained from medical records.

Results: Serum ferritin and folate levels in the patient group were found to be statistically significantly lower than the controls (34.0 ng/ml versus 46.9 ng/ml, 8.5±2.2 ng/mL versus 10.4±2.8 ng/mL, respectively), unlike serum vitamin B12 levels.

Conclusion: Our initial findings may be scientifically important for further studies, which will show that low ferritin and folate levels are associated with childhood anxiety disorders. Whether there is a causal relationship between childhood-onset anxiety disorders and nutritional deficiencies should be investigated in longitudinal studies with larger samples.

Keywords: Folic acid; ferritin; anxiety; child; risk factors.

Özet

Amaç: Vitamin B12, folat ve demir eksiklikleri hem erken yaşamda hem de sonraki dönemde sinaptogenez, miyelinasyon ve nörotransmisyonun bozulmasına ve artmış nörotoksisite ve oksidatif strese neden olan potansiyel mekanizmalar aracılığıyla beyin gelişimi ve idamesini etkileyebilir, bilişsel bozulma, depresyon ve anksiyete gibi nöropsikiyatrik bozukluklara neden olabilir. Bu çalışmanın amacı, anksiyete bozukluğu olan çocuklar ve sağlıklı kontroller arasında serum B12 vitamini, folat ve ferritin düzeylerini karşılaştırmaktır.

Gereç ve Yöntem: Hasta grubu ilk kez anksiyete bozukluğu tanısı alan, anksiyete bozuklukları dışında bedensel veya ruhsal hastalığı olmayan 8-17 yaş arası 40 çocuktan oluşurken, kontrol grubunu hasta grubuyla yaş ve cinsiyet açısından eşleştirilen bedensel ve ruhsal olarak sağlıklı 40 olgu oluşturmaktadır. Psikiyatrik tanılar için yarı yapılandırılmış bir görüşme kullanılırken, hasta grubuna öz-bildirim ölçekleri uygulanmıştır. Serum vitamin B12, folat ve ferritin düzeyleri tıbbi kayıtlardan elde edilmiştir.

Bulgular: Hasta grubunun serum ferritin ve folat düzeyleri kontrollere göre istatistiksel olarak anlamlı derecede düşük bulunmuştur (sırasıyla 34,0 ng/ml'ye karşı 46,9 ng/ml, 8,5±2,2 ng/mL'ye karşı 10,4±2,8 ng/mL). Serum vitamin B12 düzeyleri açısından hastalar ve kontroller arasında anlamlı bir farklılık saptanmamıştır.

Sonuç: İlk bulgularımız, düşük ferritin ve folat düzeylerinin çocukluk çağı anksiyete bozuklukları ile ilişkili olduğunu gösterecek daha sonraki çalışmalar için bilimsel olarak önemli olabilir. Çocukluk çağı başlangıçlı anksiyete bozuklukları ile beslenme eksiklikleri arasında nedensel bir ilişki olup olmadığı daha geniş örneklemli uzunlamasına çalışmalarda araştırılmalıdır.

Anahtar Kelimeler: Folik asit; ferritin; anksiyete; çocuk; risk faktörleri.

Introduction

Fears and worries are very common in childhood. While developmentally normal anxiety is short-lived and non-impairing, anxiety disorders are characterized by fears and worries that cause significant distress or a decrease in the functionality of daily life. Anxiety disorders

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develop as a result of complex interactions between all individual, familial and environmental risk factors, and environmental factors in the pathophysiology of anxiety disorders may be targets for prevention and treatment interventions. Of these factors, nutritional deficiencies both in the early stages of life and afterward may cause some psychiatric disorders by affecting brain development. When nutrient requirements such as iron, zinc, copper, choline, iodine, and certain B vitamins are not adequately met in the critical period for rapidly developing brain regions, the damage may be permanent even if it is compensated in the next period (1). Also, nutritional deficiencies (e.g. long-chain PUFAs, folate, choline, and iron) may impair brain regulation through epigenetic mechanisms such as DNA methylation and histone modification (2, 3). Iron is one of the most important micronutrients for brain energy and metabolic processes such as myelination and neuronal development (4, 5). Iron deficiency may result in social, emotional, and behavioral problems and academic difficulties in childhood (6, 7). Moreover, iron administration may improve some symptoms, such as anxiety, low concentration, depression, fatigue, and insomnia in children with low serum ferritin levels (8). Folate and vitamin B12 deficiencies may also cause some neuropsychiatric problems, such as depression and cognitive impairment through impaired homocysteine metabolism (9, 10). Some researchers have reported the relationship between anxiety and low folate and vitamin B12 levels in adults (11, 12). Our study aimed to compare serum vitamin B12, folate, and ferritin levels between children and adolescents with anxiety disorders and healthy controls.

