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Effects of Iron Supplementation on Attention Deficit Hyperactivity Disorder in Children

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Iron deficiency has been suggested as a possible contributing cause of attention deficit hyperactivity disorder (ADHD) in children. This present study examined the effects of iron supplementation on ADHD in children. Twenty-three nonanemic children (aged 5-8 years) with serum ferritin levels <30 ng/mL who met DSM-IV criteria for ADHD were randomized (3:1 ratio) to either oral iron (ferrous sulfate, 80 mg/day, $n = 18$) or placebo (n = 5) for 12 weeks. There was a progressive significant decrease in the ADHD Rating Scale after 12 weeks on iron (-11.0 ± 13.9; $P < 0.008$), but not on placebo (3.0 ± 5.7; $P = 0.308$). Improvement on Conners' Parent Rating Scale ($P = 0.055$) and Conners' Teacher Rating Scale ($P = 0.076$) with iron supplementation therapy failed to reach significance. The mean Clinical Global Impression-Severity significantly decreased at 12 weeks ($P < 0.01$) with iron, without change in the placebo group. Iron supplementation (80 mg/day) appeared to improve ADHD symptoms in children with low serum ferritin levels suggesting a need for future investigations with larger controlled trials. Iron therapy was well tolerated and effectiveness is comparable to stimulants.

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Introduction

Attention deficit hyperactivity disorder is the most common childhood neurobehavioral disorder [1], affecting 5-10% of school-aged children [2]. It is characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity with onset before age 7 and impaired functioning in two or more settings [3].

The pathophysiology of attention deficit hyperactivity disorder is complex and not completely understood [2,4]. However, several lines of evidence suggest an imbalance in the dopaminergic and noradrenergic systems [2]. Iron modulates dopamine and noradrenalin production, as a cofactor for tyrosine hydroxylase, the rate-limiting enzyme of monoamine synthesis. In addition, in animal models iron deficiency decreases dopamine receptor density and activity, as well as monoamine transporter function, resulting in alterations of monoamine uptake and catabolism [5,6]. Brain iron stores are therefore expected to influence the monoamine-dependent functions that are altered in attention deficit hyperactivity disorder.

Significantly lower serum ferritin levels (a marker of iron store) have been observed in children with attention deficit hyperactivity disorder than in controls [7]. Indeed, 84% of attention deficit hyperactivity disorder children had serum ferritin levels of <30 ng/mL, compared with 18% of controls ($P < 0.001$). In addition, iron deficiency correlated with the severity of both attention deficit hyperactivity disorder and restless legs syndrome. This sensorimotor disorder, characterized by an irresistible urge to move the legs at rest, relieved by movement and worse in the evening or night, focusing on the role of dopamine systems and of iron metabolism in brain, may be strongly associated with attention deficit hyperactivity disorder [8,9]. All children in our study had normal hemoglobin levels, suggesting that low ferritin levels, more than anemia, could be associated with attention deficit hyperactivity disorder symptoms. However, the cross-sectional design of the study did not allow us to infer causality between iron deficiency and attention deficit hyperactivity

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disorder; only a clear benefit of iron supplementation therapy in attention deficit hyperactivity disorder children would provide strong evidence for this causality. In one open-label study, Sever et al. [10] observed a significant decrease of the Conners' Parent Rating Scale scores after iron supplementation in attention deficit hyperactivity disorder children without iron deficiency. The hypothesis for the present study was that attention deficit hyperactivity disorder children with iron deficiency also would benefit more from iron therapy. The objective was to assess the effects of iron supplementation on attention deficit hyperactivity disorder symptoms in iron-deficient nonanemic children in a double-blind, placebo-controlled, randomized design.

Methods

Patients

Subjects were outpatient children with attention deficit hyperactivity disorder aged 5-8 years who met DSM-IV diagnostic criteria for attention deficit hyperactivity disorder [3] by clinical assessment and had serum ferritin levels <30 ng/mL (retaining the definition of iron deficiency from a previous study) [7] with normal hemoglobin levels at the screening.

