

Restless Legs Syndrome and Attention-Deficit/Hyperactivity Disorder: a Review of the Literature

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Study Objective: To review evidence on the association between restless legs syndrome (RLS) and attention-deficit/hyperactivity disorder (ADHD), to discuss the hypothetical mechanisms underlying this association, and to consider the potential interest for common pharmacologic treatments of RLS and ADHD when co-occurring.

Method: A PubMed search.

Results: In clinical samples, up to 44% of subjects with ADHD have been found to have RLS or RLS symptoms, and up to 26% of subjects with RLS have been found to have ADHD or ADHD symptoms. Several mechanisms may explain this association. Sleep disruption associated with RLS might lead to inattentiveness, moodiness, and paradoxical overactivity. Diurnal manifestations of RLS, such as restlessness and inattention, might mimic ADHD symptoms. Alternatively, RLS might be comorbid with idiopathic ADHD. Subjects with RLS and a subset of subjects with ADHD might share a common dopamine dysfunction. Limited evidence suggests that some dopaminergic agents, such as levodopa/carbidopa, pergolide, and ropinirole, may be effective in children with RLS associated with ADHD

symptoms.

Conclusions: Although still limited, evidence from clinical studies demonstrates an association between RLS and ADHD or ADHD symptoms. Further clinical studies using standard criteria and procedures are needed to better estimate the degree of association. Epidemiologic studies are required to assess the relationship between ADHD and RLS symptoms in nonclinical samples. Further investigations should address the mechanisms underlying the relationship between RLS and ADHD. Several dopaminergic agents seem to be promising treatment for RLS associated with ADHD symptoms. To date, however, the absence of randomized and blinded controlled studies does not allow evidence-based recommendations.

Keywords: Attention-deficit/hyperactivity disorder (ADHD), restless legs syndrome (RLS), dopaminergic agents

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INTRODUCTION

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IS ONE OF THE MOST COMMON PSYCHIATRIC DISORDERS OF childhood and adolescence.¹ It is estimated to affect 3% to 5% of school-aged children in the United States.² ADHD is characterized by a persistent pattern of inattention, hyperactivity-impulsivity, or both. Onset before the age of 7 and impaired functioning in 2 or more settings are essential for the diagnosis.³ Symptoms of ADHD may persist into adulthood in about two thirds of patients.⁴⁻⁶ Sleep disruption has been reported in patients with ADHD.⁷⁻⁹

Restless legs syndrome (RLS) is a common sensorimotor disorder with a prevalence of 10% to 15% in the general population.¹⁰ It is characterized by uncomfortable leg sensations with an irresistible urge to move the legs.¹⁰⁻¹³ These leg sensations are worse when sitting or lying, are relieved at least partially by movement, and are typically worse at night in adults.¹³ Patients with RLS may also have involuntary periodic limb movements while awake, and

about 80% of patients with RLS also have periodic limb movements in sleep (PLMS).¹⁴ To allow for a more-uniform diagnosis of RLS, the International Restless Legs Syndrome Study Group (IRLSSG) first developed a set of diagnostic criteria in 1995.¹³ The criteria were subsequently revised in 2002 (Table 1).¹⁵ Although RLS is traditionally believed to be a disorder of middle to older age,¹⁶ several reports have documented its occurrence in children.^{14,16-39} Children may exhibit and report symptoms of RLS differently than do adults because of their limited ability to describe the subjective symptomatology of RLS. To help overcome the difficulties of diagnosing RLS in children, the IRLSSG

Table 1—International RLS Study Group Diagnostic Criteria for RLS in Adults

An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).

The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.

The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Disclosure Statement

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have proposed a set of criteria that are specific for this population (Table 2).¹⁵

The association between ADHD and sleep disorders has inspired a series of studies examining the relationship between ADHD and RLS, the latter being also associated with sleep disturbance. Several mechanisms have been proposed to explain the association between ADHD and RLS. Moreover, growing evidence suggests that the relationship between ADHD and RLS may have relevant consequences for the treatment of these 2 conditions when they co-occur.

To date, no review of the literature is available on the association between ADHD and RLS. Therefore, the objective of this paper is to review the evidence on the relationship between RLS and ADHD, to examine the potential mechanisms underlying this association, and to discuss perspectives for a common treatment of the 2 conditions when they co-occur.

