



# Restless Legs Syndrome and Periodic Limb Movement Disorder in Children

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## Abstract

### Keywords

- ▶ limb movements
- ▶ leg movements
- ▶ periodic limb movements of sleep
- ▶ periodic limb movements during wake
- ▶ periodic limb movement disorder
- ▶ restless legs syndrome

**Introduction** Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) have been studied more than any other sleep-related movement disorder in the pediatric population. A common feature to both, periodic limb movements, occurs in many other disorders and also in reportedly healthy children and adolescents. In this review, we discuss the different types of limb movements as it pertains to pediatric RLS and PLMD and provides an update on these disorders.

**Methods** A literature search was performed with the following inclusion criteria: English publication, limb movements, leg movements, periodic limb movements of sleep, periodic limb movements during wake, PLMD, RLS, with each of the modifiers, children, pediatric, and adolescents. Identified publications were reviewed and their reference lists were searched for additional relevant publications.

**Results** A total of 102 references were included in this review. These included epidemiological studies, prospective and retrospective studies, case series, observational data, reviews, and consensus guidelines. A critical summary of these findings is presented.

**Conclusion** The limited evidence-based data support the importance of evaluating limb movements in the context of the clinical symptomatology presented by the child or the adolescent. Further research is needed to (1) better understand the pathophysiological mechanisms resulting in periodic limb movements as encountered in the pediatric PLMD or RLS patient and their impact on the overall health and well-being, (2) develop objective diagnostic criteria for RLS and differentiate it from its “mimics” in the pediatric population, and (3) establish evidence-based guidelines for treatment.

## Introduction

Most sleep-related movement disorders have been described in both adults and children. The International Classification of Sleep Disorders (ICSD) revised recently by the American Acad-

emy of Sleep Medicine (AASM) includes a sleep-related movement disorders section. Some of these disorders are more frequent or specific to the pediatric population<sup>1</sup> (–Table 1). Benign sleep myoclonus of infancy is rare and tends to resolve spontaneously within the first 6 months of life. Sleep-related

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**Table 1** Sleep-related movement disorders affecting children<sup>1</sup>

<b>Benign sleep myoclonus of infancy:</b> repetitive myoclonic jerks during quiet sleep in infants from birth to 6 months of age
<b>Sleep-related rhythmic movement disorder:</b> repetitive stereotyped and rhythmic motor behaviors that are not tremors, but occur predominantly during drowsiness or sleep and involve large muscle groups
<b>Sleep-related bruxism:</b> repetitive jaw–muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible
<b>Sleep related leg cramps:</b> painful sensations caused by sudden and intense involuntary contraction of muscles during which there is muscle spasm and hardness for several seconds
<b>PLMD:</b> periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep in conjunction with clinical sleep disturbance or fatigue
<b>RLS</b> is a sensory motor disorder that can impact sleep and is characterized by a strong, irresistible urge to move, mostly the legs that is relieved by movement, triggered by rest or inactivity, most frequently in the evening hours

Abbreviations: PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

rhythmic movements such as body rocking, head banging, or head rolling are common in infants and toddlers, less common in older children, and in some cases can interfere with sleep, impair daytime functioning, or result in self-inflicted injury. Sleep-related bruxism is also common in children (14–17%), tends to occur in families and despite an overall benign course can result in pain and dental damage. Children, 8 years and older, can present with sleep-related leg cramps and associated tenderness.<sup>2</sup> Growing pains can be frequent in children 4 to 14 years (2.6–49.4%) causing painful middle of the night awakenings.<sup>3,4</sup> Also, parasomnias such as sleep terrors and sleepwalking may present a sleep-related movement component. Yet, restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are the more studied sleep-related movement disorders in children, and are the focus of this review. Although there are similarities with adults, the purpose of this review is to examine the different types of limb movements as it pertains to the pediatric population diagnosed with either RLS or PLMD and to provide an update on these disorders.

**Methods**

The literature search was based on the PubMed database as of August 31, 2018. The following search terms were used: limb movements, leg movements, periodic limb movements of sleep (PLMS), periodic limb movements during wake

(PLMW), PLMD, RLS, with each of the modifiers, children, pediatric, and adolescents. Identified publications pertinent to children were reviewed and their reference lists were searched for additional relevant publications.

**Results**

A total of 102 references were included in this review. These include epidemiological studies, prospective and retrospective studies, case series, observational data, reviews, and consensus guidelines. A critical summary of these findings is presented in this review.

