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CASE REPORTS

Terrible twos: intravenous iron ameliorates a toddler's iron deficiency and sleep disturbance

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The relation between iron deficiency and restless legs syndrome has been widely described and investigated in both adults and children. However, the diagnosis of restless legs syndrome relies on patients voicing their symptoms, which is very difficult for patients younger than age 5 years. Frequently, we evaluate children between ages 2 and 4 years whom parents describe as "restless sleepers," "difficult to settle down," or having "frequent awakening" or "bedtime resistance." Parents are concerned that their child's poor sleep quality is leading to daytime dysfunction such as increased sleepiness, behavioral outbursts, or hyperactivity. Many of these children are diagnosed with behavioral insomnia of childhood, and behavior modification therapy is recommended with variable degrees of success. Herein, we describe a 2-year-old with similar symptoms of restless sleep, bedtime resistance, and daytime sleepiness who was found to have an underlying iron deficiency without anemia that was treated successfully with iron infusion. We highlight the importance of evaluating for underlying iron deficiency even without anemia in patients with restless sleep and associated poor daytime behavior. We also describe some common challenges associated with iron therapy and clarify iron therapeutic targets.

Keywords: iron deficiency, ferritin, intravenous iron, children, restless legs syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Iron deficiency is associated with restless legs syndrome, periodic limb movements, and newly recognized restless sleep disorder in children. The adverse effects and intolerance to oral iron therapy remain a challenge especially in children.

Study Impact: This case report highlights the role of iron deficiency in toddlers' sleep disturbances and the associated daytime behavioral consequences. It also highlights the ease and safety of intravenous iron treatment for patients who do not respond to oral iron.

INTRODUCTION

Iron deficiency continues to be a common problem that may have detrimental and potentially irreversible effects on long-term neurodevelopment and behavior in growing children.[1] The effect of iron deficiency on sleep has been well documented, especially in the pathogenesis of restless legs syndrome (RLS).[2] The diagnostic criteria of RLS rely on patient description of an often unpleasant urge to move the legs that leads to significant disturbance not explained by another medical or behavioral condition.[3] However, children younger than age 5 years frequently have difficulty expressing such symptoms and may instead complain about sleep difficulties, such as insomnia, restless sleep, frequent awakenings, or frequent movements during sleep with associated poor daytime function. It has been well recognized that problem sleepiness presents differently in toddlers than in older children or adults and usually presents as hyperactivity/inattention, behavioral outbursts, or emotional lability.[4]

Parents colloquially refer to children in their second and third year of life as being in their "terrible twos," with behavioral manifestations that include hyperactivity, tantrums, and outbursts.[5,6] Although behavioral therapy has been the mainstay for these patients, we consider other possible contributing factors, like poor sleep, that could stem from an easily diagnosed and treatable cause such as iron deficiency. Here, we present a case report that highlights the importance of identifying and correcting iron deficiency to improve overnight sleep and daytime behavior.

REPORT OF CASE

A 2.5-year-old child presented to the sleep disorder clinic for difficulty falling asleep and restless sleep. His symptoms began at approximately age 18 months with difficulty falling asleep and bedtime resistance. The parents reported a very consistent bedtime routine and a cool, quiet sleep environment. They put him into his own bed at approximately 7 PM. The parents would leave him in the room, but he continued to move around or played in his bed for almost an hour before falling asleep. He tossed and turned frequently in his bed throughout the night, and he usually woke up 2–4 times per night. These awakenings were brief, and he usually fell back to sleep by himself without parental intervention. The child

would wake up at approximately 6:30 AM and seemed unrefreshed to the family. As the day progressed, his behavior typically deteriorated and manifested as hyperactive, with bursts of anger and being oppositional. The parents believed that these behaviors stemmed from a lack of sleep and therefore tried to put him down for a nap, which is a typical practice for a 2-year-old. The patient's behavior improved significantly if he napped, but frequently he refused to even lie down for a nap. The child himself never complained of leg pain or discomfort. The parents reported that he had intermittent snoring and mouth breathing but no night sweating. There was no known family history of RLS or periodic limb movements in first-degree relatives.

