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Review

Restless Sleep Disorder and the Role of Iron in Other Sleep-Related Movement Disorders and ADHD

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Abstract: In the last few years, restless sleep has been described as the key element of many clinical issues in childhood, leading to the recognition of "restless sleep disorder" (RSD) as a new proposed diagnostic category. The essential aid of video-polysomnographic recordings enables detection and quantification of the "large muscle group movements" (such as limb movements and repositioning) frequently described by parents of children with RSD. Strong evidence links iron deficiency to the pathophysiology of sleep-related movement disorders such as RSD, restless legs syndrome, periodic limb movement disorder, and attention deficit hyperactivity disorder (ADHD) due to the important role played by the brain dopamine production system. Serum ferritin is the main parameter used to evaluate iron deficiency in patients with sleep-related movement disorders. Iron supplementation is recommended when the serum ferritin level is <50 ng/mL, since the literature emphasizes the correlation between lower levels of serum ferritin, serum iron, and cerebrospinal fluid ferritin, and increased symptom severity. Moreover, several studies report an improvement in symptoms when ferritin levels are kept above 50 ng/mL. In this narrative review, we discuss the role of iron in sleep-related movement disorders, as well as ADHD, highlighting not only the connection between these two conditions, but also the relevance of iron supplementation for symptom improvement.

Keywords: restless sleep disorder; restless legs syndrome; periodic limb movements; iron deficiency; iron supplementation; ferritin; ADHD; sleep-related movement disorders; children

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1. Restless Sleep Disorder

Restless sleep is a common disturbance frequently found in the medical literature since the 1970s [1]. In 1979, the first Diagnostic Classification of Sleep and Arousal Disorder, defined restlessness during sleep as "*persistent or recurrent body movements, arousals, and brief awakenings (that occur) in the course of sleep* [2]". Restlessness has been associated with several sleep-related disorders [1], such as sleep apnea syndrome, psychophysiological insomnia, or sleep-related myoclonus [3]. Restless sleep has also been linked to other medical conditions, such as asthma, food allergies [4], eczema [5], neurodevelopmental disorders (particularly autism spectrum disorder and attention deficit hyperactivity disorder [6]), and psychiatric disorders such as anxiety and obsessive–compulsive disorder [7,8]. At the conceptual level, any movement in sleep theoretically disturbs sleep as a cause or consequence of an arousal. At the clinical level, excessive movement in sleep is often accompanied by nocturnal awakenings, especially in early childhood. Excessive motor activity in sleep is often associated with other sleep disorders such as insomnia, arousal disorders, and breathing disorders in sleep. While respiratory disorders and arousal disorders can be

easily diagnosed and defined in the link with movement in sleep, insomnia at an early age is often difficult to attribute to a sleep-related movement disorder.

In the last few years, the literature has highlighted the importance of restless sleep as the key element of many clinical issues in childhood, and this has led to the recognition of a new sleep disorder named "restless sleep disorder" (RSD), which has been proposed as a new diagnostic category [1,8,9].

In order to define the specific features of RSD, DelRosso et al. performed a polysomnographic study of RSD, restless legs syndrome (RLS), and control children; according to this study, both patient groups, RSD and RLS, showed lower total sleep time, increased number of awakenings, and decreased REM sleep. Increased periodic leg motor activity and increased rate of daytime hyperactivity and positive family history of RLS were significantly more evident in RLS children compared to RSD children. Furthermore, the number of large body movements through the night reported by RSD children's parents was significantly higher than in those of children with RLS. RSD children did not report difficulty of sleep onset or nocturnal awakenings, which are criteria that are necessary to hypothesize behavioral insomnia.

From a clinical point of view, the parents of children with RSD frequently complain about "excessive nocturnal motor activity", reporting the occurrence of body movements occurring throughout the whole night, almost every night; they are described as "large movements" (including limb movements, frequent repositioning, bed sheet disruption, or falling out of bed) but the children do not actually get up from bed and do not complain about night awakenings [8].

