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Original Article

Early manifestations of restless legs syndrome in childhood and adolescence ☆

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Abstract

Objective: To describe the symptomatology reported by a series of children and adolescents who at initial consultation did not meet full diagnostic criteria for pediatric restless legs syndrome (RLS) but subsequently did so over the course of clinical follow-up.
Methods: Retrospective assessment of all patients with pediatric RLS receiving ongoing care in a pediatric sleep/neurology practice at a large multispecialty clinic ($n = 50$). Eighteen children and adolescents who met inclusion and exclusion criteria were identified by chart review. All but one had undergone polysomnography.
Results: Detailed sleep histories were available for 10 girls and 8 boys, all of whom presented initially with clinical sleep disturbance. Mean age at the initial sleep evaluation was 10.3 years and mean age at RLS diagnosis was 14.7 years. Detailed descriptions of the sensory RLS symptoms were recorded. Retrospective age of onset for chronic clinical sleep disturbance was a mean of 3.1 years, with 10 families reporting onset in infancy. Of the 18, 16 reported chronic sleep-onset problems and eight sleep-maintenance problems at the time of initial evaluation. Ten had a history of growing pains. Thirteen were found to have a family history of RLS. Eleven of 17 had periodic leg movements in sleep (PLMS) $\geqslant 5$ per hour. Comorbidities included parasomnias (7), attention-deficit/hyperactivity disorder (ADHD) (13), oppositional defiant disorder (ODD) (4), anxiety disorders (6), and depression (5). Serum ferritin levels of <50 ng/mL were found in 16 of 18.
Conclusions: In this group of 18 children and adolescents, clinical sleep disturbance preceded a diagnosis of *definite* RLS by an average of 11.6 years. Many had a diagnosis of periodic limb movement disorder (PLMD) or met research criteria for *probable* or *possible* RLS prior to meeting criteria for *definite* RLS. These findings suggest that some aspects of RLS can occur long before full diagnostic criteria are present. Comorbidities were common, with parasomnias, ADHD, ODD, anxiety, and depression each found in more than 20% of these cases. The 2003 National Institutes of Health (NIH) diagnostic criteria for pediatric RLS are supported by this work.

Keywords: Restless legs syndrome; Periodic limb movements in sleep; Periodic limb movement disorder; Sleep disorder; Children; Adolescents; Growing pains; Parasomnia; Attention-deficit/hyperactivity disorder; Anxiety; Depression; Ferritin

1. Introduction

Restless legs syndrome (RLS) is a neurological, sensorimotor disorder affecting sleep, which was first described over 300 years ago by Thomas Willis and further delineated by Karl Ekbom in the 1940s and 1950s [1,2]. Although several large population-based studies

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have shown RLS to occur in 5–10% of adults in the United States and Western Europe [3–9], it has remained an underdiagnosed disorder [10,11]. Age of onset has been reported retrospectively in three adult RLS studies, with onset prior to age 20 found in 27–38% and before age 10 in 8–13% [12–14]. Although Ekbom mentioned childhood RLS, it was not until the mid-1990s that detailed case reports of children and adolescents with RLS were published [15,16], followed by several other pediatric studies [17–26]. The first population-based epidemiological data on RLS in children and adolescents indicates a remarkable 2% prevalence in 8–17-year olds [27]. While emerging literature has begun to describe the clinical aspects of childhood RLS, much remains unknown.

In adults, RLS is a clinical diagnosis based on the patient's history [28,29]. There are four essential criteria for diagnosis: (1) an urge to move the legs, usually accompanied by uncomfortable leg sensations, (2) symptoms are worse when sitting or lying down, (3) symptoms are at least partially relieved by movement, and (4) symptoms are worse in the evening or at night than during the day. Other associated features commonly found in adults with RLS include sleep disturbance, periodic limb movements in sleep (PLMS), and a positive family history of RLS. While RLS can be mild in some cases, decreased quality of life ratings, cognitive deficits, attentional problems, and mood disorders are common in moderate to severe adult RLS [3,30–34]. Problematic sleep is typical in individuals seeking treatment for RLS, with this feature present in more than 90% of patients in two large clinical series [13,35]. Similarly, a recent population-based study reported sleep disturbance in 76% of adults with moderate to severe RLS [3]. "Secondary RLS" may occur in pregnancy, uremia, and spinal cord and peripheral nerve injuries, and due to some medications. Approximately 80–90% of adults with RLS have PLMS, which are brief extremity jerks that may be accompanied by transient arousals from sleep, cardiac acceleration, spikes in blood pressure, and sleep disruption [13,36]. Periodic limb movement disorder (PLMD) is diagnosed when the following conditions are present: (1) PLMS exceeding norms for age, (2) clinical sleep disturbance, and (3) the absence of another primary sleep disorder or reason for the PLMS, including RLS [37]. Thus, an individual can have RLS with PLMS or have PLMD, but not both disorders.

