Pediatric Restless Sleep Disorder

Lourdes M. DelRosso, MD, PhD[a,*], Maria P. Mogavero, MD[b,c], Oliviero Bruni, MD[d], Raffaele Ferri, MD[e]

KEYWORDS

• Restless sleep disorder • Diagnostic criteria • Treatment strategies • Iron supplementation • Neurophysiology • Comorbidities • Large muscle group movements during sleep

KEY POINTS

- Pediatric Restless Sleep Disorder (RSD) is emerging as a distinct entity in pediatric sleep medicine, characterized by restless and disruptive sleep patterns.
- RSD presents unique challenges in diagnosis and management due to its distinct features of large muscle movements during sleep.
- Studies have highlighted the prevalence, clinical presentation, and diagnostic criteria for RSD.
- Treatment options for RSD include oran and intravenous iron supplementation.
- Future research should focus on the natural course and long-term outcomes of RSD.

INTRODUCTION

In the field of pediatric sleep medicine, our understanding continues to evolve as we uncover novel sleep disorders that impact the health and well-being of children and adolescents. Among these emerging conditions, pediatric Restless Sleep Disorder (RSD)[1] has garnered increasing attention as a distinct entity separate from Restless Legs Syndrome (RLS) or Periodic Limb Movement Disorder (PLMD). Characterized by restless and disruptive sleep patterns in the absence of typical RLS or PLMD criteria,[2] RSD presents unique challenges in diagnosis and management, necessitating a deeper exploration of its clinical features, underlying mechanisms, and therapeutic approaches.

Recent clinical observations have highlighted a subgroup of children and adolescents who exhibit restless sleep behaviors distinct from RLS or PLMD criteria.[3] These individuals often experience frequent awakenings, excessive movement during sleep, and daytime fatigue, leading to impaired functioning and diminished quality-of-life. Yet, the etiology and optimal management of these restless sleep symptoms in pediatric patients remain unclear.

The identification of RSD as a distinct clinical entity underscores the need for specialized attention to pediatric sleep disorders beyond traditional diagnostic frameworks. By delineating the unique characteristics of RSD and elucidating its potential implications on child development and behavior, we can better tailor interventions to address the specific needs of affected individuals and their families.

In this review, we aim to comprehensively examine the current understanding of RSD, including its clinical presentation, diagnostic criteria, underlying pathophysiology, and treatment strategies. By synthesizing existing literature and integrating clinical insights, we aim to advance knowledge in the field of pediatric sleep medicine

[a] University of California San Francisco-Fresno, Fresno, CA 93721, USA; [b] Vita-Salute San Raffaele University, Milan, Italy; [c] Division of Neuroscience, San Raffaele Scientific Institute, Sleep Disorders Center, Milan, Italy; [d] Sapienza University of Rome, Developmental and Social Psychology, Rome, Italy; [e] Oasi Research Institute-IRCCS, Sleep Research Center, Troina, Italy

* Corresponding author. University of California San Francisco-Fresno, Inspire Health Sleep Center, 6733 N Willow Avenue Suite 107, Fresno, CA 93710.

E-mail address: lourdesdelrosso@me.com

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Abbreviations	
ADHD	attention-deficit/hyperactivity disorder
ASD	autism spectrum disorder
CAP	cyclic alternating pattern
FCM	ferric carboxymaltose
FS	ferrous sulfate
HRV	heart rate variability
IRLSSG	International Restless Legs Syndrome Study Group
IV	intravenous
LMM	large muscle group movement
PLMD	Periodic Limb Movement Disorder
PSG	polysomnography
RLS	Restless Legs Syndrome
RSD	Restless Sleep Disorder
vPSG	video-polysomnography

and promote optimal care for children and adolescents affected by RSD.

Clinical Presentation of Restless Sleep Disorder

In 2018, DelRosso and colleagues[2] presented the first clinical description of RSD, a condition that posed a challenge for pediatric sleep specialists due to its distinct features not fitting into existing diagnostic criteria for other sleep disorders. Children with "restless sleep" were commonly referred to pediatric sleep centers, presenting a perplexing scenario for clinicians.