In order to better characterize and quantify the motor activity of RSD children, a further polysomnographic study with the support of video recordings (video-polysomnography, vPSG) was performed by comparing night movements of RSD, RLS, and control children. By means of vPSG, it was possible to demonstrate the increased limb and body movements persisting the whole night and a higher total movement index in all sleep stages in RSD children compared to RLS and control children. The threshold of five movements/hour discriminated RSD patients from RLS patients and controls [9].

The diagnosis of RSD is hence based both on parental reports and on the results of vPSG. With the acknowledgement of this new evidence, the International RLS Study Group (IRLSSG) formed an RSD task force composed of 10 sleep experts in order to establish diagnostic criteria for this newly described disorder [1].

It is not possible to make a diagnosis of RSD based on clinical history alone. This criterion stresses the crucial importance of vPSG for this diagnosis, since it provides objective data on the large body movements and allows the differentiation from other disorders that may mimic RSD, such as obstructive sleep apnea (OSA), RLS, and periodic limb movement disorder (PLMD).

The large muscle movements should begin during sleep, be clearly visible, last a minimum of 1 s, and involve the whole body, arms, legs, or head; they should not be associated with respiratory events or seizures, and should not meet the criteria for periodic leg movements during sleep (PLMS), sleep-related rhythmic movements, hypnagogic foot tremor, alternating leg muscle activation (ALMA), sleep motor tics, or REM sleep behavior disorder [10,11].

The worldwide prevalence of RSD in the general population is yet to be established; however, the prevalence of RSD has been estimated to be 7.7% in children referred to a sleep disorders center [12].

RSD Pathophysiology

The pathophysiology of RSD is currently under investigation. Three potential mechanisms underlying RSD have been hypothesized to date, namely, sleep instability, sympathetic activation, and iron deficiency.

In order to clarify daytime symptoms experienced by RSD children, sleep instability was studied by evaluating the so-called cyclic alternating pattern (CAP) in RSD and RLS children, and typically developing children as a control group [13].

CAP is a physiological endogenous rhythm of NREM sleep detected during PSG. It is described as a quasi-periodic EEG activity with sequences of phasic EEG activations (phase A) interrupting the continuous EEG activity (phase B) [14]. These sequences are systematically organized in NREM sleep, thus rendering the percentage of total NREM sleep time occupied by CAP (CAP rate) a physiologic indicator of NREM sleep instability [15]. CAP sequences are organized in a recurrent pattern and undergo several repetitions during the course of the whole night, alternating with non-CAP (NCAP) periods, instead defined as periods of stable sleep with no phasic EEG activations [16]. CAP A phases are subdivided into three distinct subtypes according to their frequency content [17,18]; specifically, the A1 subtype is composed predominantly of slow waves, A3 contains predominantly fast EEG activities, and A2 consists of a combination of both subtypes [17].

DelRosso et al. [13] have shown that RSD children present a considerably shorter REM sleep latency and notably higher percentage of REM sleep than RLS children and controls. Moreover, CAP analysis showed a higher number of CAP cycles, with shorter duration but organized in longer sequences. Movements were not found to be correlated with CAP in the analysis and tended to also occur during NCAP periods; however, when occurring within CAP sequences, they were most often associated with the CAP A2 and A3 subtypes, which are more similar than A1 to arousals [18].

Another important feature of RSD recently reported by DelRosso et al. [19] is the presence of a complex sleep microstructure alteration that might play a role both in the excessive nocturnal motor activity and in diurnal symptoms peculiar to RSD. Sleep microstructure is composed of different electroencephalographic transient events such as spindles, K-complexes, arousals, and slow-wave bursts. Sleep spindles are a train of electroencephalogram (EEG) waves characterized by a frequency in the range of 11–16 Hz and lasting for more than 0.5 s [20]. Sleep spindles are implicated in sleep stability [21], as well as learning, memory, behavior, and emotion [22,23]. This study demonstrated that frontal spindles were longer in children with RSD vs. controls [19]; the longer duration might correlate with a compensatory mechanism aiming to stabilize sleep during the NCAP periods [17].

A further study by DelRosso et al. [24] demonstrated that children with RSD have increased sympathetic activation during sleep, particularly N3 and REM, compared to individuals without disorders but, as expected, not during wakefulness. Differently, children with RLS have sympathetic activation during relaxed wakefulness preceding sleep and during sleep [25,26]. This study also supports the previously described clinical and PSG findings indicating that RSD is a disorder that disrupts sleep in children and allows speculation that it can potentially have cardiovascular consequences [24,27].

