

# Iron Deficiency in Children with Attention Deficit Hyperactivity Disorder

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**ABSTRACT:** **Background:** Several studies have suggested that iron deficiency may be related to the pathophysiology of attention deficit hyperactivity disorder (ADHD) due to the role of iron in the production of dopamine and noradrenaline.

**Objectives:** To evaluate the status of iron deficiency in ADHD children, using ferritin levels, a reliable measure of iron storage in body tissue, as an iron status marker, and to investigate a possible correlation between ferritin levels and the diagnosis of ADHD.

**Methods:** The study group included 113 newly referred ADHD children aged 5–15 years (mean age  $8.8 \pm 2.7$ ).

**Results:** Ferritin levels were below 20 ng/ml in 67 children (59%) and above 20 ng/ml in 46 (41%). There was a very low inverse statistical correlation between scores on Conners' Rating Scale and ferritin levels, probably without clinical significance.

**Conclusions:** Our findings suggest that low iron stores may be related to ADHD pathophysiology; therefore, ferritin should be included in the overall evaluation of children with ADHD.

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**KEY WORDS:** attention deficit hyperactivity disorder (ADHD), iron, ferritin

Attention deficit hyperactivity disorder, the most prevalent neuropsychiatric disorder worldwide, affects between 5% and 10% of school-aged children and was found to persist through adolescence and adulthood in 30%–50% of these individuals [1,2]. The disorder is characterized by developmentally inappropriate inattention, hyperactivity and impulsivity, with onset before age 7 years and impaired functioning in two or more settings (school, home, etc.) [3].

The pathophysiology of ADHD is complex and not completely understood. No specific etiology has been identified for ADHD, and findings are consistent with a multifactorial hypothesis. Indeed, all neuropsychiatric disorders are thought to be caused by a complex combination of environmental, genetic and biological factors. Therefore, the proposed etiologies related to prenatal and perinatal risk factors, genetics and

neurobiological deficits may all be involved in the pathophysiology of ADHD in different individuals [2]. However, many studies using different methodologies have indicated that dopamine is a key element of ADHD pathophysiology. The association between ADHD and the genes regulating dopamine, norepinephrine, serotonin and gamma-aminobutyric acid (GABA) has been studied [3,4]. Of these neurotransmitters, dopamine may play a central role because of its association with the modulation of psychomotor activity and executive functions, which are the main clinical features of individuals with ADHD. Several molecular genetic studies of ADHD have concentrated on the genes involved in dopaminergic function, and special attention was focused on the association of both the dopamine D4-receptor gene and the dopamine transporter gene (DAT1) with ADHD [5,6].

The association of the dopamine transporter with ADHD is of particular importance because this site is the main target for medications that are widely used by individuals with ADHD, such as methylphenidate, pemoline and dexamphetamine. Iron is a cofactor of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis [7]. Therefore, brain iron stores may influence dopamine synthesis and subsequently affect various behavioral features, in particular those described in people with ADHD.

Several studies were performed in recent years [8–12] to define the role of serum ferritin levels as a reliable measure of iron stores in body tissues, including the brain, in the absence of anemia in children with ADHD. Only a few of these found a correlation between low ferritin levels and the presence of ADHD [8–11] and one study was unable to confirm this observation [12].

Our hypothesis was that depleted iron stores measured by ferritin levels in the serum may have a causative role in children with ADHD. The purpose of the present study was to investigate a possible correlation between iron stores as measured by serum ferritin and the diagnosis of ADHD.

## SUBJECTS AND METHODS

The study was prospective and included all new consecutive patients during a 6 month period who were referred to the

ADHD = attention deficit hyperactivity disorder

Pediatric Neurology Clinic at Asaf Harofeh Medical Center, Zerifin, Israel, with a diagnosis of suspected ADHD, following their agreement to participate.

The children were diagnosed according to the DSM-IV TR criteria confirming the presence of symptoms in two settings, using Conners' Parents Rating Scale (CPRS) and Conners' Teachers Rating Scale (CTRS). The inclusion criteria were children aged 6–16 years, attending regular schools, and not taking any stimulant medications. The exclusion criteria were chronic medical problems requiring medical treatment, such as asthma, epilepsy, etc., and hemoglobin below 10 g/dl.

Blood samples for hemoglobin, iron and ferritin were obtained from all the children. The range of assumed normal values of ferritin in our laboratory was 20–165 ng/ml; therefore, values < 20 ng/ml were recorded as low.