**The Conundrum of Periodic Limb Movements**

The presence of periodic limb movements (PLMs) during wake (PLMW) and during sleep (PLMS) in patients with RLS has been the focus of many studies, and also a source of confusion in both clinical practice and sleep laboratory, more so in the pediatric population. Definitions of the leg movements are summarized in **Table 2**.<sup>5</sup> The frequently observed association of PLMS during the polysomnogram (PSG) with clinical symptoms of RLS led some to interpret PLMS as a pathognomonic sign of RLS, a presumption that is not completely supported by the evidence.<sup>6</sup> Since that

**Table 2** Definitions and scoring of PLM

<b>Limb movements (LMs):</b> an extension of the big toe often in combination with partial flexion of the ankle, the knee, and sometimes the hip reflected in an 8 mV or more increase in electromyography (EMG) voltage above resting EMG for at least 0.5 seconds up to 10 seconds
<b>Periodic limb movement (PLM) series:</b> 4 or more LMs occurring consecutively (5–90-second interval)
<b>PLMs:</b> periodic series of repetitive, highly stereotyped LMs
<b>PLMI:</b> PLMs per hour, frequently refers to hour of sleep
<b>PLMS:</b> PLMs occurring during sleep
<b>PLMA:</b> PLMs associated with arousals from sleep
<b>PLMW:</b> PLMs occurring during wakefulness

Adapted from the AASM scoring manual, 2018.<sup>5</sup>

Abbreviation: PLMA, periodic limb movements with arousal; PLMI, periodic limb movement index; PLMS, periodic limb movement of sleep; PLMW, periodic limb movements during wake.

<sup>a</sup>Caveat: Patient-related artifacts from devices like cycling feeding pumps<sup>9</sup> can mimic PLMS during the polysomnogram.

publication, there has been a great deal of work in this regard resulting in consensus definitions for PLMS by the World Association of Sleep Medicine both in 2006 and more recently in 2016. The basis for these consensus definitions was a mathematical analysis of the PLMS in adults primarily by the group led by Ferri in Italy.<sup>7</sup> This detailed mathematical analysis resulted in the proposal of allowing for a longer duration of the limb movement, a change that was accepted by the AASM; the old rule for PLMS required a duration of 0.5 to 5 seconds, while the current rule for PLMS can be 0.5 to 10 seconds in duration. More recent mathematical analyses reported in the 2016 standards<sup>8</sup> suggest that the intervals between leg movement events should be increased as well from the current 5 to 90 seconds to 10 to 90 seconds. However, the AASM has yet to adopt this proposal.

Periodic limb movements during sleep and PLMD can precede symptoms of RLS in children.<sup>10</sup> The presence of PLMS is one of the supportive criteria for the diagnosis of RLS. However, PLMS have also been observed in various disorders, and even in healthy children.<sup>11</sup>

The association of frequently asymptomatic indices of 5 or more PLMS and PLMA with other sleep disorders and medical or mental conditions in children has been puzzling. PLMS are frequently observed in healthy younger children between the ages of 1 and 10 years, and their frequency decreases in the older group, 10 to 18 years old.<sup>12</sup> They are more than twice as common in Caucasian than in African-American healthy children.<sup>13</sup> PLMS were reported in children with a history of prematurity (3.6%: 6 out of 167) without symptoms of RLS or PLMD.<sup>14</sup>

Periodic limb movements during sleep occur in a variety of sleep disorders including RLS, PLMD, narcolepsy, and obstructive sleep apnea (OSA). In a large study, PLMS were identified in 77 of 982 PSGs, with an overall prevalence of 7.8%, and evidence of male predominance (47 boys and 30 girls). The mean age was  $9.4 \pm 4.2$  years. The periodic limb movement index (PLMI) was  $9.78 \pm 7.9$  events/hour of sleep and periodic limb movement arousal index was  $4.5 \pm 8.4$  events/hour of sleep. Associated diagnoses in this pediatric cohort included OSA in 36 (46.8%), attention-deficit hyperactivity disorder (ADHD) in 10 (13%), migraine in 7 (9.1%), seizures in 7 (9.1%), autism spectrum disorders in 5 (6.5%), and narcolepsy in 7 (9.1%) patients. Twenty-nine children had evidence of decreased serum ferritin levels (mean: 26.1 ng/mL; normal levels usually  $> 50$  ng/mL).<sup>15</sup>

Periodic limb movements during sleep are 9.5 times more common in Caucasian children with sleep-disordered breathing (SDB) than in African-American children.<sup>13</sup> Emergence of PLMS was observed in 5.1% of children after initiation of positive airway pressure therapy (PAP) in a large study, including 214 PAP titrations, mostly with continuous PAP pressures  $> 7$  cmH<sub>2</sub>O.<sup>16</sup> Asymptomatic PLMS were noted in children scheduled for adenotonsillectomy. The index increased after surgery unrelated to the respiratory improvement, and there was no symptomatic correlation.<sup>17</sup> Rogers et al reported on PLMS in 5 out of 17 children with sickle cell disease without OSA.<sup>18</sup>

Some types of pain have been associated with higher incidence of PLMS. PSG recordings of 34 children affected by migraine without aura showed that 26.5% had a PLMI  $> 5$  events/hour of sleep. The presence of PLMS was associated with symptom worsening and lower treatment efficacy for migraine.<sup>19</sup> In children with juvenile fibromyalgia, 38% (6/16) had a PLMS  $> 5$  events/hour of sleep.<sup>20</sup>