In 2003, consensus criteria for the diagnosis of RLS in children and adolescents were published as the result of a meeting at the National Institutes of Health (NIH) in Bethesda, MD, USA (Table 1) [28]. Two major concepts were incorporated—more difficultly to achieve criteria for a definitive diagnosis in children 2–12 years old than in adults and separate research categories for less definitive cases. The first was agreed upon to avoid overdiagnosis in children and the second to provide a framework to investigate a potentially broader spectrum of RLS in childhood, thereby encouraging the inevitable evolution of these diagnostic criteria. Thus, *definite*, *probable*, and *possible* RLS categories were devised. In addition, anecdotal reports of PLMD developing into RLS over time in children were acknowledged, and refined PLMD criteria were developed. The NIH committee decided to use the adult criteria for adolescents, although the categories of *probable* and *possible* RLS were left open as an option for this age range of 13–18 years. PLMD criteria can be applied at any age, although frequency criteria are higher in adults than in children. These new pediatric RLS criteria and revised PLMD criteria were subsequently included in the International Classification of Sleep Disorders diagnostic manual, 2nd edition (ICSD-2) [37].

The purpose of this current study was to characterize the clinical aspects of an interesting group of children with RLS—those who presented initially with clinical sleep disturbance and did not meet *definite* RLS criteria but later in the course of follow-up did develop the essential symptoms for a *definite* RLS diagnosis. This is an important subset of children and adolescents with RLS because some of the early manifestations of RLS in childhood may help identify those who require clinical follow-up, may aid in proper diagnosis over time, and may provide insight into pediatric diagnostic criteria for RLS, especially for young children.

2. Methods

This is a retrospective chart review of cases of pediatric RLS in individuals who were initially evaluated before the age of 18 years at Carle Clinic Association, Urbana, IL, and were seen by a single physician (DLP). The practice setting is a large multispecialty clinic in a university community of approximately 110,000 with a referral base of about 300,000 from surrounding rural and small urban areas. At the time, this practice was about 40% child neurology and 60% sleep disorders. The study was approved by the Carle Foundation Institutional Review Board.

Cases were selected for detailed review if patients presented initially with a sleep complaint and did not meet *definite* RLS criteria but later in the course of follow-up did develop the essential symptoms for a *definite* RLS diagnosis. Historical data was obtained by structured interview of the child or adolescent and parents during the course of clinical assessment and follow-up. Because of our interest in pediatric RLS, we routinely asked about RLS-related symptoms in any child or adolescent with a sleep problem, both at initial assessment and at each follow-up visit. Follow-up visits were typically 3–6 months apart. Although the NIH pediatric criteria had not been developed at the time of initial assessment for these patients, these criteria could be applied

Table 1
NIH Workshop diagnostic criteria for RLS in children (2003)

DIAGNOSTIC CRITERIA FOR RLS IN CHILDHOOD AND ADOLESCENCE

Adult essential criteria

1. 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).
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. 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.
4. 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).

Definite RLS in children (age 2 to 12 years)

1) the child meets all 4 essential criteria for RLS and
2) there is a description, in the child's own words, consistent with leg discomfort. } Definite 1

or

1) the child meets all 4 essential criteria for RLS and
2) 2 of 3 criteria supportive of the diagnosis are present (see below). } Definite 2

Terms such as "wiggly", "tickle", "bugs", "spiders", "hurt", "shaky", "boo-boos", "want to run" and "a lot of energy in my legs" may be used by the child to describe symptoms. Age-appropriate descriptors are encouraged.

Supportive of the diagnosis:

1) sleep disturbance for age
2) a biologic parent or sibling has definite RLS
3) the child has a PLMS index of ≥ 5/hour on polysomnography

Definite RLS in adolescents (age 13 to 18 years)

The 4 essential criteria as above.

For pediatric and adult RLS: The condition is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

RESEARCH CRITERIA (age 0 to 18 years)

Probable RLS

1) the child meets all 4 essential criteria for RLS, except #4: "worse in the evening or at night" and
2) the child has a biologic parent or sibling with definite RLS. } Probable 1

*or**

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 2, 3, and 4 of the essential criteria and
2) the child has a biologic parent or sibling with definite RLS. } Probable 2

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

Possible RLS

1) the child has periodic limb movement disorder (PLMD) and
2) the child has a biologic parent or sibling with definite RLS but the child does not meet definite or probable childhood RLS definitions (as above).

retrospectively because they are similar to the International Restless Legs Study Group criteria used at the time [38], and the interviewer (DLP) was routinely asking for and recording all information relevant to the pediatric RLS diagnostic criteria except for "probable 2." Restless legs sensations were differentiated from mimics of RLS, such as transient nerve compression, sore muscles, leg cramps, dermatitis, joint pain, neuropathy, and radiculopathy. Available biologic parents were interviewed for RLS symptoms by one of the authors (DLP), either during one of the child's clinic visits or over the phone.