After taking a detailed history, examining the patients and evaluating all available data, a treatment plan was suggested to the family based on the clinical features of ADHD symptoms. Treatments included behavioral modification, academic support, and medication. The ethics committee of our facility approved the study.

Statistical analysis was performed using SPSS software. The Pearson test was used for correlations between symptom severity and serum ferritin levels.

## RESULTS

The number of children eligible to be included in the study was 146, of whom 33 were excluded because of refusal by their parents to participate. The study group thus comprised 113 children: 87 (75.6%) boys and 26 (24.4%) girls aged 6–15 years (mean age  $8.8 \pm 2.7$ ), all of whom met the above mentioned criteria.

Table 1 shows the hemoglobin, ferritin and iron levels and Conners' scores of the study group. There were no significant statistical differences between the age groups for these values. Sixty-seven children (59%) had ferritin levels below 20 ng/ml and 46 (41%) had ferritin levels above 20 ng/ml.

**Table 1.** Hemoglobin, iron and ferritin levels, and Conners' scores in the study group

	All subjects
No. of children	113
Males (%)	87 (75.6%)
Mean age (SD, yrs)	8.8 (2.7)
Mean hemoglobin (SD, g/dl)	12.9 (0.84)
Mean iron (SD, ng/ml)	70.5 (31)
Mean ferritin (SD, ng/ml)	20.8 (12.3)
Mean Conners' score (SD)	18 (4.4)

**Table 2.** Comparison of factors in children diagnosed with ADHD and grouped according to low and high serum ferritin levels

	Low ferritin (< 20 ng/ml)	High ferritin (> 20 ng/ml)	P value
No. of children	67	46	
Males (%)	55 (82.1%)	32 (69.6%)	0.18
Mean age (SD, yrs)	8.6 (2.7)	9.2 (2.6)	0.2
Mean hemoglobin (SD, g/dl)	12.86 (0.85)	12.88 (0.84)	0.93
Mean iron (SD, ng/ml)	74.6 (33)	64.9 (26)	0.11
Mean ferritin (SD, ng/ml)	13.6 (3.5)	31.2 (13.2)	
Median ferritin (range, ng/ml)	14 (4–19)	25 (20–79)	
Mean Conners' score (SD)	17.5 (4.5)	18.7 (4.2)	0.15

Table 2 compares these two groups (< 20 and > 20 ng/ml) in terms of several factors, including gender, mean age distribution, and mean hemoglobin, iron and ferritin levels. No statistical difference was found between the groups, except for a very weak inverse correlation between Conners' scores and ferritin values, which most likely had no clinical significance.

## DISCUSSION

The role of iron deficiency has been demonstrated in various neurologic and developmental disorders in both laboratory and clinical studies [13]. The relationship of iron deficiency to developmental delay and cognitive deficits with and without anemia has been a focus of many studies in both developed and developing countries [14,15]. Serum ferritin reflects the status of iron stores in the body: only when the level is below 10 ng/ml are bone marrow stores depleted and anemia develops [16].

In 1997, Sever et al. [8] presented a preliminary report on 14 boys aged 7–11 years with ADHD who were treated with an iron preparation, 5 mg/kg/day, for 30 days. Blood samples of ferritin, as well as their parents' and teachers' reports were obtained before and after treatment. The results showed a significant increase in serum ferritin levels (from mean  $\pm$  SD  $25.9 \pm 9.2$  to  $44.6 \pm 18$  ng/ml) and a significant decrease in symptoms according to the parents' reports only. In 2004, Konofal et al. [9] compared iron levels in 53 ADHD children, aged 4–14 years, with iron levels in a control group matched for age and gender. Serum ferritin levels were used as a parameter for iron stores, and Conners' scores were used to measure ADHD symptom severity. The results showed that the mean serum ferritin levels were low in 84% of the children with ADHD (mean  $23 \pm 13$  ng/ml) as compared to 18% of controls (mean  $44 \pm 22$  ng/ml). In addition, low serum ferritin levels correlated with more severe ADHD symptoms and greater cognitive deficits. The authors concluded from their results that low iron stores

may contribute to ADHD and that children with ADHD may benefit from iron supplementation.

Millichap and colleagues [12] investigated the role of iron deficiency in ADHD by including serum ferritin in a battery of laboratory tests performed in 68 consecutive children aged 5–16 years seeking treatment at a clinic for attention deficit disorder. Serum ferritin levels ranged from a low of 7.7 ng/ml to a high of 150 ng/ml. The mean serum ferritin level in children with ADHD ( $39.9 \pm 40.6$  ng/ml) was not different from that of the control group ( $44 \pm 22$  ng/ml) reported by Konofal et al. [9] or the U.S. national control data. However, 74% of the patients in Millichap's study [12] had serum ferritin levels below 50 ng/ml, 44% had levels below 30 ng/ml, and 18% had serum ferritin levels below 20 ng/ml. None of the children showed evidence of iron deficiency anemia.

