Restless legs Syndrome: What a pediatrician needs to know

Maxime Benoot[a], Karlien Dhondt[b]

[a] Dept of Psychiatry, div. Child & Adolescent Psychiatry, Ghent University Hospital, Ghent Belgium
[b] Dept of Psychiatry, div. Child & Adolescent Psychiatry, Pediatric Sleep Center, Ghent University Hospital, Ghent, Belgium

karlien.dhondt@ugent.be

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Abstract

Over the last two decades, there has been increasing recognition that restless legs syndrome (RLS) occurs in children. Adults who suffer from RLS often refer to their childhood as the onset of the symptoms. Epidemiologic studies indeed report that RLS symptoms are more prevalent in children than most physicians would have expected. This article challenges pediatricians to consider what role they might play in the detection and treatment of RLS. Information is provided that should be helpful to pediatricians how to detect and how to evaluate childhood RLS. With the knowledge of pathophysiological mechanisms, the impact of pharmacological treatments, common comorbidities and other pediatric conditions, children at risk can be more easily recognized. RLS should be considered as a possible cause of growing pains and/or sleep problems and should be referred to pediatric sleep specialists if necessary, but not every child with RLS needs treatment.

Introduction

Restless legs syndrome (RLS), also called Willis-Ekbom disease (WED), is usually known as a sensorimotor disorder and is characterized by an irresistible urge to move the limbs predominantly in the evening or at night. This urge to move is usually accompanied by a specific discomfort in the lower extremities, often alluded to as a 'creepy' or 'crawly' feeling. Once thought to be a rare disorder, RLS is known now as a rather common condition with considerable clinical variability. RLS is often described in adults. A large scale population-based study in Europe and the United States reported a prevalence of RLS in 7,2% in the adult population (1). However, recent research demonstrated that RLS is also a common condition in children. It has been assumed that symptoms of RLS are more prevalent than most physicians would expect. Based on different studies, epidemiologic rates of RLS in children and adolescents ranges between 2 – 4% (2). Symptoms in children mostly appear as the inability to sit still, the experience of having growing-pain-like sensations and/or disturbed or interrupted sleep (3). Based on parent information, researchers found that RLS can manifest in early childhood, even before 2 years of age (4). However, RLS diagnosis in the pediatric population is often delayed due to unawareness of this relatively common disorder. Indeed, retrospective research, showed an average interval of 4 years between the time of consultation and the time of diagnosis (4). Furthermore, retrospective studies also indicated that many adults with RLS recall that their symptoms already started in childhood or adolescence (3). Results from the Peds REST study done by Pichietti et al. indicate a percentage of 24% and 22% for a definite diagnosis for respectively children and adolescents who consulted with specific symptoms. In addition, the authors refer to an overall percentage of 11% in the general pediatric population (3). The reasons for a diagnostic delay are rather obvious. One is a rather different clinical picture of pediatric RLS compared to the adult complaints; second might be the difficulty for (young) children to express the sensations associated resulting in a lack of verbal confirmation and third is the wrong allocation of the ache and pain symptoms to other age specific conditions, such as growing pains. Together with the unawareness of the syndrome by pediatricians, these factors can easily result in a diagnostic delay or misdiagnosis.

Based on literature and clinical experience, RLS symptoms can disrupt sleep and consequently have a potential impairment on daily functioning. However, RLS is seen as a spectrum varying from latent or subclinical to severe. The clinical presentation of the syndrome together with the severity of the complaints related to sleep disruption are therefore important to identify. In children, the impact of RLS can be significant during the day (aches and pain, mostly in the lower limbs, but in the upper limbs is also possible) and the night (sleep disruption due to the aches and pain, or to an increased motor activity experienced as a need to move the limbs). The subsequent sleep disruption may result in impairment of the cognitive, behavioral and emotional functions. Consequences as poor school performances due to hypersomnolence, inadequate concentration, a negative influence on the child's mood, a lack of energy, disturbed daily activities and hyperactivity are described (4).

Given the knowledge of underdiagnosis and secondarily the impact on cognitive and emotional functioning in children and adolescents, it is clear that RLS diagnosis should be assessed regularly in the pediatric practice whenever relevant. Clinical significance should be evaluated in order to set up a diagnostic and therapeutic protocol. This review aims to inform clinicians involved in pediatric health care about RLS by giving an overview of the clinical features, insights in the pathophysiology and by providing diagnostic and treatment tools. In addition, specific pediatric conditions in which RLS is observed more frequently are also presented.

