Iron and Ferritin Levels of Children and Adolescents with ADHD and ADHD-NOS

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ABSTRACT

Aim: The aim of this study was to compare the levels of iron, ferritin levels in children with ADHD and ADHD-NOS and to assess the relationship between ADHD symptom severity, anxiety symptom severity and iron, ferritin levels.

Materials and Methods: The study was planned as a cross-sectional, retrospective study. The records of patients who applied to the study center in between January 2012 and January 2013 were screened and 205 ADHD and ADHD-NOS cases’ records were evaluated. Patients were diagnosed clinically according to DSM-IV-TR criteria. ADHD symptom severity was assessed by Turgay DSM-IV–Based Child and Adolescent Behavior Disorders Screening and Rating Scale. Anxiety symptom severity was assessed by The Screen for Anxiety Related Emotional Disorders (SCARED).

Results: Among the whole sample, 99 (48.3%) patients had ADHD and 106 (51.7%) had ADHD-NOS. The average age of the children in the ADHD group was 10.88 ± 3.02 years, while that of the children in the ADHD-NOS group was 9.93±2.49 years. Iron and ferritin were detected in 81 of 205 patients participating in the study. No statistically significant difference was determined between two groups in terms of iron, ferritin levels (p> 0.05). Statistically significant negative correlations between ADHD hyperactivity symptom severity and iron levels, and ADHD attention deficit symptom severity and ferritin levels were found. Ferritin levels correlated statistically with the total number of psychiatric diagnoses in children.

Conclusion: Iron and ferritin levels may be differentially affected in children with ADHD. Our results should be supported with future studies.

Keywords: ADHD, iron, ferritin

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is an early-onset childhood neuropsychiatric disorder that has heterogeneous clinical characteristics such as inattention, hyperactivity, and impulsivity, and is also frequently associated with cognitive deficit (1). Prevalence of ADHD is reported to vary between 8.0-12.0 % worldwide (2). In a study on school-age children in Turkey, the prevalence of ADHD was determined to be 8.1% (3). Attention-Deficit Hyperactivity Disorder Not Otherwise Specified (ADHD-NOS) was reserved for disorders with prominent symptoms of inattention/ hyperactivity-impulsivity that do not meet criteria for ADHD in DSM-IV-TR (4). Faraone et al. showed that individuals with ADHD and ADHD-NOS had similar patterns of psychiatric comorbidity, functional impairment, and familial transmission (5). ADHD-NOS which is replaced
with ADHD. Unspecified in DSM-5 appears to be used as a diagnosis for situations in which children may be experiencing moderate attention problems in school that might be better characterized as learning or executive-functioning difficulties (4). In addition, rather than being categorized as ADHD Other Specified and Unspecified types, many young people are defined as having borderline or subclinical levels of ADHD instead. Pharmacotherapy including stimulants and atomoxetine is the first choice in the treatment of both disorders (2).

The etiology of ADHD is complex and not clearly understood yet. Although there is no definite identifiable factor, there are several hypotheses that ADHD is multifactorial (6). Heritability rate of ADHD was reported to differ between 76.0 % and 80.0 %, making it one of the most highly heritable neuropsychiatric disorders (7,8). Although the exact reason still remain unknown, several prenatal and perinatal factors including exposure to toxins and heavy metals, socio-psychological stress, diet, gene variants and structural/functional abnormalities of the brain, neurotransmitter deficiency and dysregulation in the frontostriatal as well as fronto-cerebellar catecholaminergic circuits were reported to contribute to the etiology (2,7).

ADHD is also quite frequent with comorbid conditions such as epilepsy, electroencephalographic abnormalities, iron deficiency, depressive disorders, and learning disabilities (9).

Iron is required for various vital functions, including oxygen transport, cellular respiration, immune function, nitric oxide metabolism and DNA synthesis (10). It also plays a crucial role in proper brain morphology, neurochemistry, and bioenergetics (11). Poor brain myelination arising from iron deficiency in early development has long-lasting effects on behavioral functions (12,13). Brain iron concentrations are highest in the substantia nigra, globus pallidus, nucleus caudate, red nucleus and putamen (14). The rapid accumulation of iron in these areas is required for the development of the brain and may significantly contribute to behavioral organization (14). Iron is a co-factor of tyrosine hydroxylase which is a critical enzyme in dopamine synthesis. Dopamine has been implicated in the pathophysiology of ADHD (15). Several studies of the neurobiology of ADHD have suggested that nutritional factors may affect brain function and are implicated in the pathogenesis of the (16-18). Of these nutritional factors, iron deficiency is substantial as iron plays an important role in the regulation of dopaminergic activity, which is related to pathogenesis and symptoms of ADHD (19).

