Published online: 2019-07-02

Restless Legs Syndrome and Periodic Limb Movement Disorder in Children

Denise Sharon[1] Arthur Scott Walters[2] Narong Simakajornboon[3]

[1] Department of Medicine, Tulane University School of Medicine, Clinical Director Advanced Sleep Center Metairie Louisiana, PVHMC Adult and Children Sleep Disorders Center, Claremont, California, United States
[2] Division of Sleep Medicine, Department of Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee, United States
[3] Department of Pediatrics, University of Cincinnati, Director Sleep Disorders Center and Sleep Medicine Fellowship Program, Cincinnati Children Hospital, Cincinnati, Ohio, United States

Address for correspondence Denise Sharon, MD, PhD, FAASM, PVMC Adult and Children Sleep Disorders Center, 1601 Monte Vista Ave., #207, Claremont, CA 91711, United States (e-mail: denisesharon23@gmail.com).

J Child Sci 2019;9:e38–e49.

Abstract

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.

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

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 Academy of Sleep Medicine (AASM) includes a sleep-related movement disorders section. Some of these disorders are more frequent or specific to the pediatric population[1] (►**Table 1**). Benign sleep myoclonus of infancy is rare and tends to resolve spontaneously within the first 6 months of life. Sleep-related

received
November 4, 2018
accepted after revision
December 25, 2018

Issue Theme Sleep Disorders in Children; Guest Editors: David Gozal, MD, MBA, PhD (Hon), and Leila Kheirandish-Gozal, MD, MSc.

DOI https://doi.org/10.1055/s-0039-1678661.
ISSN 2474-5871.

Table 1 Sleep-related movement disorders affecting children[1]

Benign sleep myoclonus of infancy: repetitive myoclonic jerks during quiet sleep in infants from birth to 6 months of age
Sleep-related rhythmic movement disorder: repetitive stereotyped and rhythmic motor behaviors that are not tremors, but occur predominantly during drowsiness or sleep and involve large muscle groups
Sleep-related bruxism: repetitive jaw–muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible
Sleep related leg cramps: painful sensations caused by sudden and intense involuntary contraction of muscles during which there is muscle spasm and hardness for several seconds
PLMD: periodic episodes of repetitive, highly stereotyped limb movements that occur during sleep in conjunction with clinical sleep disturbance or fatigue
RLS 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.[2] Growing pains can be frequent in children 4 to 14 years (2.6–49.4%) causing painful middle of the night awakenings.[3,4] 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**.[5] 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.[6] Since that

Table 2 Definitions and scoring of PLM

Limb movements (LMs): 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
Periodic limb movement (PLM) series: 4 or more LMs occurring consecutively (5–90-second interval)
PLMs: periodic series of repetitive, highly stereotyped LMs
PLMI: PLMs per hour, frequently refers to hour of sleep
PLMS: PLMs occurring during sleep
PLMA: PLMs associated with arousals from sleep
PLMW: PLMs occurring during wakefulness

Adapted from the AASM scoring manual, 2018.[5]
Abbreviation: PLMA, periodic limb movements with arousal; PLMI, periodic limb movement index; PLMS, periodic limb movement of sleep; PLMW, periodic limb movements during wake.
[a]Caveat: Patient-related artifacts from devices like cycling feeding pumps[9] 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.[7] 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[8] 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.[10] 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.[11]

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.[12] They are more than twice as common in Caucasian than in African-American healthy children.[13] PLMS were reported in children with a history of prematurity (3.6%: 6 out of 167) without symptoms of RLS or PLMD.[14]

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).[15]

Periodic limb movements during sleep are 9.5 times more common in Caucasian children with sleep-disordered breathing (SDB) than in African-American children.[13] 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_2O.[16] 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.[17] Rogers et al reported on PLMS in 5 out of 17 children with sickle cell disease without OSA.[18]

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.[19] In children with juvenile fibromyalgia, 38% (6/16) had a PLMS $>$5 events/hour of sleep.[20]

Children with ADHD frequently have PLMS. These limb movements can disrupt sleep and may trigger or worsen symptoms of ADHD.[21–23]