Children with ADHD frequently have PLMS. These limb movements can disrupt sleep and may trigger or worsen symptoms of ADHD.<sup>21–23</sup>

The cardiovascular risk posed by transient surges in blood pressure and heart rate associated with the leg movement events has been documented in studies involving adult patients with PLMS, with many of such patients being also diagnosed with RLS. Children with hypertension were twice as likely to have PLMS.<sup>24</sup> PLMS were associated with blood pressure elevations as reported by Wing et al,<sup>25</sup> who compared ambulatory blood pressure measurements in 314 children, with ( $n = 17$ ) and without ( $n = 297$ ) PLMS. Their findings suggested that PLMS were independently associated with a wide range of blood pressure elevations during daytime, and especially at night. These results combined with data from another study which showed that hypertensive children obtain less weekend catch-up sleep and report less daytime sleepiness<sup>26</sup> raise concern regarding the cardiovascular effects of PLMS in these children.

PLMS-associated vagal inhibition was identified in a group of 10 children (7–12 years old) with PLMS referred for the assessment of SDB. Compared with the control group without PLMS, these 10 children exhibited rapid cardiac acceleration occurring concurrently with the onset of individual leg movements followed by a return to premovement levels. This finding suggests that decreased vagal activity is associated with leg movements.<sup>27</sup> Attempts to better understand the pathophysiology and the clinical significance of PLMS point to sympathetic overactivity and inflammatory cellular pathways with associated cardiovascular risk.<sup>28</sup>

Cortical arousals can precede, coincide, or follow PLMS. PLMS and cortical arousals in sleep were increased in children with monosymptomatic nocturnal enuresis and polyuria, without a significant association with the enuretic parameters. Based on these observations, the authors suggested the presence of a comorbid mechanism that is driven by a common, independent pacemaker. The authors hypothesized that the autonomic system, its sympathetic branch, and the dopaminergic system were candidates for this pacemaker.<sup>29</sup> This hypothesis has yet to be tested.

Periodic limb movements during sleep and PLMS continue to be an active focus of research, and it is worthwhile noting them in clinical practice. Pathophysiological correlates in children are still lacking and many studies did not assess for symptoms of RLS and PLMD.

## Periodic Limb Movement Disorder in Children

### Essential Features and Clinical Manifestations

Periodic limb movement disorder consists of frequent PLMS that cause sleep disturbance and/or functional impairments,

and neither the PLMS nor the symptoms can be explained by another sleep, medical, neurological, or psychiatric disorder.

Periodic limb movements during sleep generally refer to movement occurrences in the lower extremities. Similarly, periodic highly stereotyped movements can occur in the upper extremities, and have also been described in other areas of the body. To be considered for the diagnosis of PLMD, PLMS need to be documented by overnight PSG.<sup>5</sup> The pattern and frequency of PLMS can vary from one night to another.<sup>30</sup> Actigraphy with devices worn in the lower extremities can be used over several nights to collect data. However, such data are mainly contributory, and the current diagnostic criteria (► **Table 3**) require PSG documentation.<sup>1</sup>

A clinical history documenting that the PLMS are causing sleep disturbance and/or functional impairment is needed for the diagnosis of PLMD (► **Table 3**). Sleep disturbances may include sleep onset problems, sleep maintenance problems, or reports of unrefreshing sleep that may result in excessive daytime sleepiness, increased irritability, or excitability and behavioral problems, such as inattention, learning deficits, mood alterations, or increased aggressiveness or social withdrawal. Indeed, children with PLMD may present with pro-

blems focusing attention and maintaining concentration, hyperactivity, and decreased school performance.<sup>10,31,32</sup> Increased anxiety, mood disorders, and oppositional behaviors have also been reported.<sup>10,32</sup>

**Epidemiology and Predisposing Factors**

Even though sleep-related movements are frequently seen in children, PLMD is not a common disorder in the pediatric population. A series of confounding factors limits the applicability of the published epidemiological data:

- PLMD can precede the development of RLS and onset can be as early as infancy.<sup>10</sup>
- Many studies are retrospective data reviews on children referred for evaluation of SDB, that is, a biased and skewed population.<sup>33,34</sup>
- The clinical information was based on questionnaires.<sup>33</sup>
- Limited clinical information.<sup>35</sup>
- Scarce data on general population<sup>14</sup>

Overall, the prevalence of PLMD in children seems to be in the lower 10 to 20% range (► **Table 4**). However, it is important to note that mentioned studies with one

**Table 3** Diagnostic criteria for PLMD (all must be met)

1. Polysomnography demonstrates PLMS, as defined in the most recent version of the AASM manual for the Scoring of Sleep and Associated Events
2. The frequency of the PLMS is > 5/h
3. The PLMS cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning
4. The PLMS and the symptoms are not better explained by another current sleep disorder, medical or neurological disorder, or mental disorder

Abbreviations: AASM, American Academy of Sleep Medicine; PLMS, periodic limb movement of sleep; PLMD, periodic limb movement disorder; ICSD, International Classification of Sleep Disorder.

