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SCIENTIFIC INVESTIGATIONS

High prevalence of periodic limb movements of sleep in children with Down syndrome

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Study Objectives: Increased periodic limb movements of sleep (PLMS), > 5 events/h, are present in 1.2% to 7.7% of healthy children and associated with hypertension, attention deficit, and hyperactivity. This study sought to determine the prevalence of elevated PLMS in a large cohort of children with Down syndrome (DS) and their correlation with OSA and ferritin levels

Methods: Retrospective chart review of all children with DS ages 2 to 18 years in whom single baseline polysomnography (PSG) was performed at a pediatric hospital over 5 years.

Results: A total of 418 children met inclusion criteria. Three hundred fifty-six children (85%) were referred because of concerns about sleep-disordered breathing; 49 (12%) were referred for screening per American Academy of Pediatrics (AAP) guidelines; and 13 (3%) because of concerns about restless legs or periodic limb movement disorder. One hundred thirty-nine children (33.3%) had elevated PLMS; they were younger (6.3 years) than those without elevated PLMS (7.7 years). OSA was present in 176/418 (42.1%) children, including 13/49 (26.2%) asymptomatic children referred for screening PSG. Ferritin levels were only recorded in the charts of 65 of the children with elevated PLMS (46.7%); in 36 (55.4%) levels were < 50 ng/mL.

Conclusions: PLMS were increased in a substantial number of this large cohort of children with DS. Additional studies are necessary to assess utility of laboratory testing to predicting PLMS in similar, at-risk, populations. Screening PSG has value in identifying OSA in young, ostensibly asymptomatic children with DS. The prevalence of OSA increased with age in this cohort, unlike in typical children, requiring health care providers to remain vigilant for its emergence across the lifespan.

Keywords: Down syndrome, periodic limb movements of sleep, screening polysomnography, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Elevated periodic limb movements of sleep can affect attention and behavior. To date, the prevalence of this condition in children with Down syndrome has not been described, with most of the focus thus far on sleep-disordered breathing in this population.

Study Impact: In this large cohort of children with Down syndrome a much higher prevalence (33%) of increased periodic limb movements was observed relative to that described in typical children. Affecting attention and behavior, screening for low ferritin levels and treating with supplemental iron when present may yield significant benefit.

INTRODUCTION

Periodic limb movement disorder (PLMD) is a sleep disorder defined in the *International Classification of Sleep Disorders, Third Edition*, as the presence of greater than five periodic limb movements of sleep (PLMS) per hour on polysomnogram (in children) and a "clinically significant sleep disturbance or impairment…Not better explained by another current sleep… medical or neurological…or mental disorder."[1] Although the prevalence of PLMD in the general pediatric population is itself unknown, two large studies have found elevated PLMS (> 5 events/h) in 1.2%[2] and 7.7%[3] of otherwise healthy children, respectively. Increased PLMS are associated with hypertension,[4] attention deficit and hyperactivity,[5] and nocturnal awakenings and enuresis.[6] Increased PLMS are often associated with serum ferritin levels lower than 50 ng/mL and may improve after treatment with supplemental iron.[7]

Down syndrome (DS), or trisomy 21, is one of the more common genetic disorders, diagnosed in 12.6/10,000 (1/794) live births in the United States between 2006–2010.[8] Children with DS have many features distinguishing them from typical children, including some specifically related to sleep. These include a tendency toward higher baseline end-tidal carbon dioxide levels during sleep[9] and a much higher prevalence of obstructive sleep apnea (OSA), ranging from 31%[10] to 63%.[11]

A variety of genes on several chromosomes have been associated with increased PLMS.[12] Increased PLMS have also been described in children with Angelman syndrome, a genetic disorder involving chromosome 15.[13] As such, we

hypothesized that the same could be true for children with DS. If so, this would have implications with regard to screening and management, as the consequent attention deficit and hyperactivity could impair the ability of these children to participate in mainstream educational frameworks, potentially impairing their long-term development.[14]

The goals of this retrospective study were to determine:

- The prevalence of elevated PLMS in a large cohort of children and adolescents with DS referred for baseline polysomnography at a large, academic, free-standing pediatric hospital over a 5-year period
- How many of these children had undergone testing of serum ferritin levels
- How many of these children had undergone testing of hemoglobin, serum iron, and total iron binding capacity (TIBC)
- The correlation—if present—between elevated PLMS and serum ferritin levels, and to OSA
- The prevalence of OSA in this cohort and its distribution

