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Iron Deficiency in Children With Attention-Deficit/Hyperactivity Disorder

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Abstract

Background Iron deficiency causes abnormal dopaminergic neurotransmission and may contribute to the physiopathology of attention-deficit/hyperactivity disorder (ADHD).

Objective To evaluate iron deficiency in children with ADHD vs iron deficiency in an age- and sex-matched control group.

Design Controlled group comparison study.

Setting Child and Adolescent Psychopathology Department in European Pediatric Hospital, Paris, France.

Patients Fifty-three children with ADHD aged 4 to 14 years (mean \pm SD, 9.2 \pm 2.2

years) and 27 controls (mean \pm SD, 9.5 \pm 2.8 years).

Main Outcome Measures Serum ferritin levels evaluating iron stores and Conners' Parent Rating Scale scores measuring severity of ADHD symptoms have been obtained.

Results The mean serum ferritin levels were lower in the children with ADHD (mean \pm SD, 23 \pm 13 ng/mL) than in the controls (mean \pm SD, 44 \pm 22 ng/mL; $P < .001$). Serum ferritin levels were abnormal (<30 ng/mL) in 84% of children with ADHD and 18% of controls ($P < .001$). In addition, low serum ferritin levels were correlated with more severe general ADHD symptoms measured with Conners' Parent Rating Scale (Pearson correlation coefficient, $r = -0.34$; $P < .02$) and greater cognitive deficits ($r = -0.38$; $P < .01$).

Conclusions These results suggest that low iron stores contribute to ADHD and that ADHD children may benefit from iron supplementation.

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Attention-deficit/hyperactivity disorder (ADHD) affects 5% to 10% of school-aged children and may persist through adolescence and adulthood in 30% to 50% of the patients. The disorder is characterized by inappropriate impulsivity, overactivity, inattention, and altered executive functions.¹ Because the latter are possibly modulated by the dopaminergic mesocortical pathways, and because patients with ADHD have increased dopamine transporter-binding potential² and genetic polymorphisms in the dopamine receptor,³ it has been suggested that the symptoms of ADHD may be caused by dopamine dysfunction. Indeed, children with ADHD benefit from dopamine stimulants. Because iron is a coenzyme of dopamine synthesis and iron deficiency alters dopamine receptor density and activity in animals,⁴ brain iron stores may influence dopamine-dependent functions. In the brain, iron is bound to ferritin, the levels of which are decreased by iron deficiency and increased by iron supplementation. Low ferritin levels in childhood have been reported to affect the development of the central nervous system,

leading to mental retardation and behavioral disorders.⁵ We therefore investigate whether iron deficiency contributes to ADHD symptoms in children, compared with age- and sex-matched children without ADHD.

Methods

One hundred ten children from the same school district were referred to a university pediatrics hospital between March 2002 and June 2003 for school-related problems. The clinical diagnosis of ADHD and comorbid psychiatric disorders was based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*¹ and a structured diagnostic interview. Fifty-three children, 45 boys and 8 girls aged 4 to 14 years, met the criteria for definite ADHD, and 27 age- and sex-matched children, 20 boys and 7 girls aged 5 to 15 years without ADHD, met the criteria for mild reading disability. Forty children with additional behavioral disorders, mental retardation, mood and anxiety disorders, physical diseases, and malnutrition were excluded. All children with ADHD and controls had been drug-free for at least 2 months prior to the study.

The severity of ADHD symptoms was evaluated with Conners' Parent Rating Scale (CPRS), including the hyperactivity, cognitive, and oppositional subscales.⁶ After the completion of CPRS, serum ferritin levels were measured in the morning (Elecsys Enzymun-Test; Roche Diagnostics, Meylan, France), as were blood hemoglobin, hematocrit, and iron levels. Written informed consent was obtained from one or both parents or a legal guardian before the child was included in the study, which was approved by the ethics review board.

