Periodic Limb Movements during Sleep in Children with Narcolepsy

Supriya K. Jambhekar, M.D.¹; Gulnur Com, M.D.¹; Elizabeth Jones, R.N., B.S.N.²; Rithea Jackson, B.S.²; Maria Melguizo Castro, M.S.¹; Frances Knight²; John L. Carroll, M.D.¹; May L. Griebel, M.D.¹

¹University of Arkansas for Medical Sciences and Arkansas Children's Hospital Little Rock, AR;

²Arkansas Children's Hospital, Little Rock, AR

Study Objectives: In adults with narcolepsy, periodic limb movements of sleep (PLMS) occur more frequently than in control population, and presence of increased PLMS is associated with greater sleep disruption and shorter mean sleep latency. This study was performed to determine whether PLMS are common in children with narcolepsy, and whether the presence of PLMS is associated with greater sleep disruption.

Design: Demographic and polysomnographic information were collected from consecutive patients diagnosed with narcolepsy identified retrospectively by diagnosis-based search. Descriptive data were compiled, and sleep characteristics of children with and without PLMS were compared.

Setting: Sleep disorders center in a children's hospital.

Patients: 44 patients, 6-19 years old (mean 13 years, SD 3.57), were identified. Twenty-eight were African American.

Interventions: None.

Measurements and Results: Four patients had a PLMS in-

dex (PLMI) $\geq 5/h$ (considered abnormal in literature). Sixteen (36%) had "any PLMS" (PLMI $> 0/h$). The mean PLMI was 1.3/h (SD 2.5). Sleep was significantly more disrupted, and the mean sleep latency was shorter in patients with "any PLMS" as compared to those with no PLMS. There was no correlation between the PLMI and other diagnostic criteria for narcolepsy. "Any PLMS" were present equally in children of African American and Caucasian heritage, 35.7% vs. 37.5%.

Conclusions: As in adults, children with PLMS and narcolepsy have more sleep disruption and shorter mean sleep latencies than those with narcolepsy but without PLMS. Our findings also suggest that the use of adult criteria for diagnosis of "significant" PLMS in children may not be sufficiently sensitive.

Keywords: Narcolepsy, children, periodic leg movements

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Periodic limb movements during sleep were first described in adults in the 1980s, however; their occurrence in children and adolescents has only been recently appreciated.¹ The exact prevalence of these movements, consisting of repetitive small flexions of the upper and/or lower extremities, in the general pediatric population is unclear. Reported prevalence rates of PLMS at a frequency $> 5/h$ vary between 1.2% to 10% of children not referred specifically for PLMS or restless legs syndrome (RLS).^{2,3} Although the prevalence of PLMS has been reported to be increased in children with other medical comorbidities,⁴ the prevalence in children with narcolepsy is largely unknown. A study of 8 children with narcolepsy has shown occurrence of PLMS in 63% of the patients with a mean PLMS index of 49/h.⁵

In adults, increased PLMS have been shown to be more common in patients with narcolepsy than controls without narcolepsy; the presence of increased PLMS has been shown to be associated with measures of disruption of REM sleep and daytime functioning, leading to a hypothesis that PLMS are an intrinsic feature of narcolepsy.⁶⁻⁹ In addition, adult narcolepsy patients with PLMS have been shown to have more impairment of daytime functioning than those without PLMS, in that those with PLMS have a shorter mean sleep latency than those without, suggesting greater sleepiness. Furthermore, in

BRIEF SUMMARY

Current Knowledge/Study Rationale: In adults, PLMS are known to occur more frequently in patients with narcolepsy and are shown to be associated with greater sleep disruption and shorter sleep latency. This study was performed to determine if PLMS occur commonly in children with narcolepsy and whether presence of PLMS is associated with greater sleep disruption and worse daytime sleepiness.

