16 Restless Legs Syndrome and Periodic Limb Movement Disorder

Arthur Teng

16.1 Vignette

Sami is a 5 year-old otherwise healthy and normally developing boy who presented to the Sleep Clinic with a 2 year history of snoring and restless sleep. On closer questioning the snoring is present on average three nights out of an average week. He never seems to stop breathing but there is some mouth breathing and a mild increase in work of breathing. He also sweats a bit in his sleep. In addition, the parents were worried about his restless sleep: he tosses and turns, much like what the mother described as a "washing machine". In addition, he seems to kick his legs through the night and has in fact fallen out of bed on several occasions. The father reported that no one wanted to share a bed with him during their holidays! Sami has also been complaining of pains and cramps at night. These are often relieved by massage and occasional when they are severe there is some relief with paracetamol or ibuprofen.

Sami has a good sleep routine with bedtime at 7.30 PM; he is usually asleep within 15–20 min and despite his restlessness tends to sleep through the night without disturbing his parents. Sami wakes up at around 7 AM a bit tired and unrefreshed but soon "warms up". By day he is an active boy who has no trouble running around or kicking a ball. His kindergarten teachers report that he seems bright and is graded as average academically. He has a short concentration span and tends to be easily distracted. He fidgets and squirms in his seat. He is generally well-behaved but gets a bit tired after lunch, and sometimes has trouble completing his tasks on time. He is not reported to fall asleep inappropriately at school but he falls asleep often in the short car-trip home from school in the afternoons. There is no scheduled nap. Sami is otherwise well and does not suffer from recurrent tonsillitis or other medical or surgical problems.

16.2 Physical Examination

On examination Sami was afebrile and not in respiratory distress. His blood pressure was 95/50 with normal chest and heart sounds. He was cooperative but was physically busy: he was constantly moving in his chair and tended to get up and pick up things on the desk. His tonsils were grade 2 on 4 bilaterally with a slightly high-

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arched palate. Nasal airflow was demonstrated from both sides with pallor and some swelling and medialisation of his inferior turbinates. Ear drums looked normal. He had a normal gait and neurological examination including deep tendon reflexes. His weight was 18 kg (around 50th percentile) and height 118 cm (just under the 50th percentile).

Summary of clinical presentation and possible diagnoses:

1. Snoring and Sleep disordered breathing/chronic allergic rhinitis.
2. Attention deficit disorder (ADD).
3. Restless legs syndrome (RLS)/periodic limb movement disorder (PLMD)/Growing pains (GP).

16.3 Diagnostic Evaluation

Snoring and Sleep-disordered breathing

Sleep-disordered breathing is best regarded as a spectrum ranging from primary snoring to obstructive sleep apnoea (OSA). Snoring is the main presenting symptom. Restless sleep is also a common symptom. Certainly sleep disruption as well as hypoxia could result in similar daytime symptoms. Unlike adults with obstructive sleep apnoea, in children it is unusual to have excessive daytime symptoms. In fact many children exhibit hyperactive behaviour.

Investigation

An overnight sleep study (polysomnography or PSG) would be regarded as the gold standard for a diagnosis of OSA. However, this is not often available or there is often a long waiting period. Screening oximetry is much more widely available. A strongly positive result has a 98% concordance with a sleep study but a negative result has a negative predictive value of around 50%. This means that with normal oximetry, a full sleep study might still confirm OSA in around 50% of cases. (Can cross reference to OSA diagnostic chapter).

Treatment

A trial of nasal steroids such as fluticasone or mometasone would help sort out the role chronic allergic rhinitis plays in the snoring. Nasal sprays are safe in this age group with the optimal technique (such as pointing away from the nasal septum). The medication with lowest systemic absorption should be chosen. Nasal steroids have also been shown to decrease the size of the adenoids. Together with enlarged tonsils, adenoids are the main cause of snoring in children.

