Title

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Journal

Journal of Clinical Sleep Medicine, 19(3)

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Publication Date

2023-03-01

DOI

10.5664/jcsm.10444

Peer reviewed

https://doi.org/10.5664/jcsm.10444

JCSM | Journal of Clinical Sleep Medicine

CASE REPORTS

Actigraphy evaluation before and after intravenous ferric carboxymaltose in 3 children with restless sleep disorder

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Restless sleep disorder has been described in the literature as a disorder affecting children and presenting with large muscle movements during sleep with an index of 5 events/h or more, leading to daytime impairment including sleepiness or behavioral problems. Children with restless sleep disorder have been found to have low ferritin levels. Studies with iron supplementation both oral or intravenous have been shown effective in clinically improving both nighttime and daytime symptoms. However objective data of the improvement is lacking. Repeating polysomnography is expensive, and alternative methods of assessing large muscle movements are needed. In this small case series we present actigraphy results in 3 children with restless sleep disorder collected for 1 week, a week before and 8 weeks after intravenous iron supplementation. Although actigraphy parameters were not highly consistent between our 3 patients, improvement in symptoms tend to parallel sleep parameters in actigraphy.

Keywords: restless sleep disorder, actigraphy, children, iron

Citation: Chu ZYB, DelRosso LM, Mogavero MP, Ferri R. Actigraphy evaluation before and after intravenous ferric carboxymaltose in 3 children with restless sleep disorder. *J Clin Sleep Med*. 2023;19(3):633–637.

INTRODUCTION

Restless sleep disorder (RSD) is a proposed pediatric sleep disorder with consensus criteria for diagnosis that include: report of restless sleep by a caregiver or parent, presence of large muscle movements (LMM) during sleep with an LMM index ≥ 5 events/h demonstrated by polysomnography, symptoms have to be present at least 3 times a week and for at least 3 months, there must evidence be of daytime symptoms or impairment, and restless sleep cannot be explained by another comorbidity or substance.[1]

Recent research on children with RSD has demonstrated evidence of daytime sleepiness[2] and attention deficits.[3] Previous work has shown that iron supplementation, either oral or intravenous, improves the self-reported symptoms of RSD[4,5]; however, objective data are limited. Polysomnography is a very expensive test to repeat in patients reporting resolution of symptoms after treatment, and alternative methods to assess movements or daytime function in children with RSD are needed. Actigraphy is a very attractive instrument for the assessment of sleep in both adults and children because it can monitor activity levels for several days to weeks and can also assess activity during wakefulness and during sleep.[6] Actigraphy has been used to assess movements in children,[7] however, not using the new proposed criteria for LMM.

In this report we present 3 children aged 8 to 10 years, diagnosed with RSD who wore actigraphy for 1 week prior and 1 week after treatment with intravenous ferric carboxymaltose to obtain preliminary data on the utility of actigraphy in the evaluation of restless sleep in children with RSD.

REPORT OF CASES

Three children with RSD aged 8–10 years, diagnosed in agreement with current criteria,[1] underwent 1 week of actigraphy prior to intravenous iron supplementation with a single-dose ferric carboxymaltose 15 mg/kg and 1 week of repeated actigraphy and labs 8 weeks after the iron infusion. All patients had a sleep study within a month from the intravenous (IV) iron infusion. Once RSD was confirmed with PSG, fasting ferritin and iron levels were obtained (all in the same laboratory), and IV iron infusion (15 mg/kg) given. The results of the clinical assessment, actigraphy, and laboratory work-up are found in **Table 1**. The Clinical Global Impression-Severity (CGI-S) scale was used at baseline evaluation, before the iron infusion. CGI-S is a validated 7-point scale with which the same sleep physician (L.D.) rated the severity of the patient's symptoms at the time of clinical evaluation. The rating is done with reference to the same clinician's past experience with patients affected by the same condition and ranges from 1 ("normal, not at all ill"), to 7 ("among the most extremely ill patients"). At the 8-week post-IV infusion follow-up clinic visit, symptoms improvement was assessed by the Clinical Global Impression-Improvement (CGI-I) scale score. CGI-I is a validated 7-point scale allowing the clinician to assess the degree of improvement or worsening of the patient's illness, after iron infusion, relative to baseline, ranging from 1 ("very much improved") to 7 ("very much worse").[8] The authors routinely use this scale and have reported it also in previous studies.[4,9,10]

For actigraphy, the following parameters were considered: activity counts obtained by summing post-filtered accelerometer

Table 1—Summary of demographic features and changes in clinical, laboratory, and actigraphic parameters associated with iron supplementation in the 3 children with RSD.