Study Impact: This study shows that presence of PLMS in children with narcolepsy is associated with greater sleep disruption and shorter sleep latency, suggesting the need to evaluate for the presence of "any PLMS" in children with narcolepsy. This study also raises concern about the applicability of the adult threshold for normal PLMS ($<5/h$) in the pediatric population.

adult narcolepsy patients with PLMS, a higher PLMS index has been shown to be associated with a higher periodic limb movement when awake index, suggesting greater disruption of daytime functioning.⁹

Because of the importance of potential adverse effects of worsened daytime functioning on school and social achievement in children with narcolepsy, our study was undertaken to determine whether PLMS are more prevalent in children with narcolepsy and whether PLMS in children with narcolepsy are associated with more disrupted sleep and/or more daytime somnolence.

Our hypotheses were:

1. Children with narcolepsy and PLMS have more disturbed nighttime sleep than those with narcolepsy but no PLMS.
2. Children with narcolepsy and PLMS have more daytime sleepiness than those without PLMS.
3. Children with narcolepsy and PLMS have greater morbidity of narcolepsy (i.e. greater occurrence of sleep paralysis, cataplexy, and hallucinations than those without PLMS).
4. Children with narcolepsy and PLMS have greater abnormalities of REM sleep.

METHODS

Study Sample

With the local institutional review board approval, a diagnosis-based search of medical records was undertaken. Polysomnogram (PSG) and multiple sleep latency test (MSLT) reports of children aged 6-19 years (mean age 13.4 years, SD 3.8) who were diagnosed with narcolepsy in the last 10 years were reviewed. Children with a concomitant diagnosis of epilepsy on anticonvulsant medications were excluded from the study due to the confounding role of the potential sedative effect of these medications. All subjects had undergone ≥ 1 night of polysomnography followed by a MSLT on the next day. The MSLT included ≥ 4 naps of 20 min each. The fifth nap was performed if only one of the first 4 naps showed REM sleep. It was not performed if REM sleep did not occur on any of the first 4 naps, or if REM sleep occurred on 2 of the first 4 naps. The excitement of anticipating going home has been reported to confound results of last (fifth) nap.¹⁰ Eleven patients (7 without PLMS, 4 with PLMS) had been on alerting medications (6 on dextroamphetamine, 3 on methylphenidate, 1 on atomoxetine, and 2 on modafinil) prior to the study. These medications had been discontinued (dextroamphetamine and methylphenidate ≥ 72 h, atomoxetine for 5 days, and modafinil for 2 weeks—all ≥ 5 half-lives of the drug) before testing. All children met standard diagnostic criteria for narcolepsy: sleep onset latencies less than 2 standard deviations below the mean for their age/Tanner stage¹¹ and occurrence of REM sleep within 15 min of sleep onset on ≥ 2 naps. Other causes for excessive sleepiness were ruled out by careful review of sleep hygiene and medical histories, and with testing of thyroid function. Narcolepsy DNA test (Kimball Genetics) was available on 25 (7 with and 18 without PLMS) patients (16 positive- 5 with PLMS). Patient DNA was assayed for HLA alleles DQB1*0602 and DQA1*0102 by sequence-specific PCR analysis followed by polyacrylamide gel electrophoresis. Two patients who met the diagnostic criteria of narcolepsy had Chiari I malformations and had undergone microsurgical decompression surgery. One of these patients also had a positive DNA test for narcolepsy-associated alleles HLA DQB1 0602 and HLA DQA1 0201, and the other had cataplexy, which is considered pathognomonic of narcolepsy, in addition to other criteria for narcolepsy. Other co-morbidities included Asperger syndrome, gastroesophageal reflux, post-streptococcal movement disorder, obesity, sleep disordered breathing, and hypertension. Eight patients had a total AHI greater than 1/hr (1.1 to 6.5), (obstructive apnea-hypopnea index 1.1 to 4.2/hr).