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.[24] PLMS were associated with blood pressure elevations as reported by Wing et al,[25] 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[26] 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.[27] Attempts to better understand the pathophysiology and the clinical significance of PLMS point to sympathetic overactivity and inflammatory cellular pathways with associated cardiovascular risk.[28]

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.[29] 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.[5] The pattern and frequency of PLMS can vary from one night to another.[30] 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.[1]

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 problems focusing attention and maintaining concentration, hyperactivity, and decreased school performance.[10,31,32] Increased anxiety, mood disorders, and oppositional behaviors have also been reported.[10,32]

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.[10]
- Many studies are retrospective data reviews on children referred for evaluation of SDB, that is, a biased and skewed population.[33,34]
- The clinical information was based on questionnaires.[33]
- Limited clinical information.[35]
- Scarce data on general population[14]

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[33]	Louisville, KY	6–10	351	Pediatric sleep center	11.9%	Checked on questionnaire	11.9% parental report
Kirk and Bohn 2004[35]	Calgary, Canada	0–18	591	PSG at pediatric hospital	1.2%	ADHD 7.1%	Not reported
Gingras et al 2011[34]	Charlotte, NC	1–17	468	Pediatric sleep practice	14%	Criteria for PLMD met	14% ICSD 2nd edition
Marcus et al 2014[11]	Philadelphia, PA	5–17	195	Community	7.7%	None	None
Wong et al 2014[36]	Sydney, Australia	3–16	230	PSG at pediatric hospital and no neuro/dev dis	13%	GP $\times$3 more	Not reported
Cielo et al 2017[14]	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[11] surveyed special populations. Only half of the studies listed reported a diagnosis of PLMD which was based either on parental report[31] or the current ICSD criteria at publication time.[14,34] 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.[30]

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.[10,14,37–40] Replenishment of iron stores has been associated with improvement in clinical symptoms and possible remission.[40]

Pathophysiology

Periodic limb movements during sleep are the cornerstone of PLMD and are also frequently present in RLS patients.[41] Genetic factors, dopamine dysfunction, and low brain iron have all been implicated in the pathophysiology of PLMS.[38–40] In some patients, PLMS have been associated with frequent cortical and autonomic arousals resulting in nonrestorative sleep.[29] 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.[27] A few studies in children support the need for a better understanding of the cardiovascular implications of PLMS.[28]

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.[5] 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[a]

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

[a]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

Young children:
3 mg/kg/day of elemental iron divided into 2–3 daily doses; 1 hour before or 2 hours after feeds
Older children:
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
Benzodiazepine:
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
Alpha-2 delta ligands:
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.[41] Despite recent growth in the pediatric literature, pediatric RLS remains underdiagnosed and undertreated.[42] Possible causes of under recognition include mild, intermittent, poorly understood symptoms in young children combined with limited knowledge, awareness, and access to specialized care.[43,44]

Table 11 RLS diagnostic criteria: A–C must be met[1]

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.

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[1] (►**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[1,45,46](►**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[1]

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**[47]
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; PLMD, periodic limb movement of sleep; RLS, restless leg syndrome.
Adapted from Simakajornboon et al 2015.[4]

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.[1] 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.[4] 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

Probable RLS: The child meets all essential criteria for RLS, except the circadian factor (occurrence only or worsening in the evening or night)
Possible RLS: 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.[4]

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.[47] Children with ADHD have frequent symptoms of RLS, 43%, but only 7% were properly diagnosed.[48,49] 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.[49] RLS symptoms seem to be less frequent (12%) when the patient group includes both ADHD and ADD.[50] The frequent association of RLS and ADHD suggested a possible genetic linkage, but an exploratory study did not show a significant connection.[51] 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.[52]

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.[53] Similar findings were reported in children.[10] 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.[47]

A systematic review of the pediatric RLS literature provided convincing evidence of comorbidity with several somatic and neuropsychiatric conditions.[53] 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.[42,54–56] Adolescents as a group tend to have more severe symptoms.[55] Previous studies showed no gender differences in children before their late teens,[42] but more recently Xue et al[54] 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[57] and 17% of children in general pediatric clinic.[58]

Pediatric RLS is mostly familial.[56,59–61] Linkage and genotype analyses on 23 RLS diagnosed children showed that 20 (87%) had a family history of RLS.[61] 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.[62] RLS is particularly common in monozygotic twins and in first-degree relatives supporting a genetic pattern.[59,61]

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.[63] Recently, a new entity of restless sleep disorder has been proposed,[64] possibly preceding the development of RLS.