The second part of this review is devoted to highlighting the role of iron in sleep-related movement disorders, as well as in attention deficit hyperactivity disorder (ADHD), underlining the connection between these two conditions.

2. RLS and PLMD

RLS is a sleep disorder characterized by an urge to move the legs, motor restlessness, dysesthesia, or paresthesia, typically worsening at night, but possibly occurring even during daytime. These symptoms are most commonly present at rest and are partially or totally relieved by movement [28,29].

Periodic leg movements during sleep (PLMS) are defined as periodic episodes of repetitive and highly stereotypic leg movements occurring during sleep [30]; specifically, these movements are defined as brief jerks lasting between 0.5 and 5.0 s, typically occurring at intervals of 20 to 40 s, involving legs, feet, and toes rather than arms [31–33]. PLMD is associated with sleep disruption or sleepiness not related to another primary sleep disorder or etiology [34,35].

RLS and PLMD have also been described as being strictly correlated at the pediatric age. Among children and adolescents, RLS and PLMD prevalence is estimated to be up to 2–4%, without a gender difference [36–38].

Diagnostic criteria for diagnosis of RLS and PLMD in children have been proposed by the IRLSSG [39], and subsequently updated (2013) concerning the pediatric component [40], by simplification and integration with the latest revision of adult RLS criteria [41]. Children must be able to describe RLS symptoms in their own words; clinicians should therefore be aware of non-specific but age-appropriate terms used to describe these symptoms [29] such as "they won't stay still", "they want to move", "tickle", "want to run", "bugs", "spiders", "ants" [34].

RLS has a severe impact on mood [42–44]; patients report difficulty in sleeping onset and sleep disruption [45], together with adverse effects on cognitive function [46]. Sleep disruption is also correlated with being easily frustrated and difficulty in controlling impulses and emotions [47–49]. The distinctive features of RSD and RLS are reported in Table 1.

Table 1. Distinctive features of RSD and RLS.

	RSD	RLS
Clinical presentation	Restless sleep	Urge to move legs, onset insomnia
Age	School age	School age
Symptoms timing	Night	Worse in evening, but can appear during the day
Relief with movement	No	Yes
Diagnosis	Clinical + video PSG	Clinical
Gross body movements	Yes	May be
Daytime functioning	Neurobehavioral dysfunction	Hyperactivity, inattention
PSG findings	Body movement index >5 per hour	Elevated PLMI not mandatory
Pathophysiology	Iron deficiency, sleep instability	Iron deficiency, dopamine dysfunction

3. The Role of Iron in Sleep-Related Movement Disorders

Iron is implicated in different brain physiological processes, such as dopamine production, synaptic density, myelin synthesis, and energy production, and probably in norepinephrine and serotonin neurotransmitter systems [50]. There is strong evidence linking iron deficiency to the pathophysiology of RLS, PLMD, ADHD, and RSD. The brain dopamine production system is known to play an important role in these conditions [50,51]. Due to its ability to interconvert ferric and ferrous forms, iron is one of the core elements of oxygen transport (hemoglobin), oxygen storage (myoglobin), and energy production (cytochromes), and of the catabolism of several enzymes, such as tyrosine hydroxylase, which is the rate-limiting step in dopamine production. Iron levels are kept within physiologic ranges through feedback loops regulating iron absorption [52]. Hepcidin is known as the main regulator of iron homeostasis in gut and blood cells [53].

The need for iron is especially high during growth spurts or in chronic inflammatory conditions. Due to inadequate iron absorption via the divalent metal iron transporter (DMT-1) in the gut, the need may not be satisfied by dietary intake [54,55]. Following absorption into the enterocyte, transport and oxidase proteins mediate iron transfer into the blood. Transferrin is the main iron transporter protein, which provides iron storage in the liver and red cell synthesis in the marrow [56].