Materials and Methods

Participants: The patient group consisted of 40 children and adolescents (16 males, 24 females) aged 8-17 years who were newly diagnosed with anxiety disorders, had no physical or mental illness other than anxiety disorders, and whose serum vitamin B12, folate, and ferritin levels were measured in the last six months for any reason. As the control group, 40 subjects matched to the patient group for age and sex were selected from mentally and physically healthy children and adolescents, who applied to our outpatient clinic for consultancy, and whose serum vitamin B12, folate, and ferritin levels were measured in the last six months for any reason. Eighteen children and adolescents with any history of iron, vitamin B12, and folate deficits and uses, chronic, systemic, and inflammatory diseases, and neurological deficits were excluded from the study. While medical data were reviewed retrospectively, serum vitamin B12, folate, and ferritin levels were obtained from medical records.

Measures: All diagnoses were cross-sectionally determined using the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) according to the Diagnostic and Statistical Manual of Mental Disorders the fifth edition (DSM-5), and State-Trait Anxiety Scale for Children (STAI-C) and Children's Depression Inventory (CDI) were completed.

State-Trait Anxiety Scale for Children (STAI-C): STAI-C is a self-report scale consisting of two 20-item subscales that evaluate state and trait anxiety levels of children (13, 14). Cronbach's alpha coefficient for internal consistency of the Turkish version was found as 0.81 (14). Higher scores of STAI-C subscales show higher levels of state and trait anxiety.

Children's Depression Inventory (CDI): CDI is a 27-item self-report scale that measures depressive symptoms for the last 2 weeks in children aged 6-17 years. Higher scores of CDI indicate higher levels of depression (15, 16). The coefficient for test-retest reliability in the Turkish sample was found as 0.80 (16).

Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL): K-SADS-PL is a semi-structured psychiatric interview applied by a clinician, which is developed to screen for psychiatric disorders based on the DSM-5 diagnostic criteria in children and adolescents aged 6-18 years (17). The validity and reliability of the Turkish version were tested by Ünal et al. The coefficients of reliability for the Turkish version of the K-SADS-PL ranged from 0.62 to 1 (18). K-SADS-PL questions psychiatric disorders in line with the information received from the parents and the child and a psychiatric diagnosis is made by including the observations of the psychiatrist.

Procedure: The retrospective cross-sectional study was conducted in the department of child and adolescent psychiatry, University of Health Sciences Ankara Pediatric Hematology and Oncology Training and Research Hospital. Approval for the design and data collection procedures was obtained from the ethics review committee in the University of Health Sciences Ankara Pediatric Hematology and Oncology Training and Research Hospital (2019-164).

Table 1: Demographic and biochemical parameters of the sample

	Patient Group (n=40) Mean (SD)	Control Group (n=40) Mean (SD)	p value
Age (years)	12.1 (2.5)	12.2 (2.7)	0.933
Vitamin B12 (pg/mL)	249.3 (83.3)	272.8 (95.9)	0.245
Folate (ng/mL)	8.5 (2.2)	10.4 (2.8)	0.001
Hemoglobin (g/dl)	13.4 (0.9)	13.8 (1.1)	0.128
	Median (IQR)	**Median (IQR)**	
Ferritin (ng/ml)	34.0 (64.2)	46.9 (37.8)	0.013
Sex	**n (%)**	**n (%)**	
Female	24 (60.0)	24 (60.0)	1.000
Male	16 (40.0)	16 (40.0)	

SD: standard deviation, **IQR:** interquartile range

Table 2: Distribution of diagnosis and comorbidity in patients with anxiety disorders

Anxiety Disorders in the Patient Group (n=40)	n	%
Generalized anxiety disorder	27	67.5
Social anxiety disorder	8	20.0
Panic disorder	4	10.0
Separation anxiety disorder	1	2.5
Comorbidity in the Patient Group (n=40)	n	%
None	27	67.5
Yes	13	32.5
Social anxiety disorder	6	15.0
Specific phobia	4	10.0
Generalized anxiety disorder	3	7.5

Written consent from all subjects and their parents was obtained after detailed information about the purpose and procedure of the study. K-SADS-PL was applied by a child and adolescent psychiatrist. Children and adolescents with anxiety disorders completed CDI and STAI-C.