**Table 4** PLMI > 5 events/h sleep and a diagnosis of PLMD in pediatric studies

Study	Location	Ages	Total (N)	Description	PLMI > 5 events/h sleep	Clinical symptoms	PLMD diagnosis
Crabtree et al 2003 <sup>33</sup>	Louisville, KY	6–10	351	Pediatric sleep center	11.9%	Checked on questionnaire	11.9% parental report
Kirk and Bohn 2004 <sup>35</sup>	Calgary, Canada	0–18	591	PSG at pediatric hospital	1.2%	ADHD 7.1%	Not reported
Gingras et al 2011 <sup>34</sup>	Charlotte, NC	1–17	468	Pediatric sleep practice	14%	Criteria for PLMD met	14% ICSD 2nd edition
Marcus et al 2014 <sup>11</sup>	Philadelphia, PA	5–17	195	Community	7.7%	None	None
Wong et al 2014 <sup>36</sup>	Sydney, Australia	3–16	230	PSG at pediatric hospital and no neuro/dev dis	13%	GP ×3 more	Not reported
Cielo et al 2017 <sup>14</sup>	Philadelphia, PA	5–12	167	Ex-preterm cohort	26 15.6%	PLMD	13 7.8% ICSD 3rd edition

Abbreviations: ADHD, attention-deficit hyperactivity disorder; PLMD, periodic limb movement disorder; PLMI, periodic limb movement index; PSG, polysomnography; ICSD, International Classification of Sleep Disorder.

**Table 5** Differential diagnosis of PLMD

Sleep starts: limited to the transition from wakefulness to sleep, shorter, not periodic
Fragmentary myoclonus: shorter, less periodic, and lower EMG amplitude
Benign sleep myoclonus of infancy; shorter, more frequent, less periodicity, more in arms
Nocturnal epileptic seizures: not periodic, movements are not limited to legs
Sleep disorders with PLMS: RLS, SRBD, narcolepsy
Neurologic disorders with PLMS: ADHD, Asperger syndrome, Williams syndrome, spinal cord injury, dystonias, neurodevelopmental disorders
Medical conditions: sickle cell disease, end-stage renal disease, congestive heart failure

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EMG, electromyography; PLMD, periodic limb movement disorder; PLMS, periodic limb movement of sleep; RLS, restless leg syndrome; SRBD, sleep related breathing disorders.

exception<sup>11</sup> surveyed special populations. Only half of the studies listed reported a diagnosis of PLMD which was based either on parental report<sup>31</sup> or the current ICSD criteria at publication time.<sup>14,34</sup> Considering these caveats, and using current diagnostic criteria, clinically significant PLMD in children is probably even less common than currently assumed.

Periodic limb movement disorder tends to run in families. A positive family history of PLMD was reported in 52% of cases.<sup>30</sup>

Low brain iron as reflected by measurements of iron stores (serum ferritin, transferrin, iron binding capacity (IBC) and serum iron) has been associated with PLMD.<sup>10,14,37–40</sup> Replenishment of iron stores has been associated with improvement in clinical symptoms and possible remission.<sup>40</sup>

### Pathophysiology

Periodic limb movements during sleep are the cornerstone of PLMD and are also frequently present in RLS patients.<sup>41</sup> Genetic factors, dopamine dysfunction, and low brain iron have all been implicated in the pathophysiology of PLMS.<sup>38–40</sup> In some patients, PLMS have been associated with frequent cortical and autonomic arousals resulting in nonrestorative sleep.<sup>29</sup> Hundreds of PLMS can be observed in one night, and with them frequent autonomic and sympathetic system activations such as transient increases in blood pressure and heart rate (albeit in adults), a possible mechanism for cardiovascular risk.<sup>27</sup> A few studies in children support the need for a better understanding of the cardiovascular implications of PLMS.<sup>28</sup>

### Objective Findings

Periodic limb movements during sleep as described in ►Table 2 are observed during PSG in both legs separately or simultaneously *ad lib*. If suspected, upper extremities or other areas of the body should be also monitored. PLMS can start during stage N1 of sleep, are frequent in stage N2, less in stage N3, and generally absent in REM sleep. In infants, PLMS can occur in quiet sleep.<sup>5</sup> PLMS occur in series of at least 4, but usually longer, mostly within the first two-thirds of the

night. Other conditions in which limb movements can be present are listed in ►Table 5.

### Management and Treatment

The evaluation of patients with PLMD should include a complete history, clinical examination, PSG, and assessment of iron stores. Details of the history and examination are presented in ►Table 6 and assessment of iron stores in ►Table 7. Management and treatment are presented in ►Tables 8–10, including recommendations for iron supplementation in ►Table 9.