Clinical presentation and diagnostic assessment

Clinical features of pediatric RLS

Clinicians should bear in mind that children and their parents rarely consult spontaneously for specific RLS symptoms. The most common initial burden or complaint parents refer to is the presence of a disrupted sleep. More specific descriptions include restlessness while sleeping, insomnia with difficulties in falling asleep (>30 min.) or maintaining sleep, annoying daytime fatigue or excessive sleepiness resulting in poor school performance (3). Clinically, RLS is a typical sensory-motor disorder, consisting of sensory symptoms in the legs with consequent motoric symptoms to relieve the unpleasant feeling. Information that should be helpful to primary care physicians in the detection of RLS was provided in the ped REST study, published by Picchietti et al. (3). The disturbing sensations are described by children as 'ants in the legs', 'itchy feelings', 'legs feeling heavy, with bugs', 'have to move legs', 'legs want to kick', 'need to stretch' and so on (4). These sensations are described deep inside the limbs and can occur unilaterally or bilaterally, predominantly around the ankle, knee or affecting the entire lower limb. The authors also commented that they found asking about 'growing pains' to be a useful 'lead-in' question. Nonetheless useful, the presence of growing pains however is very common and the prevalence is much greater than what was found for

Table 1: International Restless Legs-Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome (8).

Diagnostic criteria for Restless Legs Syndrome	
Essential diagnostic criteria (all must be met)	
1)	An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs (a) (b)
2)	Begin or worsen during periods of rest or inactivity such as lying down or sitting
3)	Partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues (c)
4)	Only occur or are worse in the evening or night than during the day (d)
5)	The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping) (e)
Specifiers for clinical course of RLS/WED (f)	
A)	Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year
B)	Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events
Specifier for clinical significance of RLS/WED:	
The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/ vitality, daily activities, behavior, cognition or mood.	

Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.
(α) For children, the description of these symptoms should be in the child's own words.
(β) When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
(χ) When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.
(δ) These conditions, often referred to as "RLS/WED mimics", have been commonly confused with RLS/WED particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1 – 4. The list here gives some examples that have been noted as particularly significant in epidemiological studies and clinical practice. RLS/WED may also occur with any of these conditions, but the RLS/WED symptoms will then be more in degree, conditions of expression or character than those usually occurring as part of the other condition.
(ε) The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS/WED such as pregnancy or drug-induced RLS/WED where the frequency may be high but limited to duration of the provocative condition.
RLS/WED= Restless Legs Syndrome/Willis-Ekbom-Disease

Table 2: Special considerations for the diagnosis of pediatric restless legs syndrome (2)

- The child must describe the RLS symptoms in his or her own words
- The diagnostician should be aware of the typical words children and adolescents use to describe RLS
- Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age
- It is not known if the adult specifiers for clinical course apply to pediatric RLS
- As in adults, a significant impact on sleep, mood, cognition, and function is found. However, impairment is manifest more often in behavioral and educational domains
- Simplified and updated research criteria for probable and possible pediatric RLS are available
- Periodic limb movement disorder may precede the diagnosis of RLS in some cases

definite RLS in children (3). Growing pains have a very low positive predictive value in the sample, although the negative predictive value of 99% suggests that children who do not suffer from growing pains, mainly will not have RLS.

A certain circadian pattern of the RLS symptoms has been identified. The symptoms appear to worsen during the evening and/or night. Between 06:00 p.m. and 04:00 am with an observed peak before sleep onset, around midnight and in the morning (5). Apart from the urge to move the legs, restlessness in the arms is also reported in some (more severe) cases. The overall clinical presentation shows, in contrast to the adult population, no significant gender differences in children (3).

Nevertheless the clinical picture is highly typical, the course of the RLS symptom presentation in time can be quite variable. Adult reports of RLS frequency and severity show an increase with age (3). However, unfortunately, there is insufficient information about chronicity of the clinical course of RLS for children and adolescents (2, 4).