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

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

A history of growing pains is more frequent in children with RLS. In fact, growing pains may mask RLS symptoms.[71] Also, children with RLS tend to have more siblings with growing pains.[59] Children with RLS and children with growing pains had a high rate of decreased Vitamin D.[72] 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.[73]

Genetics and Pathophysiology

In adults, a variant of the BTBD9 gene on chromosome 6 was associated with PLMS and low ferritin in RLS patients.[74] Following a genome-wide association study, Winkelmann et al identified three genomic regions associated with RLS: MEIS1, BTBD9, and MAP2K5/SKOR1.[75] A subsequent study has shown the same regions had some relation to PLMS.[76] The link between MEIS1and SKOR1 was further elucidated by Catoire et al potentially implicating them in the modulation of pain and sensory input processing of RLS.[77] Interestingly, one study on childhood-onset RLS showed the association with MEIS1 and what is currently referred to as SKOR1, but not with BTBD9.[61]

Iron deficiency has been the single best documented biological abnormality for RLS.[78] Several studies confirmed brain iron deficiency, mostly in the substantia nigra and less in the putamen, caudate, and thalamus.[79–85] 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.[78,86]

Inadequate brain iron may have consequences beyond the dopaminergic system.[87] 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.[88] A study in adult females with RLS showed reduced daytime intramuscular blood flow as measured in the tibialis anterior muscles,[89] suggesting a potential role for nitric oxide alterations in the pathophysiology of RLS.[90] Peripheral hypoxia was associated with the appearance of RLS symptoms in adults and correlated with RLS severity.[91]

Objective Findings

Polysomnographic studies demonstrate increased latency to persistent sleep and a higher arousal index.[91,92] 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.[93] 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.[94–96]

A specific protocol for children consisting of parental narratives, structured behavioral observations, and suggested clinical immobilization test has been presented by Ipsiroglu et al.[97] 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,[98–101] 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.[102]

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 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.[65]

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.

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.

References

1 Sateia M, et al for the American Academy of Sleep Medicine. Sleep Related Movement Disorders in International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014:281–337

