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Restless Sleep Disorder (RSD): a New Sleep Disorder in Children. A Rapid Review

Lourdes M. DelRosso[1] · Maria P. Mogavero[2] · Raffaele Ferri[3] · Oliviero Bruni[4]

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Abstract

Purpose of Review Restless sleep disorder (RSD) is a recently identified pediatric sleep disorder characterized by frequent movements during sleep associated with daytime symptoms. In this review we summarize the expanding evidence of the clinical presentation of RSD, potential pathophysiology, associated comorbidities, and current treatment options that will help the pediatrician identify children with RSD in a timely manner.

Recent Findings RSD is diagnosed in 7.7% of children referred evaluated in a pediatric sleep center. Children with RSD present with frequent nightly movements during sleep for at least 3 months, and have daytime symptoms related to poor sleep quality including excessive sleepiness, hyperactivity, irritability among other symptoms. Current evidence shows an increased sympathetic predominance, increased NREM sleep instability, and iron deficiency, as well as increased prevalence in parasomnias and attention deficit hyperactivity disorder.

Summary Consensus diagnostic criteria were recently published to diagnose RSD and emergent evidence suggests that iron supplementation improves its nighttime and daytime symptoms.

Keywords Restless sleep disorder · Sleep-related movement disorders · Restless legs syndrome · Periodic leg movements during sleep · Iron supplementation

Introduction

Research in the last decades has shown the importance of adequate amount of sleep for health, behavior, cognition, and other areas of functioning [1]. Expert consensus guidelines on sleep duration requirements by age have been published by the American Academy of Sleep Medicine (AASM) [2]. In general, it recommended for adolescents to sleep an average of 8–9 h, school age children to sleep an average of 10 h at night, and younger children to achieve longer hours of sleep [2]. Research has also demonstrated that length of sleep is only one aspect when discussing the restorative properties of sleep and other qualities such as continuity and depth need to be equally assessed [3, 4]. In children, healthy sleep contributes to healthy development, growth, cognition, and appropriate behavior [5–7] and poor sleep quality, as evidenced by sleep disorders causing awakenings or arousals, has shown unwanted daytime consequences [8].

Restless sleep has been studied for decades in the context of comorbid medical or sleep disorders [9••] but only in the past few years restless sleep has been identified as a primary sleep disorder that affects children's quality of

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✉ Raffaele Ferri
rferri@oasi.en.it

Lourdes M. DelRosso
lourdesdelrosso@me.com

Maria P. Mogavero
paola_mogavero@libero.it

Oliviero Bruni
oliviero.bruni@uniroma1.it

[1] Pulmonary and Sleep Medicine, University of Washington, Seattle Children's Hospital, Seattle, WA 98105, USA

[2] Istituti Clinici Scientifici Maugeri, IRCCS, Scientific Institute of Pavia, Via Salvatore Maugeri 10, 27100 Pavia, Italy

[3] Sleep Research Centre, Department of Neurology I.C., Oasi Research Institute - IRCCS, Via Conte Ruggero 73, 94018 Troina, Italy

[4] Department of Developmental and Social Psychology, Sapienza University, Via dei Marsi 78, 00185 Rome, Italy

sleep and daytime behavior, a disorder that has been called "restless sleep disorder" (RSD) [10••]. Historically, restless sleep has been assessed mainly with the use of questionnaires, such as the Child's Sleep Habits Questionnaire [11, 12], Pediatric Sleep Questionnaire [13], and the Sleep Disturbance Scale for Children [14], that include screening sleep quality or "restless sleep." For this reason the International Restless Legs Study Group (IRLSSG) designated a taskforce to review restless sleep in the pediatric medical literature, to evaluate the scientific evidence that supported the diagnosis of RSD, and to establish expert consensus criteria [10••]. The criteria for diagnosis of RSD must include the following: a complaint of restless sleep reported by the parent of caregiver, frequent movements that involve large muscle groups and occur during sleep at a frequency of at least three nights a week for at least 3 months, and importantly, video-polysomnography must show at least five movements or repositioning per hour of sleep. To be diagnosed with RSD, the child must present with daytime symptoms of sleepiness, hyperactivity, mood disturbance, difficulty concentrating, or other daytime impairment attributed to the poor sleep quality. Finally restless sleep must not be secondary to another disorder or medication effect. The prevalence of RSD in a sleep center–referred pediatric population has been estimated to be 7.7% [15•]. Recent research has identified the clinical characteristics, potential pathophysiology, current treatment options, and some associated comorbidities of RSD. Importantly, data show that treatment with iron both orally and intravenously improved both nighttime and daytime symptoms [16••].

