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Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers

Meir H. Kryger[a,*], Kazuo Otake[b], John Foerster[c]

[a]*Sleep Disorders Centre, St. Boniface General Hospital, R2034, 351 Tache Avenue, Winnipeg, Manitoba, R2H 2A6, Canada*
[b]*Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada*
[c]*St. Boniface General Hospital Research Center, St. Boniface General Hospital, Winnipeg, Manitoba, Canada*

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Abstract

Background: It has been shown that restless legs syndrome (RLS) in adults may be linked to abnormalities in iron stores. Whether reduced iron stores play a role in children is not clear.

Methods: We evaluated the status of iron stores and sleep in three teenagers who presented with severe sleep onset insomnia, subjective sleep latency exceeding 60 min and excessive daytime sleepiness.

Results: The three teenagers were found to have RLS and laboratory evaluation confirmed reduced body stores of iron with a low percent iron saturation (mean value 9.7%) and a low serum ferritin level (mean value 17 μg/l). None had marked anemia. The three patients were treated with oral iron for 4–5 months. As a group they had an increase in percent iron saturation (from a mean of 9.7 to 22.7%) and serum ferritin (from a mean of 17 to 27 μg/l) and a marked reduction of the symptoms of RLS, with mean subjective sleep latency decreasing from 143 to 23 min, sleep efficiency increasing from 75.7 to 84.0% and the number of periodic movements per hour of sleep decreasing from 20.5 to 10.5.

Interpretation: These findings support the hypothesis that abnormal iron stores or metabolism may result in RLS causing insomnia in teenagers. We recommend evaluation of iron status including serum iron, total iron binding capacity and ferritin levels in teenagers with chronic insomnia of unexplained origin even when anemia is mild or absent.

Keywords: Low body stores of iron; Restless legs syndrome; Insomnia; Anemia

1. Introduction

It was suggested many years ago that iron deficiency anemia is linked to restless legs syndrome (RLS), a disorder that may result in severe sleep onset insomnia [1,2]. The minimal diagnostic criteria for RLS include the following: an unpleasant sensation in the legs at night or difficulty in initiating sleep; disagreeable sensations of creeping (or crawling) are present in the calves often associated with aches and pains in the legs; the discomfort is relieved by movement of the limbs [3]. More recently studies have suggested that low body stores of iron and/or a dysregulation of iron transport or metabolism in the absence of anemia may lead to RLS [4–6]. The hypothesis is that the stores of iron in RLS patients or the transport and metabolism of iron may be sufficient to maintain red blood cell production, but not sufficient to maintain normal brain iron stores, which in turn may lead to reduced dopamine synthesis or receptor function.

We evaluated three consecutive teenagers in our sleep disorders center, two males (both age 14) and one female (age 19) who were referred with severe sleep onset insomnia and were found to have RLS. They were evaluated with comprehensive polysomnography including the recording of EEG, submental EMG, EOG, EKG, right and left anterior tibialis EMG, SpO_2 (using fiberoptic ear oximetry), chest wall motion and abdominal motion (using inductance plethysmography), measures of airflow (oronasal capnometry and nasal pressure), and sound (for snoring) using standard techniques [7]. The main abnormal finding was increased movements in the anterior tibialis muscles. Because there has been a great deal of recent interest in iron dysregulation in sleep movement disorders, we performed iron studies on these patients. None of these individuals had marked anemia by conventional definition, but all had findings consistent with abnormal iron metabolism. The only management recommendations made to the referring doctors for these patients were the suggestions that the cause of the iron deficiency be investigated and the patient be started on an iron supplement. The three patients

* Corresponding author. Tel.: +1-204-237-2760; fax: +1-204-235-0021.
E-mail address: kryger@sleep.umanitoba.ca (M.H. Kryger).

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had improvement in their symptoms of insomnia. Although iron dysregulation has been emphasized as a cause of RLS in the elderly [4] and adults [5], to our knowledge it has not been reported in youths.

2. Case reports

2.1. Case 1

DG, a 14-year-old male student with a body mass index (BMI) of 38, was referred with a 4 month history of severe insomnia and excessive daytime sleepiness (EDS). The patient stated that he normally went to bed at 22:00 h and it took him 2–4 h to fall asleep. This insomnia was present every night, and the patient stated that every night he had restlessness in both legs that was relieved by walking. In addition, for at least two nights a week the patient had an unpleasant disagreeable crawling sensation in his legs as he was trying to fall asleep. He had been noted to snore but had never been observed to be apneic. His mother stated that she had a great deal of difficulty in getting him out of bed at 07:00 h to go to school. He nodded off frequently at school. On weekends he would sleep in until 11:00 h.

