

Effectiveness of Iron Supplementation in a Young Child With Attention-Deficit/Hyperactivity Disorder

Eric Konofal, MD, PhD*‡; Samuele Cortese, MD*§; Michel Lecendreux, MD*; Isabelle Arnulf, MD, PhD‡; and Marie Christine Mouren, MD*

ABSTRACT. A 3-year-old child was referred to consultation for hyperactivity, attention deficit, impulsivity, and sleep problems. He met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for attention-deficit/hyperactivity disorder. At baseline, the Conners' Parent Rating Scale and the Conners' Teacher Rating Scale raw total scores were 30 and 32, respectively. The child had low a serum ferritin level (13 ng/mL). After 8 months of treatment with Tardyferon (ferrous sulfate, 80 mg/day), his serum ferritin increased to 102 ng/mL. Both parents and teachers reported considerable behavioral improvement. The Conners' Parent and Teacher Rating Scale raw total scores decreased to 19 and 13, respectively. This is the first report of the effectiveness of iron supplementation in a young child with attention-deficit/hyperactivity disorder. *Pediatrics* 2005;116:e732–e734. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0715; ADHD, iron deficiency.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; RLS, restless legs syndrome.

Preliminary evidence supports a significant iron deficiency in children with attention-deficit/hyperactivity disorder (ADHD).¹ The symptoms of ADHD may be related to a dopamine dysfunction or to an imbalance in dopaminergic function.^{2–5} Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Moreover, iron deficiency has been described to alter dopamine D₁ and D₂ receptor density and activity in animals.^{6,7} Therefore, brain iron stores might influence dopamine-dependent functions and, consequently, the expression of ADHD symptoms.

Previous neuropsychological studies reported an improvement in children's attention span after iron supplementation.^{8,9} However, no study thus far has addressed specifically the effectiveness of iron supplementation in iron-deficient children with ADHD

diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria.¹⁰ This study reports on the effect of iron supplementation in a 3-year-old child with ADHD.

CASE REPORT

A 3-year-old male was referred to the outpatient clinic of the child psychopathology unit for symptoms of inattention, hyperactivity, and impulsivity at school and home.

His father, a 28-year-old-employee, presented with symptoms of inattention and impulsivity. In childhood, he also was hyperactive. These symptoms caused a functional impairment first at school and subsequently in his work and social life. Therefore, the father was very worried about the symptomatology presented by his son. The mother, a 29-year-old housewife, reported no relevant psychiatric symptoms. The child was the only son in the family. No other relevant psychiatric symptoms or disorders in the family were reported. No medical problems during pregnancy or after the birth of the child were reported. The physical and neurologic development of the child was normal. At the time of the consultation, the child was in his first year of kindergarten. After consultation with the teachers, who also were very worried about the behavior of the child at school, the parents decided to come to our unit.

Although the diagnosis of ADHD in preschoolers is complex and still debated, evidence supports the validity of the DSM-IV¹⁰ diagnosis of ADHD in these children.^{11,12} Therefore, we looked for DSM-IV criteria of ADHD in this young child. According to the American Academy of Pediatrics recommendations,¹³ we obtained evidence from the parents and teachers. We directly interviewed both parents and obtained written reports from teachers.

According to the parents, the child had difficulty sustaining attention, seemed not to listen, had difficulty awaiting his turn, was easily distracted, had difficulty playing quietly, and was always on the go. The child also had sleep problems (ie, delayed sleep onset and excessive motility in sleep). The parents reported that some of these symptoms, such as hyperactivity and excessive impulsiveness, were present from the age of ~2 years. The parents agreed that the behavior of the child caused a significant functional impairment.

According to the teachers, the child had attention problems and difficulty finishing his activities (such as painting and putting together puzzles), he was usually out of his seat, and he frequently interrupted others in class. The teachers reported that the child was clearly more hyperactive, inattentive, and slower in his activities than his peers.