Since the demand for iron in the body might not be immediate, iron storage plays a fundamental role in cellular iron homeostasis [57]; in fact, iron may be retained within ferritin, the most important intracellular iron-storage protein. Iron storage allows iron accumulation in a nontoxic form, guaranteeing iron availability for future requirements. Moreover, cells secrete small amounts of ferritin, strictly correlated with intracellular iron concentrations; for this reason, serum ferritin concentrations represent the most reliable marker of stored iron [58].

The homeostasis of brain iron takes advantage of regional regulation involving both cellular energy demand and blood–brain barrier accessibility [59], and depends on intricate genetic factors, circadian rhythms, and, most critically, the body's iron supply [60–62]. Even in brain regions where iron levels appear to be appropriate, iron is continually taken up into the brain on a minute-by-minute basis [61]. This request for additional iron appears to be dependent on circadian changes [63] and is therefore likely to correspond with variations in circadian patterns regarding energy and metabolic demand [64]. Accurate measurements of local cellular iron demands in the brain, as well as measures of how each of these mechanisms and the genetic factors affect brain iron stores, are lacking [60]. Extending from animal studies, it is possible to state that, for humans, serum iron and ferritin indicate brain iron status very approximately, with genetic variants leading to significant individual variances [65–67]. Consequently, peripheral iron indices are weakly related to the expression of sleep-related movement disorders [51]. According to animal studies, striatal D1 and D2 receptor (D2R) density and dopamine transporter (DAT) density decrease in response to iron deficiency [68].

After analyzing the literature on iron deficiency (ID) and RLS, Allen and Earley [67] came to the conclusion that iron deficiency increases dopamine synthesis and extracellular dopamine levels. Dopamine levels naturally increase in the morning and decrease in the evening, following a circadian pattern. Dopamine activity augmentation results in both intracellular and receptor downregulation; the post-synaptic response to this mechanism in RLS was found to be adequate during daytime, but abnormal during night hours, leading to a nighttime dopaminergic deficit, notwithstanding the global dopamine excess [69].

Brain iron deficiency also involves an increased presynaptic glutamatergic function related to neuropathic pain, a state of hyperarousal with insomnia and sleep fragmentation. Iron deficiency appears to cause an increase in A2A receptors and a decrease in A1 receptors, leading to a reduction in slow-wave sleep and slow-wave activity [70].

According to both human and animal studies, iron storage depletion (ferritin levels below 12 μg/L), results in decreased hemoglobin production, reduction in physical working capacity, cognitive impairment, and retarded psychomotor development. The peripheral iron reserves are not completely replenished until a much higher level of serum ferritin is reached, in the range of 50 to 100 μg/L. The transition of iron from peripheral reserves to the central nervous system may be affected by the degree of peripheral iron saturation. Therefore, an adequate ferritin level for hemoglobin and myoglobin synthesis may not be enough to ensure the smooth functioning of neurotransmitters in the brain. Nevertheless, the mechanism that regulates the entry of iron in the CNS is probably even more complex; in fact, some cases are reported of RLS with low cerebrospinal fluid ferritin, despite adequate peripheral ferritin levels [71–73].

Iron Supplementation

Serum ferritin indicates the condition of iron reserves and is the first parameter that is reduced in case of iron deficiency. The normal range for serum ferritin levels varies depending on the age and is lower for children. Ferritin levels in the age groups of 1–5 years, 6–11 years, and 12–19 years have been reported to be approximately 24.7 ng/mL (95% confidence interval, 23.4–26.0; n = 535), 31.4 ng/mL (95% confidence interval, 29.4–33.3; n = 411), and 35.0 ng/mL (95% confidence interval, 29.6–40.4; n = 112), respectively [74].

In addition, ferritin is an acute phase reactant and thus may not be specific to co-occurring inflammation or infection, hyperthyroidism, hepatocellular disease, or malignancies. In uncertain conditions, obtaining a concomitant C-reactive protein level may also be useful to establish that inflammation is not influencing the measure [75].

Due to circadian changes in serum iron levels (highest in the morning and lowest in the evening) [76], serum iron parameters should be measured in the morning after an overnight fast [51].

At initial evaluation of a patient with a diagnosis of sleep-related movement disorders, and every time symptoms worsen, it is required to measure the full iron panel.