In 1997, Sever et al. found importantly increased serum ferritin levels and decreased ADHD symptom scores in children with ADHD after iron supplementation, suggesting that non-anemic children with ADHD may benefit from iron supplementation (20). Cortese et al. published a systematic review of studies examining the relationship between iron and ADHD. However, they did not perform statistical analyses on indices of iron status (21).

There is strong evidence that iron deficiency gives rise to developmental delays in young children (22). Iron deficiency is also related to cognitive alterations in adolescents (23). It was shown in a study on rats that although the condition of iron deficiency can be later corrected by supplementation, behavioral alterations persist (24). Iron-deficient children have increased anxiety and/ or depression with social and attentional problems (25).

In this study, we aimed to compare the levels of iron, ferritin and hemoglobin in children with ADHD and ADHD-NOS. We also aimed to assess the relationship between ADHD symptom severity, anxiety symptom severity and iron, ferritin and hemoglobin levels.

**Materials and Methods**

**Study Center and Time-frame**

The study was planned as a cross-sectional, retrospective study. It was conducted at the outpatient department of Child and Adolescent Psychiatry in Abant Izzet Baysal University Medical Faculty. The records of patients who applied to the study center in between January 2012 and January 2013 were screened and 205 ADHD and ADHD-NOS cases’ records were evaluated. The diagnosis of 205 patients’ records and their comorbid psychiatric disorders was made clinically by the consensus of child psychiatry residents and the clinical supervisor according to DSM-IV-TR criteria (4). The diagnosis of ADHD was based on 6 of the 9 attention deficit criteria, 6 of the 9 hyperactivity criteria, onset of symptoms before the age of 6 years, presence of symptoms in at least 2 different settings, symptoms being at least 6 months and impairment of functionality. The ADHD-NOS was diagnosed the patients who did not meet the criteria for ADHD (e.g. age, number of symptoms), but has a behavioral pattern marked by sluggishness, daydreaming, and hypoactivity.

Inclusion criteria were a primary diagnosis of ADHD or ADHD-NOS according to DSM-IV-TR criteria, adequate information on laboratory values and psychometric measures in patient records, application to the outpatient department between the specified time-frame. Patients with comorbid medical and psychiatric disorders were included. Both ADHD and ADHD-NOS groups received...
methylphenidate treatment at 1 mg / kg / day. Patients with inadequate records were excluded.

**Ethic Committee Approval:** Ethics committee approval of the study was obtained from Bolu Abant Izzet Baysal University Clinical Trials Ethics Committee (Date: 16.05.2018, Number: 164).

**Measures**

Turgay DSM-IV–Based Child and Adolescent Behavior Disorders Screening and Rating Scale: This parent and teacher-reported scale was developed by Turgay by transforming the DSM-IV criteria (T-DSM-IV-S) into questions without changing their meanings and includes 9 items for attention deficit, 6 items for hyperactivity, 3 items for impulsivity, 8 items for oppositional defiant disorder, and 15 items for conduct disorder. Each item is rated on a scale of 0 = none, 1 = occasional, 2 = much, and 3 = very much. When subscales are evaluated, 2 to 3 points per item are assessed as symptomatic (1), while 0 to 1 are assessed as no symptomatic (0) (26). The validity and reliability study of this scale was established previously (27).

The Screen for Anxiety Related Emotional Disorders (SCARED): This instrument consists of 41 items asking the parent (or caregiver) to indicate how often a descriptive phrase regarding how their child may have felt over the course of the previous three months is true. Respondents may select from the options of “Not True or Hardly Ever True (0 point)”, “Somewhat True or Sometimes True (1 point)”, and “Very True or Often True (2 point)” (28). When subscales are evaluated, 2 point per item are assessed as symptomatic (1), while 0 to 1 are assessed as no symptomatic (0). Both child and parent’s report were used. The scale also includes somatic/ panic, generalized anxiety, separation anxiety, social anxiety and school fear subscales. SCARED Turkish forms’ validity and reliability was established by Cakmakci (2004) (29).