We excluded potential subjects if they had an IQ < 80 by the French version of the Wechsler Intelligence Scale, third edition, for children [3,11], relevant psychiatric comorbidities (depressive, anxiety, and sleep disorders according to DSM-IV criteria), or chronic medical conditions (including malnutrition). We also excluded children who had received iron supplementation in the past 3 months or previous treatment with psychotropic agents or psychostimulants.

This double-blind, placebo-controlled, randomized pilot trial was conducted in the Child and Adolescent Psychopathology Service of the Hospital Robert Debré (APHP, Paris, France) from May 2, 2004, to December 2, 2004.

The Ethical Committee of the Pitié-Salpêtrière University Hospital (Paris, France) reviewed and approved the study protocol. Written informed consent was obtained from the parents or legal guardian with assent from the patient before enrollment. This study was conducted in accordance with the Helsinki Declaration, the Good Clinical Practice guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, and the French Huriet laws on clinical research.

Laboratory Measures

Estimation of iron status was based on several measures of biochemical and hematological variables, including serum iron, ferritin, transferrin, and soluble transferrin receptors. In particular, the normalization of serum ferritin level (i.e., a value ≥30 ng/L) was considered the indicator of iron storage.

Complete blood count and measurement of serum ferritin levels, as well as serum iron, soluble transferrin receptors and transferrin levels, were obtained during the screening visit. Serum ferritin and soluble transferrin receptor levels were determined using the Tina-quant method (Roche, Basel, Switzerland). Serum iron and transferrin levels were measured using the ferrozine method (Roche).

An experienced child psychiatrist performed the clinical evaluation in all patients.

Iron Supplementation

Outpatients who satisfied all entry criteria were randomly assigned (in a 3:1 ratio in blocks of 4 patients) from baseline to 12 weeks of treatment with iron in the form of ferrous sulfate tablets (80 mg; Tardyferon; Robapharm, Les Ulis, France) or placebo tablets (identical even when sliced) once daily in the morning. The 3:1 ratio was chosen for ethical reasons, given that the children had documented iron deficiency. The size of the trial was calculated on the assumption of a benefit equal to usual stimulants. The five study visits were at screening, baseline, and weeks 4, 8, and 12 of treatment. Routine biochemical and hematological tests were done at baseline and at week 12. Iron measures included serum iron, ferritin, transferrin, soluble transferrin receptors levels. The investigators were kept blinded to iron status after the screening visit.

At weeks 4, 8, and 12, the patients and parents were instructed to report any adverse events between visits. Adverse events were classified as mild (no limitation of usual activities), moderate (some limitation of usual activities), and severe (inability to carry out usual activities). Vital signs, weight, and height were collected at each visit.

Questionnaires

The primary outcome measure was the Conners' Parent Rating Scale (CPRS), a questionnaire measuring the severity of attention deficit hyperactivity disorder symptoms on a 0-3 scale. As secondary outcome measures, we used the Attention Deficit Hyperactivity Disorder Rating Scale (ADHD RS), Conners' Teacher Rating Scale (CTRS), Clinical Global Impression-Severity (CGI-S), and iron status measured at baseline and after 4, 8, and 12 weeks of treatment. The Clinical Global Impression-Improvement (CGI-I) subscale score was measured after 12 weeks of treatment.

The ADHD RS [12] is a semistructured interview with the patient's parent or parents, or other primary caregiver; it is rated by the investigator. The scale covers the 18 symptoms of DSM-IV criterion A [3]. Each item is scored on a 4-point scale (0 = never or rarely, 1 = sometimes, 2 = often, and 3 = very often). The CPRS [13] is a widely used questionnaire, filled out by parents, which assesses attention deficit hyperactivity disorder symptoms. It contains 48 items scored on a 4-point scale similar to that of the ADHD RS, but with slightly different wording of anchors: 0 = not at all, 1 = just a little, 2 = pretty much, or 3 = very much. The primary efficacy assessment was the change from baseline to final visit in total score on the CPRS. CPRS score was assessed at screening, baseline, and weeks 4, 8, and 12.