Statistical Analysis: For the considered variables (features) in the study, the normality tests were performed using the Kolmogorov-Smirnov test. Descriptive statistics for the normally distributed continuous variables (features) are presented as Mean ± Standard deviation, while they were given as the median and interquartile range (IQR) for non-normally distributed features. Descriptive statistics of categorical variables were given as count and percentage. Comparisons of groups were performed using One-way ANOVA for normally distributed (continuous) variables, while the Kruskal-Wallis test was for non-normally distributed variables. Chi-Square and Fisher's exact (when 2 × 2 table cells with an expected frequency below 5 are more than 20%) tests were used for determining the linear relationships between the categorical variables. Statistically, the significant level was considered as 5% and the SPSS (ver: 21) package program was used for all statistical computations.

Results

A total of 80 children and adolescents (including 40 cases with anxiety disorders and 40 healthy controls) participated in our study. Demographic variables and biochemical parameters of the sample are given in Table 1. No significant differences were found between the two groups in terms of age and sex. When the distribution of anxiety disorders in the patient group was examined (Table 2), generalized anxiety disorder (n = 27, 67.5%) was the most common anxiety disorder, and thirteen (32.5%) cases were determined to have at least one comorbid anxiety disorder. There were no significant differences between the Hb levels (the reference range: 12-15.5) of the patients and controls (13.4±0.9 g/dl and 13.8±1.1 g/dl, respectively; p = 0.128). Compared to the control group, the median level of serum ferritin (the reference range: 11-306.8) was significantly lower in the patient group (34.0 ng/ml versus 46.9 ng/ml; p = 0.013). There were no significant differences between vitamin B12

Table 3: Comparison of biochemical parameters and scale scores between the three diagnostic subgroups in the patient group

Laboratory	GAD (n=27) Mean (SD)	SAD (n=8) Mean (SD)	Other ADs (n=5) Mean (SD)	p value
Vit-B12 (pg/mL)	237.8 (81.9)	263.8 (93.9)	288.2 (73.8)	0.408
Folate (ng/mL)	8.5 (2.4)	8.6 (2.3)	8.4 (1.4)	0.990
Hb (g/dl)	13.2 (0.7)	13.4 (0.7)	14.1 (1.9)	0.206
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
Ferritin (ng/ml)	21.8 (67.9)	14.9 (16.2)	22.3 (42.1)	0.321
Scales	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
STAI-C-state	43.3 (8.0)	36.8 (6.6)	45.2 (3.7)	0.077
STAI-C-trait	36.6 (10.3)	32.7 (6.8)	35.2 (4.0)	0.584
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
CDI	14 (21)	13 (12)	12 (8)	0.780

SD: standard deviation, **IQR:** interquartile range, **GAD:** generalized anxiety disorder, **SAD:** social anxiety disorder, **ADs:** anxiety disorders, **CDI:** children's depression inventory, **STAI-C:** state-trait anxiety scale for children

levels (the reference range: 145-914) of the patients and controls (249.3±83.3 pg/mL and 272.8±95.9 pg/mL, respectively; p = 0.245). Compared to the control group, the mean level of serum folate (the reference range: 3.1-19.9) was significantly lower in the patient group (8.5±2.2 ng/mL versus 10.4±2.8 ng/mL; p = 0.001). Reference values of biochemical parameters were arranged according to sex and age ranges. Comparisons of biochemical parameters and scale scores between the three diagnostic subgroups in the patient group are given in Table 3.

Discussion

Our study compared serum vitamin B12, folate, and ferritin levels measured in the last six months between children and adolescents with anxiety disorders and sex- and age-matched healthy peers. We determined preliminary findings that serum ferritin and folate levels in the patient group were significantly lower than those in the control group. Also, we found that the diagnosis and comorbidity distributions for anxiety disorders were similar to the literature (19). A longitudinal follow-up study revealed that children who had a severe iron deficiency in infancy scored lower on measures of mental and motor functioning, and their parents and teachers rated their behaviors as more problematic in several areas, such as anxiety/depression, social problems, and attention problems (6). Moreover, a nationwide population-based study showed that current iron deficiency increased the risk of psychiatric disorders, including mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorders, and developmental disorders in children and adolescents (20). However, Öztürk et al. reported that there were no significant relationships between anxiety and serum B12, folate, TSH, zinc, and ferritin levels in adult patients (21). Similarly, Mednick et al. found no significant relationships between anxiety and depression scale scores and ferritin levels in thalassemia patients between the ages of 14-58 (22). Considering these contradictory findings in the literature, instead of iron deficiency, we found preliminary evidence that serum ferritin levels in children and adolescents with anxiety disorders were significantly lower than those in healthy peers. The serum ferritin level indicates the iron stores commonly used by body tissues such as neuron cells. Iron serves as a coenzyme for tyrosine hydroxylase (rate-limiting step in the synthesis of catecholamine) in the synthesis of dopamine and norepinephrine, and for tryptophan hydroxylase (rate-limiting step) in serotonin synthesis. As well as neurotransmission, iron also plays a role in dendritogenesis, synaptogenesis, parenchymal oxygenation, and myelination. Therefore, a marked decrease in iron stores can affect mental health in childhood, even in the absence of significant iron deficiency (23). This needs to be confirmed in prospective studies. We demonstrated the initial data that serum folate levels were significantly lower in the children and adolescents with anxiety disorders than in their healthy peers, unlike serum vitamin B12 levels. Contrary to our findings, a previous study found significant decreases in vitamin B12 levels in children and adolescents with an obsessive-compulsive disorder, while no differences in folate levels were observed (24). Low levels of folate and vitamin B12 may be associated with neuropsychiatric symptoms, because of impaired

