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PERIODIC LIMB MOVEMENTS AND RESTLESS LEGS SYNDROME IN CHILDREN WITH A HISTORY OF PREMATURITY

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Abstract

Introduction—Little is known about which children are at increased risk for restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). Polysomnographic data from the Caffeine for Apnea of Prematurity-Sleep (CAPS) study showed a high prevalence of elevated periodic limb movement index in a cohort of ex-preterm children, but the clinical importance of this finding, such as association with RLS, is unknown. We hypothesized that ex-preterm children would have a high prevalence of RLS and PLMD.

Methods—Ex-preterm children enrolled in CAPS, now aged 5-12 years, completed home polysomnography and standardized questionnaires. A diagnosis of RLS or PLMD was established by participants meeting the International Classification of Sleep Disorders, 3rd edition criteria based on questionnaires and polysomnograms. Clinically available serum ferritin levels were assessed.

Results—167 participants underwent polysomnography and completed all questionnaires. The overall prevalence of RLS was 14/167 (8.4%). An additional 13 subjects (7.8%) were found to have PLMD. Of the 26 participants who had >5 periodic limb movements/hour, 7 (26.9%) had RLS and 13 (50%) had PLMD. Serum ferritin levels were <50 mcg/L (range 11 to 38.4) for all 8 participants referred for testing.

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Conclusions—Children with a history of prematurity have a high prevalence of RLS, particularly those with elevated periodic limb movements. Iron deficiency likely contributes to RLS and PLMD symptoms in this population. Clinicians evaluating ex-preterm children with sleep disturbances should evaluate for RLS and PLMD. Further studies including serum ferritin evaluation are needed to confirm these findings.

Keywords

children; restless legs syndrome; periodic limb movement disorder; prematurity

BACKGROUND

The International Classification of Sleep Disorders, 3rd edition, lists a variety of sleep-related movement disorders that can disrupt sleep or impair daytime function.¹ Periodic limb movements are repetitive, highly stereotyped limb movements that occur during sleep. In children, periodic limb movement disorder (PLMD) is characterized by a periodic limb movement index (PLMI) greater than 5/hour seen on polysomnography (PSG) as well as sleep or daytime disturbance that is not better explained by another condition.¹ In contrast, restless legs syndrome (RLS) is diagnosed when patients report an urge to move the legs associated with an uncomfortable sensation in the legs that begins or worsens during periods of inactivity, is relieved by movement, and occurs predominantly in the evening. For RLS to be diagnosed, the symptoms must cause impairment of sleep or daytime function and cannot be accounted for by another condition.¹ While a polysomnogram documenting periodic limb movements is not necessary for the diagnosis of RLS, many people with RLS do have periodic limb movements, suggesting that RLS and PLMD are related disorders. While the prevalence of PLMD in children is unknown, it is estimated that approximately 1.9% of children have RLS.²

The Caffeine for Apnea of Prematurity trial (CAP) enrolled premature infants into a double-blinded placebo-controlled study of caffeine versus placebo for neonatal apnea. This cohort continues to be followed, and 201 of the participants in the parent study, at 5-12 years, underwent PSG and completed multiple sleep questionnaires as part of the CAP-Sleep (CAPS) study, which assessed long-term effects of caffeine on sleep architecture and breathing during sleep. CAPS showed no differences in sleep duration, obstructive sleep apnea syndrome (OSAS) or PLMI between the caffeine and placebo group. However, an increased percentage of these former preterm infants had OSAS and elevated PLMI³ compared to normative data on otherwise healthy children.⁴

Nocturnal sleep disturbances or complaints of daytime sleepiness are extremely common in children.⁵ Movement disorders such as RLS and PLMD are one cause of sleep disruption, but little is known about which children are at increased risk for movement disorders. Children with prematurity are living longer and are at increased risk for behavioral problems,⁶ cognitive delays,⁷ and a multitude of medical conditions, and this population may also be at risk for comorbidities that have not been previously identified. The aim of the current study was to assess the clinical significance of the elevated PLMI in former preterm infants. We hypothesized that there would be a high prevalence of RLS in children with a

history of prematurity. We also hypothesized that there would be a high rate of PLMD in former preterm children with a PLMI greater than 5/hour.

METHODS

Study design and participants

Participants underwent polysomnography and caregivers completed a series of questionnaires as part of the CAPS study. Children were 5-12 years old and were part of the original CAP cohort. Participants were born prematurely, weighed 500-1250 g at birth, and did not have major congenital anomalies or syndromes. Children were randomized to caffeine or placebo for a median of 6 weeks during the neonatal period.⁸ The institutional review board at Children's Hospital of Philadelphia and each clinical site approved the study, and written informed consent was obtained from parents/guardians.

