

Ferritin and Transferrin Saturation Index Levels in Children with Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Bulunan Çocuklarda Ferritin ve Transferrin Saturasyon İndeksi Düzeyleri

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ABSTRACT

Introduction: Attention deficit hyperactivity disorder (ADHD) is one of the common childhood psychiatric disorders and is believed to be caused by genetic and environmental factors. Various studies have reported that body iron levels and ADHD are correlated. In our study, we aimed to investigate the correlation of serum ferritin and transferrin saturation index (TSI) with ADHD subtypes and Conners' Teacher Rating Scale (CTRS) scores.

Material and Methods: This retrospective study included 131 boys and 16 girls between 7 and 16 years of age who were diagnosed with ADHD in accordance with DSM-IV TR diagnostic criteria. The data on serum iron, total iron-binding capacity, ferritin, and CTRS scores were obtained from the patients' hospital files. Statistical analyses were then done on these data.

Results: The mean serum ferritin level was 27.1 ± 15.6 ng/mL, and the mean TSI level was $18.1 \pm 9.1\%$. The mean serum ferritin level of those diagnosed with combined type ADHD (25.78 ± 12.90 ng/mL), in accordance with DSM-IV TR criteria, was lower than those diagnosed with predominantly inattentive type (32.75 ± 23.54 ng/mL) ($p = 0.034$). However, there was no difference in serum TSI values ($p = 0.835$).

Conclusions: In the present study, serum ferritin levels were lower in patients with ADHD than in patients with attention-deficit predominant type, and the relationship between iron parameters and ADHD was demonstrated. The necessity of evaluating iron parameters in ADHD cases has been understood once again.

Key Words: Transferrin saturation index, attention deficit hyperactivity disorder, ferritin

ÖZET

Amaç: Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) genetik ve çevresel faktörlerin neden olduğu düşünülen, çocukluk çağının sık görülen psikiyatrik bozukluklarından biridir. Vücut demiri ile DEHB'nin ilişkili olabileceği çeşitli çalışmalarda bildirilmiştir. Çalışmamızda DEHB tanısı alan çocuklarda, serum ferritin ve transferrin saturasyon indeksi (TSI) ile DEHB alt tipleri ve Conners Öğretmen Derecelendirme Ölçeği (CÖDÖ) arasındaki ilişkinin incelenmesi amaçlanmıştır.

Materyal ve Metod: Bu retrospektif çalışmaya DSM IV TR tanı kriterlerine göre DEHB tanısı alan, yaşları 7-16 arasında değişen 131 erkek ve 16 kız hasta alındı. Hastaların dosya bilgilerinden serum demir, total demir bağlama kapasitesi, ferritin ve CÖDÖ değerlerine ulaşıldı, istatistiksel değerlendirmeler yapıldı.

Bulgular: Olgularımızın ortalama serum ferritin düzeyi 27.1 ± 15.6 ng/mL ve TSI düzeyi ise 18.1 ± 9.1 olarak saptandı. DSM IV TR kriterlerine göre bileşik tip DEHB tanısı alanlarda ortalama serum ferritin düzeyi, ($25,78 \pm 12,90$ ng/mL) dikkat eksikliği baskın tipe ($32,75 \pm 23,54$ ng/mL) göre daha düşük olarak saptanırken ($p=0,034$); serum TSI değerleri arasında herhangi bir farklılık yoktu ($p=0,835$).

Sonuç: Bileşik tip DEHB olgularında serum ferritin düzeyinin, dikkat eksikliği baskın tip tanısı almış olanlara göre daha düşük olduğunun saptandığı çalışmamızda demir parametreleri ile DEHB ilişkisi ortaya konmuştur. DEHB'li olgularda demir parametrelerinin değerlendirilmesinin gerekliliği bir kez daha anlaşılmıştır.

Anahtar Kelimeler: Transferrin Saturasyon İndeksi, dikkat eksikliği hiperaktivite bozukluğu, ferritin

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the common childhood neuropsychiatric disorders and has an average worldwide prevalence of 5.2%, and its male-to-female ratio is 2.2:1 (1, 2). ADHD has three subtypes, including inattentive, hyperactive, and impulsive (3). ADHD may cause poor school performance, relationship disturbances, and social and economic problems (4,5). Various studies have shown that iron, zinc, and magnesium levels are low in children with ADHD (6, 7).

Dopaminergic systems play critical roles in the regions associated with ADHD etiology, including the areas of motor control, motivation, and reward (8). Noradrenalin and dopamine play important roles in the prefrontal cortex with regard to attention and memory (9). Iron is a cofactor of the tyrosine hydroxylase enzyme, and it plays an important role in the dopamine and norepinephrine synthesis pathway. It is also associated with the monoamine oxidase enzyme that plays a role in the electron transfer system and neurotransmitter destruction (10). It has been argued that iron deficiency is an important mechanism in the ADHD pathophysiology through dopamine synthesis (11). Since it has been understood that an iron deficiency influences dopamine transport and receptor density in the brain, and it also provokes dysfunction in the basal ganglia, certain hypotheses suggest that ADHD and iron deficiency may be correlated (12, 13). Serum ferritin levels were measured in the studies that investigated the correlation of ADHD with iron levels (14). However, it was reported that measuring only the serum ferritin levels could yield misleading results when investigating the correlation of ADHD with iron deficiencies (15). In this study, we aimed to investigate the correlation of serum ferritin levels and the transferrin saturation index (TSI) with ADHD subtypes and Conners' Teacher Rating Scale (CTRS) scores in children diagnosed with ADHD.