monoamine neurotransmitter metabolism (25). S-adenosyl-methionine (SAM), which is required for the transmethylation reactions of protein, phospholipid, DNA, and homocysteine to methionine and monoamine neurotransmitter metabolism, is synthesized from folate by a reaction catalyzed by vitamin B12-dependent methionine synthetase (25). A community-based study showed high homocysteine levels and a polymorphism (such as 677CT) of methylenetetrahydrofolate reductase (MTHFR) that is the rate-limiting enzyme in the folate metabolism, were related to depression, but not to anxiety, in adult patients (12). Similarly, another community-based study reported that low levels of folate, but not vitamin B12, were correlated with depressive symptoms in adulthood, and increased levels of homocysteine might cause DNA damage, mitochondrial dysfunction, oxidative stress in endoplasmic reticulum, and decreased methylation reactions, resulting in impaired neurotransmitter metabolism and synaptic integration and plasticity (25). Considering these contradictory findings in the literature, the effects of not only deficiencies but also low levels of folate and vitamin B12 should be evaluated with behavioral tests measuring anxiety in animal experiments. The results of our study should be considered in the light of several limitations. First, the design of our study was retrospective cross-sectional. Serum vitamin B12, folate, and ferritin levels measured for any reason in the last six months before admission to the child and adolescent psychiatry outpatient clinic were retrospectively examined and analyzed. However, psychiatric symptoms were evaluated cross-sectionally. Although the results of biochemical tests in the last six months seem appropriate for the onset of psychopathology at first glance, they can only provide preliminary evidence for further studies. Second, we found that some biochemical parameters were significantly lower, instead of the nutritional deficiencies. Third, the sample size was very small. Fourth, homocysteine levels could not be evaluated due to not being routinely measured in our hospital. Fifth, sampling from a single-center limited the generalizability of our findings. Finally, the parameters related to dietary and nutritional habits could not be evaluated in our study.

We showed preliminary data that children and adolescents with anxiety disorders had significantly lower serum ferritin and folate levels compared to their healthy peers. Our initial findings may be scientifically important for further studies, which will show that low ferritin and folate levels are associated with childhood anxiety disorders. However, it would not be correct to say that iron and folate deficiencies are the cause or consequence of anxiety disorders for now. Nutrient deficiencies can be experienced through different mechanisms that develop secondary to anxiety disorders such as anorexia or inflammation. On the contrary, iron and folate deficiencies may also be preventable environmental factors in the pathophysiology of anxiety disorders. In both cases, assessment of serum ferritin and folate levels may be a part of psychiatric evaluation for some patients in the future. Whether there is a causal relationship between childhood/adolescence-onset anxiety disorders and iron and folate deficiencies should be investigated in longitudinal studies with larger samples.

Ethical Approval: Approval for the design and data collection procedures was obtained from the ethics review committee in the University of Health Sciences Ankara Pediatric Hematology and Oncology Training and Research Hospital (2019-164).

Conflict of Interest: The authors declare no conflict of interest to disclose for this study.

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Author Contributions: SDU, OSU: conceived and designed the study; SDU, ZG: developed the study protocol, collected the data, FKK, ZG: analyzed and interpreted the data; OSU: supervised the study.