	Patient 1	Patient 2	Patient 3
Age, years	10	8	9
Sex	Male	Male	Male
CGI-Improvement	Very much	Minimally	Very much
Ferritin baseline, μg/L	20	17	28
Ferritin treatment, μg/L	119	74	122
Ferritin increase, μg/L	+99	+57	+94
Activity count, day, n	−24.6	+19.1	−15.7
Activity count, night, n	−48.7	+164.0	+23.1
Total sleep time, weekdays, min	−3.7	−40.7	+2.4
Total sleep time, weekend, min	−38.8	−50.0	+35.5
Efficiency, weekdays, %	+6.7	−5.7	+0.4
Efficiency, weekend, %	+5.6	+1.9	−4.5
Sleep fragmentation index, weekdays, %	−6.2	+1.3	−8.7
Sleep fragmentation index, weekend, %	−6.2	−4.3	+9.3

CGI = Clinical Global Impression, RSD = restless sleep disorder.

values within each 1-minute epoch, total sleep time (TST), indicating the total number of minutes scored as "asleep," sleep efficiency obtained from the number of sleep minutes divided by the total number of minutes the patient was in bed, and the sleep fragmentation index (SFI) computed from the sum of the percentage of minutes that are marked as awake in the sleep period and the percentage of 1-minute periods of sleep vs all periods of sleep in the sleep period. ActiGraph wGT3×-BT devices (Pensacola, FL) using the Sadeh algorithm were worn. The patients were scored by a single sleep physician (R.F.) who was blind to treatment and response. **Figure 1** compares the 24-hour activity levels (average of the 7 days) for each patient before (blue) and after (red) IV iron supplementation. In **Figure 1**, activity level is expressed in counts within each 1-minute epoch.

Patient 1

The first patient was a 10-year-old male with a past history of restless sleep and obstructive sleep apnea (OSA) with an obstructive apnea-hypopnea index of 5.8 events/h. He underwent adenotonsillectomy with resolution of OSA; however, the parent was concerned that sleep continued to be very restless and the child continued having behavioral problems and fatigue during the day. A post–tonsillectomy and adenoidectomy study showed resolution of OSA (obstructive apnea-hypopnea index 0.6 events/h) with evidence of increased LMM index (7 events/h). Periodic limb movement during sleep index was normal. No family history of narcolepsy, restless legs syndrome, parasomnia, or OSA was reported.

Pretreatment ferritin was 20 μg/L (normal range 16–107) and increased by 99 μg/L at 8 weeks after IV iron infusion, reaching a level of 119 μg/L. This increase was accompanied by a score of 1 (very much improved) at the CGI-I. At the same time, average actigraphic activity count decreased during both day and night. SFI and TST also decreased, but sleep efficiency increased, probably indicating a more consolidated and restful sleep.