**Table 6** Clinical and physical examination for PLMD

PLMD history
PLMS pattern and triggers if known
Sleep schedule and problems
Activity schedule and limitations
Caffeine and similar substances intake
Medications and supplements: current and previous
Medical history
Family history
Mental health assessment and history
Physical and neurological examination

Abbreviations: PLMD, periodic limb movement disorder; PLMS, periodic limb movement of sleep.

**Table 7** Iron stores<sup>a</sup>

Ferritin >50 ng/mL
Transferrin saturation >45%
IBC > 300 ng/mL
Serum iron > 70 ng/mL

<sup>a</sup>It should be performed in early morning, in a fasting state (if possible). Abbreviation: IBC, iron binding capacity.

**Table 8** Behavioral management for PLMD

Education about the disorder
Regular sleep routine
Avoid caffeinated substances
Review use of medications/supplements that may worsen PLMS
Exercise

Abbreviations: PLMD, periodic limb movement disorder; PLMS, periodic limb movement of sleep.

**Table 9** Iron supplementation

<b>Young children:</b>
3 mg/kg/day of elemental iron divided into 2–3 daily doses; 1 hour before or 2 hours after feeds
<b>Older children:</b>
325 mg ferrous sulfate + 100 mg vitamin C, 2 or 3 times per day, or in one dose

**Table 10** Medication for children with PLMD who are not candidates or did not respond to iron therapy and/or behavioral management

Clonidine 0.1–0.4 mg at bedtime in children aged 6 years and older
<b>Benzodiazepine:</b>
Clonazepam: 0.01–0.03 mg/kg at bedtime for children aged <10 years
Clonazepam: 0.25–0.5 mg at bedtime for children aged 10 year and older
<b>Alpha-2 delta ligands:</b>
Gabapentin: 5–10 mg/kg at bedtime up to 50 mg/kg for younger children
Gabapentin: 100–300 mg at bedtime for children aged 12 years and older
Gabapentin enacarbil: no data yet
Pregabalin: no data
Dopaminergic agent precautions: low dose, intermittent, ensure adequate iron stores, longer acting,
Beware of augmentation phenomena
Opiates: no data

### Restless Legs Syndrome in Children

Restless legs syndrome was believed to be a condition of middle and older age. Walters et al published in 1994 a series of RLS in three children from one family and a teenager from another family.<sup>41</sup> Despite recent growth in the pediatric literature, pediatric RLS remains underdiagnosed and undertreated.<sup>42</sup> Possible causes of under recognition include mild, intermittent, poorly understood symptoms in young chil-

**Table 11** RLS diagnostic criteria: A–C must be met<sup>1</sup>

A. An urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms should be in the child’s own words. These symptoms must:
a. Begin or worsen during periods of rest or inactivity such as lying down or sitting
b. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues and
c. Occur exclusively or predominantly in the evening or night rather than during the day.
B. The above features are not solely accounted for as symptoms of another medical or behavioral condition
C. The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in functioning

Abbreviation: RLS, restless leg syndrome.

dren combined with limited knowledge, awareness, and access to specialized care.<sup>43,44</sup>

### Essential Features and Clinical Manifestations

Restless legs syndrome is a circadian sleep-related sensorimotor dysregulation disorder characterized by a complaint of a strong, nearly irresistible urge to move the limbs<sup>1</sup> (→Table 11). It is a clinical disorder requiring time, patience, and expertise to adequately assess, especially in younger children that can be more susceptible to answer affirmatively to leading questions and have limited vocabulary to describe their sensations. To adequately differentiate RLS from other disorders that may mimic the symptoms, it is essential to have the children describe the urge to move in their own words<sup>1,45,46</sup> (→Table 12). →Table 11 presents the RLS diagnostic criteria unrelated to age. Special considerations for the diagnosis of pediatric RLS are mentioned in →Table 12. Supportive criteria for the diagnosis of RLS in children are

**Table 12** Special considerations for the diagnosis of pediatric RLS<sup>1</sup>

1. The child must describe the RLS symptoms in his/her own words
2. The diagnostician should be aware of the typical words children and adolescents use to describe RLS
3. Language and cognitive development determine the applicability of the RLS diagnostic criteria rather than age
4. Adult specifiers for clinical course may not apply to pediatric RLS
5. As in adults, a significant impact on sleep, mood, cognition, and function is found. However, impairments manifest more often in behavioral and educational domains
6. Simplified and updated research criteria for probable and possible pediatric RLS are listed in →Table 14 <sup>47</sup>
7. PLMD may precede the diagnosis of RLS in some cases

Abbreviations: PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

**Table 13** Clinical features supporting the diagnosis of pediatric RLS

The following features, although not essential for diagnosis, are closely associated with pediatric RLS and should be noted when present:
1. PLMS > 5 events per hour
2. Family history of RLS among first-degree relatives
3. Family history of PLMS $\geq$ 5 per hour
4. Family history of PLMD among first-degree relatives

Abbreviations: PLMD, periodic limb movement disorder; PLMS, periodic limb movement of sleep; RLS, restless leg syndrome. Adapted from Simakajornboon et al 2015.<sup>4</sup>

listed in **Table 13**. Children may develop symptoms of RLS over a period of time and **Table 14** lists criteria for the diagnosis of probable and possible RLS in these cases.

