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Iron Treatment in Children with Attention Deficit Hyperactivity Disorder

A Preliminary Report

Key Words
Iron
Attention deficit hyperactivity disorder
Connors Rating Scale

Abstract
Iron plays a role in the regulation of dopaminergic activity. In the present study, nonanemic children with attention deficit hyperactivity disorder (ADHD) were evaluated with regard to heme and nonheme iron metabolism and the effect of short-term iron administration on behavior. The study group consisted of 14 boys aged 7–11 years. All first underwent testing to rule out other psychiatric and medical problems. The severity of the ADHD symptoms was determined by parent and teacher scores on the Connors Rating Scale. Thereafter, each patient received an iron preparation (Ferrocal), 5 mg/kg/day for 30 days. Blood samples were taken before and after drug administration. Results showed a significant increase in serum ferritin levels (from 25.9 ± 9.2 to 44.6 ± 18 ng/ml) and a significant decrease on the parents' Connors Rating Scale scores (from 17.6 ± 4.5 to 12.7 ± 5.4). There were no changes in other blood parameters or in the teachers' scores on the rating scale. The effect of iron supplementation on the behavioral and cognitive symptoms in noniron-deficient ADHD children merits further investigation using a placebo-controlled study.

Introduction

Evidence has recently been accumulating that iron deficiency has behavioral effects. Nonheme iron is unevenly distributed in human brain, with high concentrations in the extrapyramidal regions (globus pallidus, substantia nigra, putamen and caudate nucleus), sometimes exceeding those in the liver [1]. Most of the available iron in the brain seems to be in the ferric form and is deposited in granular structures in neurons and oligodendrocytes [2]. In the rat brain, the synaptosomal and myelin subcellular fractions are richest in iron [3]. Since brain iron accumulates from birth to early adulthood [1], young animals are more vulnerable to iron deficiency.

Iron is a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, the rate-limiting enzymes in catecholamine and serotonin synthesis. However, iron deficiency does not affect their activities, nor those of other brain enzymes such as monoamine oxidase, succinate dehydrogenase, and aldehyde oxidase, or the turnover rate of dopamine, serotonin and norepinephrine [4]. Nutritional iron deficiency is associated with a reduction in brain

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(nonheme) iron, diminished density of D_2 dopamine receptors, and lowered behavioral responses to the dopamine agonists apomorphine and *d*-amphetamine [5, 6]. Iron-deficient rats, similar to animals treated with neuroleptics, display an increase in serum prolactin levels and prolactin-binding sites in the liver, which may indicate a reduction in dopaminergic tone in the pituitary [7].

On the behavioral level, iron deficiency impairs learned motor behaviors and cognitive function [8], and iron level may play a role in motor hyperactivity, poor cognitive learning, and attention deficit. This possibility is supported by the finding that the administration of iron supplements to nonanemic iron-deficient infants can improve their developmental scores [9, 10], as well as their cognitive development and attendant behavior [11]. Recently 2 adolescents with conduct disorder were found to have subnormal hemograms [12]. The authors suggested that, besides the other therapeutic drugs, the nutrient deficit needed to be corrected in order to alleviate the behavioral systems.

Iron supplement given to iron-deficient rats restored blood hemoglobin levels faster than brain iron levels; improvement in learning deficits lags behind blood hemoglobin by at least 2 months. This may explain the delayed benefit of iron treatment on cognitive function [13].

Attention deficit hyperactivity disorder (ADHD) is a behavioral syndrome characterized by developmentally inappropriate degrees of inattention, impulsiveness and hyperactivity. Many children with ADHD have low levels of magnesium, zinc, copper and iron; deficiencies in trace elements are noted in hair [14]. ADHD can be dramatically alleviated by dopamine releasers such as the psychostimulants amphetamine and methylphenidate. It has been suggested that hypoactivity of the brain dopaminergic system may be implicated in the pathophysiology of ADHD [15].

Since iron is important in the regulation of dopaminergic activity, we evaluated heme and nonheme iron metabolism parameters in nonanemic ADHD children. The behavioral effects of short-term iron administration were also examined.

Methods

Subjects

Fourteen boys aged 7–11 years (mean ± SD, 8.9 ± 1.4 years) with ADHD were included in the study. Detailed information from the patients, their parents and teachers, and the medical reports was obtained prior to the investigation. Each patient underwent a thorough neurological and psychiatric examination, and diagnosis of ADHD was established according to DSM-III-R criteria. Additional criteria for entrance into the study were: Regular attendance at school; cooperative parents and teachers who were willing to complete the Connors Rating Scale; IQ over 80; absence of any medical or neurological disease; drug-free for at least 3 months.

Children with an additional conduct disorder and/or specific developmental disorders were also excluded.

Procedure. The severity of the ADHD symptoms was assessed by the parent and teacher scores on the abbreviated Connors Rating Scale (1, 2). The scale was completed before and 30 days after treatment. All patients received Ferrocal (ferrous-calcium citrate; Teva, Petah Tikva, Israel) 5 mg/kg daily (active elemental iron, 0.05 mg/kg/daily).

