Sleep Medicine 63 (2019) 57–63

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Clinical presentation, diagnosis and polysomnographic findings in children with migraine referred to sleep clinics☆,☆☆

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ARTICLE INFO

Article history:
Received 9 December 2018
Received in revised form
24 April 2019
Accepted 29 April 2019
Available online 8 June 2019

Keywords:
Migraine
Children
Obstructive sleep apnea
Insomnia
Polysomnography
Sleep architecture

ABSTRACT

Objective: An association between migraine and sleep disturbances in children was reported, yet limited clinical data exist. The current study addresses the clinical presentation, polysomnographic (PSG) characteristics, and comorbid sleep diagnoses of children with migraine referred to the sleep clinic.
Patients: A retrospective review was performed of headache center patients evaluated by the sleep center between 2007 and 2017. Children ≤18 years old, diagnosed with migraine headache, and who had PSG within one year of evaluation in the headache clinic, were included. PSG findings, as well as demographics, were compared to a group of controls aged 5-14 years-old.
Results: In sum, 185 children with a diagnosis of migraine were included: 39% males, 75% Caucasian, mean age 13.5 ± 3.4, and 57% obese. Additionally, 180 children were included in the control group. The common presenting sleep symptoms were snoring (66%), sleep onset and sleep maintenance problems (25%), and excessive daytime sleepiness (20%). For the sleep diagnosis, 40% had obstructive sleep apnea (OSA), 27% had insomnia, 15% had periodic limb movement disorder (PLMD), and 6% had a central disorder of hypersomnolence. In terms of sleep architecture, children with migraine had significantly higher NREM 2 ($p < 0.001$) and a lower percentage of NREM3 ($p < 0.001$) compared to controls after adjustment for demographics and the presence of sleep-disordered breathing.
Conclusions: Children referred to the sleep clinic who also had migraine, experience various types of sleep complaints. OSA, insomnia, and PLMD were relatively common in this population. Changes in sleep architecture, specifically increased NREM2 and decreased slow wave sleep compared to the control group, were also observed.

1. Introduction

Migraine is a recurrent, episodic headache disorder characterized by moderate to severe, pulsating pain lasting 2–72 h; which may be associated with nausea and/or photophobia and phonophobia [1]. It is estimated to affect 1–3% of children between the ages of three and seven, 4–11% between the ages of seven and 11, and 8–28% of adolescents (13–18 years of age) [2,3]. Several studies have suggested an association between migraine and sleep

☆ The work was performed in Cincinnati Children's Medical Center, Cincinnati, Ohio.

☆☆ All authors have seen and approved the manuscript.

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https://doi.org/10.1016/j.sleep.2019.04.023
1389-9457/

List of abbreviations

AHI	apnea-hypopnea index
BMI	body mass index
NREM	non-rapid eye movement
REM	rapid eyes movement
OAHI	obstructive apnea-hypopnea index
OSA	obstructive sleep apnea
PedMIDAS	pediatric migraine disability score
PLMD	periodic limb movement disorder
PLMI	periodic limb movement index
RLS	restless leg movement
SDB	sleep disorder breathing

disturbances in the pediatric population [4], with a bidirectional relationship between headache and poor sleep, with headache negatively impacting sleep and vice versa. Specifically, there is evidence that disturbed sleep in migraine patients is associated with an increase in frequency and disability of the migraine [5–11]. A recent study showed that sleep disturbances in migraine were significantly associated with higher levels of functional disability, anxiety, and depression compared to other types of headaches in children [12]. It was speculated that the common anatomical structures and neurochemical processes, such as the serotonergic system involved in the pathophysiology of sleep and headache, could explain this link [13,14].

Several studies in children with migraine have shown an association with comorbid sleep disorders. For instance, primary snoring, obstructive sleep apnea (OSA), restless legs syndrome (RLS), and parasomnias [15–19] are more prevalent among children with migraine. The periodic limb movement index (PLMI) in adolescents with migraine positively correlates with migraine severity when compared to healthy controls [20]. In term of polysomnographic (PSG) findings, a study by Vendrame et al., on 90 children with headache (of those, 60 with migraine and 11 with chronic migraine) showed changes in sleep architecture with reduced rapid eye movement (REM) and slow-wave sleep in severe and chronic migraine compared to children with mild/moderate migraine [21].