The child was counseled to start melatonin 3 mg to help with his sleep onset difficulty and was referred to a sleep psychologist for additional behavioral sleep interventions. Because of his reported restless sleep, a ferritin level was ordered and found to be very low, at 9 ng/mL. The child was started on ferrous sulfate at 3 mg/kg daily, and a repeat ferritin level after 3 months showed some improvement to 17 ng/mL. However, he continued to have similar sleep concerns. He also developed significant adverse effects (constipation) to iron therapy. Eventually, he was evaluated by the hematology service and offered treatment with intravenous iron infusion, which the family agreed with. He was given 15 mg/kg ferric carboxymaltose as an intravenous infusion over 15 minutes and had no apparent complications or adverse effects during or after the infusion.

The patient's ferritin level after 3 weeks postinfusion was improved to 135 ng/mL. At clinical follow-up 2 weeks postinfusion, the parents reported that the child was falling asleep much sooner than before, usually within 15 minutes. His frequent nighttime movements and restlessness were also much improved. The parents reported that he was waking up refreshed. Notably, his daytime demeanor improved, with less hyperactivity and fewer oppositional behaviors, and he was able to follow directions very well (**Table 1**). The parents were impressed with the patient's reported significant improvement of his appetite and growth (weight and height improved from 13.1 kg and 92.3 cm, respectively, on the day of iron infusion to 13.8 kg and 95.5 cm after 1 month).

He was re-evaluated 3 months postinfusion, at which point he continued to indicate clinical and biochemical improvement, with a ferritin level of 67 ng/mL. An overnight polysomnography was ordered, but unfortunately, because of the COVID-19 pandemic, it was delayed until after the patient received the iron infusion. The sleep study did not show significant sleep-disordered breathing (obstructive apnea-hypopnea index, 1 event/h; mean oxygen saturation, 98%, with minimum saturation, 91%) or periodic limb movements (periodic limb movement index, 3.1 events/h; periodic limb movement arousal index, 0.7 events/h) and indicated normal sleep architecture (sleep stage N1, 1.3%; sleep stage N2, 52.1%; sleep stage N3, 26.2%; rapid eye movement sleep, 20.4%; sleep efficiency, 96.4%; sleep onset latency, 1 minute; total arousal index, 6.4 events/h; wake after sleep onset, 17.5 minutes). The results of the sleep study mirrored the clinical improvement after iron infusion.

Table 1—Pre– and post–iron infusion laboratory and PSQ results.

Items (Laboratory or PSQ Selected Questions)	Pre–Iron Infusion	Post–Iron Infusion
Hemoglobin (g/dL)	12.9	12.7
Ferritin (ng/mL)	18 (9 before oral iron)	135
Ever snoring	Yes	Yes
Snore loudly	Yes	No
Heavy/loud breathing	Yes	Yes
Stop breathing at night	Yes	No
Restless sleep	Yes	Yes
Restless legs	Yes	Yes
Unexplained leg pain	No	No
Unexplained leg pains worse in bed	No	No
Kick legs while sleeping	Yes	Yes
Kick legs regularly while sleeping	Yes	No
Leave bed	Yes	No
Difficulty falling asleep	Yes	No
Bedtime inappropriate behavior	No	No
Time to fall asleep	45 min	15 min
Change time for bed	Yes	No
Change wake time frequently	Yes	No
Bedtime during week	7 PM	7 PM
Bedtime during weekend/vacation	7 PM	7 PM
Leave bed weekday	6:30 AM	6:30 AM
Leave bed during weekend/vacation	6:30 AM	6:30 AM
Unrefreshed in the morning	Yes	No
Sleepy during the day	Yes	No
Naps during the day	No	No
Hard to wake child	No	No
Parasomnia symptoms questions	No	No
Periodic limb movement score	0.83	0.17

PSQ = Pediatric Sleep Questionnaire.