The Clinical Global Impression-Severity Scale (CGI-S): CGI-S is the most widely used clinician-rated measure of treatment-related changes in functioning (30). The CGI-S score rates illness severity on a 7-point scale, ranging from 1 (“normal”) to 7 (“among the most severely ill patients”). CGI-S is usually used in Turkish Child and Adolescent outpatient and inpatient clinics. It is also used in a lot of Turkish clinic studies in this area. CGI-S was used to indicate symptom severity in present study.

**Data Analysis**

The data of the study were evaluated using the Statistical Package for the Social Sciences (SPSS) version

22.0. Continuous variables are presented by means of summary statistics. This (unless otherwise stated) refers to the number of patients (n), mean, standard deviation (SD). Categorical data are presented using either absolute or relative frequencies. Demographic data were compared using Chi square tests, Yates’ and Fisher’s corrections were applied when required. The distribution of the data was evaluated by the Kolmogorov-Smirnov method. As the distribution of the data was normal distribution, between group comparisons were evaluated by Student’s t test or one-way ANOVA depending on group numbers. Pearson correlation analysis was used to determine the relationship between continuous variables. All tests were two tailed with p values < 0.05 considered significant.

**Results**

The records of 205 patients were analyzed. Of these, 99 (99%) patients were ADHD and 106 (51%) patients were ADHD-NOS. The average age of the children in the ADHD group was 10.88±3.02 years, and the average age of the children in the ADHD-NOS group 9.93±2.49 years. Significant difference was determined between the average ages of the groups (p = 0.015). 34 children in the ADHD group were female, and 34 children in the ADHD-NOS group were female. No statistically significant difference was determined between the groups in terms of sex (p = .73). There were 45 cases having positive family history and 51 cases having medical disease history in the ADHD group. In the ADHD- NOS group, there were 54 cases having positive family history and 48 cases having medical disease history. Both family history and medical disease history between two groups did not display statistically significant difference (respectively p = 0.095, p = 0.958) (Table I). T- DSM-IV-S-parent subscales, SCARED subscales and CGI_S scores between two groups are presented in Table II.

Comorbid psychiatric disorder was detected in 144 cases (70.24%) of 205 cases included in the study. It was found that conduct disorder (28.29%) and specific learning difficulties (21.95%) were the most common comorbid psychiatric disorders. While 71 of these 144 cases had one comorbid psychiatric disorder, others had multiple comorbid psychiatric disorder. It was found that 76 cases in the ADHD group and 68 cases in the ADHD-NOS group had comorbid psychiatric disorder. No statistically significant difference was determined between the groups in terms of comorbid psychiatric disorder (p = 0.531).

Iron and ferritin was detected in 81 of 205 patients participating in the study. Hemoglobin was detected
in 61 of 205 patients participating in the study. While the averages of iron and ferritin level were respectively 65.53±33.21, 38.77±44.66 in the ADHD group (n: 47), they were respectively 73.04±27.08, 32.83±17.11 in the ADHD-NOS group (n: 34). No statistically significant difference was determined between the groups in terms of iron and ferritin level (p > 0.05). While the average of hemoglobin level was 13.66±4.24 in the ADHD group (n: 39), it was 12.77±1.06 in the ADHD-NOS group (n: 22). No statistically significant difference was determined between the groups in terms of hemoglobin level (p = .339) (Table III).

When the relationship between iron and ferritin levels and comorbidity was evaluated, iron and ferritin levels were 75.18±33.51, 33.56±16.39 respectively in the non-comorbid group (n: 27), were 63.89±29.70, 33.91±20.82 in the one comorbid group (n: 24), and were 65.81±29.48, 40.61±53.90 in the multiple comorbid group (n: 30). No statistically significant difference was determined between the three groups in terms of iron and ferritin levels (p = 0.453, p = 0.709 respectively). When the relationship between hemoglobin level and comorbidity was evaluated, hemoglobin levels were 13.91±5.31 in the non-comorbid group (n: 25), were 12.90±1.04 in the one comorbid group (n: 20), and were 13.02±0.73 in the multiple comorbid group (n: 16). No statistically significant difference was determined between the three groups in terms of hemoglobin levels (p = 0.217).