Key parental concerns in RSD revolved around nocturnal large body movements involving limbs, head, and trunk, coupled with restless sleep and a perception of sleep disruption despite the absence of nocturnal awakenings. These symptoms were often accompanied by daytime impairment, notably daytime sleepiness, which significantly affected the child's functioning and quality-of-life.

Notably, all children diagnosed with RSD exhibited low ferritin levels, with a mean of 20 μg/L and a standard deviation of 8.87. This finding suggested a potential association between RSD and iron deficiency, highlighting a novel avenue for further investigation and treatment intervention.

Polysomnography (PSG) data revealed decreased sleep efficiency in children with RSD, a characteristic shared with the RLS group. However, unlike RLS, RSD did not exhibit prolonged sleep latency, indicating a unique sleep architecture profile in affected individuals.

The study by DelRosso and colleagues[2] proposed RSD as a new diagnostic category with specific clinical and video-PSG (vPSG) features, emphasizing the importance of recognizing and characterizing this distinct sleep disorder. By delineating the clinical presentation, associated parental concerns, daytime impairments, and laboratory findings, the authors provided valuable insights into the diagnostic approach and management of RSD in pediatric populations.

Subsequently, through a retrospective review of sleep diagnoses in 300 consecutive children evaluated at a single sleep disorders center, the same authors shed light on the prevalence and clinical characteristics of RSD in a clinical setting.[4] With 252 children undergoing PSG, the research highlighted an RSD prevalence rate of 7.7% among pediatric patients, providing valuable insights into its frequency relative to other common sleep disorders encountered in similar clinical settings. Furthermore, the study elucidated that RSD can coexist with other sleep disorders, such as habitual snoring and parasomnia, without complicating the diagnostic process, thus emphasizing the importance of recognizing and addressing RSD as a distinct entity within the spectrum of pediatric sleep disorders.

The Diagnosis of Restless Sleep Disorder

In another study, DelRosso and colleagues[5] aimed to refine the diagnostic approach for RSD through a detailed analysis of sleep-related movements using vPSG. The researchers reviewed vPSG recordings from 15 school-aged children diagnosed with RSD, 15 age-matched and sex-matched children with RLS, and 15 controls. Data collected included routine PSG parameters and video assessments of movements, such as their timing, type (involving arms, legs, or body position changes), and duration. The results revealed distinctive patterns in sleep-related movements among the 3 groups, with children diagnosed with RSD exhibiting prominent movements across all sleep stages. Notably, the total movement index—calculated by summing all types of movements and dividing by total sleep time—was significantly elevated in children with RSD, particularly with a threshold of 5 movements per hour, which demonstrated high accuracy in distinguishing RSD from other disorders, including RLS.

This study's findings provide valuable insights into the characterization of sleep-related movements in children with RSD compared to those with RLS and controls. By demonstrating the continuous course of movements throughout the night and establishing a quantitative threshold for distinguishing RSD, the research contributed to refining the diagnostic workflow for this distinct sleep disorder. These findings underscore the importance of incorporating vPSG and quantitative movement analysis in the evaluation of

pediatric sleep disorders, facilitating more accurate diagnosis and targeted interventions for children experiencing restless sleep disturbances like RSD.

In 2020, the International Restless Legs Syndrome Study Group (IRLSSG) initiated a pivotal effort to address the diagnostic challenges surrounding restless sleep disturbances. To achieve this, an esteemed task force comprising international sleep experts was assembled. This committee, consisting of 10 seasoned sleep clinicians, embarked on a meticulous process to establish consensus-based diagnostic criteria for a newly designated clinical entity termed "restless sleep disorder". The resulting recommendations were subjected to rigorous review and endorsement by the IRLSSG Executive Committee, culminating in a comprehensive framework aimed at enhancing diagnostic clarity and clinical management of RSD.[1]

Through a synthesis of medical literature and expert clinical insights, the task force identified 8 essential diagnostic criteria integral to defining RSD (**Box 1**). These criteria encompassed key aspects such as the presence of a complaint of restless sleep, observation of large body movements during sleep, and confirmation through vPSG documentation of at least 5 large body movements per hour. Additionally, the diagnostic criteria stipulated the frequency and duration of symptoms, along with the requirement for clinically significant impairment and differentiation from secondary causes of restless sleep.