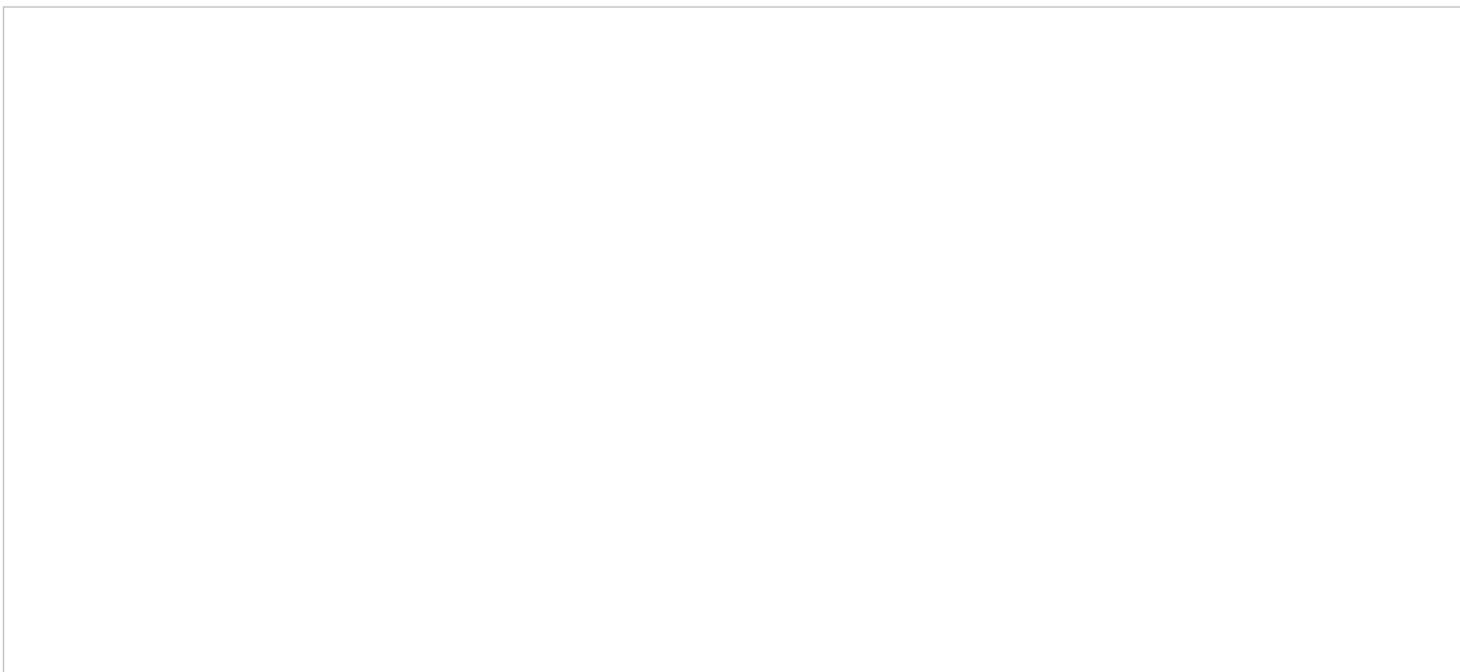
Statistical analyses were performed using the t test and χ^2 test for between-group comparison of biological measures and Pearson test for correlations between symptom severity and serum ferritin levels.

Results

The mean serum ferritin levels, shown in **Figure 1**, were lower in the children with ADHD (mean \pm SD, 23 \pm 13 ng/mL) than in the controls (mean \pm SD, 44 \pm 22

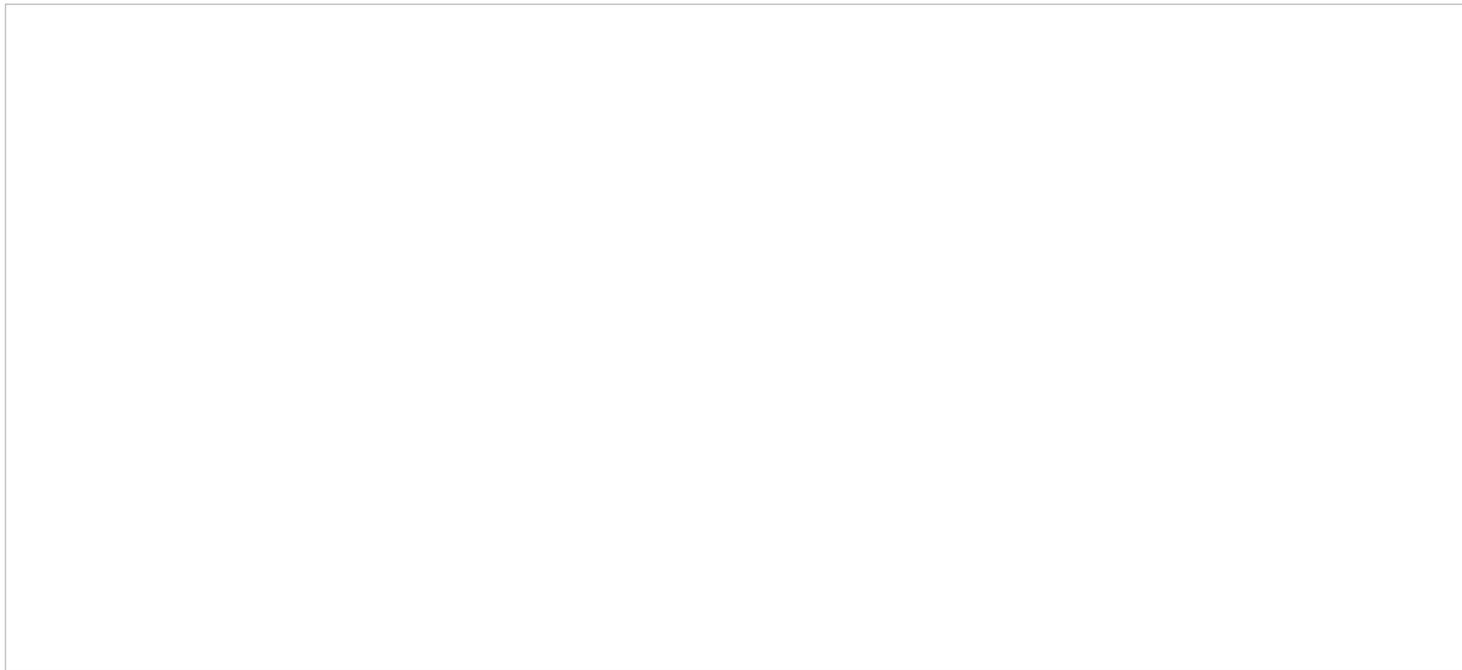
ng/mL; $P < .001$), while serum iron, hemoglobin, and hematocrit levels were within normal ranges in both children with ADHD and controls and did not differ between groups (data not shown). In the ADHD group, 42 (84%) of 53 children had serum ferritin levels lower than 30 ng/mL, a value considered abnormally low,⁷ vs 5 (18%) of 27 controls ($P < .001$). In addition, 17 (32%) of 53 children with ADHD had serum ferritin levels lower than 15 ng/mL, a value considered extremely low, compared with 1 (3%) of 27 controls.