2 Leung AK, Wong BE, Chan PY, Cho HY. Nocturnal leg cramps in children: incidence and clinical characteristics. J Natl Med Assoc 1999;91(06):329–332
3 Mohanta MP. Growing pains: practitioners' dilemma. Indian Pediatr 2014;51(05):379–383
4 Simakajornboon N, Dye TJ, Walters AS. Restless legs syndrome/Willis-Ekbom disease and growing pains in children and adolescents. Sleep Med Clin 2015;10(03):311–322, xiv
5 Berry RB, Albertario CL, Harding SM, et al. American Academy of Sleep Medicine. The AASM Manual for Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Version 2.5, Darien, IL: American Academy of Sleep Medicine (ASSM); 2018:49–53
6 Chervin RD, Hedger KM. Clinical prediction of periodic leg movements during sleep in children. Sleep Med 2001;2(06): 501–510
7 Ferri R, Zucconi M, Manconi M, Plazzi G, Bruni O, Ferini-Strambi L. New approaches to the study of periodic leg movements during sleep in restless legs syndrome. Sleep 2006;29(06): 759–769
8 Ferri R, Fulda S, Allen RP, et al; International and European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). Sleep Med 2016;26:86–95s
9 Karroum EG, Phan HC, Torrez DM, Trotti LM. Perfect periodicity: to be or not to be periodic leg movements. J Clin Sleep Med 2016; 12(03):452–455
10 Picchietti DL, Stevens HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med 2008;9(07): 770–781
11 Marcus CL, Traylor J, Gallagher PR, et al. Prevalence of periodic limb movements during sleep in normal children. Sleep (Basel) 2014;37(08):1349–1352
12 Scholle S, Scholle HC. Leg movements and periodic leg movements during sleep in the development across childhood and adolescence from 1 to 18 years. Sleep Med 2014;15(09): 1068–1074
13 O'Brien LM, Holbrook CR, Faye Jones V, Gozal D. Ethnic difference in periodic limb movements in children. Sleep Med 2007;8(03): 240–246[PubMed]
14 Cielo CM, DelRosso LM, Tapia IE, et al; Caffeine for Apnea of Prematurity – Sleep Study Group. Periodic limb movements and restless legs syndrome in children with a history of prematurity. Sleep Med 2017;30:77–81
15 Bokkala S, Napalinga K, Pinninti N, et al. Correlates of periodic limb movements of sleep in the pediatric population. Pediatr Neurol 2008;39(01):33–39
16 Pai V, Khatwa U, Ramgopal S, Singh K, Fitzgerald R, Kothare SV. Prevalence of pediatric periodic leg movements of sleep after initiation of PAP therapy. Pediatr Pulmonol 2014;49(03):252–256
17 Chervin RD, Chung S, O'Brien LM, et al. Periodic leg movements during sleep in children scheduled for adenotonsillectomy: frequency, persistence, and impact. Sleep Med 2014;15(11): 1362–1369
18 Rogers VE, Lewin DS, Winnie GB, Geiger-Brown J. Polysomnographic characteristics of a referred sample of children with sickle cell disease. J Clin Sleep Med 2010;6(04):374–381
19 Esposito M, Parisi P, Miano S, Carotenuto M. Migraine and periodic limb movement disorders in sleep in children: a preliminary case-control study. J Headache Pain 2013;14:57
20 Tayag-Kier CE, Keenan GF, Scalzi LV, et al. Sleep and periodic limb movement in sleep in juvenile fibromyalgia. Pediatrics 2000;106 (05):E70
21 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(06):1000–1007
22 Golan N, Shahar E, Ravid S, Pillar G. Sleep disorders and daytime sleepiness in children with attention-deficit/hyperactive disorder. Sleep 2004;27(02):261–266
23 Miano S, Esposito M, Foderaro G, Ramelli GP, Pezzoli V, Manconi M. Sleep-related disorders in children with attention-deficit hyperactivity disorder: preliminary results of a full sleep assessment study. CNS Neurosci Ther 2016;22(11):906–914
24 Hartzell K, Avis K, Lozano D, Feig D. Obstructive sleep apnea and periodic limb movement disorder in a population of children with hypertension and/or nocturnal nondipping blood pressures. J Am Soc Hypertens 2016;10(02):101–107
25 Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep 2010;33(06):759–765
26 Gupta N, Maranda L, Gupta R. Differences in self-reported weekend catch up sleep between children and adolescents with and without primary hypertension. Clin Hypertens 2018;24:7
27 Walter LM, Foster AM, Patterson RR, et al. Cardiovascular variability during periodic leg movements in sleep in children. Sleep 2009;32(08):1093–1099
28 Figorilli M, Puligheddu M, Congiu P, Ferri R. The clinical importance of periodic leg movements in sleep. Curr Treat Options Neurol 2017;19(03):10
29 Dhondt K, Van Herzeele C, Roels SP, et al. Sleep fragmentation and periodic limb movements in children with monosymptomatic nocturnal enuresis and polyuria. Pediatr Nephrol 2015;30 (07):1157–1162
30 Picchietti MA, Picchietti DL, England SJ, et al. Children show individual night-to-night variability of periodic limb movements in sleep. Sleep 2009;32(04):530–535
31 Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 1999; 22(03):297–300
32 Gaultney JF, Merchant K, Gingras JL. Parents of children with periodic limb movement disorder versus sleep-disordered breathing report greater daytime mood and behavior difficulties in their child: the importance of using ICSD-2nd Edition criteria to define a PLMD study group. Behav Sleep Med 2009;7(03):119–135
33 Crabtree VM, Ivanenko A, O'Brien LM, Gozal D. Periodic limb movement disorder of sleep in children. J Sleep Res 2003;12(01): 73–81
34 Gingras JL, Gaultney JF, Picchietti DL. Pediatric periodic limb movement disorder: sleep symptom and polysomnographic correlates compared to obstructive sleep apnea. J Clin Sleep Med 2011;7(06):603–9A
35 Kirk VG, Bohn S. Periodic limb movements in children: prevalence in a referred population. Sleep 2004;27(02):313–315
36 Wong MW, Williamson BD, Qiu W, Champion D, Teng A. Growing pains and periodic limb movements of sleep in children. J Paediatr Child Health 2014;50(06):455–460
37 Simakajornboon N, Gozal D, Vlasic V, Mack C, Sharon D, McGinley BM. Periodic limb movements in sleep and iron status in children. Sleep 2003;26(06):735–738
38 Simakajornboon N. Periodic limb movement disorder in children. Paediatr Respir Rev 2006;7(Suppl 1):S55–S57
39 Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. Semin Pediatr Neurol 2008;15(02):91–99
40 Dye TJ, Jain SV, Simakajornboon N. Outcomes of long-term iron supplementation in pediatric restless legs syndrome/periodic limb movement disorder (RLS/PLMD). Sleep Med 2017;32:213–219
41 Walters AS, Picchietti DL, Ehrenberg BL, Wagner ML. Restless legs syndrome in childhood and adolescence. Pediatr Neurol 1994;11 (03):241–245
42 Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in