In our study, a comparison of the clinical characteristics of the 12 children with the lowest serum ferritin levels ( $< 20$  ng/ml) and the 12 with the highest levels ( $> 60$  ng/ml) revealed no significant difference in severity or frequency of ADHD and comorbid symptoms, or in response to medications. In this patient cohort study, a causative role for low serum ferritin was not confirmed. Nevertheless, because therapy with iron has been beneficial for some neurologic disorders despite the absence of anemia, a controlled trial of ferrous sulphate supplement may be justified in ADHD children with ferritin levels below 20 ng/ml.

In another recently published controlled case study from India [10], serum ferritin levels were measured in children newly diagnosed with ADHD and compared with those of controls. A correlation was sought between serum ferritin levels and ADHD symptom severity as determined by Conners' Rating Scale. Serum ferritin was found to be significantly lower in children with ADHD (mean  $\pm$  SD  $6.04 \pm 3.85$  ng/ml) as compared to controls (mean  $\pm$  SD  $48 \pm 41.64$  ng/ml). There was also a significant inverse correlation between serum ferritin levels and oppositional subscores on Conners' Rating Scale.

The assumed low normal values of ferritin suggesting the presence of iron deficiency are variable in different studies investigating its relationship to ADHD, ranging from 12 ng/ml [10,17,18] to 30 ng/ml [12]. The value of 20 ng/ml as a low normal in our study represents an average of the values that were used in the other studies.

Recently, a new computerized continuous performance functions test [19], which includes a multitask approach, was found to be a valid and reliable tool for the diagnosis of ADHD in children and may be used for better assessment in future studies.

Our results support the assumption that iron status may play a role in the pathophysiological processes underlying ADHD. The majority of the children (59%) had ferritin levels below 20 ng/ml with no significant difference between the age groups. Moreover, hemoglobin and iron values were also

similar in all age groups. There was no strongly significant statistical correlation between ferritin levels and symptom severity, as described by Millichap and co-researchers [12] and in contrast to the results of Konofal et al. [9] and Juneja et al. [10].

The variability of the results in the different studies may reflect differences in age, gender, race/ethnicity and nutritional status due to socioeconomic conditions as well as the contribution of other factors, such as type of symptoms and associated comorbidity, that may have some influence on ADHD features.

Only one study [11] examined the effects of iron supplementation on ADHD in children. In this study 23 non-anemic children aged 5–8 years with serum ferritin levels below 30 ng/ml were randomized (3:1 ratio) to treatment with either oral iron supplements (ferrous sulphate, 80 mg/day,  $n=18$ ) or placebo ( $n=5$ ) for 12 weeks. There was a significant progressive decrease in the ADHD rating scale after 12 weeks on iron, but not in the placebo group; however, improvement on Conners' Parent Rating Scale and Conners' Teacher Rating Scale with iron supplementation therapy failed to reach significance. The limitations of this study was the small sample, particularly that of the placebo group.

The results of most studies, including the present one, support the hypothesis that depletion of iron stores, although not so severe as to cause anemia, may be related to the pathophysiological processes underlying the development of ADHD symptoms. Other studies [17,18] have suggested that lower ferritin levels are associated with higher rates of behavioral problems and that the presence of comorbid conditions might increase the effect of lower iron stores on behavioral measures.

The absence of a control group and the size of the study group are points of weakness in the design of the present study. Larger samples are required to investigate the possibility that in the population at large, the same proportion of normal children without ADHD have low levels of ferritin as found in the different study groups of children with ADHD.

Recently, it was suggested that low levels of iron and zinc might be associated with ADHD since both are related to dopamine metabolism [20]. Since ADHD constitutes a heterogeneous group of conditions with different features and clinical expressions, it may be assumed that depleted iron stores, as reflected by a significant low level of ferritin, are not a constant finding in every child with ADHD.

In conclusion, we suggest that ferritin, as a marker for iron stores, be included in all baseline evaluations of children with clinical presentation of ADHD. Furthermore, children with ferritin levels below 20 ng/ml should be required to undergo a careful dietary iron evaluation, followed by a diet that features appropriate amounts of iron sources. Additional larger controlled double-blind trials are necessary to demonstrate

the value of iron supplements in treating ADHD children with depleted iron stores as reflected by low ferritin levels.

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