Attention Deficit Disorder (ADD)

At the age of 5 years, the diagnosis of ADD is difficult to confirm. Certainly Sami does exhibit several of the symptoms, including the inattentiveness, fidgeting and physical "busy-ness". Restless sleep is also a common symptom. However, as he seems to be keeping up academically there is no daytime "impairment" as such. The aim is to improve his sleep and see how age and neuro-maturation improves his functioning in the next 12 months [1].

Restless Legs Syndrome (RLS)/Periodic Limb Movement Disorder (PLMD)/Growing Pains (GP)

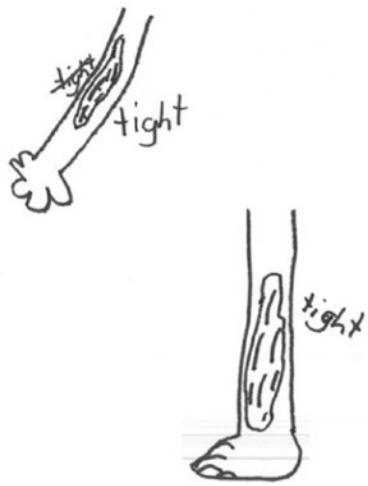
There is often some confusion between RLS and PLMD. The important thing to note is that RLS is diagnosed only on history and clinical features. Therefore it is a difficult diagnosis to make in a preschool child. Most people with RLS (around 80% or more) also have PLMD, however only around 60% of PLMD sufferers have RLS [2]. PLMD on an objective measure such as PSG in children is considered to be supportive of an RLS diagnosis in both children and adults [3] and there is some evidence that PLMD may be an early manifestation of RLS with PLMD [4].

RLS: there are five generally agreed criteria for the diagnosis of RLS in children:

1 An urge to move the legs, usually accompanied by unpleasant sensations
2 The urge to move or the sensations worsen during periods of rest or inactivity
3 The urge to move or the sensations are partially or totally relieved by movement
4 The urge to move or sensations are worse in the evening or during the night
5 The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition

In children who cannot readily voice these symptoms, the occurrence of periodic limb movements on a sleep study and a family history in first degree relatives of RLS are supportive of the diagnosis [5].

Reproduced below are drawings from two school-aged children with RLS produced from my own clinic. This method of eliciting clinical information was first published by Picchietti et al. [6]



Cross Cultural Differences in RLS

Population-based studies using the full standard diagnostic criteria for RLS report a prevalence of 4% to 11% in western industrial countries, but a lower prevalence in Asian populations [7] Prevalence tends to decrease towards the equator [8].

Periodic Limb Movement Disorder (PLMD). Unlike RLS, PLMD is not a clinical diagnosis but is defined by polysomnography (sleep studies). In adults more than 15 PLMs/h and in children more than 5/h is considered abnormal, and must by definition cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioural, or other important areas of functioning. The PLMs are not better explained by other concurrent disorders [9].

On a PSG, periodic limb movements are defined where:

1. There are more than or equal to 4 limb movements in a series
2. Each movement is separated at intervals of not less than 5 s but not more than 30 s
3. Each movement must last at least 0.5 s but not longer than 10 s [10].

4. The amplitude of the movement must be 8 μV above the resting electromyogram (EMG).

Periodic limb movements must not be confused with sleep starts or hypnic jerks, sleep myoclonus and cannot be part of an arousal from an obstructive breath. PLMs have also been reported in narcolepsy and use of antidepressants.

The prevalence of PLMS could be 4% to 11% [11]. A European study estimated the prevalence to be 3.9% in the general population [12]. In this study, patients were diagnosed with PLMD based on a telephone-based screening questionnaire without any PSG evidence. So, this might not accurately reflect the prevalence. Older age, female gender, shift work, stress, and caffeine intake were thought to be some risk factors in this study. Some studies have found a reduced prevalence of PLMS in African Americans compared to Caucasians [13].