We aimed to examine the clinical presentation, diagnosis, and PSG characteristics of children diagnosed with migraine who were independently referred to our sleep center. To better understand the changes in sleep structure in pediatric migraine, we compared these sleep characteristics results to a group of control subjects.

2. Methods

2.1. Study participants

Following institutional review board approval by the Cincinnati Children's Hospital Medical Center, we performed a retrospective chart review of all Cincinnati Children's Headache Center patients ≤18 years of age who had also been evaluated in the Cincinnati Children's Sleep Center and undergone polysomnography within ± one year of their Headache Center evaluation. Patients with significant comorbidity such as a major neurologic disease, genetic syndrome, and patients who were not diagnosed with migraine according to the International Classification of Headache Disorders (ICHD) [1], were excluded. The control group included healthy children aged 5–14 years old who had PSG showing an obstructive apnea-hypopnea index (OAHI) ≤1 per hour of sleep from our research registry (n = 180).

Demographic and medical history information were collected, and diagnostic PSGs were reviewed. In addition, for the migraine group, we evaluated the following information: (1) Chart review for primary sleep diagnoses through the sleep clinic for each individual encounter, (2) Headache characterization including migraine severity, duration, frequency, type and the Pediatric Migraine Disability Assessment (PedMIDAS) score. The headache visit for obtaining the headache characterization was the visit which occurred in closest proximity to the PSG within the period from one year before to one month after PSG, which corresponded to the period before the initiation of sleep management.

2.2. Polysomnography interpretation

PSGs were performed in the sleep laboratory at Cincinnati Children's Sleep Center with the use of a digitized system (Twin Software, Grass Technologies, West Warwick, Rhode Island, USA). The standard pediatric montage was used, and the following parameters were simultaneously recorded during the study: electroencephalogram (F3A2, F4A1, C4A1, C3A2, O1A2, O2A1), right and left electrooculogram (ROC/A1, LOC/A2), submental, tibial and intercostal electromyograms, electrocardiography, airflow with thermistor and nasal pressure transducer, end-tidal pCO2 (BCI Capnocheck, Smiths Medical, St. Paul, MN, USA), oxygen saturation by pulse oximeter, oximeter pulse waveform, and video monitoring using an infrared video camera digitally recorded. Rib cage and abdominal volume changes were recorded with a computer-assisted respiratory inductance plethysmograph (RIP). All PSGs were scored by a certified sleep technologist according to the American Academy of Sleep Medicine (AASM) guidelines and interpreted by board-eligible/board-certified sleep specialists. The AASM standard definitions were used for sleep efficiency, sleep efficiency after onset, total sleep time, percentages of sleep stages (NREM1%, NREM2%, NREM3%, or REM %), apneas, hypopneas, periodic limb movements during sleep (PLMS), and arousals [22]. Indices based on the number of events per hour of sleep were calculated for apneas/hypopneas (AHI), obstructive apneas/hypopneas (OAHI), PLMS (PLMS index), and arousals.

OSA was defined as mild (OAHI of 1 to <5/hr), moderate (OAHI five to <10/hr), or severe (OAHI OI ≥ 10/hr). Periodic limb movement disorder (PLMD) was defined by the presence of a PLMS index of >5/hr in association with clinically significant sleep disturbance or impairment in daytime functioning [23].

2.3. Migraine-related disability questionnaire

The PedMIDAS questionnaire measures the impact of migraine disability among children and adolescents. It is composed of six questions that evaluate the impact of migraine on school absenteeism, school performance, socialization, and sport-related activity. Total scores range between 0 and 270, with the following grading scale: 0–10, little to none; 11–30, mild; 31–50, moderate; >50, severe [24,25].