In addition to disturbed sleep, as mentioned above, symptoms can account for psychosocial distress as well. Cross-sectional research using the Pediatric Quality of Life inventory (PedsQL), a self-report scale for children, found RLS patients to be significant more 'feeling sad or blue', 'feeling angry', 'worrying about what will happen to me', compared to a control population (6).

Diagnostic tools and classification

Since 1960, diagnostic criteria for RLS have been published and revised by the International RLS Study Group (IRLSSG) (7). Given the concern that children <12 years of age would not be able to understand and verbally confirm the essential adult criteria, specific pediatric criteria were considered and formulated. Three diagnostic categories ("definite RLS", "probable RLS", "possible RLS") are formulated to capture the full spectrum of RLS. The two latter are mainly used in research. In 2014, a consensus was published to formulate integrated diagnostic criteria for adults, children and adolescents (Table 1) (8). In addition, special considerations for pediatric aspects of RLS were published (Table 2) (2). In particular, attention was put on their communication skills. Language and cognitive development determine the applicability of the RLS diagnostic criteria rather than age does. Moreover, physicians should be aware of the typical words children and adolescents use to describe RLS.

The International Classification of Sleep Disorders, 3rd Edition (ICSD-3) includes diagnostic criteria for RLS based on the IRLSSG criteria as shown in Table 1. To establish the ICSD-3 diagnosis of RLS, a significant impairment on daily functioning is required.

Above all, RLS is predominantly a clinical diagnosis. It is established based on the verbal confirmation of diagnostic criteria with no additional tests required per se. The presence of a positive familial history for RLS may also help to confirm the diagnosis. The patient's history and examination can be used to exclude secondary causes such as underlying diseases, risk factors or mimics. Neurologic disorders can mimic RLS symptoms such as lysosomal storage disease (Fabry), polyneuropathies, lumbosacral radiculopathies, and more common conditions such as sore leg muscles, positional discomfort or local problems (sprain, tendon, dermatitis) (2). Pharmacological side effects of prescribed medications in the pediatric population can also provoke or aggravate RLS (neuroleptics, antihistamines, beta-blockers) (9).

Besides the decisive importance of the clinical presentation in the diagnostic process, there are also some tools that can be used in the assessment of a patient with RLS symptoms. The RLS-Diagnostic Index (RLS-DI) and the international restless legs rating scale (IRLS) are validated helpful assessment tools to differentiate RLS among other sleep problems. These adult tools can be used in adolescents but are not adjusted for use in younger children. Arbuckle et. al. developed the pediatric RLS severity scale (P-RLS-SS) to properly measure RLS severity in children (10). The questionnaire items include 17 morning and 24 evening items as well as a separate parent questionnaire to asses RLS severity in children. The P-RLS-SS provides an age-appropriate tool that can contribute to the diagnostic process in pediatric RLS. However, the instrument has not been validated to date.

In addition, a positive family history among first degree relatives is frequently reported in the assessment of children with RLS. Picchietti et al. reported a biological parent with RLS in respectively 71% and 77% of cases of two different study samples (3, 4).

Another supporting feature of RLS is the presence of periodic limb movements in sleep (PLMS). PLM are described as repetitive, involuntary leg movements during sleep with a typical appearance of dorsiflexion of the toes, ankle and/or partial flexion of the knee and hip (11) (Figure 1). Polysomnographic (PSG) studies can objectify PLMS and a PLM Index (PLMI) is calculated by dividing the total number of PLMS by sleep time in hours. Studies based on PSG examination reported two-thirds of children with RLS to have a PLMI greater than 5/hour (12). However, a positive PLMI alone is not sufficient for a RLS diagnosis as it is also seen in other sleep disorders e.g. narcolepsy. Nevertheless, when a RLS diagnosis remains uncertain after rigorous clinical assessment, a PSG can be a supportive and objective additional test in the diagnostic process.

Pathophysiology

Numerous studies contributed to a better understanding of the pathophysiology of RLS. Today, there is evidence that iron as well as the neurotransmitter dopamine play a role in the pathophysiology of RLS. Additionally, a genetic susceptibility has recently been discovered as well.