Three months after beginning oral iron supplementation, it is important to obtain serum iron and ferritin levels and adjust the iron dose accordingly, in order to decrease the risk of iron excess. In clinical practice, the dose of iron is reduced when serum ferritin reaches the level of 50 ng/mL, and the iron panel is repeated over time every 3 and 6 months [30]. In addition, if the patient is undergoing intravenous (IV) iron supplementation, the iron panel should be obtained 8 weeks after the iron injection to evaluate the iron storage, and again 8 weeks later to check the iron level stability [51]. The challenge for clinicians is to identify non-responders and factors that may hinder oral iron absorption [77]. Physiologically, only 2% to 20% of oral iron is absorbed; it is assumed that the remainder of the iron is not absorbed in the duodenum and passes through the colon, where it can cause inflammation and negatively modify the gut microbiome. This limited iron absorption is the determining factor of the common gastrointestinal side effects of diarrhea, abdominal pain, constipation, and increased morbidity from gastroenteritis [78], which are complained about by approximately 10% of children taking oral iron [52]. The adherence of children to oral iron treatment could be compromised by the difficulty in swallowing pills, especially in early childhood, bad taste, and the possibility that liquid iron may stain the teeth. Some patients seem not to respond to oral iron and persist with low ferritin levels despite adequate adherence [77]. Oral iron supplementation is not recommended in children with impaired absorption, such as patients with celiac disease or gastrointestinal reflux [79]. Iron treatment is not advised in patients with hemolytic anemia and hemochromatosis. According to the most recent studies, the recommended dose of oral iron supplementation is about 3 mg of elemental iron/kg/day, corresponding to the dose for iron deficiency anemia [30]. The oral iron supplements should be taken on an empty stomach in conjunction with vitamin C to improve its absorption [79].

Recent guidelines suggest the use of IV iron infusion rather than oral administration in children who do not tolerate oral iron, in patients with compromised absorption, in the case of significant side effects, or in situations of no clinical response after 12 weeks of oral iron treatment [75]. Similar to the current adult guidelines, IV iron would be an appropriate approach as a first-line therapy for children with moderate to severe symptoms, or in patients with a severe comorbidity that would compromise iron absorption.

Concerning side effects, severe hypersensitivity infusion reactions are extremely rare with newer formulations, and minor infusion reactions occur infrequently, in 1% of administrations [51]. There is a wide choice of IV iron formulations such as iron sucrose, ferric gluconate, low-molecular-weight iron dextran, ferric carboxymaltose, and ferumoxytol. At a pediatric age, IV iron sucrose (recommended dose of 3–6 mg/kg, max 120 mg) must be administered in a pediatric infusion center [75]. IV iron sucrose should be used cautiously in children with mitochondrial disorders, or in patients with a significant systemic inflammatory process, because iron supplementation might exacerbate infections [51].

Given the current scientific evidence, serum ferritin $\geq$50 ng/mL is considered to be an adequate therapeutic target in children [35]. However, the literature recommends treatment for patients with sleep disorders, such as RLS, PLMD, and RSD, based on iron supplementation to obtain a level of ferritin of at least 50–100 ng/mL.

4. The Role of Iron in RLS, PLMD, and RSD

The literature has emphasized that lower levels of serum ferritin, serum iron, and CSF ferritin are correlated with the severity of RLS symptoms or the number of PLMS [80,81].

Patients with iron deficiency have been reported to show a six-fold increase in the prevalence of RLS/SRMD [82]. A number of studies have shown that RLS patients, although they have peripheral iron stores within the normal range, have lower brain iron levels, compared to normal controls, and also present an impaired iron passage from peripheral reserves to the brain [83,84]. The dopamine abnormalities seen in RLS are probably determined by this alteration in brain iron homeostasis [51,85]. The IRLSSG guidelines on iron supplementation for adults and the pediatric population, observing the current lack of evidence concerning the recommendation of iron treatment for RLS in children [51]. How-

ever, iron supplementation in children remains the first-line therapy in an RLS pediatric population, as long as iron is optimally absorbed and symptoms improve [77,79].