2.4. Sleep architecture comparison

To define differences in sleep architecture, we compared the sleep parameters of sleep efficiency, sleep efficiency after onset, total sleep time, percentages of sleep stages and arousal index between migraine patients and the control group. Factors that could potentially affect sleep architecture such as age, race, gender, obesity status, and also AHI and PLMI were adjusted in a multiple linear regression model.

2.5. Statistical analysis

Descriptive statistics for the migraine patients and controls were reported as a mean ± SD for continuous variables and as a percentage for categorical variables. Fisher's exact tests were used to compare the demographic variables, gender, race, and obesity status between the cases and controls. Wilcoxon signed rank tests were used to examine the difference in sleep architectures between migraine patients and controls. To further explore the association of migraine and sleep architectures while controlling for other potential confounders, stepwise variable selection methods were used in a multiple linear regression model to find the best subset of predictors among the explanatory variables including migraine patients group indicator, age, gender, race, obesity status, AHI, and PLMS index. We defined the entry criteria of α level as 0.15 and the level of staying in the model of the stepwise variable selection procedure as 0.05. For each sleep architecture variable, we reported the p-value of the migraine effect as well as those significant covariates which were kept in the best-fitted model. Spearman correlation was used to explore the correlation between headache severity parameters (migraine severity, duration, frequency, and total PedMIDAS score), and PSG parameters (AHI, arousal index, max EtCO2, mean oxygen saturation, PLMI, AHI, OAHI and sleep architecture parameters). The statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC) with $\alpha \leq 0.05$ used as the level of significance for statistical inference.

3. Results

One hundred eighty-five children met the inclusion criteria for entry into the analysis (Fig. 1). For the control group, 180 children from our research registry were included. Comparison of the demographic characteristics between the migraine group and the control group is presented in Table 1.

3.1. Presenting symptom and sleep disorders

The common presenting symptoms were snoring or respiratory pauses, sleep onset or maintenance problem, and excessive daytime sleepiness (Fig. 2). The typical sleep disorders diagnosis based on the PSG results and clinical evaluations were OSA (40%), insomnia (27%), PLMD (15%), primary snoring and Central Disorders of Hypersomnolence (6%) (Fig. 3). The typical sleep diagnosis was OSA (40%), of those, 75% had mild OSA and 25% had moderate to severe OSA. In terms of obesity and OSA, 32% of the non-obese children were diagnosed with OSA compared to 52% of the obese children (p = 0.007). Table 2 shows the sleep study characteristics of children with migraine. No significant correlations were found between body mass index (BMI) percentile and headache severity parameters, including migraine severity, duration, frequency, and total PedMIDAS score (p = 0.78, p = 0.24, p = 0.35, p = 0.98, correspondingly).

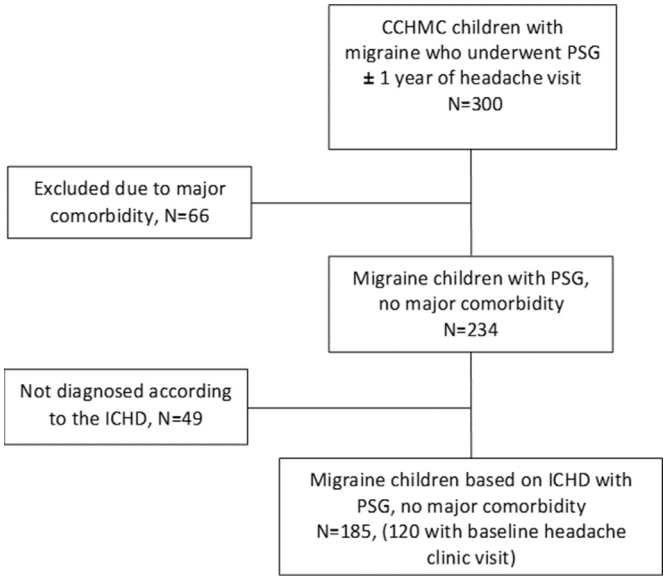

Fig. 1. Flow chart of selection of subject. CCHMC, Cincinnati Children's Hospital Medical Center; ICHD, International criteria headache diagnosis; PSG, polysomnography.