He and his mother had both noted that his legs were moving constantly during the daytime, especially his right leg. In addition he continuously chewed plastic or rubber at school. He completely chewed up one or two plastic ballpoint (Bic®) pens every day and when he had the opportunity he chewed the rubber wheels of his Lego® sets for hours on end. This chewing behavior may have been a manifestation of pica [8].

The physical examination revealed a well-nourished male student who could not stop moving. He continuously moved both of his legs, at times with a scissoring motion at the hips. He tapped his heels and could not sit still.

The Epworth Sleepiness Score (a subjective measure of sleepiness) was 15, which is in the range that is often seen in patients with daytime sleepiness due to obstructive sleep apnea syndrome. The patient had an overnight sleep study that showed a 48 min sleep latency, 67% sleep efficiency, and a great deal of activity in his anterior tibialis muscle during the first and seventh hours of sleep. The PLMs index (periodic limb movements per hour of sleep) was 19.5. The arousal index (arousals per hour) was 15.2. Although the patient was documented to snore during the night study, sleep respiration was considered within normal limits.

Hematological evaluations were consistent with iron deficiency (see Table 1). Dietary history did not explain iron deficiency, nor was there any history consistent with gastrointestinal bleeding. Investigation for celiac disease has not confirmed that diagnosis. The patient was found to have a bezoar most likely caused by the eating of the plastic mentioned above, which in turn may have been the source of the iron loss.

2.1.1. Follow-up

The patient was started on 300 mg ferrous sulfate by mouth twice a day. After 4 months of treatment the symp-

Table 1
Cases of insomnia and iron deficiency[a]

	Patient			Normal values (male/female)[b]
	1	2	3	
Age (years)	14	19	14	
Gender	Male	Female	Male	
BMI	38	27	29	<28
RBC ($\times 10^{12}$/l)	5.13/5.45	3.71/4.47	5.34/5.21	4.7–6.2/4.2–5.4
HGB (g/l)	137/148	108/137	151/151	140–180/120–160
HCT (l/l)	0.42/0.44	0.32/0.40	0.44/0.44	0.42–0.52/0.37–0.47
MCV (fL)	80.8/80.6	86.0/89.9	82.9/85.3	80–96
MCH (pg)	26.7/27.1	29.2/31.0	28.4/20.0	27–31
MCHC (g/l)	331/336	339/344	342/339	320–360
RDW (%)	14.8/13.6	11.8/12.3	13.2/12.8	11.5–14.5
Ferritin level (μg/l)	22/35	3/14	26/36	20–175/20–95
Iron (μmol/l)	5.2/5.0	9.9/22.0	9.7/18	7.0–27.0
TIBC (μmol/l)	79/57.3	93/80.2	92.4/79.1	47–72/47–80
% iron saturation	7/9	11/27.4	11/23	>16
Sleep latency (min)	48/11	23/7	56/36	15[c]
Total sleep time (min)	284/367	427/407	351/413	
Sleep efficiency (%)	67/77	86.6/82.6	73.4/89	95[c]
AHI	5.4/0.4	4.6/5.4	5.0/1.5	<5
PLMI	19.5/11.4	11.1/4.6	31.0/10.6	<5
ArI	15.2/18.1	12.8/6.6	5.0/13.6	<5

[a] Where there are two values in a cell they refer to pre-treatment/post-treatment with iron supplement.
[b] Where there are two values in the 'normal values' column, they refer to male/female normal laboratory values.
[c] Normal values for sleep latency and sleep efficiency are taken from Ref. [34], pages 180 and 184.

toms of RLS and insomnia resolved entirely and subjective sleep latency was reduced to 10 min. The daytime sleepiness resolved completely and the patient no longer fell asleep in class. His mother stated that his average grade at school went from 45% to over 90%. On evaluation the continuous movements while awake were no longer present. His post-treatment sleep study showed that sleep latency was now 11 min and sleep efficiency increased from 67% to 77%. The PLMs index was now 11.4.