Figure 1.



Mean (horizontal line) \pm SD (vertical line) and individual (dots) serum ferritin levels (nanograms per milliliter) measured in children with attention-deficit/hyperactivity disorder (ADHD) and controls (Pearson t test, $P < .001$).

In children with ADHD, the mean \pm SD CPRS score was 67 ± 15 (range, 40-110). Serum ferritin levels were correlated with ADHD symptoms severity measured with CPRS (Pearson correlation coefficient, $r = -0.34$; $P < .02$) (**Figure 2**). Serum ferritin levels also correlated with the cognitive subscore ($r = -0.38$; $P < .01$) and tended toward a correlation with the hyperactivity subscore ($r = -0.57$; $P = .055$) but did not correlate with the oppositional subscore.



Serum ferritin levels (x-axis) were inversely correlated ($r = -0.31$; $P < .02$) with the severity of attention-deficit/hyperactivity disorder symptoms (y-axis, total Conners' Parents Rating Scale).

In contrast to children with ADHD, controls had a mean \pm SD CPRS score of 41 ± 15 (range, 2-58), and their serum ferritin levels were not correlated with CPRS score.

Comment

To our knowledge, this is the first clinical study demonstrating abnormally low serum ferritin levels in children with ADHD. Serum ferritin levels were twice as low in children with ADHD as in controls. They were extremely low in one third of them, indicating low iron stores. In contrast, serum ferritin levels in control children were within published normal ranges.⁷ Because hemoglobin and hematocrit levels were normal, ruling out anemia, the low ferritin levels should be considered a specific and primary abnormality. The reason for low serum ferritin levels in children with ADHD is unclear. There was no evidence of malnutrition or intestinal malabsorption, although the latter should be investigated further. If serum ferritin levels should prove to be decreased in cerebrospinal fluid as well, this would

suggest that a brain iron deficiency may underlie the symptoms of ADHD. Because dopaminergic neurotransmission is affected by brain iron levels,⁸ we hypothesize that low ferritin levels might alter brain dopaminergic activity in children and contribute to ADHD symptoms.

A major finding was that serum ferritin levels were inversely correlated with the severity of ADHD. The children with the most severe iron deficiency were the most inattentive, impulsive, and hyperactive. This result suggests that low iron stores may explain as much as 30% of ADHD severity. The CPRS scale of ADHD includes 3 subscores: hyperactivity, oppositional, and cognitive. Only the cognitive subscore correlated significantly with low ferritin levels. This correlation suggests that the iron-deficient children are mainly inattentive and distractible and suffer from learning disabilities, a finding consistent with the role of iron deficiency in cognitive deficits and mental retardation.⁷ A causal relationship between iron deficiency and poor cognitive development and/or behavioral problems has been well established over the past 3 decades.⁹ There was also a trend toward a correlation between the hyperactivity subscore and serum ferritin levels, the children with more severe iron deficiencies suffering from increased motor restlessness. Iron deficiency is known to cause motor restlessness in rats.⁴ Of interest, restless legs syndrome, a disorder associated with a compelling urge to move the extremities and motor restlessness that is temporarily alleviated by activity and that is worse in the evening or during the night, can also be caused by iron deficiency in adults¹⁰ and in children.¹¹ It would be interesting, therefore, to look for restless legs symptoms in children with ADHD and iron deficiency and, conversely, to evaluate ADHD symptoms in iron-deficient adults suffering from restless legs syndrome.

Finally, our findings could have a major and immediate impact on the treatment of children with ADHD. Iron supplementation has been reported incidentally to decrease the CPRS and cognitive deficiency in children with ADHD with an iron-deficient diet, although serum ferritin levels were not measured in this study.¹² We suggest that iron supplementation might also improve central dopaminergic activity in children with ADHD, decreasing the need for psychostimulants.

What This Study Adds

Iron deficiency has been previously considered a potent cause of poor cognitive impairment, learning disabilities, and psychomotor instability. We need to consider that iron deficiency (low serum ferritin level) could lead to ADHD symptoms in relationship with central dopaminergic dysfunction. Also, iron supplementation could be considered a first-line treatment for children with ADHD and iron deficiency.

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