Material and Methods

This retrospective study included 147 patients between 7 and 16 years of age who were diagnosed with ADHD according to DSM IV-TR criteria and had been accepted to the Pediatric Psychiatry Department of Gazi University, Faculty of Medicine between 2010 and 2012.³ Exclusion criteria were mental retardation, neurological and/or metabolic diseases, iron treatment, or any active systemic diseases. There were 131 (89.1%) males and 16 (10.9%) females. The patients' files were retrospectively examined to obtain data, and those that were supposed to have an iron deficiency and

had related biochemical tests were included in the study. The data on serum total iron-binding capacity, iron, ferritin, and CTRS scores were obtained from the patients' hospital files (16-18). TSI was calculated by dividing the serum iron level by the total iron-binding capacity. Serum ferritin levels < 20 ng/mL and TSI < 16% were regarded as low.

Statistical Analysis: Data analysis was made with the SPSS 15.0 package program. The means of the two groups were compared with independent samples t-tests. The means of more than two groups were compared with one-way analysis of variance (ANOVA). The correlations of both ferritin levels and TSI values with CTRS subscale scores were analyzed with Pearson's correlation analysis. P values < 0.05 were considered statistically significant.

Results

The mean age of the 147 patients included in the study was 9.2 ± 2.0 years. Analysis of the patients in accordance with ADHD subtypes revealed that 119 (80%) patients had combined type, while 28 (20%) patients had a predominantly inattentive type. The mean CTRS hyperactivity score of the patients was 1.8 ± 3.2 , the mean inattention score was 15.5 ± 4.6 , and the mean behavioral problem score was 9.2 ± 3.5 . The mean serum ferritin level was 27.1 ± 15.6 ng/mL, and the TSI was $18.1 \pm 9.1\%$. The sexes were similar for ferritin and TSI levels. Analysis of ADHD subtypes with ferritin and TSI levels revealed that the mean ferritin level was lower in the combined type when compared to the predominantly inattentive type ($p = 0.034$). TSI levels were similar in all ADHD subtypes (Table 1). Pearson's correlation analysis analyzed the correlation of ferritin and TSI levels with CTRS subscale scores but did not reveal any significant correlations (Table 2). Comparisons of subscale CTRS scores in those with or without an iron deficiency did not reveal any significant differences among the groups (Table 3).

Discussion

In this study, serum ferritin and TSI levels were investigated together firstly and found a significant difference for serum ferritin levels between the mixed type and the predominantly inattentive type ADHD groups. Many different studies have researched the relationship between ADHD and iron, which is associated with dopamine and noradrenaline synthesis, the monoamine oxidase enzyme, and the electron transfer system (10). In the neurobiology of ADHD,

Table 1. Distribution of the iron parameters in relation with ADHD subtypes and gender

ADHD subtype	Ferritin ($\mu\text{g/l}$), M \pm SD*	p	TSI, M \pm SD*	p
ADHD-mixed	25.78 \pm 12.90	0.034+	18.22 \pm 9.60	0.835+
ADHD-ad	32.75 \pm 23.54		17.82 \pm 7.38	
Male	27.20 \pm 15.88	0.842	17.95 \pm 9.22	0.463
Female	26.37 \pm 13.94		19.75 \pm 9.10	

*Mean and standard deviation; +The means of the groups are compared "Independent samples T Test"

Table 2. Correlation of iron parameters with CTRS subscale scores

		CTRS -hyp	CTRS -ad	CTRS -cd
Ferritin	Correlation coefficient	-0.94	0.086	0.063
	p*	0.259	0.298	0.445
TSI	Correlation coefficient	0.034	-0.077	-0.050
	p*	0.684	0.353	0.547

*Pearson correlation test

Table 3. Comparison of CTRS subscale scores between the patients with or without iron deficiency

	CTRS -hyp	p	CTRS -ad	p	CTRS -cd	p
FER low (L)	11.98 \pm 4.09	0.808+	15.03 \pm 4.82	0.345+	8.81 \pm 3.55	0.350+
FER normal (N)	11.82 \pm 3.62		15.79 \pm 4.60		9.41 \pm 3.49	
TSI L	12.20 \pm 3.44	0.375+	15.95 \pm 4.50	0.316+	9.46 \pm 3.19	0.446+
TSI N	11.64 \pm 4.04		15.16 \pm 4.82		9.01 \pm 3.74	
FER L TSI L	12.60 \pm 3.79	0.728*	15.64 \pm 4.62	0.567*	8.92 \pm 3.53	0.634*
FER N TSI L	11.94 \pm 3.22		16.15 \pm 4.47		9.81 \pm 2.93	
FER L TSI N	11.48 \pm 4.31		14.54 \pm 4.99		8.80 \pm 3.62	
FER N TSI N	11.73 \pm 3.91		15.52 \pm 4.72		9.13 \pm 3.84	