Animal and Human Rights Statement: All procedures performed in this study were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Georgieff MK. Iron assessment to protect the developing brain. Am J Clin Nutr 2017; 106(suppl_6): 1588S-1593S.
2. Barua S, Kuizon S, Chadman KK, Flory MJ, Brown WT, Junaid MA. The single-base resolution of mouse offspring brain methylome reveals epigenome modifications caused by gestational folic acid. Epigenetics Chromatin 2014; 7(1): 3.
3. Tran PV, Kennedy BC, Lien Y-C, Simmons RA, Georgieff MK. Fetal iron deficiency

induces chromatin remodeling at the Bdnf locus in adult rat hippocampus. Am J Physiol Regul Integr Comp Physiol 2015; 308(4): R276-R282.
4. Chiou B, Neely EB, Mcdevitt DS, Simpson IA, Connor JR. Transferrin and H-ferritin involvement in brain iron acquisition during postnatal development: impact of sex and genotype. J Neurochem 2020; 152(3): 381-396.
5. Beard JL, Connor JR. Iron status and neural functioning. Annu Rev Nutr 2003; 23(1): 41-58.
6. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000; 105(4): E51.
7. Lozoff B, Clark KM, Jing Y, Armony-Sivan R, Angelilli ML, Jacobson SW. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. J Pediatr 2008; 152(5): 696-702.
8. Mikami K, Okazawa H, Kimoto K, Akama F, Onishi Y, Takahashi Y, et al. Effect of oral iron administration on mental state in children with low serum ferritin concentration. Glob Pediatr Health 2019; 6: 1-5.
9. Black MM. Effects of vitamin B12 and folate deficiency on brain development in children. Food Nutr Bull 2008; 29(2_suppl1): 126-131.
10. Lim SY, Kim EJ, Kim A, Lee HJ, Choi HJ, Yang SJ. Nutritional factors affecting mental health. Clin Nutr Res 2016; 5(3): 143-152.
11. Baldewicz TT, Goodkin K, Blaney NT, Shor-Posner G, Kumar M, Wilkie FL, et al. Cobalamin level is related to self-reported and clinically rated mood and to syndromal depression in bereaved HIV-1+ and HIV-1− homosexual men. J Psychosom Res 2000; 48(2): 177-185.
12. Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, vitamin B12, homocysteine, and the MTHFR 677C--->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. Arch Gen Psychiatry 2003; 60(6): 618-626.
13. Spielberger DC, Edwards CD, Luschene R, Mountouri J, Platzek D. Preliminary test manual for the State-Trait Anxiety Inventory for Children. California: Consulting Psychologists Press; 1973.
14. Özusta Ş. Çocuklar için Durumluk-Sürekli Kaygı Envanteri'nin uyarlama, geçerlik ve güvenirlik çalışması. Ankara: Hacettepe Üniversitesi Sosyal Bilimler Enstitüsü; 1993.
15. Kovacs M. Rating scales to assess depression in school-aged children. Acta Paedopsychiatrica: International Journal of Child & Adolescent Psychiatry 1981; 46(5-6): 305-315.
16. Öy B. Çocuklar için depresyon ölçeği: Geçerlik ve güvenirlik çalışması. Turk Psikiyatri Derg 1991; 2(2): 132-136.
17. Kaufman J, Birmaher B, Brent D, Rao UMA, Flynn C, Moreci P, et al. 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(7): 980-988.
18. Unal F, Oktem F, Cetin Cuhadaroglu F, Cengel Kultur SE, Akdemir D, Foto Ozdemir D, et al. Reliability and Validity of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, DSM-5 November 2016-Turkish Adaptation (K-SADS-PL-DSM-5-T). Turk Psikiyatri Derg 2019; 30(1): 42-50.
19. Bilaç Ö, Ercan ES, Uysal T, Aydın C. İlköğretim öğrencilerinde anksiyete ve duygudurum bozuklukları yaygınlığı ve sosyodemografik özellikler. Turk Psikiyatri Derg 2014; 25(3): 171-180.
20. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study. BMC Psychiatry 2013; 13(1): 161.
21. Ozturk P, Orhan FO, Ozer A, Akman Y, Kurutas E. Evaluation of anxiety and levels of serum B12, folate, TSH, ferritin, and zinc in telogen alopecia patients with trichodynia. Int J Trichology 2012; 4(4): 251.
22. Mednick L, Yu S, Trachtenberg F, Xu Y, Kleinert DA, Giardina PJ, et al. Symptoms of depression and anxiety in patients with thalassemia: prevalence and correlates in the thalassemia longitudinal cohort. Am J Hematol 2010; 85(10): 802-805.
23. Hergüner S, Keleşoğlu FM, Tanıdır C, Çöpür M. Ferritin and iron levels in

children with autistic disorder. Eur J Pediatr 2012; 171(1): 143-146.
24. Esnafoğlu E, Yaman E. Vitamin B12, folic acid, homocysteine and vitamin D levels in children and adolescents with obsessive compulsive disorder. Psychiatry Res 2017; 254: 232-237.
25. Bottiglieri T. Homocysteine and folate metabolism in depression. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29(7): 1103-1112.