Table 2—Criteria for the Diagnosis of RLS in Children

Criteria for the diagnosis of definite RLS in children

The child meets all four essential adult criteria for RLS **and** The child relates a description in his or her own words that is consistent with leg discomfort (The child may use terms such as *oowies*, *tickle*, *spiders*, *boo-boos*, and *a lot of energy in my legs* to describe symptoms. Age-appropriate descriptors are encouraged)

or

The child meets all four essential adult criteria for RLS and

Two of three following supportive criteria are present

(see below)

Supportive criteria for the diagnosis of *definite* RLS in children

(a) Sleep disturbance for age

(b) A biologic parent or sibling has definite RLS

(c) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep

Criteria for the diagnosis of probable RLS in children

The child meets all essential adult criteria for RLS, except criterion # 4 (the urge to move or sensations are worse in the evening or at night than during the day) **and**

The child has a biologic parent or sibling with definite RLS **or**^a

1. The child is observed to have behavior manifestations of lower-extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs, the discomfort has characteristics of adult criteria 2, 3 and 4 (ie is worse during rest and inactivity, relieved by movement, and worse during the evening and at night) **and**

2. The child has a biologic parent or sibling with definite RLS

^a This last *probable* category is intended for young children or cognitively impaired children who do not have sufficient language to describe the sensory component of RLS

METHOD

We performed a PubMed search using the following key words in various combinations: *restless legs syndrome*, *RLS*, *attention-deficit/hyperactivity disorder*, *ADHD*, *attention deficit disorder*, *ADD*, and *hyperactivity*. References from each paper were examined to find additional studies. An association may exist between RLS and ADHD considered as diagnostic categories. Alternatively, a significant association between symptoms of ADHD and symptoms of RLS may be found. Therefore, we included both those studies that considered ADHD and RLS according to standardized criteria and studies that took into consideration symptoms of ADHD and RLS. As a consequence, we did not exclude papers published before 1994 (when the American Psychiatric Association published the *Diagnostic and Statistical Manual of Mental Disorders* [DSM], *Fourth Edition* criteria for ADHD) or 1995 (when the IRLSSG developed diagnostic criteria for RLS), but we reviewed all relevant papers published up to February 2005. Because ADHD may persist into adulthood, we searched for studies conducted in children as well as for studies of adult samples. We excluded studies examining the association between ADHD and PLMS or periodic limb movement disorder (PLMD), which did not consider RLS as well.

RESULTS

Two studies examined the prevalence of RLS in ADHD subjects.^{16,40} Three studies assessed the prevalence of RLS symptoms in ADHD subjects.^{33,41,42} Two studies explored the prevalence of ADHD symptoms in RLS subjects.^{20,33} One study (the only one conducted in adults) measured the prevalence of ADHD in RLS subjects.⁴³

Table 3a reports the studies examining the prevalence of RLS or RLS symptoms in ADHD patients. Table 3b reports the studies examining the prevalence of ADHD or ADHD symptoms in RLS patients. It also specifies whether studies took into consideration associated PLMS or PLMD.

DISCUSSION

In the following sections, we discuss the prevalence of RLS or RLS symptoms in subjects with ADHD, the prevalence of ADHD or ADHD symptoms in subjects with RLS, the hypothetical mechanisms underlying the association between RLS and ADHD, and the potential interest of common pharmacologic treatments for these conditions.

Table 3a—Studies Examining the Prevalence of RLS or RLS Symptoms in Patients With ADHD

Author (year)	N*	Age range, y	Prevalence of RLS in ADHD patients, %	Prevalence of RLS symptoms in ADHD patients, %	PLMS or PLMD
Chervin et al (1997) ⁴¹	27	2-18		15	-
Picchietti et al (1998) ¹⁶	69	2-16	11.5†		+
Harnish et al (2001) ⁴²	19	6-14		10.5	+
Chervin et al (2002) ³³	98	2-14		24	+
Konofal et al (2003) ⁴⁰	43	6-14	44‡		-

*N refers to patients ADHD (attention-deficit/hyperactivity disorder), not to the total sample.

†According to the pediatric version of the diagnostic criteria for restless legs syndrome (RLS).

‡According to International RLS Study Group criteria.

PLMS refers to periodic limb movements of sleep; PLMD, periodic limb movement disorder.

Table 3b—Studies Examining the Prevalence of ADHD or ADHD Symptoms in Patients With RLS

Author (year)	N*	Age range, y	Prevalence of RLS in ADHD patients, %	Prevalence of RLS symptoms in ADHD patients, %	PLMS or PLMD
Chervin et al (2002) ³³	147†	2-14		18%	+
Wagner et al (2004) ⁴³	62	>17	26%		-
Kotagal and Silber (2004) ²⁰	32	<18		25%	+

*N refers to patients with restless legs syndrome (RLS), not to the total sample.

†Patients with a positive RLS score (item A13 of Pediatric Sleep Questionnaire)

ADHD refers to attention-deficit/hyperactivity disorder; PLMS, periodic limb movements of sleep; PLMD, periodic limb movement disorder.