Tilma et al. [86] reported that 22 children, aged 0–40 months, with RLS and low ferritin levels (median 21 ng/mL), treated with oral iron, benefited in terms of their symptoms. The improvement in symptoms was ferritin-concentration dependent and significantly better in children with a baseline ferritin level above 50 ng/mL.

A number of studies have shown that patients with RLS, although with peripheral iron storages in the normal range, had lower brain iron levels compared to normal controls and presented an impaired iron passage from peripheral reserves to the brain [79,83,84].

Approximately three months or more of iron treatment are needed to obtain an improvement of symptoms [86–88]. Several studies have proven the benefit of iron therapy in decreasing the PLMS index and reducing RLS symptoms in children [56], as well as in adults, at 3–6 months follow-up [35]. For children and adolescents, oral iron therapy has been shown to improve RLS symptoms in several case series [89–91]. In a retrospective review of 30 consecutive cases, Mohri et al. [87] emphasized a clinical improvement in 90% of subjects assuming a mean dose of 3.2 $\pm$ 1.3 mg of elemental iron/kg/day of oral ferrous sulfate. This symptomatic improvement correlated with a rise from a mean pretreatment ferritin level of 26.6 $\pm$ 12.8 ng/mL to a post-therapy mean of 83.5 $\pm$ 49.8 ng/mL [30].

Amos et al. [88], studying a cohort of 97 children with RLS (aged 5–18 years), showed that about 80% of patients had a sleep quality benefit after receiving iron supplementation (3–4 mg/kg/day). In this analysis, the mean ferritin level was 22.7 ng/mL and 71% of children had ferritin levels lower than 30 ng/mL. Patients with lower ferritin levels (18.9 ng/mL) showed improved symptoms while children with higher ferritin levels (27.4 ng/mL) did not [79].

However, the majority of studies performed on iron supplementation in children with RLS and PLMD have evaluated the effectiveness of iron therapy in the short term. Studies analyzing the long-term effect of iron therapy are still limited in number. The first long-term study that evaluated children with sleep-related movement disorders undergoing iron treatment was performed by Dye et al. [35]. The goals of the study were to assess whether oral iron supplementation leads to long-lasting improvement of the PLMS index and clinical symptoms, and sustained resolution of serum ferritin levels in children with RLS and PLMD. The authors reported clinical symptoms and PLMS index improvements at 3–6 months, 1–2 years, and >2 years, with mean serum ferritin levels increasing from 27.4 to 45.6, 52.0, and 54.7 mcg/L, respectively. A retrospective, open-label chart review of 105 pediatric patients was conducted on the basis of the authors' clinical practice of using iron as first-line therapy for pediatric RLS and PLMD. Iron was started at 3 mg/kg/day (elemental) and titrated over the following 2 years with the target of keeping ferritin at or above 50 mcg/L. The findings suggest an "ideal" iron status in RLS/PLMD of serum ferritin >50–75 mcg/L, rather than accepting "normal" values of >12 mcg/L (which were established considering iron deficiency anemia).

To date, no guidelines are available concerning RSD treatment in children; however, in clinical practice, iron supplementation has been applied to the management of pediatric RSD patients with successful outcomes [92].

In the study performed by DelRosso et al. [8], mean ferritin level in RSD patients was below the normal range and even lower than that of RLS patients, thus suggesting the possible dysregulation of the motor dopamine-dependent pathway, similar to other sleep-related movement disorders such as RLS [93].

DelRosso et al. [77] investigated the response to oral iron supplementation concerning ferritin levels in a cohort of pediatric restless sleepers. They analyzed a group of pediatric patients (age between 2 and 18 years) diagnosed with RSD, RLS, periodic leg movements during sleep (PLMS) or PLMD, OSA, and other sleep disorders. A total of 77 children were included in this study, of whom 42 were classified as responders (increase in ferritin $\geq$ 10 µg/L) and 35 were non-responders. Responders to oral iron showed an improvement in symptoms and also an increased level of ferritin, as early

as 2–3 months after supplementation. Responders also showed a low incidence of side effects and a consequent increased adherence to therapy. Non-responders complained that there was no symptomatic improvement in sleep quality, despite a long-lasting treatment. Finally, it should be considered that adherence is closely linked to the effectiveness and side effects, which were indeed observed more frequently among non-responders.