In this manuscript we describe a literature review of pediatric RSD, including the recently published consensus diagnostic criteria, proposed pathophysiology, and current treatment options.

Methods

Because of the relatively recent identification of RSD, a large number of papers were not expected. For this reason, a rapid literature search was performed in PubMed on March 20th, 2022, using the string "restless sleep disorder"; all fields were searched ensuring that any article mentioning it in the title or abstract was retrieved. Reference lists were examined and citation searching was performed.

Exclusion criteria were as follows: studies in adults and animals, in languages other than English, and with less than five participants. Review papers, guidelines, and editorials were not excluded but congress proceedings, abstracts, comments, and statements were.

Results

In total, 19 studies were retrieved: 11 journal articles [15•, 16••, 17••, 18–25], five reviews [9••, 26–29], two guidelines [10••, 30], and one editorial [31]. Table 1 reports a synthesis of the 11 studies that were included in the final analysis and will be discussed in detail in this and the following sections of this paper.

Publications assessing the clinical manifestations of children with RSD showed that children present for evaluation to sleep clinics with parental concern of restless sleep characterized by moving all night, trashing the bed, "sleeping like a helicopter," among other terms used by parents to denote the frequent body movements at night [17••]. Restless sleep at night was associated with daytime symptoms of fatigue, sleepiness, or behavioral problems [17••]. When compared to children with restless legs syndrome (RLS) or normal controls, children with RSD do not show difficulty falling asleep, nor symptoms of RLS, or nocturnal awakenings [17••]. Video polysomnography confirmed that children with RSD moved in their sleep frequently and through the whole night [20]. In fact, these movements contributed to decreased total sleep time and increased awakenings, when compared to controls. When compared to children with RLS, as expected, children with RLS had increased leg movement activity during sleep that was not found in children with RSD. Total body movement index of 5 or more identified RSD from controls with 100% accuracy [20].

It has also been reported that children with RSD have more pronounced daytime sleepiness (with an Epworth Sleepiness Scale greater than or equal to 10) than those with RLS and periodic limb movement disorder (PLMD) and a worse quality of life while, compared to patients with RLS and PLMD, children with RSD tended to have fewer chronic comorbid diseases; the authors also reported a higher percentage of REM sleep and a higher number of arousals in RSD than in the other groups of patients and controls, particularly those associated with large muscle group movements (LMM) during sleep, which contributed to the higher percentage of wakefulness after sleep onset [24].

In consideration of the clinical manifestations of RSD, a study evaluated the prevalence of this disorder in children with attention-deficit/hyperactivity disorder (ADHD) and, although restless sleep was a common disorder reported in 81.1% of these children, only 9.1% of them had RSD; in fact, in most cases restless sleep was iatrogenic or attributable to other sleep disorders and psychiatric comorbidities [23]. These data are very important for both the clinical setting (especially for differential diagnostics) and treatment of the patient.