Prevalence of RLS or RLS Symptoms in Subjects With ADHD

In the first large-scale study suggesting comorbidity between ADHD and PLMD or RLS, Picchiatti et al¹⁶ examined the prevalence of RLS and PLMD in a sample of 69 children with ADHD (according to DSM-III-R criteria) and in a control group of 38 patients aged 2 to 16 years referred to a sleep laboratory. For the ADHD group, subjects with a principal complaint related to sleep were excluded to minimize selection bias toward sleep problems. For the control group, the exclusion criteria were technically unsatisfactory anterior tibialis electromyogram, obstructive sleep apnea, neuromuscular diseases, cerebral palsy, Down syndrome, or documented seizures. RLS was diagnosed using a modified version for children of the diagnostic criteria of RLS for adults. Children were defined as having RLS according to the following criteria. Firstly, they had at least 1 parent who had RLS (as defined by the adult criteria). Secondly, they had 5 or more PLMS per hour of sleep, could describe leg discomfort in their own words, had motor restlessness, and had RLS discomfort that was worse at rest with relief by activity. An all-night polysomnogram was used to detect periodic limb movements in children found to have repetitive twitches by parents during the night. The authors reported that 8 of the 27 patients with ADHD who underwent polysomnograms (11.5% of the total ADHD group) had RLS according to the above-mentioned criteria. Only 1 of the 38 controls (2.6 %) met the criteria for RLS. No evidence for a condition known to cause or exacerbate PLMD or RLS was found in any patient.

In another clinical study, Konofal et al⁴⁰ assessed 43 children with ADHD according to DSM-IV criteria. The mean age of the children was 9.2±2.2 years. Nineteen (44%) met RLS criteria according to IRLSSG criteria. All children were medication free for at least 2 months. The authors considered diagnostic criteria for both *definite* and *probable* RLS. This may explain the relatively high prevalence reported in this study. Moreover, the authors have known interests in both ADHD and RLS; therefore, a selection bias cannot be excluded.

In a sample of 19 children with a confirmed diagnosis of ADHD (age range=6-14 years), Harnish et al⁴² found a prevalence of RLS symptoms of 10.5 %. ADHD patients were not selected on the basis of sleep complaints or symptoms of sleep disorders. All children were medication free for at least 48 hours. However, unlike the previous 2 studies, the authors did not use formal diagnostic criteria for RLS.

Chervin et al⁴¹ administered validated questionnaire items about snoring, restless legs, and daytime sleepiness to the parents of 70 children attending a child psychiatry clinic and 73 children attending a general pediatric clinic. Inclusion criteria included age 2 to 18 years, absence of mental retardation, and presence of a

parent or guardian able to provide the requested information. Pediatric patients with ADHD were excluded. No sleep complaint or disorder was used as a criterion for inclusion or exclusion. Among the 70 psychiatric patients, 27 (39%) had a diagnosis of ADHD according to DSM-IV criteria. To define the severity of the ADHD symptoms, the authors used an inattention-hyperactivity score given by the mean response to the 18 DSM-IV items rated on a 4-point Likert scale for each item. Fifteen per cent of ADHD patients, 5% of non-ADHD psychiatric patients, and 10% of pediatric clinic patients reported a positive RLS score. RLS score was not significantly different among children with ADHD in comparison with either of the other groups (psychiatric patients without ADHD and pediatric patients). Logistic regression analysis showed a significant association between inattention-hyperactivity score and the RLS score when the ADHD subjects were grouped with the non-ADHD psychiatric subjects but not when grouped with the general pediatric clinic subjects. The inattention-hyperactivity scores were not associated with the RLS score in the general pediatric group. Thus, this study showed a less-consistent association between RLS symptoms and ADHD. However, in this study, the RLS symptoms were assessed using only 1 item. As noted by the authors themselves, the use of additional validated question items for RLS symptoms may have yielded less-ambiguous results.

In a subsequent cross-sectional survey,³³ Chervin et al examined a broader sample of 866 children aged 6.8 ±3.2 years attending 2 general pediatric clinics. Inclusion criteria were age between 2 and 14 years, parental ability to read and write English, and absence of mental or physical impairment severe enough to preclude interpretation of information collected. Parents of the children completed the Pediatric Sleep Questionnaire and 2 measures of inattention/hyperactivity: the inattention/hyperactivity scale (as previously described) and the short form of the Parent Conner's Rating Scale, a tool widely used in ADHD research, which provides a 10-item hyperactivity index. Item A13 of the Pediatric Sleep Questionnaire asks specifically about leg restlessness when in bed. Twenty four percent of hyperactive subjects (defined as an inattention-hyperactivity score > 1.25) gave a positive reply to the restless legs item, in comparison with 17% of nonhyperactive subjects. The association between restless legs item score and inattention-hyperactivity score and hyperactivity index was statistically significant. In spite of the strengths of this study (validated instruments, adequate sample size), some methodologic limitations were suggested by the authors. Notably, they did not use the most rigorous diagnostic criteria for ADHD (ie, DSM-IV criteria) and RLS (ie, IRLSSG criteria).