METHODS

After receiving internal review board approval, the charts of all children with DS between the ages of 2 to 18 years who had undergone baseline polysomnography (PSG; without the use of positive airway pressure) at a large, free-standing, academic pediatric hospital from August 1, 2013 through July 31, 2018 were reviewed. All studies were clinically indicated, per symptoms or in accordance with the 2011 guidelines of the American Academy of Pediatrics (AAP) on health screening in children with DS, which recommend baseline PSG in all children with DS by the age 4 years.[15]

All studies were performed without sleep deprivation or sedation. PSG was conducted and scored using the 2012 update to the 2007 American Academy of Sleep Medicine guidelines.[16] Parameters measured included: 10-lead electroencephalogram (EEG); electrooculogram; submental electromyogram (EMG) and anterior tibial electromyography; airflow measurement with oronasal thermistor and nasal pressure transducer; thoracoabdominal movement measured via impedance plethysmography; pulse oximetry; capnography; and video and microphone recording to assess snoring, breathing patterns, and movement. PSG was performed using digital polysomnographic equipment (Natus Sleepworks, Natus Medical Incorporated, San Carlos, California), and oximetry was done using Masimo Rad-9 with SET Technology, using a 2-second window. Sleep stages, total sleep time, leg movements, and arousal index were routinely scored. Limb movements were scored when they met the following criteria: Appearing in clusters of ≥ 4 movements within 5 to 90 seconds of each other; having a duration of 0.5 to 10 seconds with a minimum amplitude of an 8-microvolt increase in EMG voltage above baseline, lasting for at least 0.5 seconds, beginning at the ≥ 8 microvolt increase above baseline and ending when the EMG voltage < 2 microvolts above baseline. Obstructive respiratory events were scored as follows. Events were scored as obstructive apneas when lasting for two breath cycles or greater; associated with > 90% reduction in airflow measured by thermistor compared to baseline for ≥ 90% of the discrete respiratory event; and were associated with ongoing respiratory effort for the duration of the decreased flow. Respiratory events were scored as obstructive hypopnea when lasting for two breath cycles or greater; associated with > 30% reduction in airflow measured by nasal pressure signal amplitude compared to baseline for ≥ 90% of the discrete respiratory event; were associated with ongoing respiratory effort for the duration of the decreased flow; and associated with arousal, awakening, or desaturation of ≥ 3%. Sleep was scored in 30-second epochs. Only epochs in which definable EEG and respiratory signals were present longer than 50% of the 30-second period were counted. A minimum of 480 scored epochs (240 minutes) were necessary for a polysomnogram to be included in this study. Studies with less than 4 hours of total sleep time were excluded.

Data collected were: sex; age at time of study; periodic limb movement index (the number of periodic limb movements per hour of sleep, PLMI); obstructive apnea-hypopnea index (number of obstructive apneas and hypopneas per hour of sleep, OAHI); whether or not ferritin, hemoglobin, serum iron, or total iron binding capacity (TIBC) had been tested within a 6-month period, either before or after PSG; the ferritin, hemoglobin, serum iron levels, and TIBC, if available. Sleep parameters including total sleep time (TST), sleep efficiency (SE), percentage of time spent in each sleep stage (N1, N2, N3, R), and arousal index (AI) were collected.

Polysomnograms in children younger than 2 years were excluded from the analysis, as leg movements are not routinely scored in this age group in our sleep center due to their extremely high prevalence and questionable significance.[17] Likewise, we elected to include in the analysis only those children who had undergone a single study, due to the inability to control for treatments given between one study and another (many of the studies were ordered by outside physicians, and these data were unavailable for review).

Statistical analysis

Methods

Summary statistics include frequency and percentages for categorical data and quantiles and interquartile range for continuous data. Because of the nonnormality of the continuous variables (age, PLMI, OAHI, and ferritin), nonparametric tests were used to compare groups. Comparisons of categorical and continuous data between groups were performed using the Fisher exact test, Kruskal-Wallis test, and Wilcoxon rank-sum test. Association of continuous variables was evaluated using the Spearman correlation. Values of $P \leq .05$ were considered statistically significant and values of $P \leq .10$ were considered marginally significant. Statistical analysis was performed using R version 3.5.2 (2018-12-20).