The urge to move can be accompanied by painful or uncomfortable, difficult to describe, sensations felt deep in the limbs, mostly in the legs, but sometimes in the arms.<sup>1</sup> Clinicians should be aware of age-specific vocabulary used to describe these sensations in children. Some examples of young children descriptions include “oowies,” “boo-boos,” “tickle,” “ants crawling,” “legs feel funny,” and “spider in the legs.” Older children may describe the sensations as “legs need to stretch,” “fidgety,” “restless,” “uncomfortable,” and “need to move.” The urge to move starts or becomes worse during inactivity and in the evening hours. However, approximately two-thirds of children and adolescents with RLS report daytime symptoms possibly related to long hours in class. Children can become more restless later in the day during car rides or while doing homework. Symptoms at bedtime may interfere with the ability to stay in bed and fall sleep. Disturbed sleep is a frequent and very distressing complaint.<sup>4</sup> PLMs can occur during sleep and/or during wakefulness further affecting both sleep and daytime functioning. Difficulties with sleep onset and with sleep maintenance along with difficulty waking up in the morning cause sleep deprivation and can stress the parent-child relationship.

**Table 14** Research diagnostic criteria for probable and possible pediatric RLS

<b>Probable RLS:</b> The child meets all essential criteria for RLS, except the circadian factor (occurrence only or worsening in the evening or night)
<b>Possible RLS:</b> The child is observed to have behavior manifestation of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort is characterized by all other RLS criteria (is worse during rest and inactivity, relieved by movement, worse in the evening or night, and is not solely accounted for as primary to another medical or a behavioral condition), but no verbalization of the urge

Abbreviation: RLS, restless legs syndrome. Adapted from Simakajornboon et al 2015.<sup>4</sup>

The restlessness of children with RLS can be mistakenly diagnosed as ADHD, but also increased rates of ADHD up to 25% were reported in children with RLS.<sup>47</sup> Children with ADHD have frequent symptoms of RLS, 43%, but only 7% were properly diagnosed.<sup>48,49</sup> Oner et al reported that 33% of their 87 patients with ADHD, aged 6 to 16 years, had RLS according to the International Restless Legs Syndrome Study Group criteria.<sup>49</sup> RLS symptoms seem to be less frequent (12%) when the patient group includes both ADHD and ADD.<sup>50</sup> The frequent association of RLS and ADHD suggested a possible genetic linkage, but an exploratory study did not show a significant connection.<sup>51</sup> One may speculate that a shared common dopamine dysfunction between RLS, PLMD and a subset of ADHD could explain the relationship between RLS and ADHD.<sup>52</sup>

Restless legs syndrome has been associated with significantly increased incidence of anxiety and mood disorders in adults. The severity of these symptoms seemed to correlate with the severity of RLS symptoms.<sup>53</sup> Similar findings were reported in children.<sup>10</sup> In an extensive review of medical records in 374 children who met the diagnostic criteria for RLS, 29% had a reported mood disturbance and 11.5% had anxiety disorder.<sup>47</sup>

A systematic review of the pediatric RLS literature provided convincing evidence of comorbidity with several somatic and neuropsychiatric conditions.<sup>53</sup> These included growing pains, kidney disease, diabetes, epilepsy, rheumatologic disorders, cardiovascular disease, liver and gastrointestinal disorders, neuropsychiatric disorders such as ADHD, depression, and conduct disorder.

Symptoms of RLS in children can start at any age. Once symptoms start, they usually progress slowly into adulthood with variable severity. Occasional remissions may occur, but complete remissions are rare.

### Epidemiology and Predisposing Factors

The prevalence of RLS in children is approximated to 2 to 4% and 0.5 to 1% may have moderate or severe symptoms.<sup>42,54-56</sup> Adolescents as a group tend to have more severe symptoms.<sup>55</sup> Previous studies showed no gender differences in children before their late teens,<sup>42</sup> but more recently Xue et al<sup>54</sup> noted a significantly higher prevalence in females (2.7%) than in males (1.7%) in a large population study in Chinese children aged 8 to 17 years. Independent of the reason for referral, RLS was diagnosed in 5.9% of children referred to a sleep clinic<sup>57</sup> and 17% of children in general pediatric clinic.<sup>58</sup>