In summary, most of these studies reported a higher prevalence of RLS symptoms in ADHD groups than in control groups. Ac-

cording to Picchietti et al,¹⁶ RLS symptoms are usually underdiagnosed in ADHD children because the complaint of RLS dysesthesia in children is usually mild and intermittent. RLS is usually progressive, and it is thus likely that these children will become more symptomatic in the future. Furthermore, in certain children, RLS symptoms may appear only when the children are sleep deprived or have received caffeine.²⁷

All the discussed studies were performed in clinical settings. To the best of our knowledge, epidemiologic data on broader non-clinical samples (ie, general-population surveys) are not available. Moreover, the above-mentioned studies were carried out before the publication of the IRLSSG criteria for the diagnosis of RLS specifically in children. Therefore, further investigation using IRLSSG criteria for children is needed to better estimate the prevalence of RLS in subjects with ADHD both in clinical and in nonclinical samples.

Prevalence of ADHD or ADHD Symptoms in Subjects with RLS

In the above-mentioned study of Chervin et al,³³ high hyperactivity index scores (>60) were found in 13% of all subjects, 18% of children with restless legs, and 11% of children without restless legs; this difference was statistically significant.

In the first study exploring the association between ADHD and RLS in adults, Wagner et al⁴³ evaluated 62 patients with RLS (according to IRLSSG criteria), 32 patients with insomnia, and 77 control subjects. Exclusion criteria included a history of sleep apnea, narcolepsy, severe frontal-lobe head trauma, epilepsy, stroke, brain tumor, and poor English-language skills. Also excluded were patients seeking treatment for ADHD. The authors administered the DSM-IV current symptoms scale for ADHD and the Brown Attention Deficit Disorder Scale (ADD) for the assessment of ADHD. Because the restlessness associated with RLS could be confused with hyperactivity, the prevalence of ADHD was determined primarily by using the Brown ADD, which places a heavier emphasis on attention than on hyperactivity/impulsivity. Subjects with a Brown ADD score > 40 (probable ADHD) also completed questionnaires on depressive symptoms and anxiety and a psychometric test battery. Diagnosis of ADHD was confirmed by a structured interview. The main Brown ADD score was significantly greater in RLS patients than in patients with insomnia or controls. A significantly greater number of RLS patients (26%) than insomnia patients (6%) or control subjects (5%) also met DSM-IV criteria for ADHD. The association was independent of the presence or absence of anxiety or depression (conditions that may mimic ADHD symptoms). Moreover, the severity of RLS symptoms (as measured by the IRLSSG rating scale) was greater in RLS patients with ADD Brown Scores > 40 than in those with Brown scores < 40. Because 30% of the RLS patients had an onset of RLS in childhood and 75% had a childhood onset of ADHD, there seemed to be no direct relationship between childhood onset of RLS and childhood onset of ADHD. As noted by the authors, it is possible that the prevalence of ADHD in their RLS sample was underestimated because about half of the patients were treated with dopaminergic medications, which may improve ADHD symptoms.

In a retrospective study of a sample of 32 children with definite or probable RLS (according to the IRLSSG modified criteria for children), Kotagal and Silber²⁰ found that 25% of the children presented with inattentiveness. As noted by the authors, the retro-

spective design is a weakness of this study and limits the validity of the data.

In summary, although still limited in number, most studies examining the prevalence of RLS or RLS symptoms in ADHD subjects and the prevalence of ADHD or ADHD symptoms in RLS patients show a significant association between these conditions. The degree of association differs from one study to the other. It is possible that some differences in study methodology (ie, criteria for inclusion and exclusion, measures of RLS or ADHD symptoms, age range of the subjects) may explain these differences. Therefore, further studies using more-standardized methods are needed to better estimate the degree of association between RLS and ADHD symptoms.

Hypothesis for the Association Between RLS and ADHD Symptomatology

The first hypothesis to account for the association between RLS and ADHD symptoms takes into consideration the effect of RLS or PLMS on sleep. An association between RLS and PLMS and sleep disturbances has been reported extensively.^{16,24,25,33,41,44} In fact, patients with RLS often have severe insomnia because of their leg discomfort and periodic limb movements while trying to fall asleep. Associated PLMS may disrupt sleep, with multiple accompanying arousals.^{15,45} Although sleep deprivation in adults usually results in excessive daytime somnolence,⁴⁶ in normal children, it can lead to inattentiveness, moodiness, and paradoxical overactivity.^{8,47-52} Therefore, RLS might lead to symptoms of ADHD through sleep disruption. However, not all studies have provided evidence for an association between sleep disturbance and ADHD symptoms, whether in children⁵³ or in adults.^{54,55} In the above-mentioned study of Wagner et al,⁴³ the RLS patients reported higher Brown scores than did insomnia patients. This suggests that patients with RLS may have an increased risk of ADHD, independent of insomnia associated with RLS. The authors noted that insomnia is a problem of sleep quantity. It is possible that the small arousals associated with PLMS, which are a problem of sleep quality, fragment sleep and lead to ADHD symptoms.