Table 1
Demographic characteristics of children with migraine and healthy controls.

	Migraine N = 185	Control N = 180	p-value
Average age at PSG assessment (years)	13.5 ± 3.4	9.7 ± 2.6	<0.001
Gender (% males)	39%	48.9%	0.06
Race (% Caucasian)	74.6%	66%	0.086
Mean BMI percentile (%)	84.1 ± 24.3	70.5 ± 26	<0.001
Rate of obesity (%)	57%	23%	<0.001
Mean number of sleep clinic visits	2.7 ± 2.4	NA	

BMI: body mass index; NA: not applicable; PSG: polysomnography.

3.2. Migraine characteristics

Information regarding migraine characteristics prior to initiation of sleep management was available for 120 children (65%). For the remaining 65 children (35%), the migraine characteristics were reported only after sleep management was initiated, hence they are not included. No differences in age (p = 0.15), race (p = 0.86), gender (p = 0.75), BMI percentile (p = 0.33), OAHI (p = 0.23), or PLMS index (p = 0.49) were observed between children with a complete baseline headache visit and children with an incomplete headache visit.

The mean frequency of migraine was 13.4 ± 10.9 per month; mean duration was 7.1 ± 11.3 h. The mean PedMIDAS score was 37 ± 53. Of those, 23% were scored with a severe disability. Table 3 describes the migraine characteristics of patients who were referred to the sleep clinic. No significant correlations were found between headache severity parameters, including migraine severity, duration, frequency, and total PedMIDAS score and PSG parameters, including arousal index, max EtCO2, mean oxygen saturation, PLMI, AHI, oAHI and sleep architecture parameters (p-values > 0.05 for all the correlations). We also did not find any significant correlations between the aforementioned headache severity parameters and a diagnosis of OSA or PLMS. Also, there were no significant differences in PSG parameters, OSA diagnosis, or PLMS between children with and without chronic migraine.

3.3. Sleep architecture

Table 4 shows the comparison of sleep architecture according to PSG between children with migraine and controls. Sleep cycle and the distribution of sleep stages differed between the two groups. Compared to the control group, children with migraine had significantly higher sleep efficiency and shorter sleep latency. Children with migraine also had a higher percentage of NREM2 and a lower percentage of NREM3 and REM as well as a smaller number of REM cycles. In order to adjust for factors that could impact the sleep architecture, we examined our results using a multiple

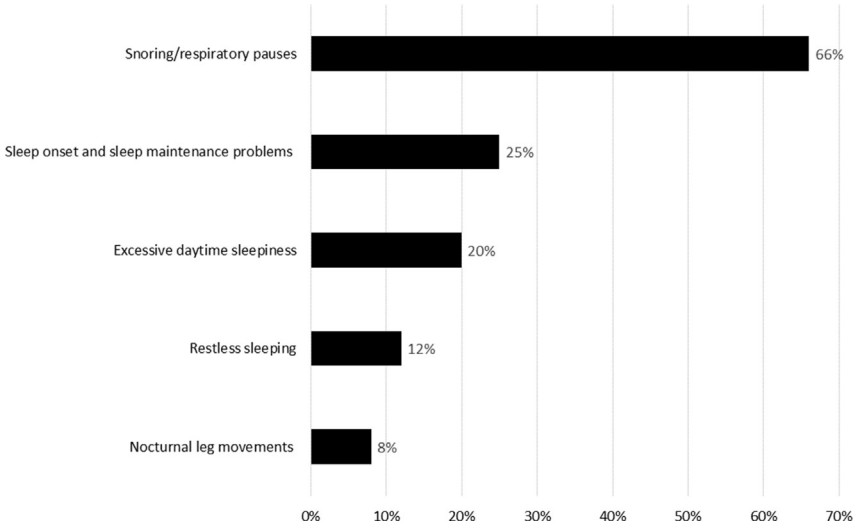

Fig. 2. Distribution of the most common causes for referral to the sleep clinic (N = 185).