Growing pains are common in children but lack consensus definition, with the diagnosis often made after the exclusion of other diagnoses. Typically the pains are bilateral, and intermittent with some pain-free days and nights. The typical location is the anterior thigh, calf, or posterior knee and with no joint involvement. There is no loss of function by day and the physical examination, laboratory and imaging tests are normal [14]. The overall incidence of GP in children is estimated at around 2%, which is similar to the incidence of GP in people with RLS [15]. There is some association between GP and PLMD though with our own studies suggesting an odds ratio of more than 3.0 [16].

16.4 Sami's Progress

Investigations

1. The overnight sleep study showed no evidence of obstructive sleep apnoea with preservation of oxygen saturation above 95% through the night. However, there were periodic limb movements. There averaged more than 16/h of sleep (Fig. 16.1).
2. Investigations included a full blood count (normal) with iron studies:

   This confirmed low iron stores with a ferritin of 10 μg/L, transferrin saturation of 12%. C-reactive protein was less than 1 mg/L (normal).

Notes

1. It is important to note that normal values of ferritin are under-reported in most pathology labs. In symptomatic children in particular the level should be well above 50 μg/L (ng/ml)
2. As ferritin is an acute phase reactant it is important to request a c-reactive protein (CRP). A so-called "normal" or even high level of ferritin in the context of inflammation and high CRP potentially represents a spurious result [17].
3. Transferrin saturation or iron saturation should be above 20%. A low iron saturation with high ferritin and usually high CRP represents low iron stores [18, 19].

Research Gaps

1. Does iron supplementation lead to improvement in restless legs syndrome? Rosen et al. showed that although the mean ferritin levels improved in children with RLS, the improvement in RLS symptoms was noted but not statistically significant [20].
2. How good is the evidence that ferritin levels should be greater than 50 μg/L?

   One of the first papers linking low iron to PLMS suggested in their dataset that 50 μg/L or less was related to evidence of PLMS [21].

   If one defines normal ferritin as above 50 μg/L then a significant proportion of a normal population of children would fall below this [22].

   In the important paper by Lipschitz [17], the geometric mean ferritin in normal controls, 59 ng per millilitre (59 μg/L) with a 95% con-