While the consensus criteria represent a significant advancement in the field, their application is presently restricted to individuals aged 6 to 18 years, reflecting the limitations of available evidence.[1] The study's conclusions underscore the importance of consensus-based diagnostic frameworks in guiding clinical practice and fostering further research endeavors to deepen our understanding of RSD and refine its diagnostic and therapeutic approaches.

Box 1
Diagnostic criteria for restless sleep disorder in children and adolescents aged 6 to 18 years

Criteria (all must be met for the diagnosis of RSD)

1. A complaint of "restless sleep", observed by the patient's parent, caregiver, or bedpartner, or reported by the patient.
2. Movements associated with restless sleep involve large muscle groups of the whole body, all 4 limbs, arms, legs, or head.
3. Movements associated with restless sleep occur during sleep or when the individual seems to be asleep.
4. Video-polysomnography analysis shows a total movement index >5/h of sleep.
5. Restless sleep is reported to occur at least three times per week.
6. Restless sleep lasts for at least 3 months.
7. Restless sleep causes clinically significant impairment in a series of areas, such as behavior, education, academic, social, occupation, or other important areas of functioning (eg, daytime sleepiness, irritability, fatigue, mood disturbance, impaired concentration, or impulsivity).
8. The condition is not better explained by another sleep disorder, medical disorder, mental disorder, behavior disorder, environmental factor, (eg, sleep-disordered breathing, restless legs syndrome, periodic limb movement disorder, sleep-related rhythmic movement disorder, insomnia disorder, atopic dermatitis, seizure disorder, etc.), or the physiologic effects of a substance (eg, caffeine).

These findings support the diagnosis of RSD:

a. Large body movements during sleep normally occur throughout the night without particular clustering.
b. Delayed sleep onset is nt frequently reported.

Adapted from DelRosso et al.[1]

Diurnal Symptoms in Restless Sleep Disorder

Regarding diurnal consequences of RSD, Liu and colleagues[6] conducted a retrospective analysis comparing children with RSD to those with periodic PLMD or RLS. They found that children with RSD exhibited increased daytime sleepiness compared to both PLMD and RLS groups, despite similar serum ferritin levels. Additionally, all 3 disease groups demonstrated decreased quality-of-life, underscoring the profound impact of sleep disturbances on overall well-being. While further research is warranted to explore the long-term consequences of RSD, these findings emphasize the importance of recognizing and addressing daytime dysfunction in children with RSD to improve their quality-of-life.

In a complementary study, DelRosso and colleagues[7] evaluated neurocognitive functions in 13 children diagnosed with RSD, mean age 10.6 years, standard deviation (SD) 2.7, using the National Institute of Health Toolbox. Their findings

revealed significant impairments in selective attention, cognitive flexibility, and inhibitory control among children with RSD compared to expected frequencies, as supported by the impaired performance at the Flanker test.[8] These results underscore the detrimental effects of RSD on executive and cognitive functions, highlighting the need for clinicians to promptly intervene and address sleep disorders and associated daytime impairment to mitigate potential cognitive impairments. Together, these studies emphasize the multifaceted impact of RSD on daytime functioning, including increased daytime sleepiness and cognitive deficits, underscoring the importance of comprehensive assessment and management strategies to improve outcomes for children affected by RSD.

Table 1 shows a synopsis of symptoms, PSG features, family history, comorbid conditions, pathophysiology, and treatment of RSD compared to those of other common sleep-related movement disorders that will be treated in this article.

Restless Sleep Disorder Neurophysiology

Some studies have approached the neurophysiologic underpinnings of RSD in children, offering insights into the mechanisms underlying this newly recognized sleep disorder.

The first study investigated cyclic alternating pattern (CAP) in RSD children,[9] a marker of sleep instability that may correlate with the motor episodes characteristic of RSD and contribute to daytime symptoms. Through PSG analysis, the researchers found that RSD patients exhibited increased sleep instability during NREM sleep, characterized by shorter CAP cycle durations and a higher frequency of CAP cycle sequences compared to controls and individuals with RLS. These findings suggest that sleep instability may play a pivotal role in the emergence of motor episodes seen in RSD, shedding light on its pathophysiology.