DISCUSSION

Substantial evidence implicates iron deficiency as an important contributing factor in the pathophysiology of RLS, periodic limb movements disorder, and, more recently, the newly recognized restless sleep disorder.[7,8] However, most of these disorders are very difficult to diagnose in patients younger than age 5 years because of a lack of classic presentation, an inability to rule out RLS symptoms without patients verbalizing such symptoms, and the need to perform an overnight polysomnogram. In this case report, we highlight the importance

of iron deficiency without anemia in a 2-year-old with symptoms of sleep-onset insomnia, bedtime resistance, and frequent awakenings and movements during sleep that were associated with daytime dysfunction in the form of hyperactivity, restlessness, and inattention.

Iron therapy has been the mainstay for treatment in children with RLS/periodic limb movements disorder in whom iron deficiency has been identified.[8] Ferritin levels vary by age, as shown by national surveys and our own previously published data,[9] with ferritin levels in the age groups 1–5 years, 6–11 years, and 12–19 years of 24.7 (95% confidence interval, 23.4–26.0; n = 535), 31.4 (95% confidence interval, 29.4–33.3; n = 411), and 35.0 (95% confidence interval, 29.6–40.4; n = 112), respectively. The typical low-normal level of serum ferritin is 13 ng/mL, with iron deficiency anemia unlikely unless the ferritin level falls below 13 ng/mL. However, the literature supports treating patients who have sleep complaints of RLS/periodic limb movements disorder/restless sleep disorder with iron supplementation to achieve a higher level of ferritin of at least 50–100 ng/mL.[10] Notably, inflammatory states may also influence ferritin level, so waiting to obtain laboratory results at least 3–4 weeks after any infection will help avoid spuriously elevated results. Obtaining a concurrent C-reactive protein level in ambiguous situations may also be helpful to ensure that inflammation is not affecting the measure. Beyond the serum ferritin level, other measures of iron stores such as serum iron, total iron binding capacity, and transferrin saturation may help more fully characterize iron stores; in this case a fasting level obtained in the morning may be more accurate.

The current consensus guidelines support the use of oral iron and revert to the use of intravenous iron infusion only in the patients who do not tolerate oral iron, in patients who have significant adverse effects, in conditions that prevent its absorption, or after 12 weeks with oral iron with no significant clinical response or a persistent ferritin level < 50 ng/mL.[8] In our clinical practice, patients on oral iron typically experience significant adverse effects of constipation, abdominal pain, and bad taste that may hinder adherence and subsequent clinical response. In addition, some patients seem not to respond to oral iron and continue to have a suboptimal ferritin level despite adequate adherence.[10] Therefore, we submit that consideration of intravenous iron as first-line therapy for children with moderate to severe symptoms similar to the current adult guidelines would be a reasonably prudent approach. There are various intravenous iron formulations available (iron sucrose, ferric gluconate, low-molecular-weight iron dextran, ferric carboxymaltose, and ferumoxytol) that are alternatives to oral iron therapy. Severe hypersensitivity infusion reactions are extremely rare with newer formulations, and minor infusion reactions occur infrequently in ~1% of administrations.[8]

Just as ferritin levels may vary by age, limb movements during sleep may be dependent on child age as well. Although periodic limb movements > 5 per hour are generally considered elevated in children, more frequent limb movements may be normal in very young children. For instance, Scholle and Scholle (2014) performed sleep studies on healthy children with no clinical sleep problems over a wide age range. In their sample, the frequency of periodic limb movements decreased with increasing age in childhood.[11] Specifically, in children younger than age 2 years, the average periodic limb movement index was 9.6 events/h with a 90th percentile of 10.9 events/h. Therefore, in very young children, frequent limb movements during sleep signify an area of needed future investigation to help define normal vs excessive movements.

CONCLUSIONS

Although the American Academy of Pediatrics recommends screening for anemia between ages 9 months and 1 year by checking a hemoglobin level, this approach will miss children with a potential underlying nonanemic iron deficiency. Therefore, we believe that screening for iron deficiency by checking a ferritin level in conjunction with hemoglobin would be helpful for early diagnosis of iron deficiency. Further studies are needed to determine whether such an approach would help in the earlier identification and treatment of iron deficiency without anemia, especially for children with sleep-related challenges.

ABBREVIATION

RLS, restless legs syndrome

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DISCLOSURE STATEMENT

All authors have seen and approved the final manuscript. The authors report no conflicts of interest.