Blood samples were obtained at 8–9 a.m. before and after the drug treatment. Hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, serum iron level, iron-binding capacity and ferritin levels were measured, as were blood count, glucose, urea, creatinine, uric acid, sodium, potassium, calcium, phosphorus, albumin, and globulin.

Statistical Evaluation. Statistical analysis of the data was performed using Student's paired t test for intragroup variations. Pearson correlation test was used for correlation analysis. All results are expressed as mean ± SD.

Results

Thirty days of Ferrocal treatment resulted in a significant increase in mean serum ferritin levels (from 25.9 ± 9.3 to 44.6 ± 18.1 ng/ml; $t = 4.14$, d.f. = 13, $p < 0.005$) and a significant decrease in the mean parents' score on the Connors Rating Scale (from 17.6 ± 4.5 to 12.7 ± 5.4; $t = 3.34$, d.f. = 14, $p < 0.005$). There was no significant correlation between these two factors ($r = 0.174$; d.f. = 12; $p > 0.55$). The mean teachers' score on the Connors Rating Scale remained unchanged after Ferrocal treatment (16.8 ± 3.7 vs. 15.6 ± 7.4). Hemoglobin, hematocrit, red and white blood count, total iron-binding capacity, globulin, albumin, and urea, and glucose, creatinine, uric acid, sodium, potassium, calcium and phosphorus levels were not significantly altered by the iron treatment, all remaining within the normal range [data not shown].

Discussion

Oral iron treatment for iron deficiency in nonanemic infants has been reported to significantly improve behavior and intellectual attainment [8, 10, 16]. The ADHD children in our study (aged 7–11 years) displayed normal serum iron, iron-binding capacity, ferritin and mean corpuscular volume values. Administration of oral iron supplement resulted in an increase in ferritin levels accompanied by an improvement in the parent score on the Con-

nors Rating Scale. Thus, there may be some benefit to iron supplementation in non-iron-deficient ADHD children. However, we cannot rule out a placebo effect, because the teacher score on the Connors Rating Scale did not improve, and no placebo control group was included in the study.

We conclude that iron deficiency does not play a role in the pathophysiology of ADHD, and oral iron treatment for affected children is not recommended. The effect of iron supplement on the behavioral and cognitive symptoms in iron-deficient ADHD children merits further investigation.

References

1 Hallgren B, Sourander P: The effect of age on the nonhaeme iron in human brain. J Neurochem 1958;3:41–51.

2 Youdim MBH: Brain iron metabolism: Biochemical and behavioral aspects in relation to dopaminergic neurotransmission; in Lajah A (ed): Handbook of Neurochemistry. New York, Plenum Press, 1985, vol 10, pp 731–755.

3 Rajan KS, Colburn RW, Davis JM: Distribution of metal iron in the subcellular fractions of several rat brain areas. Life Sci 1976;18:423–432.

4 Youdim MBH, Green AR, Bloomfield D, Mitchell D, Hill J, Grahame-Smith DG: The effects of iron deficiency on brain biogenic monoamine biochemistry and function in rats. Neuropharmacology 1980;19:259–267.

5 Youdim MBH, Yehuda S: Iron deficiency induces several dopamine dependent circadian cycles: Differential response to *d*-amphetamine and TRH. Peptides 1985;6:851–855.

6 Ashkenazi R, Ben-Shachar D, Youdim MBH: Nutritional iron and dopamine binding sites in rat brain. Pharmacol Biochem Behav 1982;17:43–47.

7 Barkey RJ, Amit T, Ben-Shachar D, Youdim MBH: Characterization of the hepatic prolactin receptors induced by chronic iron deficiency and neuroleptics. Eur J Pharmacol 1986;122:259–267.

8 Yehuda S, Youdim MBH, Mastofsky DI: Brain iron-deficiency causes reduced learning capacity in rats. Pharmacol Biochem Behav 1986;25:141–144.

9 Oski FA, Honig AS, Helu B, Howanitz P: Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. Pediatrics 1983;71:877–880.

10 Deinard AS, Murray MJ, Egeland B: Childhood iron deficiency and impaired attentional development or scholastic performance: Is the evidence sufficient to establish causality? Pediatr 1976;88:162–163.

11 Deinard A, Gilbert A, Dodds M, Egeland B: Iron deficiency and behavioral deficits. Pediatrics 1981;68:828–833.

12 Shafey H, Van Dewetering C: Iron deficiency in two adolescents with conduct, dysthymic and movement disorder. Can J Psychiatry 1994;39:371–375.

13 Youdim MBH, Ben-Shachar D: Minimal brain damage induced by early iron deficiency: Modified dopaminergic neurotransmission. Isr J Med Sci 1987;23:19–25.

14 Kozielec T, Starbrat E, Herhelin B: Deficiency of certain trace elements in children with hyperactivity. Pol J Psychiatry 1994;28:345–353.

15 Shaywitz BA, Cohen DJ, Bowers MB: CSF monoamine metabolites in children with minimal brain dysfunction. Evidence for alteration of brain dopamine. J Pediatr 1977;90:67–71.

16 Pollit E, Leibel RL: Iron deficiency and behavior. J Pediatr 1976;88:372–381.