Patient 2

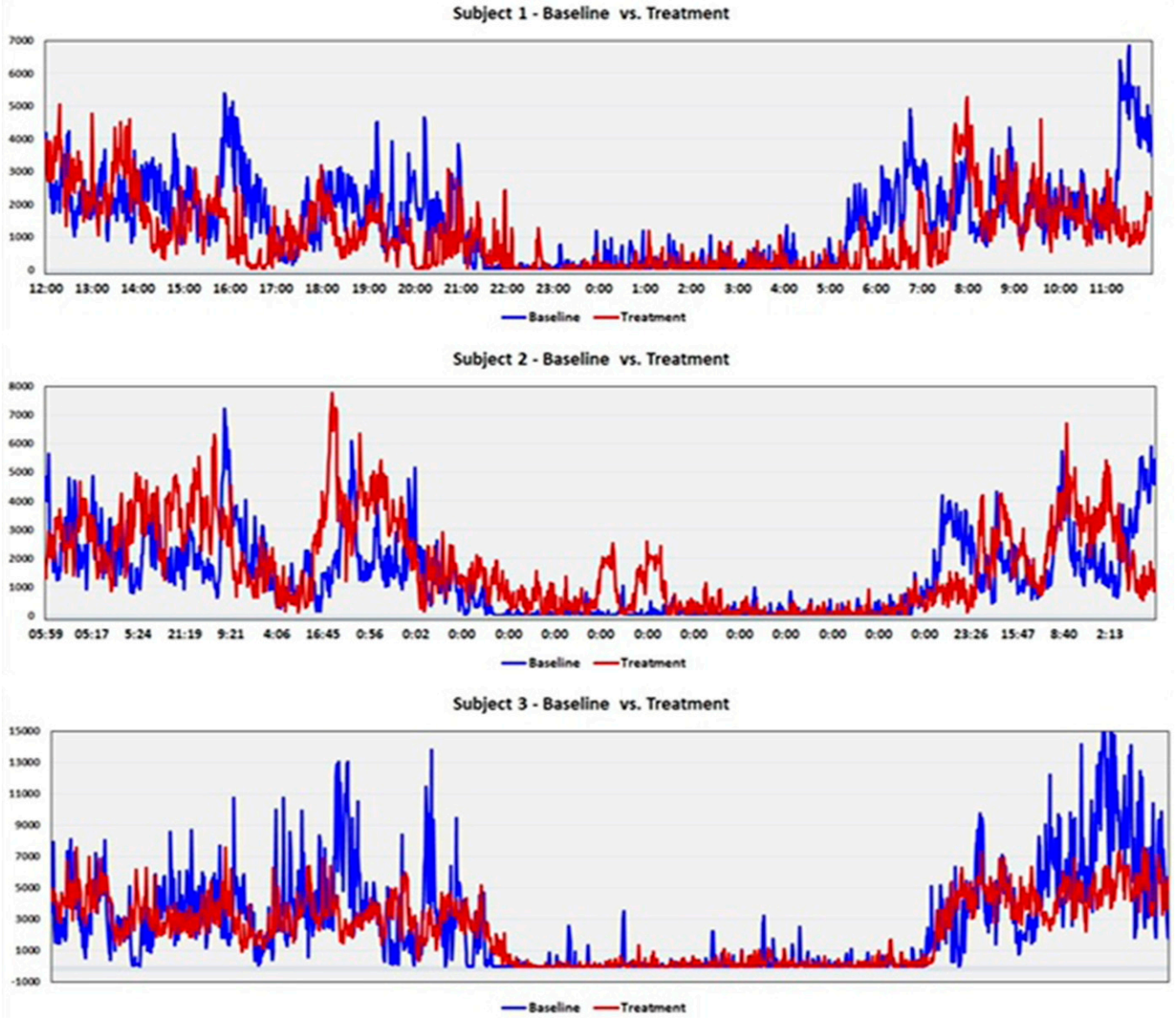
RSD (LMM index 6 events/h) with sleep fragmentation was diagnosed in this 8-year-old boy, who was referred for intravenous iron due to lack of improvement in ferritin levels with oral iron supplementation. Bedtime was 8:00 PM with a 10–20 minute sleep latency, there were no nocturnal awakenings, and wake-up time was at 7:30 AM. Daytime symptoms included sleepiness and a past medical history of anemia was reported at age 4 years. No family history of narcolepsy, restless legs syndrome, parasomnia, or OSA was reported.

Ferritin level initially was 17 μg/L (normal range 16–107) and increased to 74 μg/L after IV iron supplementation. In this patient, clinical improvement was minimal, activity and TST increased during both day and night, sleep efficiency decreased on weekdays and minimally increased in the weekend. Conversely, SFI minimally increased in weekdays and decreased in weekend.

Patient 3

Also in this 9 year-old male, RSD (LMM index 7 events/h) and iron deficiency were diagnosed, and he was referred for consideration for intravenous iron infusion due to lack of improvement in iron levels after 10 months of oral iron supplementation. Bedtime was 8:00 PM, he denied symptoms of restless legs syndrome, and reported falling asleep within 20 minutes. There were no nocturnal awakenings reported. Wakeup was at 6:30–7:00 AM to go to school. On the weekends the same schedule was kept. Daytime symptoms were not severe but included distractibility and poor attention. School performance was average. In the MAST

Figure 1—Activity level for each patient expressed in "counts" (vertical axis scale) obtained by summing post-filtered accelerometer values within each 1-minute epoch.



The figure for each patient represents the week average activity count before (blue) and 8 weeks after (red) IV iron infusion.

medical history, frequent nosebleeds lasting for 15–20 minutes had been reported. There was no family history of narcolepsy, restless legs syndrome, parasomnia, or OSA.