children and adolescents–the Peds REST study. Pediatrics 2007; 120(02):253–266
43 Dosman C, Witmans M, Zwaigenbaum L. Iron's role in paediatric restless legs syndrome - a review. Paediatr Child Health 2012;17 (04):193–197
44 Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. 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(02):101–119
45 de Weerd A, Aricò I, Silvestri R. Presenting symptoms in pediatric restless legs syndrome patients. J Clin Sleep Med 2013;9(10): 1077–1080
46 Picchietti DL, Bruni O, de Weerd A, et al; International Restless Legs Syndrome Study Group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med 2013;14(12): 1253–1259
47 Pullen SJ, Wall CA, Angstman ER, Munitz GE, Kotagal S. Psychiatric comorbidity in children and adolescents with restless legs syndrome: a retrospective study. J Clin Sleep Med 2011;7(06): 587–596
48 Kwon S, Sohn Y, Jeong SH, Chung US, Seo H. Prevalence of restless legs syndrome and sleep problems in Korean children and adolescents with attention deficit hyperactivity disorder: a single institution study. Korean J Pediatr 2014;57(07):317–322
49 Oner P, Dirik EB, Taner Y, Caykoylu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med 2007;213(03):269–276
50 Silvestri R, Gagliano A, Aricò I, et al. Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video-polysomnography. Sleep Med 2009;10(10): 1132–1138
51 Schimmelmann BG, Friedel S, Nguyen TT, et al. Exploring the genetic link between RLS and ADHD. J Psychiatr Res 2009;43 (10):941–945
52 Cortese S, Konofal E, Lecendreux M. Effectiveness of ropinirole for RLS and depressive symptoms in an 11-year-old girl. Sleep Med 2009;10(02):259–261
53 Angriman M, Cortese S, Bruni O. Somatic and neuropsychiatric comorbidities in pediatric restless legs syndrome: a systematic review of the literature. Sleep Med Rev 2017;34:34–45
54 Xue R, Liu G, Ma S, Yang J, Li L. An epidemiologic study of restless legs syndrome among Chinese children and adolescents. Neurol Sci 2015;36(06):971–976
55 Yilmaz K, Kilincaslan A, Aydin N, Kor D. Prevalence and correlates of restless legs syndrome in adolescents. Dev Med Child Neurol 2011;53(01):40–47
56 Turkdogan D, Bekiroglu N, Zaimoglu S. A prevalence study of restless legs syndrome in Turkish children and adolescents. Sleep Med 2011;12(04):315–321
57 Kotagal S, Silber MH. Childhood-onset restless legs syndrome. Ann Neurol 2004;56(06):803–807
58 Chervin RD, Archbold KH, Dillon JE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep 2002;25(02):213–218
59 Champion D, Pathirana S, Flynn C, et al. Growing pains: twin family study evidence for genetic susceptibility and a genetic relationship with restless legs syndrome. Eur J Pain 2012;16(09): 1224–1231
60 Steinlechner S, Brüggemann N, Sobottka V, et al. Restless legs syndrome as a possible predictor for psychiatric disorders in parents of children with ADHD. Eur Arch Psychiatry Clin Neurosci 2011;261(04):285–291
61 Muhle H, Neumann A, Lohmann-Hedrich K, et al. Childhood-onset restless legs syndrome: clinical and genetic features of 22 families. Mov Disord 2008;23(08):1113–1121, quiz 1203