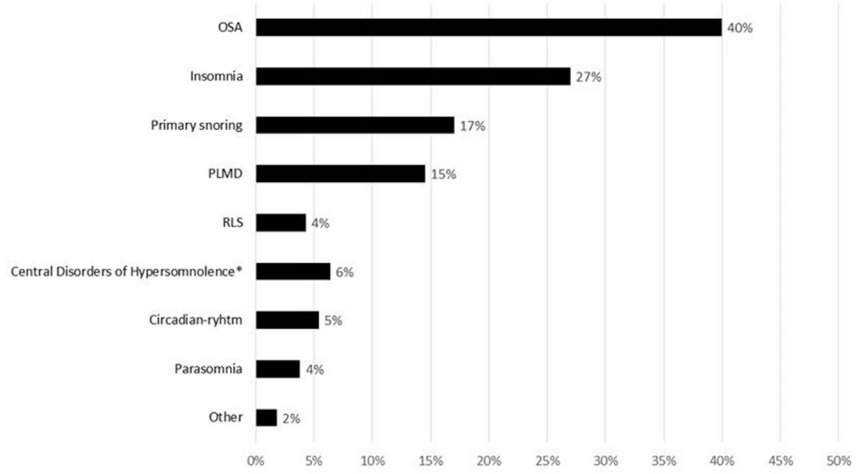

Fig. 3. Distribution of the major clinical sleep diagnosis based on the PSG analysis and sleep clinic visit (N = 185). Footnote: PLMD, periodic limb movement disorder; RLS, restless leg syndrome. * Three children with narcolepsy, five with idiopathic hypersomnia, and three - nonspecific.

regression model including age, gender, race, obesity status, AHI, and PLMI. Differences between the migraine and control group in sleep efficiency, sleep latency, and percentage of NREM2 and NREM3 remained significant even after adjustment for the aforementioned variables.

Table 2
Polysomnographic characteristics of Children with Migraine (n = 185) reported as mean with SD.

Polysomnographic Outcomes	
Mean SaO2 (%)	97.6 ± 0.96
Mean EtCO2 (mmHg)	41.2 ± 4.36
Maximum EtCO2 (mmHg)	483 ± 5.5
AHI (events/hour)	2.4 ± 2.05
Obstructive AHI (events/hour)	2.09 ± 2.11
% OSA (OAHI>1)	74 (40%)
% mild OSA (5>OAHI>1)	54 (29%)
% moderate-severe OS(oAHI≥5)	20 (11%)
Central sleep apnea	1 (0.5%)
Hypoventilation (%)	4 (2%)
% PLMS (PLMI>5)	34 (18%)
Mean PLMI (events/hour)	2.56 ± 6.1

AHI, apnea hypopnea index; EtCO2, end tidal carbon dioxide; PLMS, periodic limb movement in sleep; PLMI periodic limb movement index.

4. Discussion

The current study has shown that children referred to the sleep clinic with migraine present with various types of sleep complaints including snoring or respiratory pauses, sleep onset and sleep maintenance problems, excessive daytime sleepiness, and restless sleep. For the common sleep diagnosis in this group, OSA, insomnia, RLS/PLMD, and Central Disorders of Hypersomnolence are relatively common. Altered sleep architecture was notable in children with migraine, specifically, a decreased proportion of slow wave sleep compared to the control group.

Almost 70% of children referred to the sleep clinic with migraine presented with symptoms of sleep disorder breathing, mostly snoring and respiratory pauses. Of those, 40% were ultimately diagnosed with OSA. The association between migraine and OSA in adults has been controversial [26], and limited data is available in children. A retrospective study by Vendrame et al., reported a prevalence of 56% of sleep disorder breathing (SDB) in 60 children

Table 3
Characteristics of migraine patients (n = 120) prior to initiation of sleep management.