Polysomnography

Data were obtained utilizing the Sandman Elite 9.1 digital sleep system, Embla Systems, Denver, CO. The following variables were recorded: electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1), right and left electroculograms, submental electromyogram, tibial +/- upper extremity electromyograms, electrocardiogram, abdominal and chest respiratory effort (Sensormedics inductance plethysmography), end-tidal CO₂ (BCI capnograph), airflow (Dymedix thermistor), and SpO₂ (Nellcor pulse oximetry). Expanded 8-channel EEG monitoring and nasal pressure monitoring (ProTech PTAf2) were added in studies performed after publication of the new AASM criteria.¹² Continuous time-linked sound/visual recordings were also obtained using audio and infrared technology. All PSGs were rescored for PLMS by a single board-certified PSG technologist, blinded to the results of the MSLT, using the criteria in the 2007 AASM manual.¹²

Data Collection and Statistics

Forty-four children and adolescents 6 to 19 years of age with narcolepsy diagnosed between January 2000 and May 2009 without a concomitant diagnosis of seizure disorder or any other medical condition responsible for excessive daytime sleepiness were included. Demographic data, clinical signs and symptoms of narcolepsy, sleep characteristics from the PSG reports, and multiple sleep latency scores were collected and tabulated. Four children had PLMI > 5 /h. Due to the small number of children with PLMI > 5 /h, we compared children with “any PLMS” to those with no PLMS in order to assess the impact of “any PLMS” on daytime alertness and sleep study variables in our population.

Statistical Methods

Statistical analyses were performed using the Design, Hmisc and foreign libraries available on the free open-source statistical software “R version 2.11.1 (The R Foundation for Statistical Computing)”. For each one of the continuous variables (sleep efficiency, spontaneous arousal index, stage REM percent, REM latency minus awake and number of REM periods), a Wilcoxon rank test was used to compare patients with and without “any PLMS.” At the 0.05 level, the significant variables were spontaneous arousal index (higher in children with PLMS) and mean sleep latency (lower in children with PLMS). For the categorical variables (sleep paralysis, cataplexy, or hallucinations), χ^2 test was used to compare differences between the proportions in every group.

Six patients had OSA according to the current definition for OSA in children (AHI > 1). Our study did not have enough patients to perform subgroup analysis and compare patients with AHI > 1 per hour with those who had AHI < 1 per hour.

RESULTS

Demographic data are shown in **Table 1**. The predominant patient race was African American (63.6%, 28 children). Twenty-seven (61%) of the participants were male. Four of the 44 patients (9.1%) had PLMI > 5 /h; 16 (36%) had “any PLMS.” The mean PLMI was 1.3/h (SD 2.5) (range 0.6-18.2). Six of the 16 (37.5%) children with any PLMS were Caucasian, and 10

(62.5%) were African American. Ten of the 28 (35.7%) African American children with narcolepsy and 6/16 (37.5%) of Caucasian children with narcolepsy had “any PLMS,” i.e. PLMI > 0/h.

Notably, those children with “any PLMS” (n = 16) had more disturbed sleep (i.e., increased arousal index) than children with no PLMS. They also had shorter mean sleep latencies during the day (**Table 2**). The difference was most striking in the second nap, i.e., during that period of the day when diurnal wakefulness is maximal. There were no differences in other sleep study variables between the 2 groups. The presence of PLMS did not correlate with the occurrence of cataplexy, sleep paralysis, or sleep related hallucinations (**Table 3**). The frequency of PLMS (PLMI) did not correlate with the mean sleep latency.