The dopaminergic pathway

Prior therapeutic trials with dopaminergic agents in RLS patients provided pharmacological evidence that supports a dopaminergic mediation in RLS. Randomized, double-blind trials of dopamine (DA) agonists, such as pramipexole and ropinirole, showed a significant decrease of symptoms in RLS patients (13, 14). In contrast, DA antagonists, such as neuroleptics, worsen RLS symptoms. However, today, the precise physiological mechanism underlying the dopaminergic dysfunction in RLS patients, still remains partially unrevealed. To get more insight in the involvement of DA in RLS, we have to take a detailed look at the central and peripheral DA neurotransmitter system.

DA is known to play a central role in affecting mood, executive functions as well as locomotor activity. Central dopaminergic pathways are complex and the system includes 5 different receptors classified as D1-like (D1-D5) and D2-like (D2-D3-D4) with inhibitory and excitatory dose specific actions (15). Dysfunctions in DA activity are hard to investigate since there is no reliable manner to directly measure DA levels or activity in the brain. Recent research was able to demonstrate increased presynaptic dopamine production. Increased 3-O-Methyldopa (3-OMD) and homovanillic acid, major DA-metabolites, were found on CSF measurements in RLS patients (16). Autopsy studies in RLS patients demonstrated significant elevations in striatal tyrosine hydroxylase (TH), the rapidly limiting enzyme in DA biosynthesis, as well as a decrease in total dopamine D2 receptor expression (17). These results might most likely be caused by an increased level of intrasynaptic DA.

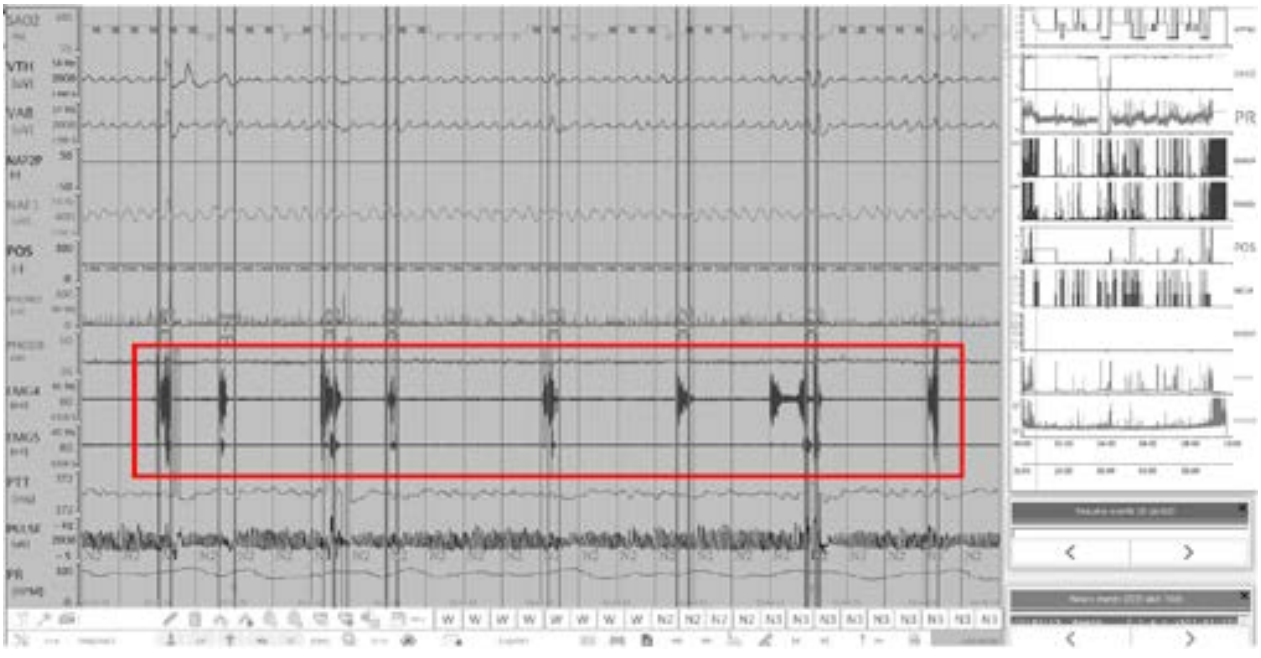
From the spinal cord perspective, DA projections from the hypothalamic A11 regions go to the dorsal (sensory) horn and ventral (motor) horn of the spinal cord and to the intermediolateral nucleus of the spinal grey matter, the final common output of the spinal sympathetic system (15). This pathway exercises an inhibitory role on the neuron excitability. According to the research of Clemens et al. an impairment of this descending control might have two consequences that are of interest in RLS: 1/ a reduced inhibitory modulation of the sensory and motor input and 2/ an increase in the sympathetic output resulting in higher blood pressure and heart rate (15). Both are reflected in the patient's complaints (higher sensory and motor activity) and/or in polysomnographic characteristics (increased heart rhythm). The urge to move the legs as well as the sensory symptoms can be understood as a dysfunctional 'gate control' mechanism that inhibits the increased sensory input due to a dopaminergic hypofunction.