In another study, DelRosso and colleagues[10] explored heart rate variability (HRV) during sleep in children with RSD, RLS, and controls to assess autonomic changes. The results revealed increased sympathetic activation during sleep in RSD children, particularly during N3 and REM sleep, compared to controls. Conversely, children with RLS exhibited sympathetic activation during relaxed wakefulness preceding sleep and throughout sleep, highlighting distinct autonomic patterns between the 2 sleep disorders. These findings underscore the role of sympathetic activation in RSD and its potential contribution to daytime symptoms, providing further insights into its neurophysiologic mechanisms.

Building upon these findings, DelRosso and colleagues[11] focused on analyzing sleep spindles, a hallmark of NREM sleep, in children with RSD, RLS, and controls. The study revealed longer frontal spindle durations in RSD children compared to controls, indicating alterations in thalamocortical oscillations. Additionally, frontal spindle density and intensity tended to be increased in RSD children, potentially contributing to excessive movement activity during sleep and daytime symptoms. By detailing differences in sleep spindle characteristics, this study enhances our understanding of the pathophysiology of RSD and its impact on daytime impairment, further corroborating previous findings of increased NREM instability and sympathetic activation in RSD.

In summary, these studies collectively provide valuable insights into the neurophysiologic mechanisms of RSD, highlighting sleep instability, sympathetic activation, and alterations in thalamocortical oscillations as key contributors to the pathophysiology of this relatively newly recognized sleep disorder in children. Such insights are crucial for developing targeted interventions aimed at alleviating symptoms and improving the quality-of-life for children affected by RSD.

Restless Sleep Disorder Comorbidities

Several studies have examined the comorbidities associated with RSD in children, shedding light on the multifaceted nature of this sleep disorder and its interplay with various underlying conditions. Kapoor and colleagues[12] conducted a retrospective study focusing on children with attention-deficit/hyperactivity disorder (ADHD) referred to a sleep center. Although restless sleep was a prevalent complaint among children with ADHD, with 81.1% reporting it, the prevalence of diagnosed RSD was substantially lower, at 9.1%. Notably, the majority of restless sleep cases were found to be secondary to other sleep disorders, psychiatric comorbidities, or medication use, underscoring the need for comprehensive evaluation when assessing children with ADHD.

Benbir Senel and colleagues[13] explored the relationship between RSD and NREM sleep parasomnias, revealing that RSD was present in almost one-third of children with these parasomnias. Furthermore, children with NREM parasomnias and RSD exhibited worse sleep quality and increased arousals compared to those without RSD, suggesting a complex interaction between RSD and parasomnias that warrants further investigation. Similarly, Benbir Senel and colleagues[14] found a high prevalence of RSD among children experiencing epileptic and non-epileptic nocturnal

Table 1
Symptoms, polysomnography features, family history, comorbid conditions, pathophysiology, and treatment of restless sleep disorder compared to those of other common sleep-related movement disorders

	RSD	RLS	PLMD	RMD	Bruxism
Symptoms					
Nocturnal	Large body movements during sleep	Urge to move legs with leg discomfort in the evening	Disrupted sleep Insomnia	Repetitive, stereotyped, and rhythmic movements	Tooth grinding during sleep
Diurnal	Sleepiness, Behavioral concerns	Sleepiness, Hyperactivity	Sleepiness, fatigue, or cognitive impairment		Jaw pain, headache, fatigue
PSG features	Large Muscle Movement index >5 No PLMS	↑ Awakenings ↓ Total sleep time ↑ Total leg movements, and isolated leg movements	PLMI >5	Rhythmic movements, particularly in N1 and N2 at vPSG	↑ Masseter muscle activity
Family history	Unknown	Often positive	Suspected	Rare	20% – 30% familial pattern
Comorbid conditions	ADHD Epilepsy Parasomnia	ADHD, renal disease, hypothyroidism	Narcolepsy ADHD	RLS, OSA, Narcolepsy, ADHD	Upper airway resistance
Pathophysiology	Iron deficiency Other unknown	Iron deficiency Medication effect Genetic Other unknown	Iron deficiency Medication effect Genetic Other unknown	Self-soothing Other unknown	↑ Sympathetic activity during arousals? Other unknown
Treatment	Iron supplementation	Iron supplementation Others	Iron supplementation Others	None	Mouth guard Muscle relaxants

Abbreviations: ↑, increased; ↓, decreased; PLMD, periodic leg movement disorder; PLMS, periodic leg movements during sleep; RMD, rhythmic movement disorder; vPSG, video-polysomnography.