DISCUSSION

PLMS, first described in children by Pichietti and Walters¹³ have been reported with a variable prevalence in this population. Genetic factors, altered iron metabolism, and dopaminergic dysfunction have been thought to be involved in the pathophysiology of PLMS. OSA, autism, ADHD, William syndrome, Tourette syndrome, narcolepsy, and medications such as selective serotonin reuptake inhibitors, lithium, and tricyclic antidepressants are thought to be risk factors for PLMS.¹⁴ PLMS have been suggested to be an intrinsic feature of narcolepsy—the two probably related by the commonality in dopaminergic pathway dysfunction in both conditions.⁹

The main new finding of this study is the effect of PLMS on nighttime sleep and daytime sleepiness in children with narcolepsy. These findings may suggest that PLMS in children with narcolepsy lead to worsening of sleep quality and daytime sleepiness. However, it may also suggest that PLMS are a feature of more severe narcolepsy, as has been suggested for adults.⁹

Based on the commonly used criterion of PLMI $\geq$ 5/h, our group of children did not have a higher prevalence of PLMS as compared to most of the previously reported prevalence rates in control population or children with other co-morbid conditions. The prevalence of PLMS at a rate $\geq$ 5/h (9%) in our sample compares to the reported prevalence of 12% of children 4 to 7 years of age in a community-based sample,¹⁵ a prevalence of 5.6% in a sample of 591 children who underwent PSG for various reasons,² and a 10% prevalence seen in 100 consecutive children undergoing PSG for various reasons.³ It is higher than a prevalence of 1.2% of children (7 of 591 children) referred with a predisposition to sleep disorders but who had no other disorder identifiable except PLMS.⁶ It is actually lower than the prevalence of PLMS reported in children with attention deficit hyperactivity disorder (ADHD) and obstructive sleep disordered breathing (OSDB).^{3,15-17} Studies have reported PLMS (PLMI > 5/h) in 26% of a sample of children with OSDB¹² and as high as 64% of children with ADHD.¹⁷

A large proportion, i.e., 36% (CI 22.15% to 50.57%) of the patients in our study had “any PLMS” (PLMI > 0/h); however, we do not have prevalence data available for a control population, as previous studies have looked for PLMI $\geq$ 5/h as the definition of the group of patients with PLMS. The mean PLMI in our group of patients was 1.3/h (SD 2.5/h), compared with 1.3/h (SD 2.2/h) reported in a group of 70 normal children 2-9 years of age.¹⁸ It is lower than that quoted by a study with a

Table 1—Demographic data

	N	Range	Median (SD)
Age (years)	44	6-19	13.41 (3.8)
Weight (kg)	39	20-151	67.2 (31.3)
Height (cm)	39	113-190	157.1 (19.3)
BMI (kg/m ²)	39	13.9-45.1	25.4 (7.5)

N, number; kg, kilogram; m, meter; cm, centimeter.

Table 2—Comparison of demographic and sleep descriptors in children with and without PLMS

	NO PLMS (n = 28)	ANY PLMS (n = 16)	p-value
Characteristics			
Age, years, (SD)	13.3 (3.9)	14.1 (4.0)	NS
Sex (male %)	71	44	0.070
African American (%)	61	69	0.594
BMI	26.2 (8.2)	24.3 (6.4)	NS
SDB			
AHI	0.7 (1.3)	0.5 (1)	NS
Nadir SpO ₂	93.2 (2.2)	94.3 (2.2)	NS
Sleep			
TST (min)	398 (50.1)	384 (54.7)	NS
Sleep efficiency (%)	83.4 (8.7)	82.3 (9.4)	NS
Arousal Index			
Spontaneous arousal	6.9 (5.9)	11.2 (5.8)	0.003
RERA	2.1 (6.3)	0.6 (0.8)	0.435
EDS			
Mean sleep latency (min)	4.7 (3.8)	2.3 (1.5)	0.033
Sleep latency nap 1 (min)	3.9 (4.2)	2.0 (1.3)	0.089
Sleep latency nap 2 (min)	5.5 (5.7)	1.8 (1.3)	0.009
Sleep latency nap 3 (min)	5.0 (4.8)	2.4 (2.3)	0.045
Sleep latency nap 4 (min)	4.5 (4.8)	3 (3.1)	NS

p values are based on a Wilcoxon Rank test for continuous variables and a χ^2 test for categorical variables. BMI, body mass index; AHI, apnea hypopnea index; TST, total sleep time. Numbers in parentheses indicate standard deviation.