Polysomnography

Participants underwent a night of comprehensive ambulatory home polysomnography. Details of the polysomnography technique and quality have previously been published.⁹ These studies included electroencephalograms, electro-oculograms, tibial and submental electromyograms, airflow (nasal pressure transducer and oronasal thermistor), chest and abdominal wall movement by inductance plethysmography, electrocardiogram, and arterial oxygen saturation with pulse waveform. Bilateral anterior tibial electromyograms were used to assess for limb movements. Limb movements were scored if they were 0.5-10 sec and had an EMG amplitude ≥ 8 micro-volts above the resting EMG; periodic limb movements were scored if limb movements occurred as part of a series ≥ 4 , with 5-90 sec between each movement in a series.¹⁰ Polysomnograms were scored and interpreted centrally according to the American Academy of Sleep Medicine pediatric specifications.¹⁰ OSAS was defined as an obstructive apnea hypopnea index (AHI) ≥ 2 /hour.¹¹

Questionnaires

Caregivers completed a standardized questionnaire addressing the International Classification of Sleep Disorders, 3rd edition (ICSD3) Criteria for Restless Legs Syndrome¹. To meet the criteria for RLS, the child had to endorse an urge to move the legs and the symptoms must be: (i) worse during inactivity, (ii) improve with movement, (iii) be worse at night and (iv) stated in the child's own words. The child also had to endorse evidence of sleep or daytime disturbance in his or her own words.

Caregivers also completed the Sleep Related Breathing Disorder Scale of the Pediatrics Sleep Questionnaire (PSQ)¹². The PSQ is a 22-item survey that asks questions related to snoring and observed apnea, daytime sleepiness, growth, and attention. Questions related to sleepiness or impaired daytime function were used to assess for PLMD (Appendix Table). These included questions about feeling sleepy during the daytime or being difficult to wake up in the morning, as well as distractibility or difficulty paying attention.

PLMD was diagnosed in participants with a PLMI > 5 /hour on PSG, who exhibited evidence of sleep or daytime disturbance and who did not have another sleep disorder, such as OSAS

(i.e., an AHI ≥ 2 /hr on the polysomnogram) or RLS. For the diagnosis of RLS or PLMD, daytime disturbance was determined by answering one or more questions referring to daytime disturbance in the affirmative on the PSQ. Participants with elevated PLMI were referred for clinical assessment, which often included serum ferritin measurement at the discretion of the clinical provider.

Statistical analysis

Statistical analysis was performed using Stata version 13.1 (College Station, TX). Two-sample test for equality of proportions with continuity correction was used to compare the proportion of participants with a PLMI >5 /hr or ≥ 5 /hr with RLS and to compare the results of the current study with other published studies. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 201 children in the CAPS cohort, 167 participants completed all procedures and were included in this study. Participants were school-age, had a mean gestational age of 27 weeks, and were primarily Caucasian (Table 1). 95 (56.9%) were male. 26 (15.6%) had a PLMI > 5 /hour, including 7 (4.2%) with a PLMI > 15 /hour. Of this group, 17 (65.4%) were female and nine (34.6%) were male. Nine participants used daily inhaled corticosteroids, four used only albuterol as-needed, four were taking methylphenidate, two were taking levothyroxine, and one patient reported taking each of the following: nasal fluticasone, lansoprazole, carbamazepine, an oral antihistamine, and dimenhydrinate. Two of the participants with an elevated PLMI had OSAS (and were therefore excluded from the group diagnosed as having PLMD) As previously reported, there was no difference in the percentage of participants with a PLMI >5 /hour between the caffeine (17.5%) and placebo (11%) groups ($p=0.19$) in the total cohort ($n=201$)³; therefore, both groups were combined for this analysis.

The prevalence of RLS in the cohort was 8.4%. Of the 14 children in the cohort with RLS, 7 (50%) were male and 7 were female. Descriptions of symptoms in the child's own words included phrases such as “tingling” and “bugs crawling” (Table 2). There was a greater prevalence of RLS in the group that had an elevated PLMI (Figure 1). Seven (26.9%) of the 26 participants with a PLMI > 5 /hr met the criteria for RLS versus 7 (5.0%) of the 141 participants with a normal PLMI ($p<0.001$).

The prevalence of PLMD in the total cohort was 7.8%. Of the 26 participants with a PLMI >5 /hr, 13 (50%) had PLMD (Figure 2), including 10 (76.9%) females and 3 (23.1%) males.

8 participants with an elevated PLMI had a clinical serum ferritin evaluation, and levels were in all cases <50 mcg/L, ranging from 11 – 38.4 mcg/L.