A subsequent study compared the effects of oral ferrous sulfate and IV ferric carboxymaltose [92]; both iron supplementation treatments led to laboratory and clinical beneficial effects, but greater and faster clinical response and a greater effect on iron status were obtained in patients treated with IV ferric carboxymaltose. A significant increase in serum ferritin from baseline was reported both with oral and IV iron supplementation; specifically, oral ferrous sulfate provided an increase in ferritin levels from 16.0 (13–23 μg/L) to 34.0 (25–44 μg/L) (median (interquartile range); $p < 0.005$), while IV ferric carboxymaltose provided an increase in ferritin levels from 16.0 (13–20 μg/L) to 124.0 (90–143 μg/L) (median (inter quartile range); $p < 0.001$).

Even though oral iron and IV iron supplementation are considered successful, several studies continue to document an important number of non-responders. Thus, alternative methods to improve brain iron status and to increase the efficacy of iron supplementation in patients with SRMD should be sought [51].

5. Sleep-Related-Movement Disorders and the Role of Iron in ADHD Patients

ADHD is a neurodevelopmental disorder characterized by inattention and/or hyperactivity/impulsivity, which can lead to subsequent impairment of education, drug abuse, criminality, bullying, and accidents [94].

According to the various presentations, three possible phenotypes have been identified: inattentive, hyperactive-impulsive, and combined type. Nevertheless, the diagnosis of ADHD should be made on the basis of behavioral criteria only after other mental disorders have been excluded, according to the DSM-5 or the ICD 10/11 [95].

The worldwide prevalence of ADHD among children and adolescents is estimated to be approximately 2–7% [96,97], and up to 25–50% of this population reports sleep-related disorders [98,99]. Specifically, young ADHD patients report high rates of daytime sleepiness, increased rate of sleep movements, and sleep-related breathing problems [99–101].

Not surprisingly, the DSM [102] initially defined ADHD precisely with some features in common with the description of RSD ("moves excessively during sleep") and RLS ("has difficulty staying seated"). Nowadays, there is a global trend to overtreat young patients with disruptive behaviors in order to control their symptoms, thereby providing just a temporary benefit, despite causing long-term side effects for both nocturnal and daytime symptoms. Sleep has rarely been considered as an outcome measure to evaluate the effect of diagnostic and therapeutic interventions in routine clinical protocols for the treatment of neurodevelopmental disorders such as ADHD. Nevertheless, sleep disorders such as RLS seem to also adversely affect ADHD comorbidity and final outcomes [70,103,104].

Insomnia and RLS are reported as the most common sleep disorders in children with a clinical diagnosis of ADHD (11%) [105–107]. RLS symptoms appear to be more common in males [108], with a higher prevalence in adolescents and adults (the limitation of detection in younger children lies in reporting symptoms in their own words) [95].

Many studies report that up to 44% of children diagnosed with ADHD show RLS symptoms, whereas 26% of children diagnosed with RLS show ADHD symptoms [109,110]. Moreover, ADHD patients were reported to be more symptomatic when also suffering from RLS, maybe due to their repeated sleep interruptions [95]. However, until 2005 no correlation between sleep problems and ADHD subtype (hyperactive, inattentive, or mixed) was demonstrated [106]. There may be a potential pathophysiological link between RLS and some subtypes of ADHD because BTBD9 risk alleles have been linked to decreased iron storage [111].

Attention [112], inhibition [113], and working memory are involved in both RLS and ADHD, resulting in a similar daytime compromission involving changes in daytime

activities, inattention, mood regulation problems, and outbursts of hyperactivity, and also often poor academic performance [69].

Kapoor et al. [114] examined the prevalence of RSD in 66 children with ADHD. Although restless sleep was reported in up to 81.1% of patients, only 9.1% of these were diagnosed as RSD; however, restless sleep was often iatrogenic or caused by other sleep disorders or psychiatric conditions.