The complex findings for the putative role of dopamine in RLS may also indicate different phases or expressions of RLS, different underlying disease processes and complex neurophysiological interactions.

Iron deficiency and the dopaminergic neurotransmission

From a clinical perspective, secondary causes for RLS such as anemia, renal failure and pregnancy lead to the assumption of iron deficiency as a contributing factor in RLS symptoms. Indeed, MRI studies showed reduced iron in the striatum of RLS patient's brains (18). Since no neurodegenerative abnormalities could be detected in RLS patients, a dysfunctional iron uptake is plausible. In addition, the found similarities in dopaminergic abnormalities in RLS patients as well as in iron deficient conditions are tantalizing. Significant increases in tyrosine hydroxylase (TH) and phosphorylated TH (known to be the rate limiting enzyme in the biosynthesis of DA) were seen together with decreased extracellular levels of dopamine and dopamine transporter functioning. These findings indicate the potential role of iron deficiency in the impaired dopaminergic transmission in RLS.

Figure 1 : *Periodic limb movements in sleep, a marker of restless legs in polysomnography*



Genetic susceptibility

At the turn of the century, a twin study described a concordant rate of 83% for RLS in monozygotic twins (19). A genetic susceptibility was further elaborated by a genome wide association study that confirmed genetic risk factors within six loci: *MEIS1*, *BTBD9*, *PTPRD*, *MAP2K5/SKOR1* and *PTPRD* (20). Single nucleotide polymorphisms in these six loci were shown to increase the risk of RLS and were strongly linked to increased PLMS, the polysomnographic hallmark of RLS. Interestingly the locus *BTBD9* encodes a protein domain related to the circadian rhythm genes which might explain the circadian pattern of the RLS condition. These findings contribute to a gene-environment interaction hypothesis underlying the pathophysiology of RLS and strengthen the clinical suspicion of a hereditary cause.

Co-phenomenal conditions

Primary RLS is an isolated syndrome, however a few co-occurring conditions are described in literature. The most commonly are chronic kidney disease and attention-deficit/ hyperactivity disorder (ADHD).

A systematic literature review shows consistent evidence of an increased prevalence of sleep disorders in children with chronic kidney disease (CKD), with a prevalence of 10-35% for RLS (21). The exact pathophysiology of RLS in CKD patients remains unclear; there doesn't seem to be any correlation between RLS and iron deficiency in CKD patients. This suggests a different pathogenesis of RLS in these patients (22). Symptoms of RLS especially increase during periods of rest, for example during dialysis. Adjustment of the dialysis schedule earlier in the day, short daily hemodialysis, distraction tasks during dialysis and intradialytic exercise programs are described as successful interventions that ameliorate RLS symptoms (23).

A higher prevalence of RLS in children and adolescents with ADHD was demonstrated with rates of 11.5% to 44% (24). Here, iron deficiency was described as playing a role in both ADHD and RLS (24). The mechanism of dopamine hypo-activity, in which iron is an important co-factor for dopamine synthesis, as well as a common genetic determinant may be considered as a common pathophysiology for ADHD and RLS.

In addition, there are a few other diseases in which a higher prevalence of RLS has been shown compared to the general population. These include Tourette syndrome and nocturnal enuresis (25, 26). However, extensive evidence for these associations remains limited. Furthermore, RLS frequently co-occurs with psychiatric disorders. Among these, ADHD, mood and anxiety disorder were the most common with a prevalence of respectively 25%, 29.1% and 11.5% (27). The authors emphasize the mutual impact of disturbed sleep, mood and attention difficulties. When RLS is present in patients with comorbid psychiatric conditions, it is important to consider the enhancing effect of antipsychotics and the possible amplifying effect of selective serotonin reuptake inhibitors on RLS symptoms.