Another possible explication for the association between RLS and ADHD symptoms is that the diurnal manifestations of RLS might mimic ADHD symptoms or be misclassified as symptoms of hyperactivity. Picchietti et al¹⁶ reported that RLS can lead to symptoms of hyperactivity and inattentiveness during the daytime in children. For example, some children who are seriously affected with RLS cannot sit in school during the day for extended periods because they get up and walk around to relieve their leg discomfort. Hyperactivity might thus lead to inattention through the mechanism of leg discomfort.⁴³ In the study of Wagner et al,⁴³ RLS patients showed both increased inattention on the Brown ADD scale and hyperactivity on the DSM-IV scale for ADHD. As a consequence, the authors stated that this result does not discriminate whether there is a direct connection between inattention and RLS or whether the hyperactivity in RLS indirectly leads to inattention.

A third possibility is that RLS is comorbid with idiopathic ADHD or that they are both manifestations of common central nervous system pathology.³³ Children with RLS and a subset of children with ADHD might share a common dopaminergic deficit.⁴³ Several studies have provided evidence for decreased dopa-

minergic function in the midbrain, frontal, and prefrontal regions of the brain in patients with ADHD.⁵⁶⁻⁶⁰ This may be related to gene polymorphism in the dopamine receptor or dopamine transporter system.⁶¹⁻⁶³ There is also evidence for dopamine deficiency in the pathophysiology of RLS.^{64,65} Interestingly, both ADHD and RLS have been found to be associated with iron deficiency. Konofal et al first reported lower ferritin levels in children with ADHD than in normal controls.⁶⁶ Magnetic resonance imaging studies in RLS have suggested that iron deficiency may also occur in certain forms of RLS.^{56,64} Further research on iron deficiency in these 2 conditions may help to elucidate their potential common physiopathology, at least for a subgroup of subjects. The hypothesis of iron deficiency is not incompatible with the hypothesis of dopaminergic hypoactivity, since 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.⁶⁷

When associated with idiopathic ADHD, RLS may exacerbate ADHD symptoms or cause a later onset of symptoms of ADHD.⁴³ Vice versa, it is also possible that ADHD worsens RLS symptoms. Chervin et al³³ noticed that adult patients with RLS sometimes report that increased daytime activity worsens their nocturnal symptoms. In the study of Wagner et al,⁴³ the RLS symptoms were more severe in RLS patients with ADHD symptoms than in RLS patients without ADHD symptoms.

The hypothesis that medications for ADHD or other medications may cause RLS symptoms seems weak, since, in the reviewed studies, the patients were free of drugs that are known to cause RLS symptoms.^{16,65}

Finally, Wagner et al⁴³ criticized the hypothesis that the association between ADHD symptoms and RLS is simply an artifact of similar symptomatology and that the diagnostic criteria for ADHD are not sufficiently specific to discriminate adequately between ADHD and RLS. In their study, they reported that RLS was associated with inattention as well as hyperactivity. If the association were due only to similar symptomatology, this would imply that RLS is also characterized by inattentiveness, a finding that has not been reported previously in studies of RLS. Moreover, it is important to point out that, although some symptomatic overlap may exist between these 2 conditions, hyperactivity in ADHD is not associated with the leg discomfort characteristic of RLS.⁶⁸

Implications of the Association Between RLS and ADHD Symptoms for Pharmacologic Treatment

The association between RLS and ADHD symptoms may have important consequences for the treatment of these conditions when they co-occur and when the standard treatments for ADHD symptoms are not effective.

Most patients with RLS have a positive therapeutic response to dopaminergic drugs. These medications improve both the sensory and motor symptoms of RLS. The drugs that have been found to be effective are dopamine precursors (levodopa) and dopamine-receptor agonists, including ergoline derivatives (bromocriptine, pergolide) and nonergoline derivatives (pramipexole and ropinirole).^{15,69} Given the association between RLS and ADHD symptoms, dopaminergic therapy may be effective in RLS patients with ADHD symptoms.

Walters et al²⁹ reported the cases of 7 children diagnosed with ADHD according to DSM-IV criteria and presenting with RLS or

PLMS (5 had both the conditions, 1 only RLS, and 1 only PLMS). Five of the 7 children had previously been treated with stimulants that had either been determined to be ineffective (n=4) or to have intolerable side effects (n=3). Five of the 7 children were treated with levodopa/carbidopa, and 2 with pergolide. On the basis of parent and child verbal report, treatment improved RLS symptomatology in all 6 children with RLS. It also significantly reduced the PLMS index. After treatment, 3 of the 7 children no longer met the DSM-IV criteria for ADHD. All 7 children significantly improved on the total score of Conner's Parent Rating Scale and on the total score of the Child Behavior Check List.