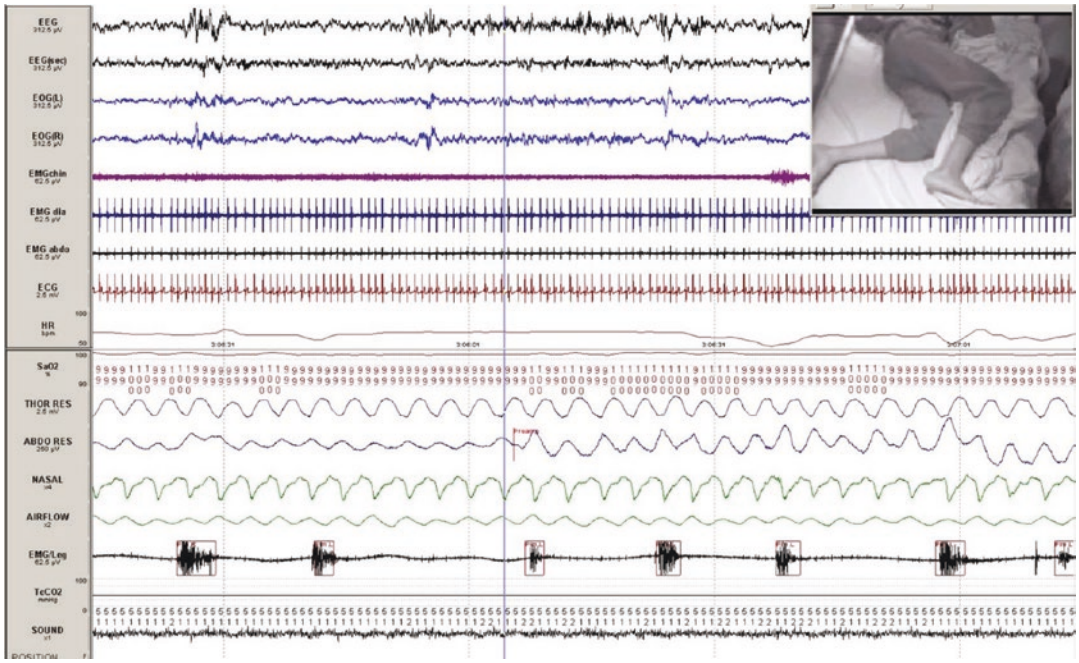


Fig. 16.1 Periodic limb movements showing 7 PLMs is a 1-min epoch of light (N2) sleep. PLMs are most commonly recorded in light sleep

fidence range of 12 to 300 ng/ml). It has been suggested that rather than tell parents that their child is iron deficient, that their ferritin level is sub-optimal for their symptoms [23].

Serum ferritin levels of <50 μg/L should raise suspicion of iron deficiency in children with chronic disease and in high-risk populations such as Indigenous Australians [24].

There is little doubt that significant tissue iron deficiency can exist with ferritin levels less than 30 μg/L in the absence of anaemia [25].

The Australian Blood Authority clearly states that a ferritin level of 20–50 μg/L can be associated with iron deficiency [26].

Serum ferritin levels ≥30 μg/L up to the method-related upper reference limit demonstrates healthy iron stores as long as co-existing inflammatory disease or hepatocellular damage are not present is the recommendation of the Royal Australasian College of Pathologists [27].

3. It is suggested that serum ferritin levels poorly reflect cerebrospinal fluid (CSF) ferritin levels [28, 29]

16.5 Sami's Treatment and Progress

Sami was treated for 3 months on nasal mometasone. The correct technique was demonstrated, including pointing at an angle away from the nasal septum, around 25° laterally, one spray to each nostril nightly, and advised to brush his teeth after. His mother reported better nasal airflow, less mouth breathing and almost no snoring.

In addition, he was commenced on iron in the form 100 mg of elemental iron as 370 mg iron polymaltose. This is equivalent to about just under 5 mg/kg daily for 3 months. The parents were advised in writing to give this after meals

with a small volume of orange juice, and to avoid taking milk, other dairy products and calcium close to the dose. As a general precaution they were advised to keep the medication out of the reach of small children. They were also told to look out for gastric symptoms and constipation. With the newer forms of oral iron, these side effects were less common. This was well tolerated. There was also a good clinical response: the sleep was much less restless, Sami seemed less hyperactive during the day as reported by his teachers and was much more attentive during class. He also had less episodes of night cramps or growing pains. Because he had a good clinical response, a blood test was not repeated.

16.6 Summary

It is important to take a good dietary history, excluding unusual diets in the family. At Sami's age excessive cow's milk ingestion should be avoided and a varied, healthy diet encouraged. A thorough medication history is also important. Paediatricians should also be cautious in avoiding certain antidepressants like mirtazapine, venlafaxine, sertraline, fluoxetine, amitriptyline as they may aggravate periodic limb movements.

Oral iron therapy should last 3 to 6 months. There is some suggestion that there should be slow weaning after that. Ideally the iron tests should be repeated towards the end of treatment [30].

For children poorly tolerant of oral iron, there is some evidence that IV iron sucrose can have a benefit [31].

There is poor evidence at this stage for other treatment of RLS/PLM in children. In adults dopaminergic medications such as pramipexole, ropinirole, rotigotine, and other drugs like gabapentin, pregabalin that are the mainstay of treatment for RLS may also cause a reduction in periodic limb movements in patients with PLMD [32]. Medications such as clonazepam, gabapentin, melatonin, clonidine, magnesium and valproate have been rarely tested in RLS/PLMD, usually without clear results and cannot be applied with certainty to children.

For an excellent review of pharmacotherapy of PLMD/RLs in children see Ref. 33.

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