When the relationship between total number of psychiatric diagnosis and iron, ferritin and hemoglobin levels was assessed, a statistically significant negative correlation was found between the total number of diagnosis and ferritin levels (r: -351, p = 0.001), but the same relationship with iron and hemoglobin levels was not obtained (p > 0.05).

When the relationship between the symptoms of ADHD and iron, ferritin and hemoglobin was evaluated, while there was a significant negative correlation between ADHD HA subscores and iron levels (p=0.027), and between ADHD AD subscores and ferritin (p=0.011), no correlation was found between the symptoms of ADHD and hemoglobin (p>0.05) (Table IV). When the relationship between SCARED scores and iron, ferritin and hemoglobin levels was evaluated, no relationship was found between iron, ferritin and hemoglobin levels and SCARED subscales and total scores (p>0.05).

| Table I. Comparison of sociodemographic data of the ADHD-NOS and ADHD groups |
|-----------------------------|-----------------------------|-----------------------------|
|                            | ADHD-NOS group (n:99)       | ADHD group (n:106)          |
| Age                        | 10.88±3.02                  | 9.93±2.49                   | .015 |
| Sex                        |                             |                             | .73  |
| Male                       | 65                          | 72                          | .73  |
| Female                     | 34                          | 34                          | .73  |
| Family history             |                             |                             | .095 |
| Positive                   | 54                          | 45                          | .095 |
| Negative                   | 45                          | 61                          | .095 |
| Medical disease history    |                             |                             | .958 |
| Positive                   | 48                          | 51                          | .958 |
| Negative                   | 51                          | 55                          | .958 |

| Table II. Comparison of T-DSM-IV-S-parent subscales, SCARED subscales and CGI-S scores of the ADHD-NOS and ADHD groups |
|---------------------------------|-----------------------------|-----------------------------|
|                                | ADHD-NOS group (n:99)       | ADHD group (n:106)          |
| T-DSM-IV-S-parent              |                             |                             | .p  |
| Attention                      | 2.41±1.72                   | 6.28±2.15                   | <.001|
| Hyperactivity                  | 1.40±1.85                   | 4.52±3.18                   | <.001|
| Opposition-defiance            | 1.45±2.02                   | 3.56±2.99                   | <.001|
| CD                              | 0.11±0.46                   | 0.56±1.22                   | .001 |
| Total score                    | 21.34±11.41                 | 42.37±17.02                 | <.001|
| SCARED                          |                             |                             | .p  |
| Somatic/panic                  | 1.85±2.31                   | 2.29±2.47                   | .441 |
| Generalized anxiety            | 1.32±1.98                   | 3.11±2.64                   | .001 |
| Separation anxiety             | 1.43±1.68                   | 2.68±1.92                   | .003 |
| Social anxiety                 | 2.09±1.95                   | 2.85±2.22                   | .106 |
| School phobia                  | 0.53±1.31                   | 1.15±1.42                   | .050 |
| Total score                    | 25.89±12.86                 | 34.00±12.89                 | .007 |
| CGI-S                          | 3.39±0.74                   | 4.55±0.64                   | <.001|

| Table III. Comparison of iron, ferritin and hemoglobin levels of the ADHD-NOS and ADHD groups |
|---------------------------------|-----------------------------|-----------------------------|
|                                | ADHD-NOS group              | ADHD group                 | .p  |
| Iron µg/dL (r: 60-180 µg/dL)    | 73.04±27.08                 | 65.53±33.21                | .349 |
| Ferritin, ng/mL (r: 10-204 ng/mL)| 32.83±17.11                | 38.77±44.66                | .464 |
| Hemoglobin g/dl (r: 11.5-17.5 g/dL) | 12.77±1.06               | 13.66±4.24                | .339 |

r: reference range
Discussion

In this retrospective study, we aimed to compare the levels of iron, ferritin and hemoglobin in children with ADHD and ADHD-NOS, and to assess the relationship between ADHD symptom severity, anxiety symptom severity and iron, ferritin and hemoglobin levels. While we did not find significant difference between ADHD and ADHD-NOS groups in terms iron, ferritin and hemoglobin levels, we found statistically significant negative correlation between ADHD HA symptom severity and iron levels, and ADHD AD symptom severity and ferritin levels. We also found statistically significant negative correlation between the total number of psychiatric diagnosis and ferritin levels.