DISCUSSION

This is the first study to our knowledge to demonstrate an increased prevalence of RLS in children with a history of prematurity compared to the general pediatric population. The

study also showed a high prevalence of PLMD in former preterm children. Preterm children are also at risk for more sleep disruption and sleep disorders such as OSAS.^{13, 143}

The rates of elevated PLMI and RLS were substantially greater in the children in this study, who had a history of prematurity, than that reported in otherwise healthy children (Table 3). In a previous report of a cohort of 195 healthy, non-snoring children, the median PLMI was 0/hour with a range from 0 to 35.5/hour; 7.7% of those participants had a PLMI > 5/hr, as compared to 15.6% in the current study.⁴ In a large survey of school age children, RLS was found using a standardized questionnaire in 1.9% of respondents, as compared to 8.4% in the current study.² There are no good estimates for the prevalence of PLMD in a general pediatrics population. One study of 468 children referred to a sleep clinic found a PLMD prevalence of 14%,¹⁵ but it is expected that a referred clinical population would have a much higher prevalence than the general population.

Restless legs syndrome has not been well-studied in healthy children, and little is known about which pediatric groups are at increased risk for an increased prevalence of RLS or limb movements during sleep. In children, there may be overlap of RLS and related conditions, with a spectrum ranging from asymptomatic individuals with an elevated PLMI to PLMD, and RLS. There also could be a progression of symptoms over time. In a series of 18 children and young adults who developed RLS, all but two had sleep disruption that began by age 5, and the majority had symptoms even during infancy.¹⁶ Many of these patients were diagnosed with PLMD prior to having a conclusive diagnosis of RLS.

The current study found a relatively low proportion of participants with RLS who had an elevated PLMI (26.9%). Other studies have found rates of elevated PLMI in 63-74% of children with RLS.¹⁷⁻¹⁹ While the etiology of this difference is not entirely clear, one explanation may be that the current study population did not include only patients with sleep disorders, as others have done.^{17, 19} Unlike clinical studies that only perform polysomnograms in patients where there is a clinical indication, all participants in the current study had polysomnograms. Another possible explanation could be a progression of symptoms with age¹⁸. Although the cross-sectional age of the children in the current study is similar to the age of diagnosis in other pediatric RLS studies, the age of onset of symptoms often begins in the first few years of life and symptoms may change over time.^{16, 18, 19} Another possible explanation for our findings is that all children in this study were sampled using home polysomnography over only a single night. In a study that included 15 school-age children who had a PLMI >5/hour on one of two polysomnograms, 60% had a PLMI <5 on the other study²⁰. This suggests that there is significant night-to-night variability in limb movements in children, which could influence the diagnosis of PLMD.

Prematurity is increasingly common, and much remains to be discovered as preterm babies age into childhood and adulthood. Children with a history of prematurity have been shown to be at increased risk for obstructive lung disease²¹ and cognitive deficits²², among other medical conditions.²³ This population has also been shown to be at risk for disorders affecting sleep, including increased rates of OSAS^{3, 24} and differences in circadian rhythm.²⁵ Sleep-related movement disorders may be another category of disease that children with prematurity have at a higher rate than their counterparts born at term. In

addition, children with a history of prematurity may be more vulnerable to the effects of sleep disruption than those born at term. Former preterm children with poor sleep efficiency¹³ and OSAS²⁶ have a greater propensity to cognitive impairment than peers born at term.

The cause of sleep-related movement disorders in this population is not known but one plausible explanation is iron deficiency. Up to 80% of iron in neonates is accumulated during the third trimester. Premature infants are particularly vulnerable to iron deficiency; up to 85% of infants born at less than 32 weeks gestation and with a birth weight < 1500 grams have iron deficiency during infancy.²⁷ The persistence of iron deficiency in former preterm infants is unknown, but one Brazilian study found iron deficiency in 48% of former preterm infants at one year corrected age.²⁸ Iron is particularly important in the development of the fetal brain, which grows rapidly during the first two years of life. In addition to impacting areas of the brain involved in learning, memory and cognition, iron is an important co-factor in the synthesis of neurotransmitters like dopamine.²⁹ Iron supplementation and dopamine agonists have successfully treated sleep-related movement disorders. A study of 32 children (aged 10 years) with a prior diagnosis of iron deficiency during infancy revealed an increased PLMI during overnight polysomnography when compared to controls.³⁰ The current study on former premature infants revealed an increased PLMI on PSG performed at school-age. All children who were clinically evaluated had serum ferritin < 50 mcg/L, although only eight children had serum ferritin levels evaluated, which is a limitation of this study. Studies have shown that adults with RLS who have lower serum ferritin levels have more symptoms than those with higher serum ferritin levels and that supplementing with oral iron improves symptoms while increasing serum ferritin levels.^{31, 32} 50 mcg/L is often used clinically as the cutoff for treatment with iron supplementation. These findings may indicate that iron deficiency during the crucial earlier periods of brain development may produce a long-term dopamine dysfunction manifested as increased muscle activity (periodic limb movements). Because there was no difference in the number of patients with an increased PLMI between the caffeine and placebo group, neonatal caffeine administration during infancy does not seem to be a risk factor for increased limb movements during sleep.