We conducted additional investigation for the most relevant differential diagnoses. Family functioning, as assessed by a clinical interview, was adequate and seemed not to account for the symptoms of the child. Mental retardation and borderline intellectual functioning were ruled out by clinical judgment. Pervasive developmental disorders were ruled out by an interview with the parents and the observation of the child. No delayed onset of spoken language was reported. The child had no expressive-language or mixed receptive-expressive language disorder. He had only a mild phonological disorder (ie, omissions and substitutions of sounds), as evaluated by a speech therapist from our unit. Speech therapy was promptly organized for this mild phonological disorder. Although difficult to evaluate directly with the child, anxiety and depressive disorders were ruled out after an

From the *Service de Psychopathologie de l'Enfant et de l'Adolescent, Hôpital Robert Debré, Paris, France; ‡Fédération des Pathologies du Sommeil, Hôpital Pitié Salpêtrière, Paris, France; and §Servizio di Neuropsichiatria Infantile, Dipartimento Materno Infantile e di Biologia-Genetica, Università degli Studi di Verona, Verona, Italy.

Accepted for publication May 31, 2005.

doi:10.1542/peds.2005-0715

No conflict of interest declared.

Address correspondence to Eric Konofal, MD, PhD, Service de Psychopathologie, de l'Enfant et de l'Adolescent, 48 Boulevard Serurier, 75019 Paris, France. E-mail: eric.konofal@rdb.ap-hop-paris.fr

PEDIATRICS (ISSN 0031 4005). Copyright © 2005 by the American Academy of Pediatrics.

interview with the parents. Impairment of vision and hearing were ruled out by physical examination. Acute or chronic medical illnesses (including epilepsy) were not reported by parents. The child did not take any medication. As previously stated, the child presented with sleep problems such as delayed sleep onset and excessive motility in sleep. These sleep problems could have accounted for a certain part of the symptomatology, but it is unlikely that they accounted for it all, because some of his symptoms of ADHD (hyperactivity and impulsiveness) preceded the sleep problems.

Therefore, the synthesis of information from parents and teachers supported the diagnosis of ADHD according to DSM-IV criteria.

Although they are not essential for the diagnosis, we used the Conners' Teacher Rating Scale and the Conners' Parent Rating Scale as optional tools, according to American Academy of Pediatrics guidelines (recommendations 3A and 4A). We used the 1969¹⁴ and 1973¹⁵ versions, respectively, of these questionnaires, which were translated into French and validated on a French childhood population.¹⁶ At baseline, the Conners' Parent Rating Scale and the Conners' Teacher Rating Scale raw total scores were 30 and 32, respectively.

At present, there are no routinely indicated tests to establish the diagnosis of ADHD. However, after our report on iron deficiency in ADHD children, we systematically proposed a free screening of serum ferritin levels to parents of children with ADHD (or children suspected of having ADHD) who were referred to our unit. After an exhaustive explication on the potential relationship between iron deficiency and symptoms of ADHD (at least in some children with ADHD), the parents agreed to this blood test. At the first consultation, blood samples were obtained; serum ferritin levels and hemoglobin were measured. The child had a low serum ferritin level (13 ng/mL) but was not anemic (hemoglobin: 12.9 mg/dL). According to our analyzing laboratory, the normal reference range for serum ferritin in preschool-aged children is 15 to 80 ng/mL for both genders. Given the low value of serum ferritin in the child, an iron supplementation was proposed to his parents, who agreed to it. Therefore, an iron supplementation with Tardyferon (ferrous sulfate) was prescribed (80 mg/day). After 4 months of treatment, his serum ferritin increased to 97 ng/mL. At the clinical interview, the child's parents reported moderate behavioral improvements, particularly concerning impulsivity and hyperactivity. Written reports by teachers confirmed this mild behavioral improvement. Sleep problems, assessed by parental interview and sleep diaries filled out by the parents, were improved. After 8 months of iron treatment, his serum ferritin level increased to 102 ng/mL. Both the parents and teachers reported marked behavioral improvement. The Conners' Parent Rating Scale and the Conners' Teacher Rating Scale raw total scores decreased to 19 and 13, respectively. At clinical interview, the parents described the child as "transformed." He was less hyperactive, more attentive, and less impulsive, although he still presented some difficulty delaying reaction when he was frustrated. In their written reports, teachers also reported marked behavioral changes. The child was more organized in his activities (eg, painting, putting together puzzles, cutting), more attentive, and less forgetful and impulsive. His relationships with his peers were very much improved. He became progressively more collaborative during speech therapy. The quality of his sleep continued to be preserved.