The case search occurred between January 2003 and March 2003. We found a total of 199 patients younger

than age 25 years, who were in active follow-up over the previous 2 years and who were being seen for sleep problems other than obstructive sleep apnea or a primary parasomnia as the only sleep diagnosis. Fifty had a diagnosis of *definite* RLS (at most recent contact), 75 PLMD (without *definite* RLS), and 74 others had clinical sleep disturbance but not RLS or PLMD. This last group included patients with ADHD ($n = 30$), limit-setting sleep disorder or sleep-onset association disorder ($n = 10$), cerebral palsy ($n = 9$), sleep disorder not otherwise specified (NOS; $n = 8$), anxiety disorder ($n = 6$), autism ($n = 6$), delayed sleep phase syndrome ($n = 3$), depression ($n = 1$), and chronic pain ($n = 1$). None of the 50 pediatric RLS cases had evidence for secondary RLS.

Two of the 18 cases that met inclusion/exclusion criteria have been included in another publication [25]. They are reported in this article because the emphasis in this current paper is substantially different—the development of RLS symptoms over time, rather than moderate to severe PLMD. Furthermore, in both cases, the children did not meet *definite* RLS criteria at the time of the previous report.

Clinical sleep disturbance was defined as either sleep onset problems (sleep latency > 20 min, twice or more per week) or sleep maintenance problems (two or more full arousals, twice or more per week). Daytime sleepiness was defined following International Classification of Sleep Disorders diagnostic manual guidelines [39]. Comorbidities in the children and adolescents for attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), mood disorders, and anxiety disorders were assessed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [40]. Growing pains were defined as a history of recurrent lower limb discomfort that a parent and/or healthcare provider thought were "growing pains."

At the time of initial assessment for these patients, we routinely recommended polysomnography (PSG) for all cases of clinical sleep disturbance where there was no specific, definite cause found by clinical interview. Attended PSG was done at a single American Academy of Sleep Medicine–accredited center with the following parameters measured: electroencephalogram (EEG), eye movements, chin electromyogram (EMG), nasal and oral airflow, chest and abdominal movement, leg movements, electrocardiogram (ECG), and oxygen saturation. Infrared video monitoring and a sensitive intercom were also used. Leg movements were measured using anterior tibialis leg leads bilaterally. PLMS were defined as a sequence of four or more limb movements of 0.5–5.0 s in duration, separated by more than 5 and less than 90 seconds, and amplitude greater than or equal to 25% of toe dorsiflexion during calibration [37,41].

3. Results

3.1. Clinical characteristics and age of symptom onset

Eighteen children and adolescents were identified by chart review, who did not meet diagnostic criteria for *definite* RLS at initial presentation but did meet full RLS diagnostic criteria during follow-up care, out of 50 pediatric RLS cases in active follow-up. This represented 36% of our pediatric *definite* RLS cases at the time. There were 10 females and 8 males. Seventeen were Caucasian and one African-American/Caucasian.

Mean age at initial sleep evaluation was 10.3 years (range 0.2–17.1 years) and mean age at *definite* RLS diagnosis was 14.7 years (range 8.1–24.3 years) (Table 2). This represents an average 4.4 year interval (range 0.3–9.1 years) between the time of initial consultation and when the child developed the specific symptoms for a diagnosis of *definite* RLS. Age at *definite* RLS diagnosis was as follows: 8–12 years: 8 cases; 13–18 years: 7 cases; 19–20 years: 0 cases; and 21–24 years: 3 cases. The eight who met *definite* criteria at ⩽12 years of age all met "*definite 1*" criteria. Of the 10 who met full diagnostic criteria at >12 years of age, seven would have met "*definite 1*" criteria and two would have met "*definite 2*" criteria if the more restrictive criteria for the children ⩽12 years of age had been applied.

Retrospective age of onset for chronic clinical sleep disturbance was a mean of 3.1 years old, with 10 families reporting onset in infancy (i.e., less than 12 months old [Table 2]). In all but two cases, onset was before 6 years of age. This represents an average 11.6 year interval (range 1.2–23.8 years) between the time of onset of chronic clinical sleep disturbance and when the child developed the specific symptoms for a diagnosis of *definite* RLS. Fig. 1. is a frequency distribution histogram depicting age of onset for chronic sleep disturbance and age at which *definite* RLS diagnostic criteria were met. For the 10 with onset less than 12 months of age there was no obvious gender difference, with five females and five males in this younger onset group.

Clinical sleep disturbance was prominent. Of the 18, 16 reported chronic sleep-onset problems and eight reported sleep-maintenance problems at the time of initial evaluation (Table 3). Sixteen of 18 were described as "restless in sleep" by their parents (i.e., they were reported to move around a lot in bed while asleep). Mild daytime sleepiness was reported in 7 of 18, typically in sedentary situations, such as while a passenger in a car. None of these patients developed evidence for narcolepsy over the course of clinical follow-up.