While the strength of this study is its large cohort size, its limitations must be recognized. Analysis relied on review of a standardized questionnaire rather than personal interviews. Fairly lenient criteria were used to establish daytime disturbance using the PSQ, which could have overestimated the prevalence of PLMD. Comparisons were made with historical data rather than a control group of age-matched children born at term. Future studies prospectively assessing children with a history of prematurity for RLS and PLMD and evaluating sleep-related movement disorders in these patients as they mature into adulthood would be valuable. Studies evaluating the role of iron deficiency and therapy with iron in RLS and PLMD are also needed.

Infants born preterm are increasingly surviving into childhood and adulthood, and increasingly, comorbidities are being identified in these patients. This study has shown that these children are at increased risk for restless legs syndrome, which could have implications on behavior, cognition, and quality of life in this population. Clinicians caring for these

patients should consider evaluating for sleep-related movement disorders to allow for early identification and intervention.

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Appendix

Appendix Table

Pediatric Sleep Questionnaire items used in diagnosis of periodic limb movement disorder.

4. DOES YOUR CHILD:			
4a. Wake up feeling unrefreshed in the morning?	Y	N	DK
4b. Have a problem with sleepiness during the day?	Y	N	DK
5. HAS A TEACHER OR OTHER SUPERVISOR COMMENTED THAT YOUR CHILD APPEARS SLEEPY DURING THE DAY?	Y	N	DK
6. IS IT HARD TO WAKE YOUR CHILD UP IN THE MORNING?	Y	N	DK
10. DOES YOUR CHILD OFTEN :			
10a. Does not seem to listen when spoken to directly	Y	N	DK
10b. Has difficulty organizing tasks and activities	Y	N	DK
10c. Is easily distracted by extraneous stimuli	Y	N	DK
10d. Fidgets with hands or feet or squirms in seat	Y	N	DK
10e. Is "on the go" or often acts as if "driven by a motor"	Y	N	DK
10f. Interrupts or intrudes on others	Y	N	DK

DK, don't know

Abbreviations

CAPS	Caffeine for Apnea of Prematurity – Sleep
PLMI	Periodic limb movement index
EMG	electromyogram
ICSD3	International Classification of Sleep Disorders, 3 rd edition

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Highlights

- Children born prematurely are at increased risk for restless legs syndrome (RLS)
- This population also has high rates of elevated periodic limb movements in sleep
- Iron deficiency may play a role in RLS and periodic limb movement disorder

Figure 1. Presence of restless legs syndrome (RLS) by periodic limb movements index (PLMI) group

Nearly 27% of subjects with a PLMI >5/hour had RLS compared to 5% of those with a PLMI <5/hour. Solid black line represents the prevalence of 1.9% seen in the general pediatric population.

Figure 2. Sleep-related movement disorders in 26 subjects with a periodic limb movement index (PLMI) > 5/hour

PLMD, periodic limb movement disorder; RLS, restless legs syndrome

Table 1

Demographics

Characteristic	Study group (n=167)
Age (years)	9.2 ± 2.0
Male	95 (56.9)
Maternal race	
Asian	17 (10.2)
Black	10 (6.0)
White	139 (83.2)
Other	1 (0.6)
Gestational age, weeks	27.2 ± 1.6
PLMI (n/hour)	0.9 (0, 35.2)
PLMI > 5/hour	26 (15.6%)
PLMI > 15/hour	7 (4.2%)

PLMI, Periodic limb movement index. Data are shown as mean ± SD, median (range), or n (%).

Table 2

Child description of symptoms in 14 subjects with restless legs syndrome.

Subject	RLS description
1	Legs hurt
2	Legs hurt, ache, are sore
3	Legs hurt
4	Legs are tired
5	Tingling
6	Tingly
7	Legs ache
8	Tight, burning, pain
9	Pain
10	Ache/stiff
11	Tingling
12	Aches
13	Bugs crawling
14	Legs asleep

RLS, restless legs syndrome.

Table 3

Comparison of current study data with previously published studies.

	Current study	Marcus ⁴	Picchiatti ²	Gingras ¹⁵	p value
n	167	195	4325	468	
Age (y)	5-12	5-17	8-11	1-17	
Population type	Former preterm	Healthy children	Population-based survey	Sleep clinic referrals	
PLMI>5 (%)	15.6	7.7			0.018
RLS (%)	8.4		1.9		<0.001
PLMD (%)	7.8			14	0.037

PLMD, periodic limb movement disorder; PLMI, periodic limb movement index; RLS, restless legs syndrome.