DISCUSSION

To the best of our knowledge, this is the first report on the effectiveness of iron supplementation in a young child with ADHD.

Sever et al¹⁷ reported limited effectiveness of iron supplementation in a sample of 14 boys with ADHD who were 7 to 11 years of age. In their study, there was a significant decrease on the Conners' Parent Rating Scale scores, but the Conners' Teacher Rating Scale scores did not change significantly after iron supplementation, and the authors could not rule out a placebo effect. It is interesting to note that none of these boys with ADHD were iron deficient. Moreover, posttreatment assessment was performed 30

days after the beginning of iron supplementation, which could be too early to observe remarkable effects. In animal models, it has been reported that iron supplementation in 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,¹⁷ which may explain the limited improvement reported by the authors. In accordance with this hypothesis, in our child, behavioral improvements were observed after 8 months of iron supplementation, whereas ferritin levels began to increase faster.

In our study, the decrease in Conners' Parent and Teacher Rating Scale scores seems to rule out a placebo effect.

Because the parents reported an improvement in sleep, it is possible that a better quality of sleep may have contributed to the decrease in behavioral symptomatology. In fact, several sources of evidence reported an association between sleep disruption and ADHD symptoms.¹⁸ As stated in a recent review by our group,¹⁹ symptoms of restless legs syndrome (RLS) may mimic or be comorbid with ADHD symptoms. Because RLS may be associated with low ferritin levels and symptoms of RLS may improve after iron supplementation, it is possible that this young child may have had RLS instead of or in addition to ADHD and that iron supplementation acted primarily to improve the symptoms of RLS. Although the diagnosis of RLS in a 3-year-old child is very difficult given the limited ability to describe the subjective symptomatology of RLS, we found no symptoms of RLS. Moreover, neither the mother nor the father had symptoms of RLS. Therefore, our findings seem not to be accounted for by improvement in RLS symptomatology.

Otero et al²⁰ assessed the effectiveness of iron supplementation on attention function in iron-deficient children by using neurophysiological measures. They recorded visual event-related potentials in 2 groups of children (ie, iron-deficient children and a control group) while executing a continuous-performance task. The recording was performed before and after iron supplementation. Before iron treatment, iron-deficient children almost lacked a P300 in central and parietal regions. After iron supplementation, P300 clearly became evident, although its Pz amplitude remained smaller compared with that in children in the control group. It is known that P300 has been used as a means to determine attentional function. However, Otero et al²⁰ used a neurophysiological measure of neuropsychological function (ie, attention) in a group of children from the general population, whereas we assessed the behavior of 1 child with ADHD by using clinical interviews and questionnaires. Moreover, the children studied by Otero et al²⁰ were older (8–10 years) than our child. Nonetheless, findings from Otero et al²⁰ seem to be in agreement with our results, confirming the effectiveness of iron supplementation in improving attentional function in iron-deficient children.

Our report suggests the usefulness of screening serum ferritin levels in children with ADHD as well as the potential effectiveness of iron supplementa-

tion for children with ADHD who have low ferritin levels. It also provides a rationale for double-blind placebo-controlled studies of iron supplementation for children with ADHD who also have low serum ferritin levels.

