

Original Article

## Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children

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### Abstract

**Objective:** Increasing evidence suggests a significant comorbidity between attention-deficit/hyperactivity disorder (ADHD) and restless legs syndrome (RLS). Iron deficiency may underlie common pathophysiological mechanisms in subjects with ADHD plus RLS (ADHD+RLS). To date, the impact of iron deficiency, RLS and familial history of RLS on ADHD severity has been scarcely examined in children. These issues are addressed in the present study.

**Methods:** Serum ferritin levels, familial history of RLS (diagnosed using National Institutes of Health (NIH) criteria) and previous iron supplementation in infancy were assessed in 12 ADHD+RLS children, 10 ADHD children and 10 controls. RLS was diagnosed using NIH-specific pediatric criteria, and ADHD severity was assessed using the Conners' Parent Rating scale.

**Results:** ADHD symptom severity was higher, although not significantly, in children with ADHD+RLS compared to ADHD. The mean serum ferritin levels were significantly lower in children with ADHD than in the control group ( $p < 0.0005$ ). There was a trend for lower ferritin levels in ADHD+RLS subjects versus ADHD. Both a positive family history of RLS and previous iron supplementation in infancy were associated with more severe ADHD scores.

**Conclusions:** Children with ADHD and a positive family history of RLS appear to represent a subgroup particularly at risk for severe ADHD symptoms. Iron deficiency may contribute to the severity of symptoms. We suggest that clinicians consider assessing children with ADHD for RLS, a family history of RLS, and iron deficiency.

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**Keywords:** Restless legs syndrome; Attention-deficit/hyperactivity disorder; Iron; Dopamine; Ferritin

### 1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder estimated to affect approximately 5–10% of the gen-

eral population in Western Europe and the United States [1,2]. In adults, RLS is characterized by uncomfortable leg sensations with an irresistible urge to move the legs [3]. These leg sensations are worse when sitting or lying and at night and are relieved, at least partially, by movement [3]. Children may exhibit and report symptoms of RLS differently from adults, due to their limited ability to describe the subjective symptomatology of RLS [4].

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In order to help overcome the difficulties of diagnosing RLS in children, the International Restless Legs Syndrome Study Group (IRLSSG) has proposed a set of criteria specific to this population [3]. Remarkably, in childhood, RLS symptoms may not be limited to the nighttime [4,5]. For example, Picchietti and Walters reported some cases of RLS children presenting with restlessness during schooltime, leading to significant inattention and concentration difficulties [5].

The majority of studies on RLS pathophysiology have focused on the dysfunction of the dopaminergic system [6,7]. Moreover, several lines of evidence have suggested a potential role of altered brain iron metabolism [8,9]. In particular, data from magnetic resonance imaging (MRI) [10], autopsy studies [11] and analyses of cerebrospinal fluid ferritin [12–14] have shown a significant iron deficiency in RLS. Furthermore, intravenous iron therapy has been reported effective for symptomatic treatment of RLS [15,16]. The hypothesis of iron deficiency is not incompatible with a dopaminergic dysfunction since iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Moreover, iron deficiency has been described to alter dopamine D<sub>2</sub> receptor density and dopamine transport activity [17]. Iron stores may, therefore, influence dopamine-dependent functions [18].

Evidence from clinical reports indicates a significant association between RLS and one of the most frequent childhood neuropsychiatric disorders, namely attention-deficit/hyperactivity disorder (ADHD) [19]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria, this disorder is characterized by a persistent, pervasive and age-inappropriate pattern of inattention, hyperactivity and impulsivity [20].