Konofal et al⁷⁰ reported the case of a 7-year old child with ADHD according to DSM-IV criteria and RLS according to IRLSSG criteria. The child had been treated with methylphenidate for 1 year, with limited efficacy. After 12 weeks of Tardiferon (ferrous sulfate) treatment, an improvement was observed (the scores on the Conner's Parent and Teacher Scales decreased from 70 to 30 and from 28 to 21, respectively). However, after 5 months, there was a return of excessive motor activity at bedtime with RLS symptoms. Methylphenidate appeared to be less efficacious at the beginning of the afternoon and had no effect on sleep problems. Therefore, ropinirole was co-prescribed. After 1 month, the child's oppositional behavior disappeared, his attention was better, and he slept well (the scores on the Conner's Parent and Teacher Scales were 33 and 20, respectively).

In the study of Wagner et al,⁴³ the authors reported that RLS patients who received dopaminergic drugs had Brown ADD scores significantly lower than those of RLS patients without dopaminergic treatment. No other RLS therapeutic drug category or combination of drugs was related to ADD severity.

These case reports provide limited evidence that dopaminergic agents may represent promising treatment for children with both RLS and ADHD symptoms. Chervin et al³³ estimated that if RLS or associated PLMS do contribute to hyperactivity behavior, then therapy that eliminates restless legs would effectively treat 12% of all hyperactive children and 43% of hyperactive children who complain of restless legs.

However, to date, beyond case reports, evidence on dopaminergic treatment in children is very limited.⁶⁹ Therefore, caution should be used in treating children with dopaminergic agents. Another possible implication of the association between RLS and ADHD symptoms concerns iron-supplement treatment. Since, as previously seen, a subgroup of RLS subjects may have iron deficiency,^{56,64} it would be interesting to evaluate iron supplementation in subjects with both ADHD and RLS.⁶⁶ Interestingly, iron supplementation has been reported incidentally to improve symptoms in children with ADHD with an iron-deficient diet.⁷¹ In the study of Konofal et al,⁴⁰ serum ferritin levels correlated with ADHD index and RLS severity, suggesting that iron supplementation could enhance the effect of dopaminergic agents in children with symptoms of RLS and ADHD.

CONCLUSIONS

Although the number of studies is limited, clinical studies have provided evidence for an association between RLS and ADHD or ADHD symptoms. Further epidemiologic studies, using specific IRLSSG criteria for children, are needed to confirm this association both in clinical and in community samples. With respect to the explanation of this association, sleep disruption associated

with RLS may lead to ADHD symptoms, RLS may mimic the symptomatology of ADHD, or it may be comorbid with idiopathic ADHD. The 2 conditions might share a common dopamine dysfunction, which could be genetically determined, at least in subgroup of patients. Future research should consider the hypothetical common pathophysiology of the 2 conditions. The association between RLS and ADHD symptoms may have relevant implications for treatment when these conditions coexist. The reports by Walters et al²⁹ and Konofal et al⁷⁰ suggest that children with RLS and ADHD symptoms may benefit from treatment with dopaminergic agents. However, to date, the limited number of patients treated by these authors (respectively 7 and 1) and the absence of randomized and blinded controlled studies do not allow evidence-based recommendations for treatment to be made.

Other agents may be potentially interesting in the treatment of comorbid RLS and ADHD. According to the recent American Academy of Sleep Medicine Report,⁶⁹ some dopamine-receptor agonists (such as talipexole, cabergoline, priribedil, and α -dihydroergocryptine) and the dopaminergic agents amantadine and selegiline may be effective in the treatment of RLS and PLMD, but the level of effectiveness of these agents is not currently established. To the best of our knowledge, there are no published studies on the effectiveness of these agents in ADHD associated with RLS. Further studies should also address the efficacy of iron supplementation in enhancing the effect of dopaminergic agents.

No published studies have specifically addressed the effectiveness of methylphenidate or other stimulants given in the evening for the treatment of ADHD and RLS. O'Brien et al⁷² reported no significant differences in the PLMS index of 53 stimulant-medicated ADHD children, 34 nonmedicated children with ADHD, and 53 nonmedicated controls. However, RLS was not evaluated explicitly in this study. Thus, the role of methylphenidate and other stimulants seems worthy of future research.

The association between ADHD and RLS or other conditions related to sleep disruption, as well as potentially interesting implications for new pharmacologic treatments, underscore the need to consider ADHD as a disorder not just limited to the daytime but of 24-hour duration.