Results

During the review period, 418 children met the inclusion criteria, of whom 48.8% were female. The median age at the time of study was 6 years (average: 7.27; range 2–17). Of the

418 children studied, 356 (85%) were referred because of concerns about sleep-disordered breathing. Forty-nine of 418 children studied (12%) were asymptomatic and referred for screening based on the AAP guidelines, and 13/418 o the children (3%) were studied because of concerns about either restless legs or PLMD (**Table 1**).

The baseline PSG data are described in the next paragraphs and are summarized in **Table 2**. The average TST was 421.7 minutes (standard deviation [SD] 84.7; range 40.3–549.5 minutes). The average SE was 83% (SD 13.2; range 12–99.7). The average percentage of time spent in stage N1 was 8% (SD 6.6; range 0–60.4%). The average percentage of time spent in stage N2 was 37.8% (SD 13.9; range 0–100%). The average percentage of time spent in stage N3 was 34.9% (SD 14; range 0–85.5%). The average percentage of time spent in stage R was 19.3% (SD 8.7; range 0–43.1%). The average arousal index was 12 events/h (SD 1.6; range 0–56).

Of the 418 children studied, 176 children (42.1%) had an OAHI > 1 events/h: 112 (26.8%) had an OAHI between 1–5 events/h, and 64 (15.3%) had an OAHI > 5 events/h (**Table 2**). One hundred twenty-one children (50%) with an OAHI < 1 events/h were female, as were 53 (47.3%) of those with an OAHI of 1–5 events/h and 30 (46.9%) with an OAHI > 5 events/h (Fisher exact test $P = .85$). The median age was significantly different (6.3 versus 7.7 versus 10.3 years) among children with an OAHI < 1, 1–5, and > 5 events/h, respectively (Kruskal-Wallis test $P < .001$, **Table 3**). Thirteen of the 49 asymptomatic children referred for screening (26.2%) had some degree of OSA, with 9 (18.4%) having an OAHI of 1 to ≤5 events/h, and 4 (8.2%) having an OAHI > 5 events/h.

One hundred thirty-nine of the 418 children studied (33.3%) had a PLMI > 5 events/h. The PLMI was > 5 events/h in 50.4% of males versus 49.6% of females (Fisher exact test $P = .84$). The median age was significantly higher (7.8 versus 6.1 years) for those with a PLMI > 5 events/h versus < 5 events/h (Wilcoxon rank-sum test $P < .001$), and children older than 10 years had a significantly lower PLMI (3.5 events/h) compared with children ages 6 to 9 years (6.3 events/h) and with children ages 2–5 (6.35 events/h) ($P < .001$). These data are summarized in **Table 3**. The PLMI was > 5 events/h in 84 children (34.7%) with an OAHI < 1 events/h, versus 41 children (36.6%) with an OAHI between 1 to 5 events/h, versus 14 children (21.9%) with an OAHI > 5 events/h ($P = .01$).

Of the 139 children with a PLMI > 5 events/h, 65 (46.7%) had had their plasma ferritin levels tested during the 6 months prior to or following PSG. Of the 13 children referred for PSG due to concerns about restless legs or PLMD, 7 had a PLMI > 5 events/h (54%). Of these, 5 children (71%) had ferritin levels tested, with 3/5 (60%) recorded below 50 ng/mL. Of the 65 patients with elevated PLMS who had had their ferritin levels checked, the values were below 50 ng/mL in 36 (55.4%). The average ferritin value was 52.1 ng/mL. Of the 139 children with PLMI > 5 events/h, 77 had hemoglobin values recorded (average 12.9 g/dL, within normal limits, SD 1.1); 8 had TIBC values (average 331 mcg/dL, within normal limits: SD 91), and

Table 1—Baseline demographics (n = 418).

Male	214 (51.2%)
Female	204 (48.8%)
Age (years)	
Average	7.27
Median	6
Range	2–17
Reason for PSG	
SDB	356 (85%)
Screening	49 (12%)
RLS/PLMS	13 (3%)

PLMS = periodic limb movement during sleep, PSG = polysomnography, RLS = restless legs syndrome, SDB = sleep-disordered breathing.

Table 2—Polysomnographic data.