Treatment

Before deciding on a therapeutic approach, some factors should be taken into account. First, since clinical implications with impact on daily life are rather variable, one should always consider treatment only when the burden on daytime functioning (mood, school performance, hypersomnolence) is significant. Second, triggering factors such as medication, poor sleep hygiene, lack of physical condition, lack of healthy nutrition must be acknowledged and third, co-phenomenal conditions should be treated first, if possible.

According to the proposed pathophysiology and pharmacological evidence, iron supplementation and dopamine agonists are the most commonly used therapeutic agents. All pharmacological interventions in children and adolescents are off-label use. A flow chart was drawn to give an overview of the recommended therapeutic options (Figure 2).

Evidence-based guidelines conducted by the IRLSSG task force recommend iron as the first -line treatment option in RLS in children and adolescents with proven iron deficiency (28). Serum ferritin below 50µg/L is considered an indication for iron supplementation. Initially, oral iron supplementation is recommended. Ferrous sulfate at a dose of 3mg/kg/day can be given with a daily maximum of 130 mg. However, the possibility of an interfering systemic problem with iron malabsorption should be taken into account. In addition, gastro-intestinal side effects (bad taste, nausea and constipation) can be challenging for children to comply an oral iron treatment (28). When oral iron treatment for 3 months does not provide adequate benefit or has to be discontinued due to side effects, IV iron may be considered. IV iron sucrose (Venofer®) is reported as a safe and effective treatment option in children (28). The recommended dose is 3 -6 mg/kg IV iron sucrose with a maximum of 120mg. The therapeutic target is to obtain a serum ferritin level ≥ 50 µg/L. The IRLSSG Working Group emphasizes that there are no studies demonstrating the long-term benefit or safety of iron treatment. Therefore, follow-up monitoring is recommended. In absence of an iron deficiency, other pharmacological treatment options should be considered.

Guidelines for the treatment of RLS in adults reported dopamine agonists, pramipexole and ropinirole, as standard level of recommended treatment (29). No recommendations for children were made. However, some randomized, double-blind studies, are described with significant improvement of RLS symptoms with dopamine agonists (30).

When using dopamine agonists, adverse side effects (aggression) and drug augmentation can appear. The latter is due to increased dopamine resulting in postsynaptic down-regulation of dopaminergic receptors, thus possibly enhancing the underlying RLS mechanism (29). Pediatric dose should start and stay low with the main aim to restore daytime functioning and sleep. After a treatment period of 6 months, a discontinuation is advised to reevaluate symptom severity (30).

In case of augmentation, the RLS guidelines recommend an alpha-2-delta-1 ligand anti-epileptic such as gabapentin as an alternative option (29). DelRosso et.al. described a few case reports suggesting RLS-symptom relief with gabapentin therapy (30).

Due to its muscle relaxing activity, clonazepam is proposed as treatment option in RLS as well. There is however limited data on its use for pediatric RLS. Moreover, important side effects can appear in children (aggression) and benzodiazepines have a bad reputation on sleep architecture when it comes to chronic use.

Other treatment options such as melatonin, vitamin D, magnesium are not retained as there is little or no scientific evidence.