Although ADHD is a heterogeneous disorder and its pathophysiology is not completely understood, neuroimaging and genetic studies have provided evidence for a dopaminergic dysfunction in the midbrain, frontal and prefrontal cortex [21–24]. In our previous studies, we reported a significant iron deficiency in a subgroup of ADHD children; moreover, serum ferritin levels were found to correlate with ADHD symptom severity [25]. On the basis of the above-mentioned evidence, we hypothesize that, in patients with both RLS and ADHD, these two disorders may share common central nervous system (CNS) pathophysiology influenced by iron deficiency [26]. At the present time, little attention has been addressed to the clinical features of children with ADHD plus RLS (ADHD+RLS) in comparison to those with ADHD only (ADHD). In particular, no previous studies examined the effect of RLS on the clinical manifestations of ADHD in children with both of these disorders. Furthermore, no studies have assessed iron levels in children with ADHD+RLS compared to children with ADHD and controls. Finally, to our

knowledge, no studies have evaluated the family history of RLS in patients with ADHD and its impact on ADHD symptom severity. Exploring these issues could allow a better understanding of the clinical features of patients with both ADHD and RLS and may provide insight into the pathophysiological overlap between ADHD and RLS.

Therefore, the two objectives of this study were as follows:

1. To compare ADHD symptom severity and mean serum ferritin levels in three groups of children: a group of ADHD+RLS, ADHD, and age- and sex-matched controls;
2. To investigate the family history of RLS and a previous history of iron supplementation, as well as their impact on ADHD symptoms, in these three groups.

## 2. Methods

### 2.1. Patient population

Participants in the study were outpatients from the same school district referred to the child psychopathology department of Robert Debré University Hospital in Paris–France between March 2003 and April 2004 with a possible diagnosis of ADHD with or without a sleep disorder. Inclusion criterion was a diagnosis of ADHD according to the DSM-IV criteria [20]. Exclusion criteria were the presence of additional mild to moderate behavioural, mood or anxiety disorders, physical diseases and malnutrition. RLS diagnosis was based on the National Institutes of Health (NIH) consensus criteria for RLS in children [3]. For the diagnosis of RLS in children, three categories have been proposed to encompass the full spectrum of pediatric RLS: definite, probable and possible RLS.

After exclusion criteria, 22 children (17 boys and 5 girls) aged 5 years and 3 months to 8 years and 11 months participated in this study. Twelve out of 22 of these children (54.5%) met the diagnostic criteria for RLS: two definite, four probable, and six possible RLS.

Ten children referred for suspicion of behavioural disturbances or school problems, but who actually did not meet diagnostic criteria for ADHD or any other psychiatric disorders or RLS symptoms, were included in the control group. None of the children were on medication for ADHD, RLS, or sleep at the time of assessment. In addition, none were on iron supplementation at the time of assessment.

### 2.2. Procedure

In order to evaluate the ADHD symptom severity, the parents of the subjects were asked to complete the

Conners' Parent Rating Scale (CPRS) [27], which is a widely used questionnaire that assesses behavioural symptoms, including ADHD. We used the CPRS-48 items, which is the only validated French version to assess ADHD symptoms [28]. This version contains 48 items scored on a four-point Likert-type scale. The CPRS provides information on six subscales: conduct problems, learning problems, psychosomatic problems, impulsive–hyperactive behaviours, anxiety and hyperactivity index. For the purposes of this study, we included the hyperactivity index (which includes symptoms of hyperactivity, impulsivity and inattention), impulsive–hyperactive, learning and conduct problems.

Both biologic parents of the patients as well as of controls were specifically asked for their personal history of RLS as well as for a history of iron supplementation in their children, using one-to-one interview. Health records were examined to confirm a possible history of iron supplementation in infancy. We screened for any iron prescription mentioned in the health records.

After the completion of the CPRS, serum ferritin levels were measured before breakfast in the morning (Elec-sys, Enzymun-Test, France), as were haemoglobin, hematocrit, and iron levels [25]. Written informed consent was obtained from one or both parents or legal tutor before including a child in the study, which was approved by the ethics review board.