Detailed descriptions of the restless legs sensory symptoms, in the patient's own words, are listed in Table 4. Bug-like feelings, tingle, wiggle, itch, energy in the legs, and need to move are some of the reported sensations. Included in Table 4 is the age at which the

Table 2
Age at initial sleep evaluation, *definite* RLS diagnosis, and onset of clinical sleep disturbance

Patient #	Age at initial sleep evaluation	Age at *definite* RLS diagnosis[a]	Interval initial sleep eval. to RLS diagnosis	Age of onset sleep disturbance (retrospective)[b]	Interval onset sleep disturb. to RLS diagnosis
1	7.3	11.8	4.5	Infancy	11.3
2	9.0	11.3	2.3	Infancy	10.7
3	9.5	17.5	8.0	Infancy	17.0
4	7.0	8.1	1.1	Infancy	7.6
5	17.1	24.3	7.2	Infancy	23.8
6	14.8	15.6	0.8	4	11.6
7	10.2	18.3	8.1	Infancy	17.8
8	6.9	11.9	5.0	3	8.9
9	16.8	22.5	5.7	1.5	20.0
10	0.2	9.3	9.1	0.1	9.2
11	6.5	10.0	3.5	3	7.0
12	13.3	14.7	1.4	Infancy	14.2
13	13.3	21.2	7.9	Infancy	20.7
14	15.4	16.0	0.6	14	2.0
15	7.0	14.1	7.1	5	9.1
16	12.5	12.8	0.3	Infancy	12.3
17	13.2	13.5	0.3	12.3	1.2
18	6.1	12.6	6.5	4	8.6
Mean (range)	10.3 (0.2–17.1)	14.7 (8.1–24.3)	4.4 years (0.3–9.1)	3.1 years; 10 infancy, 16 < 6 years	11.6 years (1.2–23.8)

[a] *Probable* RLS, *possible* RLS, or PLMD criteria met earlier in 13 of 18.
[b] One year of age is used for calculation where 'infancy' is listed.

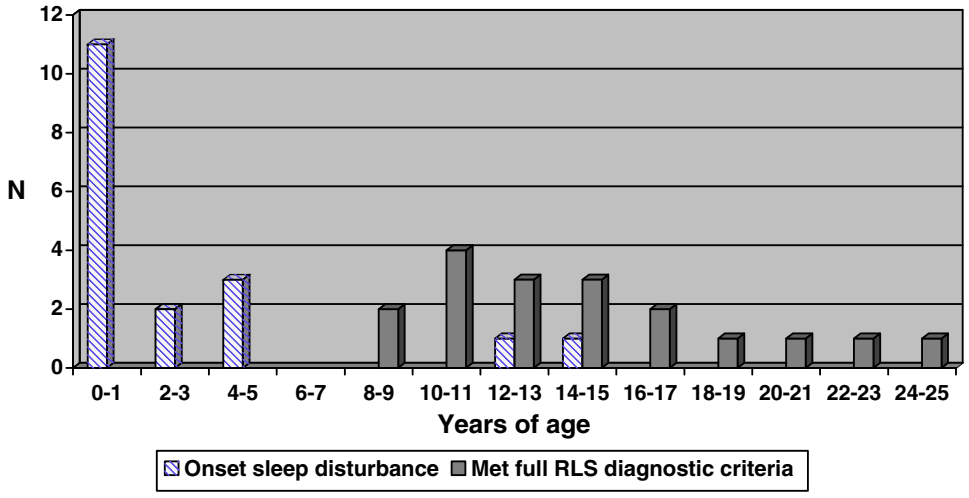

Fig. 1. Age of onset for chronic sleep disturbance and age met full RLS diagnostic criteria.

sensory component was first described consistently in these words to the examining physician, even if full *definite* RLS criteria were not yet met. All reported an "urge to move," 15 noted urge and discomfort, and 3 noted urge without discomfort.

Ten had a history of growing pains. Of these, there was insufficient information about the characteristics of the growing pains at the time of initial consultation to know if these represented RLS for nine, and for one the growing pains were not consistent with RLS. In all nine, the child or adolescent could not recall the growing pains in substantial detail. The growing pains were typically described as intermittent and variable in severity.

Presenting symptoms at the time of initial consultation were related to sleep ($n = 8$), school ($n = 3$), both sleep and school ($n = 5$), or other concerns ($n = 2$). Both in the "other" category reported "staring spells" as the main concern. Clinical seizures were ruled out in both cases. Examples of the chief complaints are as follows: "sleep problems," "sleepless wonder," "poor sleep," "school problems," "short attention," "hyper," and "school problems, lazy?"