Sleep fragmentation or insomnia may also result from PLMS [115]. Many polysomnographic studies highlighted higher frequency of PLMS in children with ADHD [101,116–118]; for example, that of Stephens et al. [116] reported the highest number of PLMS in children with ADHD, compared to the control group, especially during REM sleep. Moreover, a greater number of total arousals and more arousals from slow-wave sleep were reported. Frye et al. [119] demonstrated that the prevalence of increased PLMS is 15% higher in adolescents with ADHD compared to patients without ADHD. Moreover, a correlation was found between PLMS and ADHD severity and the presence of internalizing problems and impaired executive functions, compared to those with ADHD or PLMS alone. Microarousals leading to sleep fragmentation and sleep impairment linked to PLMS and RLS may cause ADHD symptoms [95].

Conversely, according to Fulda et al. [120], children with ADHD do not present a higher risk of frequent PLMS. This study, however, does not exclude the presence of children with ADHD and PLMS; however, in those cases, PLMS should not be considered an intrinsic characteristic of ADHD, but rather a different and additional finding.

Pediatric ADHD patients have spindle characteristics comparable to those found in RSD, thus reinforcing the association between these two conditions [121]. It has been supposed that frontal spindles, in particular, show higher activity in children with ADHD, thus representing frontal lobe hyperfunction [122]. Several studies have demonstrated that the frontal spindles are involved in attention, executive function, behavior, emotion [22], and intelligence [19,23].

Furthermore, the possible role of iron availability in the brain in a "secondary form of ADHD" has been highlighted. Thus, an estimate of iron levels in the brain could shed light on a possible role of iron deficiency in the pathophysiology of this ADHD "subtype" [123].

The nature of iron deficiency is different between RLS and ADHD. In RLS, iron deficiency is a consequence of inadequate dopamine production; ADHD is instead associated with a more rapid dopamine clearance and impaired dopamine receptor signaling [124].

Children with ADHD and RLS have been shown to have lower ferritin levels compared to those with RLS alone [70]. When compared to a control group, children with ADHD who are not anemic may have lower ferritin levels [95,125]. Among ADHD subtypes, the hyperactive and combined subtypes are more commonly associated with reduced iron levels and RLS symptoms [95].

Iron deficiency has been shown to be directly proportional to the severity of ADHD symptoms in children with co-existing ADHD and RLS [29]. Children with ADHD and low serum ferritin levels (<45 mg/L) experience more severe ADHD symptoms, cognitive impairments, and sleep–wake transition problems [89,119,126,127].

In a systematic review, Cortese et al. [128] hypothesized that an alteration of the blood–brain barrier or iron transport mechanisms in children with ADHD (with or without RLS) may lead to a possible difference between peripheral and central iron levels. Therefore, ADHD individuals might have brain iron deficiency even though their serum ferritin levels are normal or subnormal.

Recent studies [129] have shown that keeping serum ferritin above 50 ng/mL can improve symptoms of RLS, PLMS, and ADHD [130,131].

Iron supplementation might also improve cognitive and behavioral functioning in ADHD patients [95,132,133]. As a result, iron supplementation therapy should be given priority as a treatment option for childhood RLS, particularly for patients with ADHD and low serum ferritin levels [124,134].

6. Conclusions

Due to the high prevalence of restless sleep in the pediatric population and its potential negative consequences, restless sleep is an important field of research. In this review, we described three important sleep-related movement disorders, highlighting their common pathophysiology related to iron deficiency. Iron deficiency has received growing attention in the last few years in relation to the increased recognition of pediatric sleep disorders such as RLS, PLMD, and RSD, but also because of the reported evidence of its involvement in ADHD hyperactive behaviors.

Pediatricians need to be aware of children presenting with restless sleep because they can be easily treated, whereas, if untreated, they can show significant daytime impairment. Iron supplementation (in particular IV iron) has been demonstrated to be beneficial for symptoms of restless sleep related to RLS, PLMD, or RSD. Iron supplementation is generally safe in the absence of hemochromatosis or other rare disorders of iron metabolism, provided that bloodwork is performed before iron treatment and during follow-up, to monitor for iron overload.

Future studies should delineate the role of other biomarkers, such as hepcidin, elucidate the optimal ferritin level for iron treatment initiation, and carry out randomized clinical trials using iron supplementation to determine the dosage and duration of treatment.

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