PLMI	**Average**	**Median**	**Range**	**0 to < 5 events/h**	**> 5 events/h**	
All patients (n = 418)	5.45	2.45	0–48.2	279 (66.7%)	139 (33.3%)	
Screening (n = 49)	6.45	3.1	0–32.7	29 (59.2%)	20 (40.8%)	
OAHI	**Average**	**Median**	**Range**	**< 1 events/h**	**1 to ≤ 5 events/h**	**> 5 events/h**
All patients (n = 418)	3.6	0.6	0–99	242 (57.9%)	112 (26.8%)	64 (15.3%)
Screening (n = 49)	1.86	0.4	0–22	36 (73.4%)	9 (18.4%)	4 (8.2%)
Other Sleep Parameters	**Average**	**SD**	**Range**			
TST (minutes)	421.7	84.7	40.3–549.5			
SE (%)	83	13.2	12–99.7			
Stage N1 sleep (%)	8	6.6	0–60.4			
Stage N2 sleep (%)	37.8	14	0–100			
Stage N3 sleep (%)	34.9	14	0–85.3			
Stage R sleep (%)	19.3	8.7	0–43.1			
AI	12	1.6	0–56			

Average, median and range values for PLMI and OAHI given in events/h. AI = arousal index, OAHI = obstructive apnea-hypopnea index, PLMI = periodic limb movement index, SD = standard deviation, SE = sleep efficiency, TST = total sleep time.

Table 3—Comparison of age and sex composition as functions of obstructive apnea-hypopnea index and periodic limb movement index.

OAHI	< 1 events/h (n = 233)	1 to ≤ 5 events/h (n = 123)	> 5 events/h (n = 62)	Statistical Test and Significance
Mean age (years)	6.27	7.7	10.3	Kruskal Wallis $P < .001$
Male sex (%)	50	52.7	53.1	Fisher exact $P = .85$
PLMI	**< 5 events/h (n = 282)**	**> 5 events/h (n = 136)**		**Statistical Test and Significance**
Mean age (years)	6.1	7.8		Wilcoxon rank sum $P < .001$
Male sex (%)	51.6	50.4		Fisher exact $P = .84$

OAHI = obstructive apnea-hypopnea index, PLMI = periodic limb movement index.

Table 4—Laboratory data in 139 patients with periodic limb movement index > 5 events/h.

	Number Tested	Average	SD	Median	Range
Ferritin (ng/dL)	50 (36%)	52.1 (WNL)	33	45.3	17.1–154.6
Hemoglobin (g/dL)	79 (57%)	12.9 (WNL)	1.1	12.9	9–15.4
Iron (mcg/dL)	7 (5%)	71 (WNL)	41	67	43–365
TIBC (mcg/dL)	8 (6%)	331 (WNL)	91	370.5	129–389

SD = standard deviation, TIBC = total iron binding capacity, WNL = within normal limits.

7 had iron values (average 71 mcg/dL, within normal limits; SD 41) tested for (**Table 4**). The correlation between serum ferritin levels and PLMI was low (Spearman $r_s = .03$, $P = .83$, 95% confidence interval: −0.2913, 0.3538).

DISCUSSION

The prevalence of elevated PLMS in this cohort of children with DS was substantially higher (33.2%) than that described in the general pediatric population, a finding not previously reported. As noted, most of these children were referred either due to concerns about sleep-disordered breathing (85%) or per the screening recommendations of the AAP (12%); only 3% were referred because of concerns about restless legs or periodic movements of sleep. As such, the elevated PLMS in most of these children was an incidental finding.

Although most pediatric health care providers are aware of the importance of screening for and treating sleep-disordered breathing in children with DS, the high prevalence of elevated PLMS in this cohort suggests that this, too, may need to be screened for and treated. The AAP recommends obtaining a baseline polysomnogram in all children with DS by the age of 4 years,[15] primarily to screen for sleep-disordered breathing. These findings indicate the importance of attention to the limb movement data as well.