The CTRS [13] short form is a questionnaire with 28 items about attention deficit hyperactivity disorder symptoms filled out by teachers, similar to the CPRS. We used the French version of the ADHD-RS, CPRS, and CTRS [14,15].

The CGI-S [15,16] is a single-item 7-point rating (1 = normal, not at all ill; 7 = among the most extremely ill subjects) based on the experience of the clinician with attention deficit hyperactivity disorder subjects. The CGI-I similarly rates improvement on a 7-point scale, as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.

All patients were checked for restless legs syndrome, assessed at baseline and weeks 12 according to the International Restless Legs Syndrome Study Group criteria specific for children [9].

Data Analysis

The changes from baseline to weeks 4, 8, and 12 were analyzed using parametric (paired Student's test) or nonparametric (paired Wilcoxon test) methods when appropriate for both groups. The correlations between serum ferritin levels and ADHD RS scores were performed using Pearson correlation coefficients.

Table 1. Sample characteristics at baseline

Characteristics	Placebo, n = 5	Ferrous Sulfate,* n = 17
Age, years (SD)	6.4 (0.9)	5.7 (1.2)
Female, no. (%)	2 (40)	3 (16)
Height, cm (SD)	121.0 (11.9)	121.0 (11.1)
Weight, kg (SD)	23.3 (6.8)	23.3 (5.9)
Hematological values		
Hemoglobin, g/dL (SD)	12.8 (0.6)	12.6 (0.8)
Mean cell volume, fL (SD)	81.5 (3.2)	81.9 (2.8)
Serum iron, μg/dL (SD)	11.9 (5.7)	14.8 (4.5)
Serum ferritin, ng/mL (SD)	26.2 (10.2)	29.1 (17.6)
Soluble transferrin receptors, mg/L (SD)	3.5 (0.9)	3.5 (0.8)
Transferrin, mg/L (SD)	2.8 (0.3)	2.7 (0.3)
CPRS total score (SD)	79.0 (29.0)	56.2 (11.9)
ADHD index (SD)	21.6 (8.8)	19.5 (4.8)
ADHD RS total score (SD)	35.0 (8.0)	38.1 (6.6)
Inattentive subscore (SD)	17.4 (4.5)	17.1 (3.3)
Hyperactive/Impulsive subscore (SD)	18.8 (5.2)	21.7 (6.3)
CGI-S score, no. (%)		
Moderately ill	1 (20.0)	1 (5.9)
Markedly ill	2 (40.0)	8 (47.1)
Severely ill	1 (20.0)	5 (29.4)
Extremely ill	1 (20.0)	3 (17.6)
RLS criteria, no. (%)		
Definite	1 (20.0)	1 (5.9)
Probable	0 (0.0)	3 (17.6)
Possible	1 (20.0)	10 (52.9)

There were no significant differences between groups.
Abbreviations:
ADHD = Attention deficit hyperactivity disorder
ADHD RS = Attention Deficit Hyperactivity Disorder Rating Scale
CGI-S = Clinical Global Impression-Severity
CPRS = Conners' Parent Rating Scale
RLS = Restless legs syndrome
SD = Standard deviation
* Ferrous sulfate was administered in the form of Tardyferon.

Results

A total of 23 children (18 boys and 5 girls) with attention deficit hyperactivity disorder and a low serum ferritin level (<30 ng/mL) at screening (between day –7 and day –3) met the inclusion criteria and were randomized to treatment with oral ferrous sulfate 80 mg/day (n = 18) or placebo (n = 5) at baseline (day 0). Of these, 19 children (83%) had serum ferritin levels of <30 ng/mL at baseline. Two patients discontinued iron supplementation: one for constipation and one lost to follow-up. No patient discontinued placebo. The demographic and clinical characteristics of the patients at baseline are summarized in Table 1.