Migraine Characteristics	
Headache frequency (events per month)	13.4 ± 10.9
Mean headache duration (hours)	7.1 ± 11.3
PedMIDAS score (0–270)[a]	37.4 ± 53
Average severity (0–10)	5.3 ± 2.44
Chronic migraine	50 (42%)
Presence of Aura	
Migraine without aura[b]	118 (98%)
Migraine with aura[b]	7 (6%)
Medications	
Treated with amitriptyline	17 (14%)
Treated with topiramate	24 (20%)

[a] PedMIDAS, Pediatric migraine disability score. The total score range between 0 and 270, with the following grading scale: 0–10, little to none; 11–30, mild; 31–50, moderate; >50, severe.
[b] Total above 100% since some are mixed with and without aura.

with migraine. It was reported that SDB was more frequent in the migraine group compared to the group of children with nonspecific headache, chronic migraine, or tension headache [21]. In our study, 55% of the migraine patients were obese, which is in accordance with previous reports [27,28]. While a high prevalence of obesity could have contributed to the rate of OSA, 32% of the non-obese children in our cohort were also diagnosed with OSA. Several mechanisms could explain the relationship between OSA and migraine. Hypoxemia [29], hypercarbia, altered cerebral blood flow, and an increase in blood pressure could potentially contribute or aggravate headache [30]. Sleep disruption due to frequent arousals could also worsen symptoms of migraine [31].

More than a third of children with migraine in this study had insomnia or circadian rhythm disorders. The prevalence of insomnia in the general pediatric population is reported to be between 5 and 20%; secondary insomnia is more common than primary insomnia [32–34]. Adult studies showed that insomnia is the most common sleep disorder among headache suffers, affecting those who seek treatment for migraine [35,36]. However, to our knowledge, no studies have reported insomnia as a distinct sleep disorder in children with migraine.

In our cohort, PLMD and RLS were observed in 15% and 4% of the pediatric migraine group, respectively. In agreement with our findings, Sevindik et al., showed that the frequency of RLS in children with migraine was higher compared to a control group [19]. Another study showed that the PLMI was positively correlated with the migraine severity in adolescents. Hence, it was suggested that PLMD might influence the clinical presentation of migraine, including an increase in its severity, frequency, and disability, as well as affecting treatment efficacy [20]. The pathogenesis underlying the association between the two conditions is unknown. Several mechanisms, including a dopaminergic system imbalance, a common genetic background, or an iron metabolism dysfunction have been suggested [37]. In terms of parasomnia, both sleep terror and sleepwalking have been linked to migraine, presumably due to a disorder of serotonin metabolism [38]. Our results showed NREM parasomnia in only 4% of the participants. The reason for this could be related to the older average age of our cohort, as parasomnias are more common in younger children [39].

A recent retrospective population-based cohort study showed that migraine is an independent risk factor for narcolepsy developed in children with an adjusted hazard ratio of 5.3. In our study, 12 children (6%) presented with symptoms of Central Disorders of Hypersomnolence, of which three were ultimately diagnosed with narcolepsy. Our study may support this finding, however an extrapolation could not be obtained due to the low estimated incidence, 0.83 per 100,000 person-years, of narcolepsy in the pediatric population [40].

Our results showed a significant difference in sleep architecture in children with migraine compared to controls. Specifically, higher sleep efficiency with shorter sleep latency, higher NREM2 percentage, and lower NREM3 percentage were observed for the migraine group compared to controls. These differences remained significant after adjustment for the demographic variables age, gender, race, BMI percentile, AHI, and PLMS index, all of which are factors that potentially could affect sleep architecture [41]. A previous study showed that children with severe migraine have decreased REM and NREM3, and an increased arousal index compared to children with mild to moderate migraine. However, no comparison with a healthy control group was performed in this study. The role of serotonergic neurotransmission in both slow wave sleep and migraine might explain our findings [38]. Another explanation could be attributed to medication for migraine, such as amitriptyline, which can affect sleep architecture, by modifying REM sleep and Slow Wave Sleep, as was previously shown in an adult study [42]. Topomax and Elavil can also affect sleep architecture [43,44]. The retrospective nature of our study and the lack of baseline headache information for all patients, limited our ability to explore this effect. Notably, we observed a decrease in sleep latency when compared to the control group, which might be attributed to sleep fragmentation leading to sleep deprivation in children with migraine.