Another research group, instead, focused attention on the prevalence of RSD in NREM sleep parasomnias,

Table 1 Summary of the nine studies on RSD included in the analysis (in chronological order)

Section/publication	Patients	Other group(s)	Method(s)	Results/conclusions
DelRosso et al., *2018* [17••]	RSD ($n=15$), mean age 9.5 ± 3.18 years RLS ($n=15$), mean age 11.9 ± 3.52 years	Controls ($n=30$), mean age 10.6 ± 3.8 years	PSG	Children with RSD have increased movements at night and daytime impairment, decreased ferritin, and increased arousals
DelRosso et al., *2019a* [20]	RSD ($n=15$), mean age 9.5 ± 3.18 years RLS ($n=15$), mean age 11.9 ± 3.52 years	Controls ($n=15$), mean age 10 ± 3.16 years	Video-PSG	PSG showed decreased sleep time Five movements per hour 100% accuracy for RSD vs. controls and 90% vs. RLS
DelRosso et al., *2019b* [15•]	Clinical sample ($n=300$), mean age 7.9 years, range 0.33–19 years		Clinical assessment, PSG	RSD 7.7% of the total sample
DelRosso et al., *2020* [22]	Iron supplementation responders ($n=42$), median age 10 years, range 2–17 years	Iron supplementation non-responders (35), median age 6 years, range 2–17 years	PSG	RSD in 14.3% of responders and 8.6% of non-responders
DelRosso et al., *2020* [19]	RSD ($n=38$) Age range 5–17 years RLS ($n=23$) Age range 4–17 years	Controls ($n=19$) Age range 5–18 years	PSG, CAP analysis	RSD with lower percentage of A3 CAP subtypes than controls, shorter duration of the B phase and of the CAP cycle than both controls and RLS, longer duration of CAP sequences than controls. Increased NREM sleep EEG instability
DelRosso et al., *2020* [18]	RSD ($n=32$) Median age 10.0 years Interquartile range 8–13.5 years RLS ($n=32$) Median age 10.0 years Interquartile range 8–14 years	Controls ($n=33$) Median age 7.4 years Interquartile range 6–14 years	PSG, HRV	In RSD increased sympathetic activation during sleep, particularly N3 and REM, compared to controls, but not during wakefulness. In RLS sympathetic activation during relaxed wakefulness preceding sleep and during sleep
DelRosso et al., *2020* [16••]	RSD with intravenous iron ($n=15$) Median age 11 years, interquartile range 8–15 years RSD with oral iron ($n=15$) Median age 13 years, interquartile range 9–15 years		Clinical and laboratory assessment	Iron supplementation with improvement in clinical and laboratory parameters. Response greater with intravenous than oral iron
DelRosso et al., *2021* [21]	RSD ($n=38$), mean age 10.3 ± 3.57 years RLS ($n=23$), mean age 9.4 ± 4.54 years	Controls ($n=29$), mean age 10.0 ± 4.56 years	PSG, spindle count	Children with RSD had longer frontal spindles, indicating a complex sleep microstructure disturbance with possible influence on excessive movement activity during sleep and daytime symptoms

Table 1 (continued)

Section/publication	Patients	Other group(s)	Method(s)	Results/conclusions
Kapoor et al., *2021* [23]	ADHD ($n=66$), mean age 11.6 ± 3.6 years		Clinical and laboratory assessment, video-PSG	Complaint of restless sleep in 81.1% of children with ADHD, but only 9.1% had RSD. Restless sleep mostly secondary and associated with other sleep disorders, psychiatric comorbidities, or medication use
Senel et al., *2021* [25]	NREM parasomnias ($n=28$) Mean age 12.5 ± 4.4 years	Controls ($n=20$), mean age 10.8 ± 3.6 years	Clinical and laboratory assessment, video-PSG, CAP analysis	RSD in one-third of children with NREM parasomnias, associated with worse sleep quality, increased CAP phase A3, and arousals
Liu et al., *2022* [24]	RSD ($n=14$), mean age 8.72 ± 3.59 years RLS ($n=12$), mean age 9.78 ± 3.43 years PLMD ($n=34$), mean age 9.23 ± 3.98 years		Clinical and laboratory assessment, video-PSG	Children with RSD with increased daytime sleepiness compared to PLMD or RLS and all three groups showed decreased quality of life