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events, with lower ferritin levels observed in patients with RSD across all subgroups, indicating a potential association between iron metabolism and RSD pathogenesis.

Moreover, Voci and colleagues[15] examined RSD in children and adolescents with autism spectrum disorder (ASD), revealing a suspected RSD prevalence of 12.4% in the sample. Interestingly, while iron metabolism did not appear to be the primary factor implicated in RSD within this population, the study underscored the importance of further research into the prevalence, etiology, and sequelae of RSD in children with ASD. Additionally, DelRosso and colleagues[3] conducted a systematic review highlighting the high prevalence of restless sleep in children with various underlying conditions, emphasizing the need for empirical evidence-based clinical definitions to differentiate primary and secondary restless sleep and guide treatment strategies effectively.

In summary, these studies collectively underscore the diverse comorbidities associated with RSD in children, ranging from ADHD and NREM parasomnias to epilepsy and ASD. Understanding the intricate relationships between RSD and these underlying conditions is crucial for developing targeted interventions to alleviate symptoms and improve sleep quality and overall well-being in affected children. Further research is warranted to elucidate the mechanisms underlying these associations and guide the development of evidence-based diagnostic and therapeutic approaches for RSD.

Treatment of Restless Sleep Disorder

The treatment landscape for RSD in children has advanced in recent years, with studies exploring the efficacy of iron supplementation as a potential therapeutic intervention. DelRosso and colleagues[16] conducted a retrospective pilot study comparing oral ferrous sulfate (FS) and intravenous ferric carboxymaltose (IV FCM) in children with RSD. The study revealed a favorable response to iron supplementation, with both clinical and laboratory parameters showing improvement. Notably, children treated with IV FCM exhibited greater improvement in both clinical symptoms and iron status compared to those receiving oral FS. Adverse effects were more common with oral supplementation, highlighting the potential benefits of IV iron therapy for children with RSD.

Ingram and colleagues[17] further investigated the clinical response to IV iron supplementation in pediatric sleep clinic patients with RSD (n = 17), RLS (n = 30), and PLMD (n = 22). The study demonstrated significant improvements in sleep symptoms and ferritin levels post-infusion, with 73% of patients noting improvement in at least 1 symptom. Importantly, there were no significant differences in ferritin change across diagnostic subgroups, suggesting the potential efficacy of IV iron therapy across different sleep disorders. While adverse reactions to IV infusion were noted in a minority of patients, they were generally mild and manageable, reinforcing the safety profile of IV iron supplementation in this population.

Furthermore, Chu and colleagues[18] presented a small case series (n = 3) highlighting the use of actigraphy to assess the efficacy of IV iron supplementation in children with RSD. Although actigraphy parameters varied among patients, improvements in symptoms tended to parallel changes in sleep parameters, suggesting a potential role for actigraphy as a non-invasive tool to monitor treatment response in RSD.

These findings underscore the importance of objective outcome measures in evaluating treatment efficacy and suggest avenues for further research to optimize therapeutic strategies for children with RSD. Overall, the emerging evidence supports the use of IV iron supplementation as a promising therapeutic approach for children with RSD, offering potential benefits in both clinical symptoms and iron status.

Quantification of Large Body Movements

The scoring of large muscle group movements (LMM) during sleep has been a topic of interest in sleep medicine, with efforts made to establish standardized criteria for their detection and quantification. Ferri and colleagues[19] addressed this gap by developing rules for scoring LMM involving large muscle groups during sleep. These rules were formulated by a task force of the IRLSSG through a consensus-building process. The criteria defined movements characterized by an increase in electromyographic activity and/or movement artifact in recommended channels, with durations between 3 and 45 seconds in adults or 3 and 30 seconds in children. These movements, often associated with sleep stage changes and arousals, had lacked clear scoring guidelines, hindering the development of studies exploring their clinical relevance. The establishment of these rules filled this gap and provided a framework for future research in this area.