Table 3—Clinical characteristics: comparison of children with PLMS and without PLMS

	Total	PLMS	No PLMS
Cataplexy	17	6	11
Hallucinations	10	4	6
Sleep paralysis	10	2	7

small number of normal subjects that reports the mean PLMI of 4.8/h in children 5-9 years of age (n = 7) and 3.3/h in the 10-19 year olds (n = 9).¹⁹

The most important finding in this study is that those children with any concomitant PLMS had more sleep disturbance than those with narcolepsy and no PLMS, even though most of them had a PLMI < 5/hour. This finding is in keeping with the results of Dauvilliers et al., who noted that adult patients with narcolepsy and PLMS had more sleep disturbance, especially

related to REM sleep.⁹ We did not find a significant difference in specific nighttime REM sleep characteristics between the 2 groups. Despite the proclivity of patients with narcolepsy to have increased sleepiness and sleep attacks during the day, the nighttime sleep of narcolepsy patients has been recognized as abnormal, with increased arousals and stage shifts.²⁰ Any factor that further deteriorates sleep quality, such as PLMS, would thus seem inherently undesirable.

Children with narcolepsy and PLMS had shorter sleep onset latencies during daytime naps than did children who had narcolepsy but no PLMS. This again agrees with the findings of Dauvilliers et al. in their adult sample.⁹ In our study sample, the difference in sleep latency was most striking in nap 2 (**Table 2**), which usually occurs at 10:00, the period that is associated with maximum diurnal wakefulness. This occurrence may have an effect on daytime functioning, especially performance in school.

There was no correlation between the severity of PLMS (PLMI) and the measure of sleepiness (mean sleep latency). However, this may have been due to the small study sample.

We found an equal prevalence of “any PLMS” among the races. The possible differential occurrence of PLMS in otherwise normal children of different races or ethnicities is unclear. A large study looking at ethnic differences found that Caucasian children were more likely than African Americans (16.5% vs. 7%) to have PLMS (PLMI > 5), a difference that was independent of AHI, BMI, or SES.²¹ Our results suggest that African American children with narcolepsy may be more prone to have PLMS than African American children without narcolepsy, and that PLMS may occur with narcolepsy more often in African American children than in Caucasian children. However, as this was a retrospective study not designed to determine PLMS prevalence, this finding remains suggestive.

The majority (64%) of our study sample was African American. This is disproportionate to the population distribution of the state, with only 15.6% of the population being of African American descent, which may suggest a higher prevalence of narcolepsy among African Americans in the state of Arkansas.¹⁰ This has been reported in only two prior adult studies, one in 1945 using military recruits,²² and the other published in 2009, an estimated prevalence study in King County, Washington.²³ The literature has otherwise suggested no significant difference in prevalence between Caucasians and African Americans.²⁴

Our study also raises concern about the applicability of the adult threshold for normal PLMS (< 5) in the pediatric population. In our study, patients with “any PLMS” had poorer sleep quality and increased daytime sleepiness compared to those patients with narcolepsy and no PLMS in spite of a PLMI < 5/h in the majority of the group with PLMS (only 4 children had an index > 5). This suggests that PLMS of lower frequency may be disturbing to nighttime sleep. This finding may be unique to children with narcolepsy who are by definition predisposed to excessive daytime sleepiness, but suggests the need to assess all children with “any PLMS” for evidence of sleep disturbance and effect on daytime functioning.

We did not find a correlation between the occurrence of PLMS and presence of other manifestations of narcolepsy, i.e., cataplexy, hallucinations, or sleep paralysis, which may suggest that cataplexy, hallucinations, and sleep paralysis are indepen-

dent manifestations of narcolepsy not related to degree of sleep disturbance or the daytime sleepiness.