ADHD, attention-deficit/hyperactivity disorder; *CAP*, cyclic alternating pattern; *EEG*, electroencephalography; *HRV*, heart rate variability; *NREM*, non-rapid eye movements; *PLMD*, periodic limb movement disorder; *PSG*, polysomnography; *RLS*, restless legs syndrome; *RSD*, restless sleep disorder

evaluating its clinical and polysomnographic characteristics: the diagnosis of RSD was made in 28.6% (almost one-third) of children with NREM parasomnia (the most common disorder was sleepwalking), thus underlining the importance of investigating the presence of RSD in this group [25]. In this study, sleep efficiency was lower in children with RSD and NREM parasomnias than in controls; the analysis of the cyclic alternating pattern (CAP) [32] showed that its subtypes A1, A2, and A3 were significantly more expressed in children with NREM parasomnias than in controls and subtype A3 (closely related to arousals) was higher in children with RSD [25].

Children with RSD were identified to have mean ferritin levels of < 20 ng/dl which fits criteria for non-anemic iron deficiency (NAID), defined as ferritin levels < 50 ng/dl. NAID has been identified as a contributor to sleep-related movement disorders mainly by alteration of dopaminergic pathways involved in motor activity at night [33]. Our search found evidence that children with RSD improved clinically after iron supplementation, supporting the possible iron deficiency pathophysiological mechanism in RSD [22].

Other potential mechanisms underlying the pathophysiology of RSD were published and include sleep instability, studied by analyzing a physiological electroencephalographic pattern detected in polysomnography during NREM sleep which is a marker of NREM sleep instability, called cyclic alternating pattern (CAP) [32]. A recent study showed that children with RSD demonstrate abnormal CAP structure, suggesting alterations in the physiological NREM sleep instability [19]. These findings were characterized by lower percentage of A3 subtypes than controls, shorter duration of the B phase of the CAP cycle, and shorter CAP cycle. Another interesting finding was the fact that movements in children with RSD occurred mainly during NCAP periods [34], interrupting them, confirming that the large muscle group movements seen in children with RSD during sleep are associated with significant sleep disruption. Figure 1 shows, as an example, the polysomnographic aspect of a large muscle group movement in a child with RSD. The movement clearly interrupts a period of stable NREM sleep stage N2 with regular breathing, is associated to an increase in heart rate, and is followed by return to sleep.

Heart rate variability (HRV), a marker of sympathetic/parasympathetic balance, was also analyzed in a group of children with RSD [35]. In normal sleep, the transition from wakefulness to sleep is accompanied by a switch from sympathetic to parasympathetic predominance manifested by slowing in heart rate and respiration [36]. HRV in children with RSD showed increased sympathetic activation during sleep compared to controls. A recent study showed that the duration and density of frontal spindles, especially during N2 sleep stage, tended to decrease in children with RSD, compared to controls; this finding may help explain the