3.2. Comorbidity

Comorbidities included parasomnias ($n = 7$), ADHD ($n = 13$), ODD ($n = 4$), anxiety disorders ($n = 6$), and

Table 3
Symptoms and findings in 18 children and adolescents with RLS

Finding	No. of patients
Clinical sleep disturbance	18/18
Onset problems[a]	16/18
Maintenance problems[b]	8/18
Restless in sleep	16/18
Daytime sleepiness[c]	7/18
Growing pains	10/18
Comorbidities	
Parasomnias	7/18
ADHD	13/18
ODD	4/18
Anxiety	6/18
Depression	5/18
Biologic parent with RLS	13/18[d]
PLMS $\geqslant$5.0/h on PSG	11/17[d]
PLMS observed by parent	2/11[d]
Serum ferritin $<$ 20 ng/mL	5/18
Serum ferritin $<$ 35 ng/mL	13/18
Serum ferritin $<$ 50 ng/mL	16/18
Response to dopaminergic	9/11

ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; RLS, restless legs syndrome; PLMS, periodic limb movements in sleep; PSG, polysomnography.
[a] Sleep latency >20 min, twice or more per week.
[b] Two or more full arousals, twice or more per week.
[c] All seven had mild daytime sleepiness.
[d] Not comprehensively assessed in all cases.

Table 4
Descriptions of sensory complaints

Quotation	Patient age (yrs)[a]
"sand in toes"	5
"like ants on bottom of feet, tingling"	7
"tingle"	8
"itchy feeling"	11
"legs feel a little energy, bug feeling"	11
"legs hurt, like massages too hard"	12
"like spiders on legs"	12
"need to move, stiff"	12
"like spiders"	13
"feel like moving"	14
"have to move legs"	14
"legs feel funny and move a lot when sitting"	15
"need to wiggle"	16
"feels funny, a lot of energy"	17
"legs want to kick"	18
"static feeling, itch, deep ache"	21
"can't get comfortable, need to move"	22
"need to stretch to relax, achy"	24

[a] Age at which sensory component first described consistently in patient's own words, even if full *definite* RLS criteria not yet met.

depression ($n = 5$) (Table 3). A history of frequent parasomnias (greater than twice per month, for greater than three months) was present in 7 of 18. These were sleepwalking ($n = 2$), sleep terrors ($n = 2$), and nightmares ($n = 1$). Another one experienced sleepwalking and sleep-related rhythmic movement disorder, head-rolling type. An additional child experienced sleepwalking, nightmares, and sleep-related rhythmic movement disorder, body-rocking type. In all cases, these parasomnias began before *definite* RLS criteria were met but after the onset of clinical sleep disturbance. A total of eight patients had anxiety and/or depression diagnoses. The specific diagnoses were as follows: anxiety NOS ($n = 2$), generalized anxiety disorder ($n = 1$), major depressive disorder ($n = 2$), anxiety NOS plus depression NOS ($n = 2$), and generalized anxiety disorder plus major depressive disorder ($n = 1$). Thus, in 8 of 18 RLS cases, three had a comorbid anxiety disorder, two had a depressive disorder, and three had both anxiety and depressive disorders. In all eight cases, the onset of anxiety or depression symptoms occurred after the onset of clinical sleep disturbance. Onset of anxiety or depression symptoms occurred before the *definite* RLS diagnosis in four and after in four.

3.3. Family history of RLS

A positive family history (FH) of RLS in one or both biologic parents was present in 13 of 18 cases (77%). When both biologic parents were available for interview, 11 of 13 (85%) patients had a parent with RLS. In one of the eleven cases, both parents met criteria for RLS. Where at least one parent was available, there was a parental history of RLS in 13 of 17 cases. One child was adopted and neither biologic parent was available. In four other cases, only one of the biologic parents was available, all mothers. Nine mothers and five fathers were affected by RLS. Only two of these 14 parents had a previously recognized diagnosis of RLS, and in both cases they were established patients of one of the authors (DLP).

3.4. NIH research criteria and supportive features

These data were complete enough to apply the NIH research criteria for pediatric RLS (Table 1) in a retrospective manner, except for research category "*probable 2*." Four met "*probable 1*" criteria (symptoms worse in the day plus a family history of RLS) an average of 4.5 years (range 1–8 years) prior to full RLS diagnostic criteria (Table 5). Another seven met *possible* RLS criteria (PLMD plus FH of RLS) an average of 3.7 years (range 0.3–8.1 years) prior to full RLS diagnostic criteria.

Table 5
NIH category prior to meeting full RLS criteria

Diagnostic criteria prior to RLS diagnosis	
NIH *Probable* RLS (not worse night)	4
NIH *Possible* RLS (PLMD + FH of RLS)	7
Periodic limb movement disorder (PLMD)	2(11)[a]
None	5

[a] 11 met PLMD criteria if *probable* and *possible* not applied.