As expected, the serum ferritin levels increased in the iron treatment group, from 29.1 ± 17.6 ng/mL at baseline to 45.9 ± 22.6 ng/mL at week 4 and to 55.7 ± 20.4 ng/mL at week 12 (P = 0.000). In contrast, they remained unimproved in the placebo group, changing from 26.2 ± 10.2 ng/mL at baseline to 31.0 ± 13.6 ng/mL at week 4 and to 21.0 ± 8.9 ng/mL at week 12 (Table 2).

There was no statistically significant difference between groups at baseline, and most variables showed no clinically impressive differences, but there was a clinically impressive disparity on the CPRS. At baseline, the severity score on the CPRS was about 40% worse for the placebo group than for the iron supplement group.

The efficacy outcomes are shown in Table 3. CPRS tended to improve more in the iron group (−7.0 ± 14.9, P = 0.055) than in the placebo group (−3.2 ± 22.8, P = 0.769) and ADHD RS severity significantly decreased after 12 weeks of treatment in the treatment group (−10.2 ± 14.0, P = 0.008), but not in the placebo group (3.0 ± 5.7, P = 0.308) (Fig. 1A). The improvement was observed in both subscores, but was particularly marked in the inattention subscore. A similar trend for improvement of CTRS in the treatment group (P = 0.076 for within-group change) but not in the placebo group was observed.

On the CGI-S, 4 of 17 patients (23.5%) treated with iron and none of the 5 patients treated with placebo were rated as very much or much improved. In addition, 5 of 17 in the treatment group (29.4%) were rated minimally improved, compared with 2 of 5 in the placebo group (40%) (Fig. 1B).

The number of children with restless legs syndrome (whether possible, probable, or definite) decreased from 14 of 19 (75%) at baseline in the treatment group (Table 1) to 2 of 19 meeting the criteria for possible restless legs syndrome at endpoint (10.5%) (P = 0.0003 for chi-square

Table 2. Effect of treatment on iron measures from baseline to endpoint at 12 weeks

Hematological Values	Placebo, n = 5		Ferrous Sulfate,* n = 17	
	Mean (SD)	95% CI†	Mean (SD)	95% CI†
Hemoglobin, g/dL	−0.36 (0.27)	−0.70, −0.02	0.25 (0.51)	−0.03, 0.53
Serum iron, μg/dL	0.98 (9.91)	−11.33, 13.29	5.41 (9.81)	−0.02, 10.85
Serum ferritin, ng/mL	−5.20 (14.32)	−22.99, 12.59	30.53 (17.50)	20.84, 40.22
Soluble transferrin receptors, mg/L	−0.10 (1.21)	−1.59, 1.40	−0.30 (0.86)	−0.78, 0.18
Transferrin, mg/L	−0.14 (0.32)	−0.54, 0.26	−0.24 (0.27)	−0.39, −0.09

Abbreviations:
CI = Confidence interval
SD = Standard deviation
* Ferrous sulfate was administered in the form of Tardyferon.
† Confidence interval is for difference from baseline to endpoint (week 12).

with Yates correction). In contrast, 2 of 5 children (40%) had restless legs syndrome at baseline in the placebo group (Table 1), but all 5 of the children (100%) children still had a possible restless legs syndrome after 12 weeks of treatment ($P = 0.16$ for chi-square with Yates correction). To be diagnosed as having definite RLS, the child must have all four of the essential adult criteria for RLS and either be able to describe the leg sensations in their own words or, if the child cannot describe the leg sensations in their own words, they must still meet four adult criteria for RLS and must meet two of the three following criteria: (1) Sleep disturbance for age; (2) Periodic limb movement in sleep index of more than five per hour sleep; (3) A first-degree relative (parent or sibling) with definite RLS [17]. Due to effect size in both groups, no correlation was found between serum ferritin level and occurrence of restless legs symptoms.