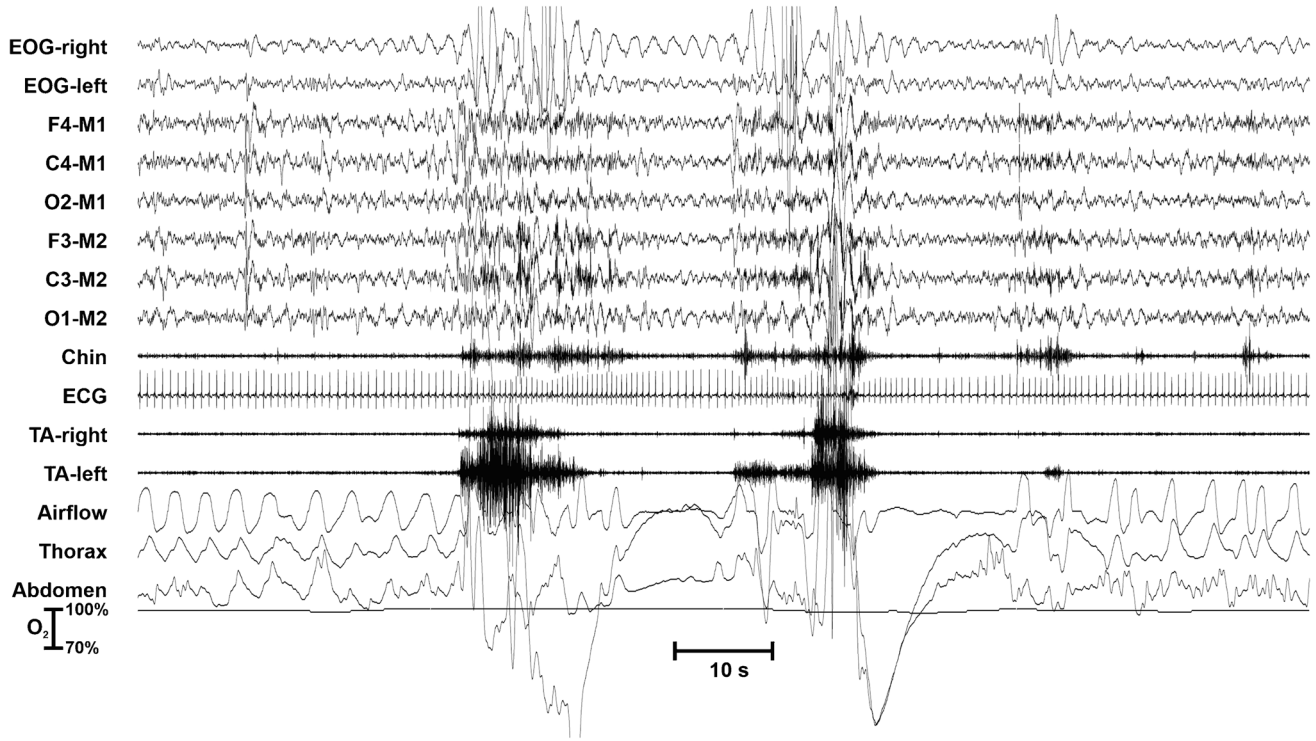

Fig. 1 Example of large muscle group movements during polysomnographic recording in a child with RSD. The movements interrupt a period of stable non-REM sleep stage N2 with regular breathing, are associated to increased heart rate, and are followed by unstable non-REM sleep

occurrence of excessive motor activity during sleep and the presence of daytime symptoms [21].

In terms of treatment options, two publications have studied iron supplementation in children with RSD [16••, 22]. In one, oral iron supplementation was evaluated in a group of children with sleep-related movement disorders but RSD was not individually assessed [22]. In the second publication, oral iron supplementation with ferrous sulfate was compared to intravenous ferric carboxymaltose [16••]. Oral iron supplementation for 3 months was given to children with RSD. Iron was in the form of ferrous sulfate 325 mg tablet daily or liquid 3 mg/kg/day (if the child could not swallow a tablet). Children who had side effects to oral iron or refused oral iron were offered intravenous treatment and received ferric carboxymaltose in a single dose of 15 mg/kg, if they weighted less than 50 kg or 750 mg if they weighted over 50 kg. When comparing both groups, it was found that serum ferritin increased with both oral and intravenous iron and symptoms improved in both groups [16••].

Discussion

The current literature review of the 11 publications (summarized in Table 1) that constitute the basis for the evidence of RSD highlights recent work in pediatric sleep medicine that led to the identification of this new pediatric sleep disorder. We have included the initial manuscripts describing the characteristics and symptoms in children with RSD and the current pathophysiology evidence. The use of CAP analysis in children with RSD and in children with parasomnias supports sleep instability in RSD. CAP is a validated assessment of sleep instability, previously studied in pediatric populations, and known to be affected by other conditions, for instance, CAP rate has also been found to be increased in other sleep disorders like insomnia [37], obstructive sleep apnea [38, 39], periodic limb movement disorder [40], and seizures [41], while it is decreased in narcolepsy [42, 43]. Heart rate variability has widely been used in the assessment of sympathetic, parasympathetic tone in sleep disorders [44, 45], providing a better understanding of the effects of sleep disruption on the autonomic nervous system, cardiac function, and potential consideration of use as biomarker. The analysis of sleep spindles provides further insight into the daytime consequences in RSD. Spindles play a role in memory consolidation, learning ability, and daytime behavior. Studies have shown abnormalities in spindles in children with neurodevelopmental disorders [46, 47] or children with sleep disorders [48]. Interestingly, the finding of long frontal spindles can postulate a delay in maturation of the frontal cortex, since spindles usually are predominant in the central hemispheres in school age children [49]. Similar spindle

characteristics found in RSD have been demonstrated in children with ADHD [50].