### 2.3. Statistics

#### 2.3.1. Statistical analyses

Statistical analyses were performed using the Stat-View<sup>®</sup> 5 software (SAS Institute Inc.) for between-group comparison of serum ferritin levels and symptom severity using analysis of variance (ANOVA). Similarly, the effects of positive family history of RLS and iron supplementation during infancy on the CPRS (index) for serum ferritin levels were assessed using ANOVA.

### 3. Results

The demographic characteristics, mean CPRS scores and biological measures for the three groups (ADHD+RLS, ADHD and controls, respectively) are shown in Table 1.

ADHD symptom severity, measured by the ADHD index on the CPRS, was higher, although not significantly, in ADHD+RLS versus ADHD. As expected, ADHD symptom severity was higher in ADHD+RLS and ADHD versus controls. The same trend was observed for the conduct disorders index. The hyperactivity–impulsivity index was slightly higher in the ADHD group compared to the ADHD+RLS group, although no significant differences were found. There were no significant differences in the three groups in the learning index.

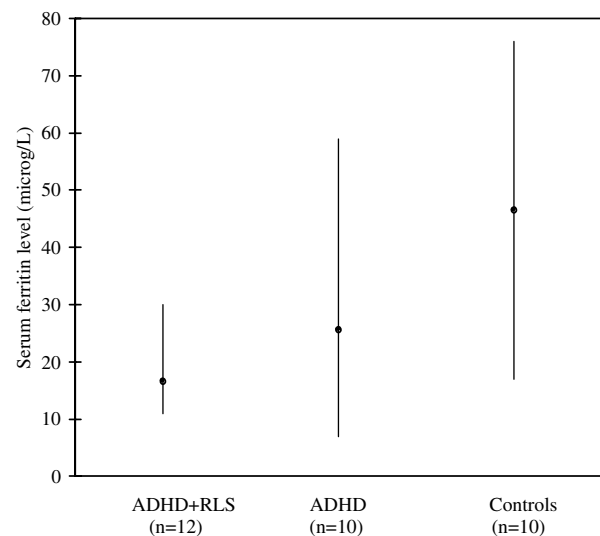


Fig. 1. Mean (plot)  $\pm$  SD (vertical line) serum ferritin levels ( $\mu\text{g/L}$ ) measured in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and Restless Legs Syndrome (RLS), ADHD and controls.

Table 1

Characteristics of children with or without ADHD and RLS

	ADHD+RLS (n = 12)	ADHD (n = 10)	Controls (n = 10)	p ANOVA		
				ab	ac	bc
Age (years)	7.3 $\pm$ 1.2	6.7 $\pm$ 0.9	7.0 $\pm$ 0.9	NS	NS	NS
Gender (M/F)	8/4	9/1	7/3	NS	NS	NS
<i>Conners' parent T scores:</i>						
Hyperactivity index	75 $\pm$ 14	67 $\pm$ 21	45 $\pm$ 22	NS	<0.0001	0.0019
Impulsive–hyperactive	21 $\pm$ 4	23 $\pm$ 3	12 $\pm$ 7	NS	0.0015	0.0026
Learning problems	8 $\pm$ 3	9 $\pm$ 3	7 $\pm$ 4	NS	NS	NS
Conduct problems	13 $\pm$ 4	12 $\pm$ 4	4 $\pm$ 3	NS	0.0001	0.0042
Positive family history of restless legs syndrome	7 (58%)	1 (10%)	0	NA	NA	NA
Iron supplementation during infancy	6 (50%)	2 (20%)	0	NA	NA	NA
Serum ferritin level ( $\mu\text{g/L}$ )	16 $\pm$ 6	25 $\pm$ 15	46 $\pm$ 18	NS	0.001	0.0155

Data are mean  $\pm$  SD; NS, not significant; NA, not applicable; a, ADHD+RLS; b, ADHD; c, controls.