Ferritin was 28 μg/L (normal range 16–107) before iron supplementation and it increased by 94 μg/L after IV iron infusion, reaching a level of 122 μg/L. This increase was accompanied by a score of 1 (very much improved) at the CGI-I. Average actigraphic activity count decreased during the day but increased at night, possibly correlated with TST, which increased minimally during the weekdays but substantially during the weekend. Sleep efficiency was practically unchanged during the weekdays and slightly decreased during the weekend. SFI was decreased during the weekdays but increased during the weekend.

DISCUSSION

In the current case reports we have shown that although there is clinically significant improvement reported by parents, actigraphy data were not highly consistent in our 3 patients. However, it is also clear that the changes in sleep parameters assessed by actigraphy seem to parallel, in some way, the clinical changes assessed by CGI-I (which showed minimal improvement) and ferritin levels. For instance, **Table 1** illustrates that there was minimal improvement in patient 2, who also had the smallest improvement in ferritin levels post–IV infusion, and was also the only patient whose sleep fragmentation index increased

+1.3 (decreased in the other 2 patients) and activity during the day increased +19, while it decreased in the other 2 patients.

Actigraphy has long been used and validated for the estimation of sleep and wakefulness in children. The American Academy of Sleep Medicine has published a clinical practice guideline on the use of actigraphy in patients with sleep-related disorders[11] and recommends the use of actigraphy in adults and children for the evaluation of insomnia, circadian rhythm disorders, and sleep-related breathing disorders, but actigraphy was not found to be helpful for periodic limb movements of sleep.[11] The scoring of periodic limb movements of sleep requires a minimum duration of 0.5 seconds and a maximum duration of 10 seconds, which is similar to the scoring of LMM in sleep in children with a minimum of 3 seconds and a maximum of 30 seconds.[12] It is possible that movements in this category are not adequately identified by the actigraphy sleep scoring algorithm, which uses 60-second epochs for analysis.

A meta-analysis on the use of actigraphy in children with attention deficit hyperactivity disorder, comparing them to typically developing children, showed that activity level during the day clearly shows a higher motor activity in patients with attention deficit hyperactivity disorder while activity during sleep presented more heterogeneous results.[13] Studies in children of similar age (7–11 years) have shown that wakefulness after sleep onset may be the best predictor of sleep quality and values ≤ 30 minutes correspond to high sleep quality.[14] However, we cannot be sure that this is valid also for RSD, because these children are reported to move but not to wake up during the night; for this reason, we also considered SFI as an indicator of sleep quality in this short case series.

It is very interesting to note that both clinical improvement and sleep parameter changes appear to be more preeminent in the 2 children who showed the higher increase in ferritin level (patients 1 and 3), who increased their ferritin by approx 100 μg/L, reaching levels approx 120 μg/L. The only child who increased his ferritin level by about 60% of the increase of the other 2 children did not improve. This might indicate that future studies should be arranged in order to confirm this preliminary finding and that a target ferritin level of approx. 120 μg/L should be sought in the clinical practice for the treatment of RSD. This is also supported by other previously reported data by our group[4] showing that intravenous iron is significantly more effective than oral iron supplementation in RSD because of the significantly higher levels of ferritin reached. Nonanemic iron deficiency usually occurs in early stages of iron deficiency during which ferritin levels drop without decrease in hemoglobin levels.[15] Although there is no consensus on the actual value for non-anemic iron deficiency, most publications agree that ferritin levels below 30 μg/L start showing hypochromia without effect on hemoglobin.[15] For restless legs syndrome in children, levels above 50 μg/L are typically pursued. There is growing evidence that low iron stores affect attention and behavior[16]; therefore, improving iron stores in children with daytime symptoms can produce an overall improvement that could be multifactorial. Further studies need to identify the direct relationship between improvement in iron levels and improvement in nocturnal movements.

Although these case reports cannot be considered conclusive, they seem to indicate that a larger and controlled study is warranted in order to better define the eventual usefulness of actigraphy for monitoring the treatment effects of intravenous iron for RSD and, perhaps, to identify patients who are responding less and may need a repeat infusion.

ABBREVIATIONS

CGI-I, Clinical Global Impression-Improvement
IV, intravenous
LMM, large muscle movements
OSA, obstructive sleep apnea
RSD, restless sleep disorder
SFI, sleep fragmentation index
TST, total sleep time

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October 26, 2022
Submitted in final revised form December 6, 2022
Accepted for publication December 6, 2022
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The work was performed at Seattle Children's Hospital. The authors report no conflicts of interest.