REFERENCES

- Dulcan M. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. *American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry* 1997; 36:85S-121S.
- Buitelar JK. Attention-deficit/hyperactivity disorder: What have we learned over the last decade? In: Sanberg S, ed. *Hyperactivity and Attention Disorders of Childhood*. Cambridge: Cambridge University Press; 2005:30-63.
- Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington: American Psychiatric Association; 1994.
- Elliott H. Attention deficit hyperactivity disorder in adults: a guide for the primary care physician. *South Med J* 2002;95:736-42.
- Spencer T, Biederman J, Wilens TE, et al. Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. *J Clin Psychiatry* 1998;59(Suppl7):59-68.
- Wender PH. Attention-deficit hyperactivity disorder in adults. *Psychiatr Clin North Am* 1998;21:761-74.
- Dahl RE, Pelham WE, Wierson M. The role of sleep disturbances in attention deficit disorder symptoms: a case study. *J Pediatr Psychol* 1991;16:229-39.
- Kaplan BJ, McNicol J, Conte RA, et al. Sleep disturbance in pre-school-aged hyperactive and nonhyperactive children. *Pediatrics* 1987;80:839-44.
- Lewin DS, Di Pinto M. Sleep disorders and ADHD: shared and common phenotypes. *Sleep* 2004;27:188-9.
- Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. *Sleep* 1994;17:739-43.
- Restless legs syndrome. In: *International Classification of Sleep Disorders, revised*. Rochester: American Sleep Disorders Association; 1997:68-71.
- Montplaisir J, Pelletier G, Warnes H. Restless Legs Syndrome and periodic limbs movements during sleep. In: Krieger MH, Roth T, Dement WC eds. *Principles and Practice of Sleep Medicine*. Philadelphia: WB Saunders; 1994:589-97.
- Walters AS. Toward a better definition of the restless legs syndrome. *The International Restless Legs Syndrome Study Group. Mov Disord* 1995;10:634-42.
- Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord* 1997;12:61-5.
- Allen RP, Picchietti D, Hening WA, et al. 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;4:101-19.
- Picchietti DL, England SJ, Walters AS, et al. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *J Child Neurol* 1998;13:588-94.
- Boghen D, Peyronnard JM. Myoclonus in familial restless legs syndrome. *Arch Neurol* 1976;33:368-70.
- Ekbom KA. Growing pains and restless legs. *Acta Paediatr Scand* 1975;64:264-6.
- Kotagal S, Rathnow SR, Chu JY, et al. Nocturnal myoclonus--a sleep disturbance in children with leukemia. *Dev Med Child Neurol* 1985;27:124-6.
- Kotagal S, Silber MH. Childhood-onset restless legs syndrome. *Ann Neurol* 2004;56:803-7.
- Montplaisir J, Godbout R, Boghen D, et al. Familial restless legs with periodic movements in sleep: electrophysiologic, biochemical, and pharmacologic study. *Neurology* 1985;35:130-4.
- Picchietti DL, Walters AS. Restless legs syndrome: parents-child pairs. *Sleep Res* 1995;24:319.
- Picchietti DL, Walters A S. Restless legs syndrome and periodic limbs movements in childhood and adolescence: comorbidity with attention-deficit hyperactivity disorder. *Child Adolesc Psychiatry Clin North Am* 1996;5:729-40.
- Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. *Sleep* 1999;22:297-300.
- Picchietti DL, Underwood DJ, Farris WA, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Mov Disord* 1999;14:1000-7.
- Sheldon S, Levy H. Periodic limb movements in childhood. *Sleep Res* 1993;22:70.
- Walters AS, Picchietti DL, Ehrenberg BL, et al. Restless legs syndrome in childhood and adolescence. *Pediatr Neurol* 1994;11:241-5.
- Walters AS, Hickey K, Maltzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. *Neurology* 1996;46:92-5.
- Walters AS, Mandelbaum DE, Lewin DS, et al. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. *Dopaminergic Therapy Study Group. Pediatr Neurol* 2000;22:182-6.
- Wise MG, Gillepsie S. Autosomal dominant restless legs syndrome in a young girl with symptoms onset at 12 months. *Sleep Res*