62 Sander HH, Eckeli AL, Costa Passos AD, Azevedo L, Fernandes do Prado LB, França Fernandes RM. Prevalence and quality of life and sleep in children and adolescents with restless legs syndrome/Willis-Ekbom disease. Sleep Med 2017;30:204–209
63 DelRosso LM, Bruni O, Ferri R. Restless sleep disorder in children: a pilot study on a tentative new diagnostic category. Sleep (Basel) 2018;41(08):xx
64 Gamaldo CE, Benbrook AR, Allen RP, Scott JA, Henning WA, Earley CJ. Childhood and adult factors associated with restless legs syndrome (RLS) diagnosis. Sleep Med 2007;8(7–8):716–722
65 Amos LB, Grekowicz ML, Kuhn EM, et al. Treatment of pediatric restless legs syndrome. Clin Pediatr (Phila) 2014;53(04):331–336
66 Tilma J, Tilma K, Norregaard O, Ostergaard JR. Early childhood-onset restless legs syndrome: symptoms and effect of oral iron treatment. Acta Paediatr 2013;102(05):e221–e226
67 Halac G, Sezer GM, Saglam NO, et al. The relationship between Willis-Ekbom disease and serum ferritin levels among children in Northwestern Turkey. Neurosciences (Riyadh) 2015;20(04): 336–340
68 Riar SK, Leu RM, Turner-Green TC, et al. Restless legs syndrome in children with chronic kidney disease. Pediatr Nephrol 2013;28 (05):773–795
69 Applebee GA, Guillot AP, Schuman CC, Teddy S, Attarian HP. Restless legs syndrome in pediatric patients with chronic kidney disease. Pediatr Nephrol 2009;24(03):545–548
70 Stabouli S, Papadimitriou E, Printza N, Dotis J, Papachristou F. Sleep disorders in pediatric chronic kidney disease patients. Pediatr Nephrol 2016;31(08):1221–1229
71 Rajaram SS, Walters AS, England SJ, Mehta D, Nizam F. Some children with growing pains may actually have restless legs syndrome. Sleep 2004;27(04):767–773
72 Evans AM, Berde T, Karimi L, Ranade P, Shah N, Khubchandani R. Correlates and predictors of paediatric leg pain: a case-control study. Rheumatol Int 2018;38(07):1251–1258
73 Işıkay S, Işıkay N, Per H, Çarman KB, Kocamaz H. Restless leg syndrome in children with celiac disease. Turk J Pediatr 2018;60 (01):70–75
74 Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med 2007;357(07): 639–647
75 Winkelmann J, Schormair B, Lichtner P, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 2007;39(08): 1000–1006
76 Moore H IV, Winkelmann J, Lin L, Finn L, Peppard P, Mignot E. Periodic leg movements during sleep are associated with polymorphisms in BTBD9, TOX3/BC034767, MEIS1, MAP2K5/SKOR1, and PTPRD. Sleep (Basel) 2014;37(09):1535–1542
77 Catoire H, Sarayloo F, Mourabit Amari K, et al. A direct interaction between two restless legs syndrome predisposing genes: MEIS1 and SKOR1. Sci Rep 2018;8(01):12173
78 Allen RP. Restless leg syndrome/Willis-Ekbom disease pathophysiology. Sleep Med Clin 2015;10(03):207–214, xi
79 Allen RP, Barker PB, Wehrl FW, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001;56(02):263–265
80 Earley CJ, B Barker P, Horská A, Allen RP. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med 2006;7(05):458–461
81 Godau J, Klose U, Di Santo A, Schweitzer K, Berg D. Multiregional brain iron deficiency in restless legs syndrome. Mov Disord 2008;23(08):1184–1187
82 Moon HJ, Chang Y, Lee YS, et al. T2 relaxometry using 3.0-tesla magnetic resonance imaging of the brain in early- and late-onset restless legs syndrome. J Clin Neurol 2014;10(03):197–202