Study Limitations

The main limitation of our study was the small number of patients. We found only 4 patients with PLMI $\geq$ 5/h, suggesting that prevalence of PLMS with a PLMI $\geq$ 5/h is equal to or lesser than that reported in general population. A larger number of subjects would have enabled subgroup analyses, separating out patients with AHI greater than 1/h, to detect the role of OSDB in the group of patients with narcolepsy. However, in spite of this small number of study subjects, we found a correlation between the presence of PLMS and mean sleep latency, suggesting a strong correlation between the two. Narcolepsy is a relatively rare diagnosis in the pediatric age group, and multicenter trials would be necessary to make more certain conclusions.

Several of the children in this group had other disorders including OSDB, which have been described with PLMS. Our study was not powered sufficiently to study the effect of OSDB (defined as AHI > 1/h in the pediatric population) on the PLMS in narcolepsy. However, we do not think that OSDB contributed to the effect of PLMS on sleepiness in our sample, as all except one of the patients with AHI > 1/h had no PLMS, and the one with PLMS was 19 years old with an AHI of 2.2. This AHI would not have been considered diagnostic of OSA in the adult population. If anything, the inclusion of these patients may have diluted the effect of PLMS on daytime sleepiness.

Another important limitation of this study is that it was retrospective in nature; hence all data (e.g., details about familial restless legs syndrome, information about presence/absence of ADHD after specific testing) were not available for all patients; we did not have all tests performed (e.g., genetic testing, MRI, ferritin levels) on all patients; we may also have been unable to exclude cases of secondary narcolepsy; and we did not have a control group. The lack of normative controls for prevalence of “any PLMS” in the general population is also limiting, as we cannot confidently infer how the prevalence of “any PLMS” in children with narcolepsy compares to the prevalence in the general pediatric population. However, based on the similar mean PLMI between our study and a study on a normal pediatric sample,¹⁸ we may infer that children with narcolepsy do not have higher incidence of “any PLMS” than do control children. Nevertheless, the presence of PLMS in children with narcolepsy appears to be associated with increased daytime somnolence.

Data in prior studies may not be comparable due to differences in the scoring criteria. The new AASM scoring rules require that PLMS be scored even if preceded by an arousal if less than 0.5 sec of time lapses between the end of one event and the beginning of another, regardless of which occurs first.¹² A PLMS arousal is defined as an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that last at least 3 seconds, with at least 10 seconds of stable sleep preceding the change. Previously the rules required that if the arousal preceded the leg movement, then the leg movement not be independently scored. This may have led to underscoring of leg movements in the past as compared to recent studies. However, the bias due to this change would have led to an overestimation of PLMS, which was not

seen; our sample actually had fewer patients with PLMI $\geq 5/h$ as compared to previously reported data.

The variables monitored during the PSGs were not uniform for all study subjects. After the introduction of the new AASM criteria, expanded 8-channel EEG monitoring and nasal pressure monitoring (ProTech PTAF2) were added to the PSG. However, we do not believe this affected the results of this study, as it did not affect the scoring of the PLMS or the MSLT.

CONCLUSIONS

Our study suggests the need for careful analysis of PLMS in children with narcolepsy. PLMS may contribute to worsening of nighttime sleep and daytime sleepiness, or the presence of PLMS may suggest greater severity of the underlying condition. However, this study is limited due to its retrospective nature and small sample size. Larger, possibly multicenter studies are needed to substantiate these suggestions. Prospective controlled therapeutic trials assessing the effect of treatment of PLMS on extent of daytime sleepiness may be necessary to appropriately define the causative role of PLMS on excessive daytime sleepiness in patients with narcolepsy and the need to treat PLMS in children with narcolepsy.

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Address correspondence to: Supriya K. Jambhekar, M.D., Associate Professor, Pulmonary Medicine, University of Arkansas for Medical Sciences, Director, Sleep Disorders Center, Arkansas Children's Hospital, 1 Children's Way, # 512-17, Little Rock, AR 72202; Tel: 501-364-1006; Fax: 501-364-3930; E-mail: jambhekar-supriya@uams.edu

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