Two out of the three supportive criteria for the diagnosis of RLS (Table 1) were met at the time of initial evaluation in 16 of the 18 patients. All patients reported significant sleep disturbance for age. In addition to this criterion, eight patients met both other supportive criteria, while four met the criterion for first-degree relative with RLS and four met the criterion for a PLMS index of $\geqslant 5$ per hour.

3.5. Polysomnography (PSG) and PLMD

All but one child had a single night of PSG. Eleven of 17 had periodic leg movements in sleep (PLMS) $\geqslant 5$ per hour, mean 13.0 per hour and range 5.5–32.8 per hour. Only 2 of the 11 with PLMS $\geqslant 5$ per hour were observed by their parents to have repeat limb jerks in sleep prior to the PSG. In addition, two of the six not shown to have PLMS $\geqslant 5$ per hour by PSG were reported by their parents to have repeated limb jerks in sleep. The one child who did not undergo PSG had PLMS demonstrated on home video recording at two and seven months of age. At the time of PSG, none were on medication known to induce, aggravate, or suppress PLMS. None of the 18 had clinical or PSG evidence for obstructive sleep apnea. For the 17 who had PSGs, the mean apnea-hypopnea index was 0.1 per hour (range 0–1.2). If the *probable* and *possible* RLS research criteria are not applied, 11 patients met PLMD criteria an average of 4.1 years (range 0.3–8.1 years) prior to meeting *definite* RLS diagnostic criteria.

3.6. Serum ferritin

Serum ferritin values were available for all 18 cases (Table 3). Ferritin less than 20 ng/mL was found for 5 of 18 and less than 35 ng/mL for 13 of 18 (range 9–107). Only 2 of 18 had ferritin levels greater than 50 ng/mL, and one of those subsequently had a drop from 82 to 38, with the lower value found at the time when she developed full criteria for *definite* RLS. For the 10 with onset of sleep disturbance in infancy, the median ferritin level was not significantly different from those with onset after infancy (16.5 and 29.5 ng/mL respectively, Mann–Whitney $z = -1.11$, $p = 0.1335$).

3.7. Overlap between ADHD, FH of RLS, and low ferritin

ADHD, FH of RLS, and serum ferritin less than 35 ng/mL each occurred in 13 of the 18 cases. Eight of 18 patients had all three factors. No combination of two factors stood out: ADHD + FH of RLS (10/18), ADHD + low ferritin (10/18), or FH of RLS + low ferritin (9/18). Having all three factors did not have an obvious association with onset of sleep disturbance in infancy (4/10 vs. 4/8).

3.8. Response to dopaminergic therapy

In 11 of 18 cases, dopaminergic medication was chosen as a clinical treatment in an open-label fashion. A positive clinical response, characterized by improved sleep and some degree of improvement in daytime function, occurred in 9 of the 11 cases. In two cases, there was no clear response, with a single dopaminergic trial in each of these two cases (carbidopa–levodopa extended release ($n = 1$), pramipexole ($n = 1$)). The responders reported results with carbidopa–levodopa extended release ($n = 3$), pramipexole ($n = 5$), and ropinirole ($n = 1$). None of the nine cases had evidence for the onset of RLS sensations secondary to medication. None of the patients were on dopaminergic therapy at the time of initial consultation, when they were determined to not meet full RLS diagnostic criteria. Seven of 18 cases were on dopaminergic medication for treatment of periodic limb movements at the time they met *definite* RLS diagnostic criteria. This could have potentially delayed onset of sensory symptoms in these cases. However, we believe this is unlikely to be a major factor due to dosing at bedtime in all cases, missed doses, and routine trials off medication in all cases.

4. Discussion

The most important finding of this case series is that in some children and adolescents clinical sleep disturbance can precede the full diagnostic manifestations of RLS by months or years. Such a clinical presentation occurred in 18 of 50 (36%) of our pediatric RLS cases at the time of this review with the interval between initial sleep consultation and development of *definite* RLS an average of 4.4 years. Remarkable was the recall of the onset of chronic clinical sleep disturbance an average of 11.6 years prior to meeting criteria for *definite* RLS, with 10 of 18 reporting onset in infancy.

This study raises some interesting questions about the relationship of disturbed sleep to restless legs. While sleep disturbance "considered to be characteristic of the full expression of the disorder" [28], is more common in more severe RLS [6], and has been found to be present in over 90% of adults seeking treatment for RLS [13,35], it is not part of the essential diagnostic criteria for RLS. Sleep onset or maintenance problems were the most common symptoms found in a large case series of pediatric RLS at Mayo Clinic, present in 87.5% [18]. Certainly, in any individual patient with RLS there could be other causes of sleeplessness that are causative or contributing factors, such as poor sleep habits. When a patient reports that the RLS feelings are interfering with sleep onset or maintenance, the relationship seems obvious. However, in our cases, the sleep disturbance preceded the onset of any RLS feelings in many, and

in all cases we were impressed by the magnitude of the sleep disturbance in relation to the severity of the RLS feelings. In many of our cases, PLMS could have contributed to the sleep disturbance, as well as sleep hygiene problems, sleep-onset association issues, anxiety, and depression in some. Nonetheless, we think our data raise the concern about the development of RLS in children and adolescents who present with clinical sleep disturbance but do not meet full diagnostic criteria for RLS at the time of initial evaluation.