To determine if children with the lowest ferritin levels would benefit more from iron supplementation therapy than the other children, we performed a Pearson correlation between baseline serum ferritin levels and endpoint ADHD RS value. This correlation was not significant ($R = -0.45$, $P = 0.090$).

Iron therapy was generally well tolerated. None of the patients had a decrease of appetite or any exacerbation of attention deficit hyperactivity disorder symptoms. The adverse events in the iron group were abdominal pain (2 of 18, or 11%) and constipation and vomiting (both in the same patient) (1 of 18, or 6%); the latter patient discontinued the trial. In the placebo group, only abdominal pain was reported, in 2 of 5 children (40%). Abdominal pain in 4 children (2 on iron, 2 on placebo) spontaneously resolved in 3 of them while they were still taking the capsules; the fourth child, a girl treated with iron still had abdominal pain at the end of the trial.

There were no clinically significant changes in heart rate or blood pressure in either group. There were no significant changes in body weight after correction for age- and gender-specific means for the general pediatric population.

Discussion

To our knowledge, this is the first double-blind, randomized, placebo-controlled trial of oral ferrous sulfate on attention deficit hyperactivity disorder symptoms in iron-deficient nonanemic children.

Table 3. Effect of treatment on primary and secondary outcome measures after 12 weeks

Rating	Placebo, n = 5		Tardyferon, n = 17		
	Mean (SD)	95% CI	Mean (SD)	95% CI	95% CI
CPRS total score	−3.2 (22.8)	−31.49, 25.09	−7.0 (14.0)	−15.81, 0.19	−21.8, 14.2
ADHD index	−0.2 (7.2)	−9.13, 8.73	−1.8 (3.8)	−3.99, 0.26	−6.7, 3.4
CTRS total score	2.0 (3.4)	−34.12, 42.12	−5.3 (11.2)	−12.89, 0.74	−19.2, 4.5
ADHD RS total score	−3.0 (5.7)	−10.13, 4.13	−10.2 (14.0)	−18.48, −3.65†	−20.5, 6.1
Inattentive	−0.8 (2.5)	−3.89, 2.29	−4.4 (7.0)	−8.57, −1.18‡	−10.2, 3.1
Hyperactive/Impulsive	−2.2 (3.7)	−6.80, 2.40	−5.8 (7.5)	−10.22, −2.15†	−10.8, 3.6

Abbreviations:
ADHD RS = Attention Deficit Hyperactivity Disorder Rating Scale
CI = Confidence interval
CPRS = Conners' Parent Rating Scale
CTRS = Conners' Teacher Rating Scale
SD = Standard deviation
*Within treatments, confidence interval is for difference from baseline to endpoint (week 12); overall confidence interval is for difference from placebo.
† $P < 0.01$.
‡ $P < 0.05$, pairwise comparison.