Table 2

Effects of positive family history of restless legs syndrome and iron supplementation during infancy on Conners' Parent Rating scales and serum ferritin levels

	<i>p</i> ANOVA Conners' parents rating scale (index)				Serum ferritin levels
	Hyperactivity index	Impulsive-hyperactive	Learning problems	Conduct problems	
Positive family history of restless legs syndrome	0.0007	0.0055	NS	0.0166	0.0235
Iron supplementation during infancy	0.0469	NS	NS	NS	NS

The plots of mean serum ferritin levels are shown in Fig. 1. The mean serum ferritin levels were significantly lower in children with ADHD (mean  $\pm$  standard deviation (SD),  $21 \pm 11$   $\mu\text{g/L}$ ) than in controls ( $46 \pm 18$   $\mu\text{g/L}$ ) ( $p < 0.0005$ ). Children with ADHD+RLS had lower mean serum ferritin levels than ADHD children, although the difference did not reach statistical significance. Moreover, the serum ferritin levels had a more restricted range in the ADHD+RLS group than in the ADHD and control groups (respectively: [11–30  $\mu\text{g/L}$ ], [7–59  $\mu\text{g/L}$ ], and [17–76  $\mu\text{g/L}$ ]).

A positive familial history of RLS was found in seven children (58%) with ADHD+RLS and in one child with ADHD (10%), while none in the control group presented with a positive familial history of RLS (Table 1). Interestingly, a positive family history of RLS was significantly associated with high ADHD index scores ( $p = 0.0007$ ) and with a low serum ferritin level ( $p = 0.0235$ ) (Table 2).

As shown in Table 1, a previous history of iron supplementation during infancy (indicating an iron deficiency status) was present in 50% of the ADHD+RLS subjects, in 20% of the ADHD patients and in none of the controls. Interestingly, as reported in Table 2, a previous history of iron supplementation was significantly associated with high ADHD index scores ( $p = 0.0469$ ).

#### 4. Discussion

To our knowledge, this is the first study that assessed iron levels, previous iron supplementation and RLS history in the family in a group of ADHD+RLS children, in a sample of ADHD children without RLS and in a control group. This is also the first study that explored the impact of RLS and positive family history of RLS on ADHD symptom severity.

We found that mean serum ferritin levels were significantly lower in children with ADHD than in controls. This finding is consistent with our previous data from a different sample. Moreover, ADHD symptoms were more severe in ADHD+RLS children compared to those with ADHD only. Although this difference did not reach statistical significance, it is possible that this study was underpowered by the limited sample size. Therefore, we suggest that further larger studies explore

this issue. As for the mechanism explaining the aggravation of ADHD symptoms, sleep fragmentation linked to RLS may negatively impact daytime behaviour, contributing to symptoms of inattention, hyperactivity and impulsivity. Moreover, since the ADHD+RLS group presented with the lowest ferritin levels and ferritin levels were associated with high ADHD index scores, we speculate that ADHD+RLS children may represent a subgroup of ADHD characterized by high symptom severity determined by the pathophysiological consequences of iron deficiency. However, given the cross-sectional nature of this study, we can not infer causality, and thus our conclusions are speculative. Nonetheless, our results suggest a role for RLS and iron deficiency screening in ADHD. Our results also suggest that a positive family history of RLS may be a marker of severity in ADHD and early-onset RLS but also may predict ADHD. Given the high genetic component in RLS, this finding converges with the hypothesis of a pathophysiological overlap between ADHD and RLS in subjects with severe forms of ADHD.

Finally, previous iron supplementation during infancy was also associated with more severe ADHD symptoms. We can speculate that patients with severe forms of ADHD are iron deprived and that iron supplementation in infancy may not be sufficient to improve the central iron status of these subjects.

We can hypothesize that a previous iron supplementation was intended to treat an acute or a chronic long-term iron deficiency at infancy which, in spite of this treatment, continued to persist during childhood. Previous animal studies indicated that a chronic and severe iron deficiency during CNS development lead to dopamine receptors decreasing, which was irreversible in spite of iron supplementation during the post-natal period [29]. Further studies assessing the appropriate modalities of iron supplementation during the CNS maturation are greatly needed to better understand how and when iron supplementation may be efficient to improve ADHD symptoms. Moreover, iron deficiency during infancy or in childhood may lead to iron misregulation in CNS, which could be not detectable using peripheral measures.