The 18 pediatric cases in our report had a gradual progression of symptoms over time. This is consistent with the medical literature where the natural clinical course of early-onset RLS, onset before age 45, has been reported as chronic and progressive in over two-thirds of cases. Most of the remaining third describe the symptoms as stable over time. Data from four clinical studies support this view [12,14,35,42], as well as the findings of increased severity with age [27,43] and increased prevalence with age [3,6]. Slow progression is typical, with long periods of stability in many [35,42]. In addition, a small minority of cases have a remission or disappearance of symptoms [12,14,35]. This possibility of remission suggests that any medical treatment should be reassessed periodically to evaluate for the ongoing need of therapeutic interventions. Intermittent, slow progression is not common with late-onset RLS, where rapid progression is typical [43]. Secondary RLS usually remits fully once the underlying condition has resolved, for example, with renal transplantation in end-stage renal disease [44] and for pregnancy [45]. None of our 18 cases had evidence for secondary RLS.

4.1. Descriptions of RLS sensations

Verbatim description of RLS urge and discomfort are included in Table 4. This adds to the growing literature on how children and adolescents describe RLS. In pediatric and adult RLS it is common for us to hear patients report that "it is hard to describe." Nonetheless, with patience and good listening skills we have typically been able to elicit responses from children and adolescents that allow us to accurately rule in or rule out RLS as the reason for their leg sensations. Descriptions that include "wiggle", "bugs", "tickle", "tingle" and "itch" have been common in pediatric RLS.

Language development and cognitive development are important in regards to the key sensory components of RLS, which need to be described by the patient for accurate diagnosis. A similar situation exists for pediatric migraine. In this study, the youngest child to meet *definite* RLS criteria was 8.1 years old and the youngest to meet *probable* RLS criteria was 5 years old. While we cannot say that other children five and above might have had RLS sensations and simply were not able to describe the feelings prior to the time described in this report, we think this is unlikely due to the careful interview technique used to examine these children and our extensive experience with headache diagnosis in children. However, in children less than 5 years or in children with developmental delays, we believe that the level of language and cognitive skills does make RLS unlikely to be diagnosed, even if the sensations are frequent. We believe this supports a role for emphasis on the motor component of RLS (i.e., PLMS) in the diagnosis of young children.

4.2. Family history of RLS

A positive family history of RLS, which was found in 77% of our cases, is typical for early-onset, primary RLS. The adult RLS literature has reported 40–92% of early-onset cases being familial and much lower rates in late-onset and secondary RLS [12,14,35,43,46,47]. In a population-based study of pediatric RLS, parental history indicative of RLS was found in 71% of children 8–11 years and 80% of 12–17 year olds [27]. Clinically, we have found a positive family history of RLS in a biologic first-degree relative to be helpful in raising our diagnostic certainty of RLS in pediatric cases, as well as alerting us to the possibility of RLS developing over time in children who do not meet full RLS criteria at the time of initial evaluation. However, there are instances where this information is not available, such as in one of our cases where the child was adopted.

4.3. Growing pains

Growing pains are a generally recognized but poorly defined entity, which has been reported to occur in 5–15% of school-aged children [48]. Ten of our 18 cases had a history of growing pains. However, there was insufficient recall of the growing pain characteristics in nine to know if these represented RLS. In addition, the exclusion criteria for this study would have eliminated any cases where there was recall of growing pains as RLS. Of interest, several other studies have reported that some children with RLS have their RLS symptoms mistakenly attributed to growing pains [12,14,15,26,49].

4.4. Comorbidity

Comorbidity is defined as the coexistence of two or more disease processes in the same individual (e.g., asthma and diabetes, ADHD and learning disabilities). This concept does not necessarily imply interaction between the comorbid conditions but does help to raise that possibility. It emphasizes the concept of "and," not "or". Comorbidity should not be confused with the differential diagnosis of conditions.

Seven of 18 had a history of frequent parasomnias, which included sleepwalking, sleep terrors, and

nightmares. This is consistent with our other work, which has shown frequent parasomnias in children with RLS and with PLMD [23,25]. An additional two cases had sleep-related rhythmic movement disorder. While parasomnias are common in childhood, the coexistence of RLS and parasomnias in these individuals raises the possibility of sleep disruption associated with RLS and PLMS triggering the parasomnias [20,37].

The high number of our cases with ADHD is an artifact of our initial interest in looking for RLS in children and adolescents who were referred for ADHD. However, the medical literature does support the likelihood of a complex relationship between ADHD, RLS, and PLMD [50]. Of interest is a recent study of adults with RLS, which found that 26% met the diagnostic criteria for ADHD [33].