2.2. Case 2

XW, a 19-year-old female student with a BMI of 27, had a 7 year history of sleep onset insomnia and EDS that began at age 12. Five nights a week she had symptoms compatible with RLS. During the time she was trying to fall asleep she tossed and turned and described an itchy, creepy, crawly unpleasant sensation in her legs primarily in her calves and shins. The sensation was often relieved by movement or walking. She stated that her sleep onset was usually in excess of 100 min. During the time she was trying to fall asleep she frequently had clear-cut hypnagogic hallucinations. Between once a week and once a month she had classic episodes of sleep paralysis. With these episodes she awakened and was conscious but could not move her extremities.

The patient had daytime sleepiness with an Epworth score of 15. She fell asleep outside of the normal nighttime sleep period virtually every day and she stated that she dreamed with almost every nap. She felt better after a nap compared to before. As a result of the sleepiness she had done very poorly at university. She was extremely sleepy in the morning and when allowed to sleep in and awaken naturally, she would awaken at 16:00 h. She would still feel sleepy after the long sleep episodes.

The overnight sleep study revealed a sleep latency of 23 min, REM sleep latency of 99 min, sleep efficiency of 86.6%, and an increase in stage 1 sleep. She had 11.1 movements per hour, consistent with periodic movements in sleep. There were 12.8 arousals per hour of sleep. Because the patient had symptoms suggesting narcolepsy, she had a multiple sleep latency test (MSLT) that yielded a mean sleep latency of 10.9 min, and on three of four of the naps she demonstrated features of REM sleep. These results were compatible with narcolepsy. Hematological studies and iron studies were consistent with iron deficiency anemia.

2.2.1. Follow-up

After 5 months of 300 mg of ferrous sulfate by mouth t.i.d., she had complete abolition of the insomnia with subjective sleep latency decreasing from 100 to 30 min but daytime sleepiness remained, as did vivid dream imagery at sleep onset and naps. The repeat overnight sleep study revealed sleep latency of 7 min, REM latency of 60.0 min, sleep efficiency of 86.0%, and an increase in stage 1 sleep. She had 6.6 movements per hour, consistent with periodic movements in sleep. There were 6.6 EEG arousals per hour of sleep. The MSLT revealed a mean value of 7.8, with no REM sleep onsets. Since sleepiness most likely related to narcolepsy was the remaining sleep complaint she was treated with modafinil, a stimulant. With this there was an improvement in daytime alertness. One year after treatment she considered both her nocturnal sleep and daytime alertness normal.

2.3. Case 3

DJ, a 14-year-old male student with a BMI of 29, had major problems in school because of EDS and insomnia that began approximately 6 months before referral. As a result of difficulty in getting up in the morning he missed 90% of his school days and he finally dropped out of school.

The patient had been going to sleep about 01:00 h, but not falling asleep for at least 1 h, frequently much longer. He would sleep in until the middle to late afternoon. The patient described that every single night he had restlessness in his legs; “I have crazy legs.” He had an itchy sensation in his skin and a crawling sensation about twice a week when he tried to sleep. This disagreeable symptom was improved by moving his legs or walking. His mother stated that he moved a great deal when he slept and his bedclothes were a mess when he awakened in the morning. The patient had been noted to occasionally snore but he had never been observed to stop breathing. There was no history of excessive movements outside of the sleep period.

The patient stated that he dreamt as he was falling asleep. He had never had sleep paralysis or cataplexy. The patient fell asleep accidentally or on purpose outside of the normal sleep period every single day. The patient stated that he dreamt during these nap episodes and he felt better after these naps compared to before.

The patient had a 1 year history of diarrhea, which had not been investigated when he was first evaluated in our center. The patient also had a history of other complex medical problems including IgA deficiency, history of recurrent infections, peptic ulcer disease and a presumably benign chronic frontal lobe mass. Hematological studies were consistent with low iron stores. An etiologic cause for the reduced iron stores was not proven but it was hypothesized that it was caused by gastrointestinal disease.

Polysomnography documented a sleep latency of 56 min and sleep efficiency was 73.4%. Once he did fall asleep he had, for a large part of the night, classic periodic movements in sleep, with 31 twitches per hour of sleep. During REM sleep he demonstrated episodes of mild oxygen desaturation that were not caused by obstructive apnea. The MSLT showed a mean sleep latency of 15 min and REM onsets in two of four naps.