The results of our study did not show any significant correlations between headache severity parameters (migraine severity, duration, frequency, and total PedMIDAS score) and PSG parameters (sleep architecture parameters, AHI and PLMI). However, these results should be interpreted with caution. Due to the retrospective nature of our study, headache severity score was not assessed on the same day as the sleep study, which potentially could affect the results.

Table 4
Comparison of polysomnographic characteristics of sleep architecture between children with migraine and each group of controls.

	Cases (n = 185)	Control1(n = 180)	p-non adjusted	Adjusted-p
Total sleep time (minutes)	416 ± 67	416.90 ± 64.17	0.95	0.08
Sleep efficiency (%)	83% ± 11	80% ± 10	**<0.001**	**<0.001**
Sleep efficiency after onset (%)	89% ± 9	90% ± 8	0.53	0.47
Sleep latency (minutes)	33.3 ± 40	49 ± 39	**<0.001**	**<0.001**
Arousal index (events/hour)	10.9 ± 5.4	9.5 ± 2.7	0.082	0.85
REM%	20 ± 7	21 ± 5	**0.046**	0.46
NREM1%	4 ± 4	3 ± 1	0.264	0.83
NREM2%	54 ± 10	46 ± 7	**<0.001**	**<0.001**
NREM3%	22 ± 8	30 ± 7	**<0.001**	**<0.001**
REM cycles (number)	3.7 ± 1.3	4 ± 1.1	**0.007**	0.595

*Adjusted-p value represents multiple linear regression analysis that was used to adjust for age, gender, race, BMI percentile, AHI and PLMI.
Bold signifies $p < 0.05$.

Several studies in adults have shown that targeted interventions of certain sleep disorders can improve migraine severity. For instance, treatment of OSA by continuous positive airway pressure has been shown to improve migraine severity [45,46] while cognitive behavioral interventions for comorbid insomnia has been shown to reduce headache frequency in adults [47]. A preliminary trial using melatonin as a prophylaxis for children with migraine showed promising results with a decrease in the frequency of headache attacks [48]. Taken together, our results and the observation from prior studies highlight the importance of addressing sleep issues in children with migraine. Recognition of the common sleep complaints and related sleep disorders frequently found in children with migraine may aid clinicians in the diagnosis and management of both conditions. Additional research is needed to evaluate the effect of sleep management on clinical outcomes of migraine in children.

This study has several limitations. First, it is a retrospective study which is subject to selection bias. Second, the migraine patients were referred to the sleep clinic, thus implying suspicion of a sleep disorder. Comparing those patients with migraine to the control patients helps mitigate this issue but does not control for patients with migraine that were not referred nor recognized to have a sleep disorder. Furthermore, due to the relatively younger age and lower BMI and rate of obesity in our control group, we could not match cases with controls; therefore, for the sleep architecture comparison, we adjusted for demographic variables (age, gender, and race) and obesity status. Due to the retrospective nature of our study, we could not compare the PSG findings of migraine children with and without sleep complaints. This should be investigated in a future prospective study. Finally, only 65% of the children in our cohort had a complete baseline headache visit. However, no difference in demographics, OAHI, or PLMS index was observed between children who had complete baseline headache visit and those who did not.

5. Conclusion

This is the first study to our knowledge that evaluated the overall clinical presentation, diagnosis, and PSG findings in a relatively large cohort of children with migraine referred to sleep clinics. Our data indicate a high prevalence of a variety of sleep disorders. Most children with migraine seen in our sleep clinic were diagnosed with OSA, insomnia, PLMD, and Central Disorders of Hypersomnolence. Furthermore, significant changes in sleep architecture were observed as evidenced by a higher NREM2 index and a lower proportion of slow wave sleep. A high index of suspicion for sleep disorders is necessary, and referral to the sleep clinic has the potential to improve both migraine and sleep disorders. Further prospective studies to determine the prevalence of sleep disorders in children with migraine and the response to sleep management are needed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

All authors disclose no potential conflicts of interest, including any financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated-including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.023.

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