*The groups were compared with "Independent samples T Test". * The groups were compared with "one-way Anova"

there is a direct relationship between dopamine function and iron, which is known to play an important role in neurocognitive functions. For example, iron is the main cofactor of the tyrosine hydroxylase enzyme, a rate-limiting step in dopamine synthesis (9). However, it has been shown in animal experiments that iron deficiency affects dopamine receptor density in the brain (10). Iron binds to the ferritin protein in the brain. In cases of advanced iron deficiency, the serum level of ferritin decreases, and ferritin levels return to normal with iron replacement. In addition, it was reported that there was a significant relationship between low serum ferritin levels and structural-developmental retardation and behavioral problems in the central nervous system. When all findings were evaluated together, it was suggested that a large number of physiological pathways using iron could be associated with ADHD symptoms.

Calarge et al. reported a negative correlation of SNAP (Swanson Nolan and Pelham) scale's attention as well as hyperactivity total ADHD scores with ferritin levels. An analysis of the correlation between CPRS

scores and ferritin revealed a statistically significant difference only in the hyperactivity/restlessness scale. The same study found a negative correlation between the severity of inattention symptoms and ferritin levels. In addition, a negative correlation was found between the baseline and week eight ferritin levels and amphetamine weight-adjusted levels at week 13 (19). Another study reported higher CPRS scores in children whose ferritin levels were under $< 45 \mu\text{g/L}$, and those children had higher scores in the "sleep-wake transition disorders" subscale of the Sleep Disturbance Scale for Children (20). In the present study, we researched the correlation between ferritin and TSI levels with ADHD subtypes and CTRS subscale scores in children diagnosed with ADHD. The mean ferritin level was lower in the combined type compared to the predominantly inattentive type. There was no correlation between ferritin and TSI levels and CTRS subscale scores. In addition, the patients were separated into groups with respect to their ferritin and TSI levels; however, they did not show significant differences for their CTRS subscale scores. In a meta-analysis study by Falkingham and

colleagues, it was evident that iron replacement in children with iron deficiency and iron deficiency anemia led to a significant increase in attention skills and total intelligence scores (21). In addition, a study was done with Halterman et al. 5398 children; It was reported that iron deficiency negatively affects the cognitive functions of children independent of anemia, and children with iron deficiency take two times lower grades than mathematics lessons compared to children without iron deficiency (22). In the long-term follow-up studies, it has been shown that the cognitive development of children with iron deficiency is adversely affected (23). In a study by Konofal and colleagues with 54 children aged 4 to 14 years, low levels of serum iron and ferritin levels were found in children with ADHD compared to the control group, and this difference was found to be related to ADHD symptom severity (24). A significant correlation was reported between low ferritin levels and CPRS hyperactivity scores by Öner et al. In the same study, no correlations were found between neuropsychological test scores and ferritin, mean corpuscular volume, hemoglobin or red cell distribution width (25). A similar study found that CPRS hyperactivity scores were correlated with low ferritin levels; however, the authors did not report any association of ferritin with attention disorders, either on CPRS or CTRS (26). In another study, low ferritin levels were correlated with high CTRS scores. However, this correlation was not found with CPRS (27). In a recent study, serum levels of iron, ferritin were significantly lower in children with ADHD, who also had significantly lower hemoglobin and hematocrit. Also, the ADHD subtype did not significantly influence these abnormalities (28). In our study, we did not find any correlation of CTRS subscale scores with either ferritin or TSI levels.

When studies that investigated ADHD and iron parameters are analyzed, it may be seen that ferritin levels were used as a variable to investigate the correlation of ADHD symptoms with iron. Cortese et al. investigated the association of brain and serum ferritin levels; however, they could not find any significant correlation between the two regarding a number of brain areas (29). A comparison of cerebrospinal fluid ferritin and TSI between patients with restless leg syndrome and healthy controls revealed lower levels of both ferritin and TSI in the patients with restless leg syndrome. However, serum ferritin and TSI levels were similar in both patients with restless leg syndrome and healthy controls (30). In our study, we investigated serum ferritin and TSI levels and found a significant difference for serum ferritin between the mixed type and the predominantly inattentive type ADHD groups. There was no difference in CTRS subscale scores. When all

of the findings are considered, we concluded that serum ferritin and TSI levels might not clearly reflect brain iron levels.

The main limitations of our study are its retrospective nature and the inclusion of patients with a suspected iron deficiency. Another limitation of the study is diagnosing the disease without a structured or semi-structured interview scale. We also did not classify the patients in relation to possible factors that could affect serum iron parameters.

In this study, we found that serum ferritin levels differed among ADHD subtypes; however, a similar association was not found for TSI. Studies that investigated the relationship between ADHD and iron parameters have established promising results that clarify the etiopathogenesis of ADHD (31-34). However, further studies with larger sample sizes are needed, using methods that can more clearly determine brain iron levels and classify patients according to factors that may affect iron parameters.

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