It is worth highlighting other important publications not included in the "Results" section of this review. The first one is a systematic literature review on restless sleep in children published by a taskforce created by the International Restless Legs Syndrome Study Group (IRLSSG) with the specific goal to assess restless sleep in children [9••]. In this manuscript, it was corroborated that restless sleep constituted a significant sleep quality disruptor and a contributor to unwanted daytime symptoms. The literature review identified that restless sleep was a common complaint in children with sleep disorders, seen in up to 80% of children with obstructive sleep apnea [51–53], restless legs syndrome (RLS) [54–60], or children with periodic leg movements of sleep (PLMS) [61, 62]. Restless sleep was also found in children suffering of medical conditions such as acute otitis media [63], asthma [64–66], neurologic disorders (headaches, nocturnal seizures) [67–70], eczema [71], among others. Other important contributors to restless sleep included psychiatric conditions such as depression or anxiety [72, 73], and substance use such as caffeine [74, 75].

The literature review by the IRLSSG offered invaluable information since it helped in setting up a pathway for the evaluation of a child presenting to the sleep specialist or pediatrician with concerns of restless sleep. The assessment should start with a thorough history and physical exam followed by exclusion of secondary causes of restless sleep. RSD must be considered when secondary causes are not identified and a sleep study or video-polysomnogram should be performed [76]. As previously mentioned, the diagnosis of RSD requires at least 5 movements per hour during sleep [17••]. The second publication from the IRLSSG is the consensus diagnostic criteria (Table 2) which includes the presence of chronic symptoms (at least 3 months) and frequent (at least 3 times a week) and emphasizes on the need to rule out other disorders [10••].

Although medical and psychiatric disorders and use of medications can be clear to differentiate, some other sleep-related movement disorders may pose a challenge to identify. Interestingly, most of the work on RSD has been done in comparison to children with RLS or PLMD. Studies have clearly shown that children with RSD do not present with PLMS or bedtime symptoms of leg discomfort. Other sleep-related movement disorders to differentiate include sleep-related rhythmic movement disorders, bruxism, and nocturnal epilepsy [77]. Sleep-related rhythmic movement disorders usually start during infancy and rarely persist after 5 years of age. They are characterized by repetitive head banging against the pillow or body rocking or rolling, usually at sleep onset or sleep stage transition presumably with the goal of self-soothing [27]. Rhythmic movement disorders are clearly differentiated from RSD by the persistence, in the latter, of body movements and repositioning through the night that do not follow a rhythmic or repetitive pattern. Also, rhythmic movement disorders are typically present at the onset of sleep or during night awakenings for resuming sleep. Another sleep-related movement disorder commonly seen in children is bruxism. The movements are confined to jaw clenching or teeth grinding, and although these movements can result in arousals or awakenings with evidence of large body movements and repositioning, the polysomnographic artifact on the chin electromyogram leads should clearly demonstrate a checkerboard-like artifact demonstrating bruxism prior to or during the arousal or movement [78]. Nocturnal epilepsy presents with stereotypical movements, dystonic positions, and postictal findings that differentiate it from the simple repositioning seen in RSD [79].

And finally, the third publication consists of new guidelines for scoring large muscle group movements which were developed with a substantial contribution from the work on the assessment of restless sleep in children [30]. These rules help in assessing sleep-related movements not only associated to RSD but also accompanying other medical conditions.