DeMeo and colleagues[20] compared the scoring of LMM on PSG with video in children with restless sleep, aiming to validate PSG criteria for LMM detection. The study found PSG-LMM to be significantly more numerous than video-

LMM, indicating a higher sensitivity of PSG in detecting these movements. Although PSG-LMM led to the detection of a greater number of movements, their duration was not statistically different from video-LMM. Moreover, a high correlation was observed between the LMM indexes and durations obtained by both methods. These findings underscore the definite utility of PSG criteria for LMM scoring, suggesting their consideration for inclusion in sleep scoring manuals and potentially serving as diagnostic criteria for RSD, although a different cut-off for abnormality might be necessary.

Furthermore, Ibrahim and colleagues[21] investigated the frequency and characteristics of LMM during sleep in healthy adults, providing normative data on LMM frequency and duration. The study found LMMs to be a common phenomenon, with indices and durations varying across sleep stages and age groups. LMMs were associated with arousals, respiratory events, and other sleep features, suggesting a potential clinical significance that warrants further investigation. The study highlighted the need for additional research to elucidate the role of LMMs in sleep physiology and their potential implications for sleep health. Even more recently, LMMs have been explored in more details in adults and an exploratory study aiming at identifying patients with a possible adult form of RSD found that these patients tend to have slightly enhanced LMMs, compared to patients with RLS or NREM sleep parasomnia, but significantly more than controls.[22] This is also in agreement with another study in adult controls and patients with RLS showing that LMMs are significantly increased in patients.[23]

Overall, these studies contribute to our understanding of LMMs during sleep and emphasize the importance of standardized scoring criteria for their detection and quantification. Further research in this area may provide valuable insights into the clinical significance of LMMs and their role in sleep disorders such as RSD.

Summary and Future Perspectives

Pediatric RSD has emerged as a distinct entity within pediatric sleep medicine, characterized by restless and disruptive sleep patterns in children and adolescents. DelRosso and colleagues[2] provided the first clinical description of RSD, highlighting its unique features and association with low ferritin levels. Subsequent studies elucidated the prevalence, clinical presentation, and diagnostic criteria for RSD, emphasizing the need for specialized attention to pediatric sleep disorders beyond traditional diagnostic frameworks.[24–27] Furthermore, investigations into the neurophysiology, comorbidities, and treatment options for RSD have expanded our understanding of this condition and paved the way for targeted interventions to improve outcomes in affected individuals.[16]

Moving forward, future research endeavors should focus on several key areas to advance our understanding and management of RSD in children and adolescents. Firstly, longitudinal studies are needed to explore the natural course and long-term outcomes of RSD, including its impact on neurodevelopment, cognitive function, and quality of life. Additionally, further investigations into the neurophysiologic mechanisms underlying RSD, such as sleep instability, autonomic dysregulation, and alterations in thalamocortical oscillations, may provide valuable insights into potential therapeutic targets. Moreover, large-scale prospective trials are warranted to evaluate the efficacy and safety of emerging treatment modalities for RSD, including IV iron supplementation and other pharmacologic interventions. Finally, the development of standardized scoring criteria for large body movements during sleep, as well as the exploration of non-invasive monitoring methods, such as actigraphy, may enhance diagnostic accuracy and treatment monitoring in RSD. In the future, additional research might show that artificial intelligence could play a crucial role in analyzing complex sleep data, identifying patterns predictive of RSD, and personalizing treatment approaches based on individual sleep profiles. By addressing these research priorities, we can advance knowledge in the field of pediatric sleep medicine and improve outcomes for children and adolescents affected by RSD.

CLINICS CARE POINTS

- Recognition of large body movements during sleep as a key clinical feature in the diagnosis of RSD.
- Utilization of vPSG to document large body movements and establish diagnostic criteria for RSD.
- Assessment of daytime symptoms, including excessive daytime sleepiness and cognitive deficits, to evaluate the impact of RSD on overall well-being and functioning.
- Comprehensive evaluation for comorbidities such as ADHD, NREM parasomnias, epilepsy, and ASD to address the multifaceted nature of RSD and guide treatment strategies effectively.
- Consideration of IV iron supplementation as a promising therapeutic approach for children with RSD, with potential benefits in both clinical symptoms and iron status.

- Implementation of standardized scoring criteria for large body movements during sleep to enhance diagnostic accuracy and treatment monitoring in RSD.

DISCLOSURE

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