ACKNOWLEDGMENT

We are grateful to Solange Cook for translation of the manuscript.

REFERENCES

1. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med.* 2004;158:1113–1115
2. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Cohen RM. High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. *Am J Psychiatry.* 1999;156:1209–1215
3. Jucaite A, Fernell E, Halldin C, Forssberg H, Farde L. Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. *Biol Psychiatry.* 2005;57:229–238
4. Russell VA. Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder—the spontaneously hypertensive rat. *Neurosci Biobehav Rev.* 2003;27:671–682
5. Solanto MV. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behav Brain Res.* 2002;130:65–71
6. Erickson KM, Jones BC, Hess EJ, Zheng Q, Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharmacol Biochem Behav.* 2001;69:409–418
7. Youdim MB, Ben-Shachar D, Yehuda S. Putative biological mechanisms of the effect of iron deficiency on brain biochemistry and behavior [published correction appears in *Am J Clin Nutr.* 1990;5:319]. *Am J Clin Nutr.* 1989;50:607–615
8. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. *Am J Clin Nutr.* 1989;50:667–673
9. Walter T, Kovalskys J, Stekel A. Effect of mild iron deficiency on infant mental development scores. *J Pediatr.* 1983;102:519–522
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994
11. Dopfner M, Rothenberger A, Sonuga-Barke E. Areas for future investment in the field of ADHD: preschoolers and clinical networks. *Eur Child Adolesc Psychiatry.* 2004;13(suppl 1):I130–I135
12. Lahey BB, Pelham WE, Stein MA, et al. Validity of DSM-IV attention-deficit/hyperactivity disorder for younger children [published correction appears in *J Am Acad Child Adolesc Psychiatry.* 1999;38:222]. *J Am Acad Child Adolesc Psychiatry.* 1998;37:695–702
13. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics.* 2000;105:1158–1170
14. Conners CK. A teacher rating scale for use in drug studies with children. *Am J Psychiatry.* 1969;126:884–888
15. Conners CK, Barkley RA. Rating scales and checklists for child psychopharmacology. *Psychopharmacol Bull.* 1985;21:809–843
16. Dugas M. *L'Hyperactivité chez l'Enfant.* Paris, France: PUF; 1987
17. Sever Y, Ashkenazi A, Tyano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. *Neuropsychobiology.* 1997;35:178–180
18. Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 1998;37:637–646
19. Cortese S, Konofal E, Lecendreux M, et al. Restless legs syndrome and ADHD: a review of the literature. *Sleep.* 2005;28:1007–1013
20. Otero GA, Pliego-Rivero FB, Contreras G, Ricardo J, Fernandez T. Iron supplementation brings up a lacking P300 in iron deficient children. *Clin Neurophysiol.* 2004;115:2259–2266

Effectiveness of Iron Supplementation in a Young Child With Attention-Deficit/Hyperactivity Disorder

Eric Konofal, Samuele Cortese, Michel Lecendreux, Isabelle Arnulf and Marie Christine Mouren

Pediatrics 2005;116:e732

DOI: 10.1542/peds.2005-0715

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/116/5/e732>

References

This article cites 18 articles, 3 of which you can access for free at:
<http://pediatrics.aappublications.org/content/116/5/e732#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Attention-Deficit/Hyperactivity Disorder (ADHD)
http://www.aappublications.org/cgi/collection/attention-deficit:hyperactivity_disorder_adhd_sub
Therapeutics
http://www.aappublications.org/cgi/collection/therapeutics_sub
Toxicology
http://www.aappublications.org/cgi/collection/toxicology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Effectiveness of Iron Supplementation in a Young Child With Attention-Deficit/Hyperactivity Disorder

Eric Konofal, Samuele Cortese, Michel Lecendreux, Isabelle Arnulf and Marie
Christine Mouren

Pediatrics 2005;116:e732

DOI: 10.1542/peds.2005-0715

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/116/5/e732>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2005 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