Eight of 18 patients had comorbid anxiety and/or depression diagnoses. In all eight cases, the onset of anxiety or depression symptoms occurred after the onset of clinical sleep disturbance, and after the *definite* RLS diagnosis in four but before diagnosis in four. Depression and anxiety are common in adults with RLS, much more frequent than in the general population [34,51]. Of interest is that persistent insomnia is a very strong predictor of depression in adults [52–54] with an odds ratio of 39.8 in one study [55]. In children, early childhood sleep problems have been found to predict the development of mood and anxiety disorders [56,57]. While causation has not been determined, such a relationship has been raised and, if accurate, suggests an interesting opportunity for prevention [58–60].

4.5. NIH research criteria

This work supports the research criteria of "*probable 1*" RLS and *possible* RLS as useful in the diagnostic scheme (Table 1). "*Probable 1*" differs from *definite* RLS in that feature four, "worse in the evening or night than during the day," is not needed but that there is a FH of RLS. Four of 18 reported their RLS as worse during the day an average of 4.5 years prior to meeting *definite* RLS diagnostic criteria. It is not clear why this aspect is different, but prolonged sitting in the classroom for elementary school age children could create the conditions where RLS is manifest, just as some adults with RLS will describe daytime symptoms during long car trips or airplane flights. Also possible is that this could be mediated by a different circadian pattern of endogenous brain dopamine in juvenile mammals than in adult mammals [61]. Seven of 18 cases met *possible* RLS criteria (PLMD plus FH of RLS) an average of 3.7 years prior to meeting *definite* RLS diagnostic criteria. Thus, both "*probable 1*" RLS and *possible* RLS appeared to be early, partial manifestations of pediatric RLS in this case series.

4.6. Polysomnography (PSG) and PLMD

Eleven of 17 cases who had undergone PSG met diagnostic criteria for PLMD prior to meeting criteria for *definite* RLS. Since PLMS are an objective motor finding in RLS and supportive of an RLS diagnosis [28], we believe these data suggest that PLMD can be an early manifestation of RLS in the pediatric age range. None of our cases had another cause for the PLMS, such as OSA, narcolepsy, REM behavior disorder or medication effect, and fairly extensive normative data in children, adolescents, and adults has shown low rates of PLMS in individuals less than 40 years of age [23,24,62–68]. This is in contrast to older adults who have a higher background rate of PLMS and where there is controversy about the significance of PLMS [69–71] . Even with the application of the "*probable 1*" RLS research criteria, there are still 9 of 18 who would not have had a specific sleep disorder diagnosis (PLMD) until *definite* RLS symptoms had developed. Only 2 of the 11 with PLMS $\geqslant 5$ per hour were observed by their parents to have repeat limb jerks in sleep prior to the PSG, supporting ours and others' previous work, which indicates history alone is not accurate for the determination of PLMS [25,72]. Of note, 6 of 17 cases who had undergone PSG did not have PLMS $\geqslant 5$ per hour on a single study. Since there is documented night-to-night variability of PLMS [73], it is possible that repeat PSG or several nights of actigraphy for PLMS would have picked up additional PLMD cases. However, repeat PSG is expensive and there is currently no actigraphy system for PLMS that has been validated in children, as there is in adults [74,75].

4.7. Serum ferritin

Serum ferritin levels below 50 ng/mL have been found to be associated with increased severity of RLS in adults [76,77] and an increased prevalence of RLS has been found in iron deficient anemia and in blood donors [78,79]. Additional evidence supporting a role of iron in RLS and PLMD, includes magnetic resonance imaging (MRI) data [80], autopsy data [81], intravenous iron studies [82,83], and the results of oral iron treatment in pediatric cases [22,84]. Of interest is that there is an emerging literature on low iron and ADHD [85,86]. The roles of iron and dopamine in the pathogenesis of RLS are potentially related by the function of iron in the brain's dopamine systems [87,88]. While we did not have concurrent control ferritin data for our cases, 13 of 18 were less than normative median values for age and gender, with 6 of 18 below the 5th percentile [89,90]. In our cases, 16 of 18 had serum ferritin values below 50 ng/mL. One of two who were above 50 ng/mL subsequently had a drop from 82 to 38, with the

lower value found at the time when she developed full criteria for *definite* RLS.

4.8. Limitations

In addition to the limitations described above, it should be noted that this is a highly selected case series with an N of 18, from a single pediatric sleep/neurology practice. As such, these results may not be easily extrapolated to the general community. Nonetheless, we believe that these data are useful and should encourage others to look at some of the issues we have raised.

5. Conclusions

In children and adolescents, clinical sleep disturbance and PLMD can precede the development of symptoms essential for a definitive diagnosis of pediatric RLS, suggesting a progression of symptoms over time.

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