- 1996;25:391.
31. Rajaram SS, Walters AS, England SJ, et al. Some children with growing pains may actually have restless legs syndrome. *Sleep* 2004;27:767-73.
 32. Bestue-Cardiel M, Sanmarti F, Artigas J. Periodic movements of the limbs during sleep in childhood. *Rev Neurol* 2002;34:244-8.
 33. Chervin RD, Archbold KH, Dillon JE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. *Sleep* 2002;25:213-8.
 34. Chervin RD, Dillon JE, Archbold KH, et al. Conduct problems and symptoms of sleep disorders in children. *J Am Acad Child Adolesc Psychiatry* 2003;42:201-8.
 35. Frolich J, Lehmkuhl G. Differential diagnostic correlations of sleep and attention disorders in childhood--comorbid psychological and organic illnesses. *Prax Kinderpsychol Kinderpsychiatr* 2004;53:48-59.
 36. Hornyak M, Schluter B, Scholle S, et al. Restless legs syndrome in childhood. *Nervenarzt* 2004;75:742-8.
 37. Kryger MH, Otake K, Foerster J. Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. *Sleep Med* 2002;3:127-32.
 38. Walters AS. Is there a subpopulation of children with growing pains who really have Restless Legs Syndrome? A review of the literature. *Sleep Med* 2002;3:93-8.
 39. Winkelmann J, Muller-Myhsok B, Wittchen HU, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. *Ann Neurol* 2002;52:297-302.
 40. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Restless legs syndrome and serum ferritin levels in ADHD children. *Sleep* 2003;26:A136.
 41. Chervin RD, Dillon JE, Bassetti C, et al. Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep* 1997;20:1185-92.
 42. Harnish MJ, Boyer S, Kukas L, Bowles AM, Orr WC. The relationship between sleep disorders and attention deficit hyperactivity disorder (ADHD): objective findings. *Sleep* 2001;24:A14.
 43. Wagner ML, Walters AS, Fisher BC. Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome. *Sleep* 2004;27:1499-504.
 44. Crabtree VM, Ivanenko A, O'Brien LM, et al. Periodic limb movement disorder of sleep in children. *J Sleep Res* 2003;12:73-81.
 45. Insufficient sleep syndrome. In: *International Classification of Sleep Disorders: Diagnostic and Coding Manual*. Rochester: American Sleep Disorders Association; 1990:87-90.
 46. Bonnet MH. Sleep deprivation. In: Krieger MH, Roth T, Dement WC eds. *Principles and Practice of Sleep Medicine*. Philadelphia: WB Saunders; 1994:50-67.
 47. Dahl RE. Sleep in behavioral and emotional disorders. In: Ferber R, Kryger MH eds. *Principles and Practice of Sleep Medicine in the Child*. Philadelphia: WB Saunders; 1995:148-9.
 48. Mindell JA, Vari CA. Sleep problems and daytime behavior problems in young children: is there a relationship? *Sleep Res* 1992;21:234.
 49. Goulding P, Mendez S, Gibbons VP. The relationship between alterations in sleep architecture and daytime neurological function in children. *Ann Neurol* 1993;34:504.
 50. Corkum P, Tannock R, Moldofsky H, et al. Actigraphy and parental ratings of sleep in children with attention-deficit/hyperactivity disorder (ADHD). *Sleep* 2001;24:303-12.
 51. Ring A, Stein D, Barak Y, et al. Sleep disturbances in children with attention-deficit/hyperactivity disorder: a comparative study with healthy siblings. *J Learn Disabil* 1998;31:572-8.
 52. Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1998;37:637-46.
 53. Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep* 2001;24:313-20.
 54. Chervin RD. Periodic leg movements and sleepiness in patients evaluated for sleep-disordered breathing. *Am J Respir Crit Care Med* 2001;164:1454-8.
 55. Mendelson WB. Are periodic leg movements associated with clinical sleep disturbance? *Sleep* 1996;19:219-23.
 56. Ernst M, Zametkin AJ, Matochik JA, et al. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *J Neurosci* 1998;18:5901-7.
 57. Ernst M, Zametkin AJ, Matochik JA, et al. High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. *Am J Psychiatry* 1999;156:1209-15.
 58. 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;27:671-82.
 59. Solanto MV. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behav Brain Res* 2002;130:65-71.
 60. Viggiano D, Vallone D, Sadile A. Dysfunctions in dopamine systems and ADHD: evidence from animals and modeling. *Neural Plast* 2004;11:97-114.
 61. LaHoste GJ, Swanson JM, Wigal SB, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Mol Psychiatry* 1996;1:121-4.
 62. Madras BK, Miller GM, Fischman AJ. The dopamine transporter: relevance to attention deficit hyperactivity disorder (ADHD). *Behav Brain Res* 2002;130:57-63.
 63. Waldman ID, Rowe DC, Abramowitz A, et al. Association and linkage of the dopamine transporter gene and attention-deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtype and severity. *Am J Hum Genet* 1998;63:1767-76.
 64. Allen RP, Barker PB, Wehr F, et al. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* 2001;56:263-5.
 65. Trenkwalder C, Stiasny K, Pollmacher T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep* 1995;18:681-8.
 66. Konofal E, Lecendreux M, Arnulf I, et al. Iron deficiency in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 2004;158:1113-5.
 67. Erickson KM, Jones BC, Hess EJ, et al. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharm Biochem Behav* 2001;69:409-18.
 68. Hickey K, Walters A, Hening W. Hyperactivity and "growing pains" as possible misdiagnoses in young-age onset restless legs syndrome. *Sleep Res* 1992;21:209.
 69. Littner MR, Kushida C, Anderson WM, et al. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 2004;27:557-9.
 70. Konofal E, Arnulf I, Lecendreux M, et al. Ropinirole in a child with attention-deficit hyperactivity disorder and restless legs syndrome. *Pediatr Neurol* 2005;32(5):350-1
 71. Sever Y, Ashkenazi A, Tyano S, et al. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. *Neuropsychobiology* 1997;35:178-80.
 72. O'Brien LM, Ivanenko A, Crabtree VM, et al. The effect of stimulants on sleep characteristics in children with attention deficit/hyperactivity disorder. *Sleep Med* 2003;4:309-16.