2.3.1. Follow-up

Five months after the initial diagnosis of RLS the patient was started on ferrous sulfate (300 mg twice daily) iron

replacement therapy. Within 6 months there was complete abolition of the symptoms of RLS and insomnia. The patient no longer walked at night and considered his nocturnal sleep normal. The patient was now going to sleep at 00:30 h and the subjective sleep latency was 30 min. The mother stated that the excessive movements during sleep had resolved and the bedclothes were no longer a mess in the morning. His mother stated that he was normally alert and he was returning to school. The repeat sleep study showed that the sleep latency was 36 min, sleep efficiency was 88.9% and the PLMs index was 10.6. The MSLT was now 14.5 min and there were no REM onsets.

3. Discussion

We have shown that chronic sleep onset insomnia in adolescents may be associated with RLS related to abnormal iron status. The combination of low serum iron, high total iron binding capacity, low percent iron saturation, and low ferritin levels is compatible with a diagnosis of low iron stores. With iron replacement, patients all had resolution of the movement disorder and the complaint of insomnia and the elimination of the disagreeable sensation in the legs. It may take months for iron stores to return to normal on treatment [9,10] and the abnormal values in our patients, although improved, had not all yet normalized with therapy. Some features of iron deficiency may improve rapidly with treatment before stores are normal [9]. In one of our patients (Case 2), although the insomnia resolved, treatment with iron did not have any effect on the symptoms and features of narcolepsy.

These cases illustrate the point that insomnia is not a disease, but a patient complaint or a symptom, and the clinician's challenge is to elucidate the cause of the symptom and, if possible, to treat the cause. In our cases iron deficiency probably caused insomnia and treating it improved the patients' sleep. Sleep disorders in children and teenagers can result in a marked deterioration in school performance and may affect their lives significantly. Our cases presented with sleep onset insomnia and EDS. The sleepiness in our cases was likely caused by chronic sleep deprivation due to a long sleep latency. In Case 2 narcolepsy was also likely present. Insomnia has many causes, but a few that require special consideration in this age group. A careful history and/or the use of a sleep diary can be very helpful in sorting out the cause of a sleep disorder. Several disorders may cause insomnia and/or EDS in children.

3.1. Delayed sleep phase syndrome

Delayed sleep phase syndrome (DSPS) is a disorder in which a patient's circadian clock is delayed causing primarily sleep onset insomnia. DSPS is important in the differential diagnosis of teenagers who fall asleep late and get up late. These individuals, when awakened in the morning to go to school, will have difficulties in getting out of bed and may have severe sleepiness at school and fall asleep in classes. Typically such patients sleep in very late on weekends and when they have a normal sleep quota are wide awake and alert. At first glance all our cases had features compatible with this diagnosis. What made them different were the symptoms of movement disorders. Case 3 still tended to go to sleep late, 00:30 h but the RLS symptoms were gone.

3.2. Narcolepsy

Narcolepsy causes EDS, but one of the manifestations can be difficulty in falling asleep and staying asleep at night. In narcolepsy there appears to be sleep/REM sleep dysregulation with some of the features of REM sleep (dream imagery, sleepiness, a reduction in muscle tone) occurring outside the normal sleep period. These patients may also demonstrate periodic movements in sleep. During multiple sleep latency testing, patients may demonstrate a short mean sleep latency (less than 5 min) and two or more sleep onset REM periods [11]. Case 2 continued to have daytime sleepiness and hypnagogic hallucinations after her RLS symptoms resolved and it is likely she had narcolepsy.

3.3. RLS/periodic limb movements in sleep

RLS/periodic limb movements in sleep has been described frequently in older populations, but it does occur in children [12–14] and can present with sleep onset or sleep maintenance insomnia and EDS, as in our cases. History may reveal restlessness at bedtime and increased motor activity during sleep, which often is periodic with a cycle of approximately 20–40 s. All of our cases had motor restlessness and noticeable movements during the daytime and had difficulty sitting still. This may not be the case in adults in whom the restlessness may be prominent only at bedtime. In adult patients this disorder has been linked with painful conditions (joint disorders), renal failure and anemia [15]. Our cases confirm that abnormalities in iron metabolism (discussed below) without marked anemia can also be associated with this syndrome. It has been suggested that abnormal movements and RLS may be common in children with attention deficit hyperactivity disorder (ADHD) [13,16]. Dopaminergic therapy which is useful in the symptomatic treatment of RLS [17] may reduce ADHD symptoms in RLS patients with ADHD [18]. Based on what we have learned from our cases, a systematic study of iron metabolism in ADHD is warranted.