Pediatric RLS is mostly familial.<sup>56,59-61</sup> Linkage and genotype analyses on 23 RLS diagnosed children showed that 20 (87%) had a family history of RLS.<sup>61</sup> In a large cross-sectional study in Brazil, 1.9% of the 383 children and adolescents (age: 5-17 years) were diagnosed with RLS and 90.9% had a family history of RLS.<sup>62</sup> RLS is particularly common in monozygotic twins and in first-degree relatives supporting a genetic pattern.<sup>59,61</sup>

Approximately 70% of children with RLS demonstrate an index of five or more PLMS on one night of PSG and nearly 90% when multiple PSGs were performed. Restless sleep in children has been associated with the development of RLS later in life.<sup>63</sup> Recently, a new entity of restless sleep disorder has been proposed,<sup>64</sup> possibly preceding the development of RLS.

Children with RLS or with restless sleep disorder tend to have lower iron stores.<sup>49,57,64–67</sup> RLS is more frequent among children with lower iron stores.<sup>67</sup>

Most studies support increased occurrence of RLS in pediatric chronic kidney disease.<sup>68–70</sup> This group of RLS patients was more likely to report sleep disruption and rated lower on quality of life by parent report.<sup>68</sup>

A history of growing pains is more frequent in children with RLS. In fact, growing pains may mask RLS symptoms.<sup>71</sup> Also, children with RLS tend to have more siblings with growing pains.<sup>59</sup> Children with RLS and children with growing pains had a high rate of decreased Vitamin D.<sup>72</sup> Among children with celiac disease, RLS rates are not higher, but age of onset was younger and symptoms were more severe. RLS symptom severity in this group seemed to correlate with decreased serum ferritin and decreased levels of Vitamin D.<sup>73</sup>

**Genetics and Pathophysiology**

In adults, a variant of the BTBD9 gene on chromosome 6 was associated with PLMS and low ferritin in RLS patients.<sup>74</sup> Following a genome-wide association study, Winkelmann et al identified three genomic regions associated with RLS: MEIS1, BTBD9, and MAP2K5/SKOR1.<sup>75</sup> A subsequent study has shown the same regions had some relation to PLMS.<sup>76</sup> The link between MEIS1 and SKOR1 was further elucidated by Catoire et al potentially implicating them in the modulation of pain and sensory input processing of RLS.<sup>77</sup> Interestingly, one study on childhood-onset RLS showed the association with MEIS1 and what is currently referred to as SKOR1, but not with BTBD9.<sup>61</sup>

Iron deficiency has been the single best documented biological abnormality for RLS.<sup>78</sup> Several studies confirmed brain iron deficiency, mostly in the substantia nigra and less in the putamen, caudate, and thalamus.<sup>79–85</sup> The iron deficiency in the brain is the result of impaired iron transport across the blood–brain barrier and into the neuromelanin cells of the substantia nigra. Decreased iron affects oxygen transport and activates hypoxic pathways increasing dopaminergic activity and producing postsynaptic down-regulation. This postsynaptic down-regulation response suffices during the day and might explain the increased arousal but seems to overcompensate in the evening and at night when dopamine levels are low due to circadian fluctuations. This iron deficiency-dopamine metabolic theory of RLS is supported by animal models, analyses of postmortem brains, biochemical, and imaging studies in adult RLS patients.<sup>78,86</sup>

Inadequate brain iron may have consequences beyond the dopaminergic system.<sup>87</sup> Iron acts as a co-factor in the regulation of the hypoxia inducible factor. Immunohistochemical analyses of substantia nigra tissue from autopsy studies on RLS patients showed an increase in the hypoxia-inducible factors suggesting activation of the hypoxia pathway.<sup>88</sup> A study in adult females with RLS showed reduced daytime intramuscular blood flow as measured in the tibialis anterior muscles,<sup>89</sup> suggesting a potential role for nitric oxide alterations in the pathophysiology of RLS.<sup>90</sup> Peripheral hypoxia was associated with the appearance of RLS symptoms in adults and correlated with RLS severity.<sup>91</sup>

**Objective Findings**

Polysomnographic studies demonstrate increased latency to persistent sleep and a higher arousal index.<sup>91,92</sup> PLMS indices of five events per hour of sleep or more are noted in 70 to 80% of adults and seem to be more frequent in children. Activity monitors attached to the ankle or foot can provide a measure of PLMs and have the advantage of recording across several nights.

The suggested immobilization test (SIT) is specific for RLS and has been used in research protocols mostly with adult patients or older teenagers. It is usually performed an hour before bedtime, even though a multiple SIT protocol has also been validated.<sup>93</sup> During the test, the patient is asked to sit awake in bed with out-stretched legs while PSG without respiratory monitoring is recorded. PLMW and sensory components of RLS are reported. PLMW > 40/h suggests a diagnosis of RLS corroborated by sensory report such as a visual analog scale.<sup>94–96</sup>

A specific protocol for children consisting of parental narratives, structured behavioral observations, and suggested clinical immobilization test has been presented by Ipsiroglu et al.<sup>97</sup> This protocol is currently being used in RLS and growing pains studies.