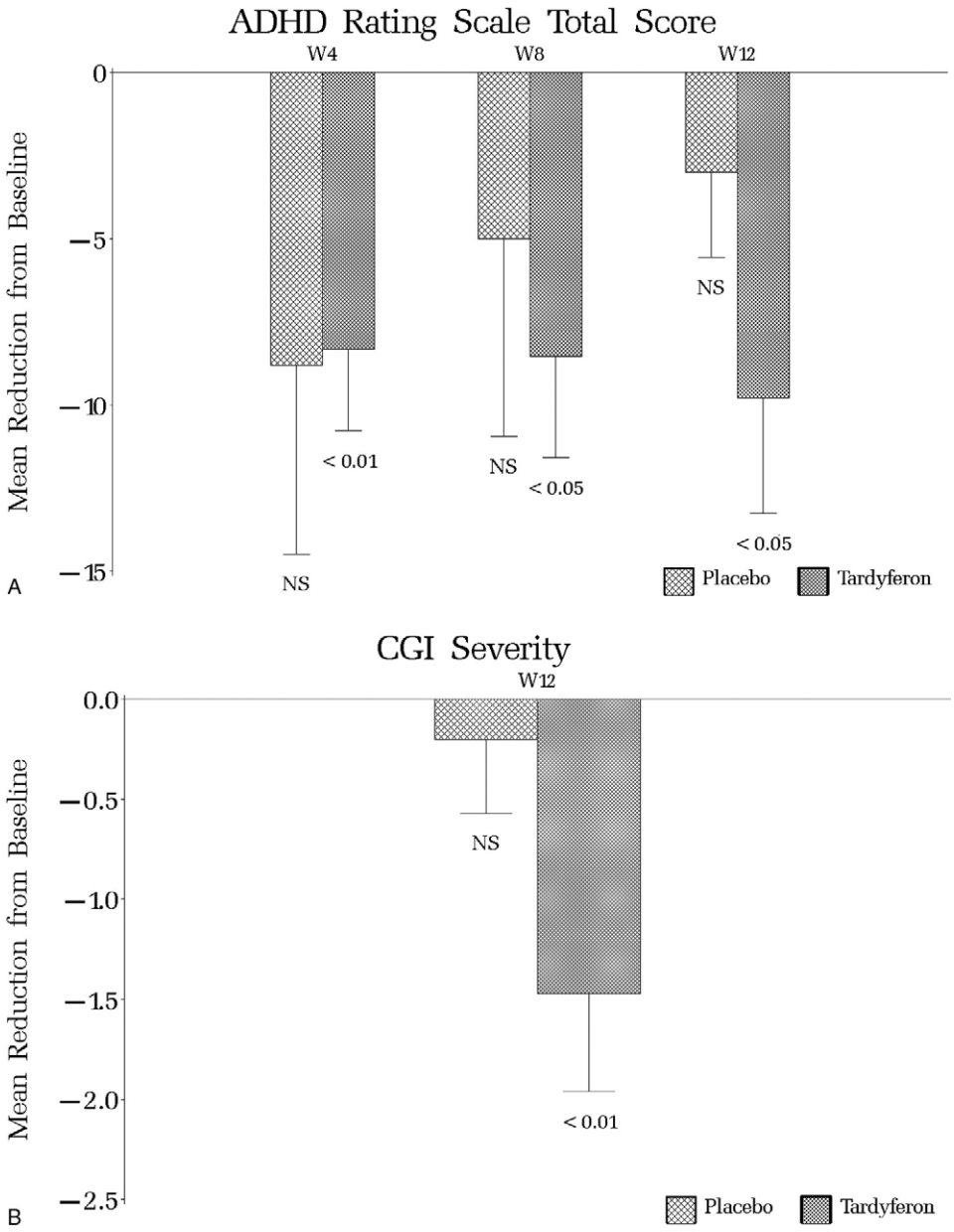

Figure 1. Change from baseline in ADHD RS score (A) and CGI-S score (B). Abbreviations: ADHD RS, Attention Deficit Hyperactivity Disorder Rating Scale; CGI-S, Clinical Global Impression-Severity.

Subjects who received iron supplementation therapy reported significant improvement on total score and on hyperactive/impulsive and inattentive subscales of the ADHD RS. Restless legs symptoms also were improved in the treatment group, but not in placebo. As previously reported, restless legs symptoms may mimic, may be mimicked by, or may hide evening motor activity of children with attention deficit hyperactivity disorder [8,9]. Therefore, we cannot exclude the possibility that the improvement of restless legs symptoms was actually accounted for by the improvement of attention deficit hyperactivity disorder motor activity in the evening. CGI-severity and improvement scores were also significantly improved in the iron therapy but not the placebo group, but CGI-I responder status (much improved or very much improved) was not significantly different between groups. The effect size of the difference between iron supplementation and placebo on the ADHD RS was large (Cohen's $d = 0.81$).