The main outcome of this study is significant negative correlation between ADHD HA symptom severity and iron levels, and ADHD AD symptom severity and ferritin levels. This means that as the iron level decreases, ADHD HA symptom severity increases, and as the ferritin level decreases, ADHD AD symptom severity increases. In studies evaluating iron, ferritin and ADHD relations, ADHD and healthy control groups were compared for iron and ferritin levels (19, 31-37). The data comparing to ADHD and healthy control in terms of iron, ferritin was inconsistent. While some studies found no significant difference between ADHD and healthy groups in terms of ferritin level (31,33), others found significantly lower ferritin levels in ADHD cases compared to healthy control cases (19, 34-37). In a meta-analysis study, it has been shown that lower serum ferritin levels in ADHD patients than healthy controls. It has also found no correlation between serum iron levels and ADHD in the same meta-analysis (38). In studies evaluating correlation between ADHD symptoms and ferritin levels, the data were inconsistent. While some studies found different from our study that ADHD hyperactivity scores were negatively associated with serum ferritin level in the ADHA (39-41), Menegassi et al. (2010) found no relationship between ADHD symptoms and ferritin level (32).

Iron is essential element, which plays a central role in brain processes (42). Therefore, iron deficiency (ID) causes structural and functional brain abnormalities such as dopamine metabolism alterations, energy metabolism and myelination (43). ID is associated with ADHD etiopathophysiology with several mechanisms (21). While there was direct relationship between ADHD symptom and ferritin, it could not be found same direct relationship for ADHD and iron level in the literature. Finding, negative correlation between ADHD HA symptom severity, we found our study can contribute to the ADHD literature.

We also observed a significant negative correlation between the total number of psychiatric diagnosis and ferritin levels. This means that as the number of psychiatric diagnosis increases, the ferritin level decreases. Comorbidities are common in ADHD (9). In a study, it was found higher serum ferritin levels in psychiatric disorders other than ADHD (19). In a meta-analysis study, it was found different from our study that patients with ADHD as well as other psychiatric comorbidities had higher serum ferritin levels than without psychiatric comorbidities. This difference in literature and our study can be explained by different diet and pathophysiologic changes related to other psychiatric disorders.

Another finding we have in our study that there is no significant difference between ADHD and ADHD-NOS groups with regard to iron, ferritin and hemoglobin levels. Our study may be a contribution to the literature on this subject. There is no study in the literature assessing the association between ADHD and ADHD-NOS in terms of iron, ferritin and hemoglobin levels.

Our findings should be evaluated within the context of limitations. Firstly, the study is lack of a healthy control group. Secondly, the study was retrospective and depended on information recorded routinely in clinical records. This dependence led to a missing data which may have affected the results. Thirdly, the study was conducted on a clinical sample evaluated at a single center and may not reflect patient populations in other centers or in the community. Fourthly, the laboratory evaluations were conducted as part of the baseline examination prior to commencing pharmacotherapy at the study center but due to dependence on patient charts we could not ascertain whether the patients were drug naïve or were receiving treatment at the time of evaluations. Despite those limitations this is the only study that we are aware of evaluating psychometric
features and laboratory values of children diagnosed with ADHD and ADHD-NOS.

**Conclusion**

In conclusion, it has been shown significant negative correlation between ADHD HA symptom severity and iron levels, and ADHD AD symptom severity and ferritin levels and an inverse relationship between the number of psychiatric diagnoses and ferritin with ADHD in our study. These findings suggest that iron and ferritin levels are associated with ADHD symptoms and assessing ferritin levels may be beneficial if the number of psychiatric diagnoses is increased in children with ADHD. However, there is a need for further study in this area because our finding and literature information are both inadequate and incoherent to generalize our findings.

**Ethics**

**Ethics Committee Approval:** Ethics committee approval of the study was obtained from Bolu Abant Izzet Baysal University Clinical Trials Ethics Committee (Date: 16.05.2018, Number: 164).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**


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