3.4. Iron deficiency and movement disorders

Although it is generally emphasized that iron deficiency anemia is associated with RLS [1,2], our cases confirm that marked anemia does not have to be present, and are consistent with the hypothesis that abnormalities in iron metabolism may play a key role [4,5]. Once anemia is present, the marrow iron stores are zero and the ferritin level is less than

10 μg/l [19]. It has been suggested that iron deficiency might be implicated in RLS if the ferritin level is less than 50 μg/l [6,20].

The pathophysiology by which abnormal iron metabolism may be associated with RLS is not clear. It has been shown that the cerebrospinal fluid concentration of ferritin is reduced while the concentration of transferrin is elevated [21]. This was interpreted to indicate low brain iron in patients with idiopathic RLS. Magnetic resonance imaging studies have demonstrated reduced iron deposits in the substantia nigra, suggesting that brain iron deficiency may cause abnormalities in dopamine metabolism in the idiopathic RLS patients [22]. It is possible that similar mechanisms are at play in patients with iron deficiency. It is known that RLS symptoms are not constant, but tend to be worse at night. The cause of this is unclear, but may be related to the observation that the plasma iron level demonstrates a circadian rhythm with evening and night values being about half of morning values [23].

The relationship between iron metabolism and movement disorders is potentially complex. Iron is involved in the conversion of tyrosine into L-dopa, which is then converted into dopamine [5]. It has thus been suggested that iron deficiency might result in a reduction of neurotransmitter production and function, especially in the dopamine-opiate systems [24,25]. When intracellular iron levels are low there is decreased ferritin production in cells [26]. Although insufficient iron can lead to abnormal neurotransmitter production and function, it has also been suggested that excess or accumulation of iron may lead to degeneration of substantia nigra dopamine neurons by oxidative damage. This has been suggested as a potential mechanism in Parkinson's disease [27]. It is possible that abnormalities in more recently described mechanisms of iron transport may play a role in some patients [19,28–30]. RLS is familial in some cases and may be due to abnormalities in iron metabolism or susceptibility to RLS if iron deficiency occurs.

3.5. Treatment of iron deficiency

As in adults, it is important to determine the etiology of iron deficiency in children and adolescents. In our cases, blood loss related to a gastrointestinal pathology was thought to be the main contributor in the two males; in the female excessive bleeding during menstrual cycles was thought to be the main factor. For children, the effective dose is 1.5–2.0 mg of elemental iron per kilogram of body weight three times daily, or five times that amount in most ferrous sulfate tablets, elixirs or pediatric drops, since ferrous sulfate contains 20% of elemental iron by weight. Adults or grown-up children are most commonly treated with 300 mg of ferrous sulfate three times daily. Although iron is best absorbed with an empty stomach (e.g. 1 h before meals) [8], this might lead to gastrointestinal symptoms. To avoid gastrointestinal irritation, experts have suggested that ferrous sulfate should be taken with meals, even though this will impair absorption somewhat [9]. There is usually an inadequate quantity of iron in multi-vitamin preparations for children. There currently does not seem to be a consensus about whether ascorbic acid (vitamin C) should be routinely used to enhance iron absorption; although absorption may be increased [31] there is also an increase in side effects [8,9]. In addition, a recent study concluded that the impact of vitamin C on iron absorption is less pronounced when vitamin C is used chronically, explaining why several studies of prolonged vitamin C use did not show positive effects on iron status [32]. In the absence of controlled clinical trials in children with iron deficiency and RLS, it seems prudent to use similar criteria as in adults, i.e. one would stop therapy at a serum ferritin level of approximately 50 μg/l [6,20]. If the symptoms resolve before the ferritin level reaches 50 μg/l, then it might be reasonable to stop the medication at that time. Because a very low serum ferritin value represents a dramatic reduction in body stores of iron, it may take several months of treatment for the iron to be repleted. The practitioner should follow-up the patient to ensure that iron overload does not occur. This would be indicated by an increased ferritin level.

3.6. Conclusions

Teenagers presenting with insomnia may have RLS. When RLS symptoms are present, iron status evaluation is recommended even when anemia is mild or absent. Screening with routine complete blood count is not sufficient [19,33] to detect reduced iron stores in children and we recommend detailed iron investigations including measures of iron, iron binding capacity and ferritin.

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