83 Rizzo G, Manners D, Testa C, et al. Low brain iron content in idiopathic restless legs syndrome patients detected by phase imaging. Mov Disord 2013;28(13):1886–1890

84 Schmidauer C, Sojer M, Seppi K, et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol 2005;58(04):630–634

85 Earley CJ, Connor J, Garcia-Borreguero D, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom Disease). Sleep Med 2014;15(11):1288–1301

86 Connor JR, Patton SM, Oexle K, Allen RP. Iron and restless legs syndrome: treatment, genetics and pathophysiology. Sleep Med 2017;31:61–70

87 Patton SM, Ponnuru P, Snyder AM, Podskalny GD, Connor JR. Hypoxia-inducible factor pathway activation in restless legs syndrome patients. Eur J Neurol 2011;18(11):1329–1335

88 Oskarsson E, Wåhlin-Larsson B, Ulfberg J. Reduced daytime intramuscular blood flow in patients with restless legs syndrome/Willis-Ekbom disease. Psychiatry Clin Neurosci 2014;68 (08):640–643

89 Trenkwalder C, Allen R, Högl B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol 2018;17(11):994–1005

90 Salminen AV, Rimpilä V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology 2014;82(21): 1856–1861

91 Hornyak M, Feige B, Voderholzer U, Philipsen A, Riemann D. Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. Sleep 2007;30(07):861–865

92 Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. Sleep 2009;32(06):772–778

93 Garcia-Borreguero D, Kohnen R, Boothby L, Tzonova D, Larrosa O, Dunkl E. Validation of the multiple suggested immobilization test: a test for the assessment of severity of restless legs syndrome (Willis-Ekbom Disease). Sleep (Basel) 2013;36(07): 1101–1109

94 Haba-Rubio J, Sforza E. Test-to-test variability in motor activity during the suggested immobilization test in restless legs patients. Sleep Med 2006;7(07):561–566

95 Michaud M, Poirier G, Lavigne G, Montplaisir J. Restless legs syndrome: scoring criteria for leg movements recorded during the suggested immobilization test. Sleep Med 2001;2(04): 317–321

96 Montplaisir J, Boucher S, Nicolas A, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. Mov Disord 1998;13(02):324–329

97 Ipsiroglu OS, Beyzaei N, Berger M, et al. "Emplotted Narratives" and Structured "Behavioral Observations" supporting the diagnosis of Willis-Ekbom disease/restless legs syndrome in children with neurodevelopmental conditions. CNS Neurosci Ther 2016; 22(11):894–905

98 Shaikh AG, Mehndiratta P, Gonzalez C, Koo BB. Analog restless legs syndrome rating scale. Eur Neurol 2013;70(3-4):195–200

99 Walters AS, LeBrocq C, Dhar A, et al; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4(02):121–132

100 Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med 2001;2(03):239–242

101 Sharon D, Allen RP, Martinez-Martin P, et al; International RLS Study Group. Validation of the self-administered version of the international Restless Legs Syndrome study group severity rating scale - the sIRLS. Sleep Med 2018;54:94–100

102 Arbuckle R, Abetz L, Durmer JS, et al. Development of the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS): a patient-reported outcome measure of pediatric RLS symptoms and impact. Sleep Med 2010;11(09):897–906