In conclusion, we believe that our results provide some insight into the possible pathophysiological over-

lap between ADHD and RLS, and into the role of iron deficiency in this association. Our findings may also be of interest from a clinical standpoint, suggesting that the clinician should consider family RLS history and previous iron supplementation as a marker of severity of ADHD. Additional studies are needed to confirm and expand upon our results. Moreover, further genetic and neurophysiological studies on the potential overlap between ADHD, RLS and iron deficiency could advance our knowledge in this complex and promising topic.

## References

- [1] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165(11):1286–92. 13.
- [2] Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. *Sleep Med Rev* 2006;10(3):153–67.
- [3] Allen RP, Picchiatti DL, Hening W, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4(2):101–19.
- [4] Walters AS, Picchiatti DL, Ehrenberg BL, Wagner ML. Restless legs syndrome in childhood and adolescence. *Pediatr Neurol* 1994;11(3):241–5.
- [5] Picchiatti DL, England SJ, Walters AS, Willis K, Verrico T. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *J Child Neurol* 1998;13(12):588–94.
- [6] Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med* 2007;120(1 Suppl. 1):S13–21.
- [7] Cervenka S, Palhagen SE, Comley RA, Panagiotidis G, Cselenyi Z, Matthews JC, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. *Brain* 2006;129(Pt 8):2017–28.
- [8] Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med* 2004;5(4):385–91.
- [9] Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep* 1998;21(4):371–7.
- [10] Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* 2001;56(2):263–5.
- [11] Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* 2003;61(3):304–9.
- [12] Clardy SL, Earley CJ, Allen RP, Beard JL, Connor JR. Ferritin subunits in CSF are decreased in restless legs syndrome. *J Lab Clin Med* 2006;147(2):67–73.
- [13] Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology* 2000;54(8):1698–700.
- [14] Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. *J Sleep Res* 2005;14(1):43–7.
- [15] Earley CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med* 2005;6(4):301–5.
- [16] Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis* 2004;43(4):663–70.
- [17] Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, et al. Iron deficiency: differential effects on monoamine transporters. *Nutr Neurosci* 2005;8(1):31–8.
- [18] Beard J. Iron deficiency alters brain development and functioning. *J Nutr* 2003;133(5 Suppl 1):1468S–72S.
- [19] Cortese S, Konofal E, Lecendreu M, Arnulf I, Mouren MC, Darra F, et al. Restless legs syndrome and attention-deficit/hyperactivity disorder: a review of the literature. *Sleep* 2005;28(8):1007–13.
- [20] American Psychiatric Association. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Press 1994.
- [21] Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. *Lancet* 1999;354(9196):2132–3.
- [22] Biederman J, Faraone SV. Current concepts on the neurobiology of Attention-Deficit/Hyperactivity Disorder. *J Atten Disord* 2002;6(Suppl. 1):S7–S16.
- [23] Khan SA, Faraone SV. The genetics of ADHD: a literature review of 2005. *Curr Psychiatry Rep* 2006;8(5):393–7.
- [24] Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2006:34.
- [25] Konofal E, Lecendreu M, Arnulf I, Mouren MC. Iron deficiency in children with attention deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 2004;158:1113–5.
- [26] Konofal E, Cortese S. Restless legs syndrome and attention-deficit/hyperactivity disorder. *Ann Neurol* 2005;58(2):341–2.
- [27] Conners CK. Manual for Conners' Rating Scales. North Tona-wanda, NY: Multi-Health Systems, Inc; 1989.
- [28] Dugas M. L'hyperactivité chez l'enfant. Paris: PUF; 1987.
- [29] Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharmacol Biochem Behav* 2001;69(3-4):409–18.