The severity of RLS symptoms has to be assessed in order to evaluate need, efficacy, and response to treatment. Several scales, including the most commonly used the International Restless Legs Syndrome Study Group RLS Severity Scale (IRLS) and more recently the self-administered version of the IRLS (sIRLS), have been validated and are available for use in adult patients,<sup>98–101</sup> but none was yet validated for the pediatric RLS patients. The Pediatric RLS Severity Scale, the P-RLS-SS, is a questionnaire with 17 morning and 24 evening items. It was developed based on detailed input from children and adolescents with RLS, their parents, and clinical experts providing it with strong content validity.<sup>102</sup>

**Differential Diagnosis and Comorbidities**

An urge or need to move one’s legs is a common symptom. Therefore, it is essential to differentiate RLS from other conditions that may “mimic” RLS and are listed in ► **Table 15**. The differential diagnosis of RLS is further complicated by the long list of RLS comorbidities listed in ► **Table 16**.

**Table 15** Pediatric conditions that may mimic or be associated with RLS

Positional discomfort
Sore leg muscles
Ligament sprain or tendon strain
Arthritis
Osgood–Schlatter Disease
Chondromalacia patella
Growing pains
Dermatitis

Abbreviation: RLS, restless legs syndrome.



**Table 16** Other common RLS mimics, comorbidities, and associated conditions

Sleep start or hypnic jerks
Phasic movements during REM
Fragmentary myoclonus
Myoclonic epilepsy
Nocturnal leg cramps
Peripheral neuropathy
Radiculopathy
Myopathy
Fibromyalgia
Complex regional pain syndrome
Sickle cell disease
Pregnancy
Renal failure and dialysis

Abbreviations: REM, rapid eye movement; RLS, restless legs syndrome.

**Table 17** RLS Clinical and physical examination

RLS history
RLS symptoms start time, pattern, and triggers if known
Sleep schedule and problems
Activity schedule and limitations
Caffeine and similar substances intake
Medications and supplements current and past
Medical history
Family history
Mental health assessment and history
Physical and neurological examination
Polysomnography and SIT or alternately actigraphy might be considered

Abbreviations: RLS, restless legs syndrome; SIT, suggested immobilization test.

**Management and Treatment**

The evaluation of patients with RLS should include a thorough, detailed clinical history, physical examination, and assessment of iron stores. Details of the examination are

**Table 18** Behavioral management for RLS

Education about the disorder, its course, and potential impact
Regular sleep routine
Avoid caffeinated substances
Review use of medications/supplements that may worsen RLS symptoms and/or PLMS
Exercise and stretch schedule

Abbreviations: PLMS, periodic limb movement of sleep; RLS, restless legs syndrome.

**Table 19** Medication for RLS children who are not candidate or not responsive to iron therapy and/or behavioral management

Generally, consider PRN use; start low, go slow
Clonidine, mostly for sleep: 50–800 µg
Benzodiazepines such as clonazepam mostly for sleep: 0.125–0.5 mg depending on age
Alpha-2 delta such as gabapentin (5–15 mg/kg) at bedtime, mostly for insomnia and pain complaints
Dopaminergics precautions: low dose, intermittent, ensure adequate iron store, longer acting and extended release
Check for augmentation: ropinirole (0.25–0.5 mg/day)
Anticonvulsants such as levetiracetam starting at 10–20 mg/kg/day
Opiates: no data in children with RLS

Abbreviations: PRN, pro re nata (as needed); RLS, restless legs syndrome.

presented in **Table 17** and assessment of iron stores in **Table 7**. Management and treatment are presented in **Tables 9, 18, and 19**. The most frequently reported and effective treatment for pediatric RLS is supplemental iron.<sup>65</sup>

**Conclusions**

- Sleep-related movement disorders occur in children.
- PLMs and PLMS are observed and scored during PSG in a variety of disorders as well as in reportedly healthy children. Their significance in the absence of clinical correlates needs further study.
- PLMS occurring in other sleep disorders such as OSA or narcolepsy; any sleep complaint is attributed to the respective sleep disorder.
- PLMS are a necessary criterion for a diagnosis of PLMD.
- PLMs can be observed in patients with RLS.
- If a diagnosis of PLMD or RLS is suspected, based on clinical history and examination, iron stores should be assessed.
- Any treatment for PLMD and RLS should include patient and family education, behavioral modification as needed, including adequate allowed time for sleep and replenishing iron stores if ferritin levels are below 50 µg.
- There is limited data on the immediate and long-term efficacy of medications and their side effect profile in children with PLMD or with RLS.
- More studies are needed on the impact of the PLMs in the general pediatric population and their relationship to sleep disorders and cardiometabolic processes.

**Conflict of Interest**

None declared.

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