Patients, parents, teachers, and investigators were totally blind to treatment and to biochemical measures during the trial, which allows confidence that the subjective scoring of ADHD symptoms was unbiased. In retrospect, the choice of the short form CPRS total score as primary outcome was not wise, because the effect was diluted by non–attention deficit hyperactivity disorder items. This problem was further complicated by a baseline discrepancy between randomized groups on this particular measure. Nevertheless, the total scores for the CPRS and CTRS tended to decrease with iron treatment from baseline to endpoint.

At present, data from the literature provide little guidance for inferring the most appropriate doses and duration

of iron treatment for cognitive and behavioral symptoms in iron-deficient nonanemic children. The available placebo-controlled randomized clinical trials of iron supplementation were conducted after the first reports in the 1970s on the relationship between iron deficiency, cognitive impairment and motor instability in children [18]. Most of these studies, however, used intramuscular iron supplementation or included iron-deficient anemic children, or included young children (generally with abnormal psychomotor development) [19-21]. In one study designed to evaluate the effectiveness of iron supplementation in iron-deficient nonanemic subjects, Bruner et al. [22] used twice daily a 650 mg oral dose of ferrous sulfate for 8 weeks (a dose 16 times greater than the 80 mg dose we used in our younger children). This trial was conducted in a sample of girls with learning disabilities, aged 13-18, and the outcomes were cognitive measures; no measures of behavior were used. Further studies should be undertaken to better estimate the appropriate doses and treatment duration of oral iron supplementation for attention deficit hyperactivity disorder symptoms in iron-deficient nonanemic children.

Oral ferrous sulfate administration was generally well tolerated in the present trial. The observed side effects (constipation, nausea, abdominal pains) were consistent with those reported in previous studies using ferrous sulfate [22]. All events were considered mild or moderate in severity, except in one patient. Oral iron supplementation has been widely used for a long time in other indications and it is considered a safe drug. We cannot, however, determine whether a long-term iron treatment could induce hemosiderosis, although the risk seems low with moderate oral doses in children documented to have low systemic levels [23].

The effectiveness of ferrous sulfate in improving ADHD RS scores provides some evidence that iron deficiency is not only associated with attention deficit hyperactivity disorder, but may also contribute to its pathophysiology.

The results of this pilot trial should be considered with caution, but provide a rationale for larger and multisite trials assessing the effectiveness of iron supplementation for attention deficit hyperactivity disorder children with nonanemic iron deficiency. The absolute change obtained here with iron (−10.2 on ADHD RS score) is about 70% of the improvement obtained with atomoxetine (−14.0 to −15.6) in two pivotal studies [24] and is comparable to that found in meta-analyses of drugs with U.S. Food and Drug Administration indication for attention deficit hyperactivity disorder. If confirmed in a larger trial, the benefit obtained with iron therapy could place iron for selected low-ferritin patients as an alternative or complement to pharmacologic therapy in attention deficit hyperactivity disorder.

A hypothesis to explore is whether iron could enhance the action of methylphenidate and amphetamine. If so, it would be worthwhile to investigate whether patients who are poorly responsive to methylphenidate or amphetamine benefit from combined therapy with oral iron—particularly in the subset of children reporting restless legs symptoms.

The major limitation of this trial is the small sample size, especially in the placebo group. Like Millichap et al. [25], we suggest launching a controlled trial with a larger sample and correlating increased iron stores with improvements in parent and teacher questionnaires.

The present study raises the question of whether young children with attention deficit hyperactivity disorder should have serum iron or ferritin levels checked. The results reported were obtained with a mild iron deficiency that did not manifest in frank anemia and could be missed clinically. A careful dietary history may provide a clue that the child's intake of iron is deficient and justify the necessary laboratory work to check for tissue deficiency. In documented cases of iron deficiency, especially in preschoolers and very young children, clinical common sense would suggest first replenishing iron stores and then re-evaluating before instituting other treatment.

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