Screening for elevated PLMS can be challenging. Parental symptom reporting has not proven effective in identifying children with increased PLMS,[18] perhaps because of the known night-to-night variability in their appearance.[19] The very weak positive correlation identified in this study between ferritin levels and PLMS is similar to what has been reported in other studies.[20,21] It is important, however, to consider the wide window in which this was tested (up to 6 months before and 6 months after the study). This may well have led to some children being treated prior to having their ferritin levels tested. Medication and treatment data for these children were mostly unavailable for review, certainly those from the primary care setting, and so this finding needs to be interpreted with caution. Similar limitations exist with the data about hemoglobin, TIBC, and serum iron levels in this study cohort. With that said, there is good evidence that long-term iron supplementation in children suspected to have PLMD results in better sleep quality and reduction of the PLMI,[7] and can bring about cognitive improvement in children with low baseline serum ferritin levels.[22] It may be that a future study analyzing ferritin, iron, TIBC, and hemoglobin levels obtained in close proximity to the PSG testing itself and controlled for iron supplementation will be able to provide a better indication about their utility in screening for elevated PLMS, especially in higher risk children such as those with DS.

Although we do not routinely score limb movements in children younger than 2 years in our laboratory, for the reasons described earlier, this approach may need to be revisited. The reasons for considering this include the relatively higher prevalence of iron-deficiency anemia in this age group; the described correlation between PLMS and low ferritin levels; and the adverse neuropsychological outcomes associated with increased PLMS in children.

The finding that most children in this cohort with increased PLMS (53.2%) had not undergone testing of ferritin levels in the 6 months prior to or following their sleep studies was unexpected. The referrals for the sleep studies came from a variety of

programs within and outside the hospital, and most were ordered with the stated objective of identifying sleep-disordered breathing. However, the lack of follow-up to this finding can and should certainly be improved upon, and we are in the process of launching a hospital-wide quality-improvement project to address this very issue.

There was no significant correlation found between the OAHI and PLMI, Indeed, the percentage of children with an elevated OAHI, whether > 1 events/h or > 5 events/h, with a concurrently elevated PLMI was actually less than that of the cohort as a whole. This is in contrast to findings by Chervin et al of increased PLMS in children scheduled for adenotonsillectomy, most with evidence of OSA on concomitant polysomnography.[23] This may be due to a number of factors, including the triggering of limb movements by obstructive hypoventilation or respiratory effort-related arousals, neither of which were included in the current analysis.

The high prevalence of OSA in this cohort is consistent with that previously reported in children with DS. We found that the prevalence of OSA in this cohort increased as they grew older. This contrasts with what Bixler et al[24] and others have reported on the natural history of OSA in the general pediatric population. This may be a finding specific to children with DS, but may also be because of the inclusion of younger, asymptomatic children referred for screening in accordance with the AAP guidelines.[15] It may also have to do with the emergence of hypothyroidism over time that may have worsened sleep-disordered breathing, and which was uncontrolled for in this study. In any case, this finding supports the need for constant vigilance for the emergence of OSA across the lifespan of people with DS.

Finally, the high prevalence of OSA in 26.2% of the 49 asymptomatic children referred for screening PSG in accordance with the AAP recommendations was especially noteworthy. It demonstrates the importance of this screening, and of an even greater awareness of the degree to which asymptomatic children with DS may experience sleep-disordered breathing. Physicians caring for young children with DS should be aware that OSA may be present yet undetected through their conventional screening process for sleep-disordered breathing, and that they may need to focus more on this finding.

Summary

Increased PLMS were present in a large cohort of children with DS referred for PSG at a much higher prevalence than described in the typical population, mostly as an incidental finding. Because of this, it is important to consider PLMD as an important cause of sleep disturbance in children with DS and as having a potentially detrimental effect on daytime function, behavior, and cognition. Additional studies tightly correlating ferritin, hemoglobin, serum iron levels, and TIBC with polysomnographic data about PLMS may provide additional information about their use in screening for this disorder in children at higher risk.

The finding that 13/49 asymptomatic children with DS (26.2%) referred for screening PSG in accordance with the AAP recommendations had mild and moderate OSA, confirms the importance of this screening in children with DS.

ABBREVIATIONS

AAP, American Academy of Pediatrics
AI, arousal index
DS, Down syndrome
EEG, electroencephalogram
EMG, electromyogram
OAHI, obstructive apnea-hypopnea index
OSA, obstructive sleep apnea
PLMD, periodic limb movement disorder
PLMI, periodic limb movement index
PLMS, periodic limb movements of sleep
SE, sleep efficiency
TIBC, total iron binding capacity
TST, total sleep time

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DISCLOSURE STATEMENT

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The authors report no conflicts of interest.