An interesting finding is the successful treatment of RSD with iron supplementation, either orally or intravenously [16••]. Previous studies on sleep-related movement

Table 2 Consensus diagnostic criteria for restless sleep disorder (RSD) [10••]

Criteria A–H must be met
A. A complaint of "restless sleep" as reported by the patient's parent, caregiver, or bedpartner, or by the patient
B. Restless sleep movements involve large muscle groups of the whole body, all four limbs, arms, legs, or head
C. The movements occur during sleep or when the individual appears to be asleep
D. Video-polysomnography shows a total movement index (by video analysis) of 5 or more per hour of sleep
E. Restless sleep occurs at least three times per week
F. Restless sleep has been present for at least 3 months
G. Restless sleep causes clinically significant impairment in behavioral, educational, academic, social, occupational, or other important areas of functioning, as reported by the patient's parent, caregiver, or bedpartner, or by the patient (e.g., daytime sleepiness, irritability, fatigue, mood disturbance, impaired concentration, or impulsivity)
H. The condition is not better explained by another sleep disorder, medical disorder, mental disorder, behavior disorder, environmental factor (e.g., sleep-disordered breathing, restless legs syndrome, periodic limb movement disorder, sleep-related rhythmic movement disorder, insomnia disorder, atopic dermatitis, seizure disorder, etc.), or the physiological effects of a substance (e.g., caffeine)

disorders, particularly RLS, have demonstrated symptomatic improvement after iron supplementation [80]. One can postulate that brain iron deficiency can contribute to various sleep-related movement disorders, possibly depending on the brain area affected. Neuro-imaging studies already support the presence of a regionally variable low brain iron content in adults with RLS, particularly in the substantia nigra and putamen [81–83]. Most recently, transcranial ultrasound performed has shown improvement in iron stores in regions of the brainstem after intravenous iron infusion in adults with RLS [84]. Iron is a cofactor in the production of various neurotransmitters including dopamine and dopaminergic pathways play a role in RLS [85]; therefore, the most logical hypothesis is that regional low iron levels in the brain similarly to RLS contribute to increased body movements during sleep. Detailed imaging studies in children with RLS or RSD are still lacking.

As a final point, we would like to add that most work in RSD was done in children older than 6 years and the diagnostic criteria specify that a child must be older than 6 years to qualify for the diagnosis. Prior the age of 6 years, the authors recommend the preliminary diagnosis of insomnia with motor restlessness which can be a precursor of a sleep-related movement disorder in children and might respond to iron supplementation as a treatment option. Further reassessment when the child is older is recommended [86].

This type of insomnia is typically found in children with a family and clinical history of RLS, iron deficient anemia, or growing pains. This type of insomnia can start at any age but usually is seen in the first years of life. Some children exhibit difficulties in falling asleep, rolling and kicking the covers off the bed, and night awakenings followed by screaming, crying, kicking, and slapping the legs or by verbally expressing that the legs hurt with a seemingly comforting effect of massage performed by parents. Furthermore, some cases of severe insomnia with falling asleep and nocturnal hyperactivity might be the early phenotypical expression of a non-diagnosed or lately recognized RLS or RSD itself. Further studies are needed to define the boundaries between these 3 types of disorders [86].

Conclusions

RSD is a pediatric sleep disorder characterized by frequent movements during sleep and significant daytime impairment, not explained by another condition, and diagnosed in children older than 6 years. There is evidence to support a pathophysiology based on iron deficiency, sleep instability, and increased sympathetic activation. RSD has been seen in children with ADHD and parasomnias. Expert taskforce consensus diagnostic criteria for RSD and for scoring large muscle group movements have been published. Iron supplementation has shown benefit improving sleep and daytime symptoms. The lack of RSD criteria for younger children could make it difficult to categorize those young children with motor hyperactivity during sleep that are often diagnosed with insomnia with motor restlessness. Further studies are needed to identify early symptoms that might be concurrent to the diagnosis of RDS or RLS.

At this stage we suggest that children younger than 6 years with similar symptoms should be diagnosed with insomnia with motor restlessness.

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Compliance with Ethical Standards

Conflict of Interest This work was partially supported by the Italian Ministry of Health (RC n. 2773798). Dr. Ferri reports personal fees from Jazz Healthcare Italy, outside the submitted work; the other authors have no relevant financial or non-financial interests to disclose.

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