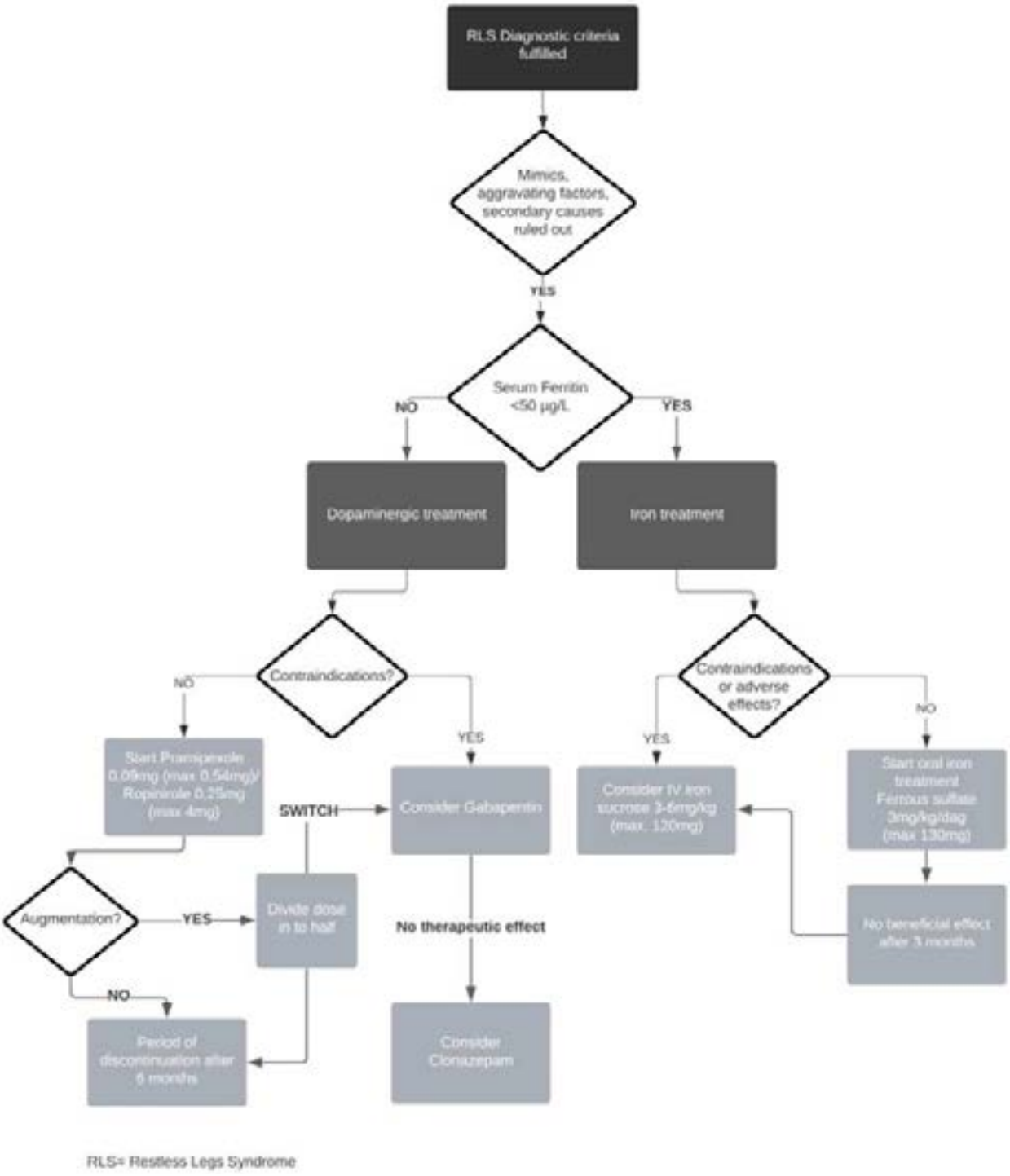
Conclusion

We aimed to provide adequate information for pediatricians to play a role in the detection and treatment of RLS in children. RLS is a sensory-motor disorder often not recognized or misdiagnosed in the pediatric population. Symptoms mostly appear as the inability to sit still, growing-pain-like sensations and/or disturbed and interrupted sleep. Apart from the diagnostic criteria published by the IRLSSG, diagnostic tools can be used to help identify RLS. Clinicians should be aware of common secondary causes, mimics and exacerbating factors. A PSG can be an additional objective diagnostic test. Due to different, yet partially unraveled pathophysiological mechanisms, the condition is likely heterogeneous. Before considering treatment options, a good assessment of sleep hygiene, sleep habits and possible exacerbating or co-occurring factors is recommended. Based on the proposed pathophysiological mechanisms, iron and dopamine agonists are the main therapeutic options. Therefore, a serum ferritin analysis, even though this cannot always be considered as the underlying cause, is worth to perform. Discontinuation of pharmacological treatment with a re-evaluation is important since the clinical features of RLS syndrome can vary during a lifetime.

Conflicts of interest

There are no conflicts of interest in this study

Figure 2 : *Flowchart treatment pediatric RLS (28, 30)*



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