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Urinary 6-Sulphatoxymelatonin Levels and Sleep Disorders in Children With Migraine

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Abstract

We conducted the present study to assess melatonin secretion in a sample of children with migraine, to describe their sleep patterns and problems, and to examine the impact of sleep problems on migraine disability. The parents of 18 children with migraine completed the Children's Sleep Habits Questionnaire and Pediatric Migraine Disability Assessment Score in Arabic. The parents of 18 healthy controls also completed the Children's Sleep Habits Questionnaire. Urinary 6-sulphatoxymelatonin levels were determined with the enzyme-linked immunosorbent assay method. There was no significant difference in urinary 6-sulphatoxymelatonin between the migraine and control groups ($Z = –0.127$, $P = .889$). There were no significant differences between groups in Children's Sleep Habits Questionnaire subscales or total scores. There were significant correlations between bedtime resistance, parasomnias subscales, and migraine disability. Our findings indicate that nocturnal production of melatonin is not reduced in children with migraine, and sleep disturbances impact the degree of migraine disability.

Keywords

migraine, 6-sulphatoxymelatonin, sleep

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Headaches in children and adolescents can be frequently disabling, with a significant impact on the quality of life of both children and parents.[1] Migraine has a high prevalence in children and is a significant source of morbidity.[2] A relationship between migraine and sleep has been established for a long time. Migraine can emerge during nocturnal sleep or following a brief period of daytime sleep, and attacks can be preceded by a lack of sleep.[3] Sleep-related risk factors have been identified for frequent and severe headache.[4] Common neurotransmitter systems are involved in pain perception, sleep organization, and mood disorders, and these systems could comprise the biochemical substrates explaining this interdependence.[5] There is evidence for a role of melatonin in headache.[6] Melatonin mechanisms are related to headache pathophysiology in many ways, including anti-inflammatory effects, toxic free radical scavenging, reduction of proinflammatory cytokine upregulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, gamma-amino butyric acid and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of melatonin's chemical structure to that of indomethacin.[7] Melatonin has been considered a good candidate for migraine and other headaches prevention because of its favorable mechanisms of action and excellent tolerability profile.[8] Miano and colleagues[9] reported that melatonin effectively reduced the number, intensity, and duration of headache attacks per month in a small series of children with primary headache. Several studies[10,11] reported low melatonin levels in adults with migraine. We hypothesized that melatonin levels are lower in children with migraine than healthy controls. The aims of this study were to assess melatonin secretion in a sample of children with migraine by measuring the overnight urinary output of 6-sulphatoxymelatonin, to describe their sleep patterns and problems, and to examine the impact of sleep problems on migraine disability.

Methods

Participants

Eighteen nonmedicated children with migraine, aged between 5 and 12 years, were recruited from a patient population referred to the neurology clinic in a tertiary hospital. Migraine was defined according to

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International Classification of Headache Disorders diagnostic criteria, second edition.[12] Children with medical disorders, with comorbid psychiatric disorders, or receiving medications that were known to affect sleep were not recruited. Parents completed informed consent and a brief survey regarding their educational attainment and any significant medical problems and/or medications for the child, in addition to completing the Children's Sleep Habits Questionnaire[13] in Arabic. The parents of 18 normal control children also completed the Children's Sleep Habits Questionnaire. Parents of both children with migraine and control children were asked to collect urine from their children into a plastic container between 8:00 PM and 8:00 AM the next day. The study was approved by the research committee at the Department of Pediatrics, Faculty of Medicine, Cairo University. Ethical approval was obtained from the Institutional Review Board for Human Subject Research at the National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt.

Measures of Sleep Patterns and Sleep Problems

The abbreviated version of the Children's Sleep Habits Questionnaire[14] was used to assess sleep habits and sleep problems as reported by parents. The Children's Sleep Habits Questionnaire consists of 33 sleep-disturbance items and 3 items asking for information about bedtime, morning waking time, and daily total sleep duration. The parents are asked to recall their children's sleep behaviors over a "typical" recent week. Each item is rated on a 3-point scale: 1 = rarely (0-1 time/week); 2 = sometimes (2-4 times/week); 3 = usually (5-7 times/week). Some items that are considered to be desirable sleep behaviors are reversed in scoring, such that a higher score reflects more disturbed sleep behaviors. Items querying needing parent to be in the room to sleep and being afraid to sleep alone were present on both the bedtime resistance and sleep anxiety subscales. The 33 sleep-disturbance items are conceptually grouped into 8 subscales: bedtime resistance (6 items), sleep-onset delay (1 item), sleep duration (3 items), sleep anxiety (4 items), night wakings (3 items), parasomnias (7 items), sleep-disordered breathing (3 items), and daytime sleepiness (8 items). The Children's Sleep Habits Questionnaire has shown adequate reliability and validity, and a cut-off total Children's Sleep Habits Questionnaire score of 41 yielded a sensitivity of 0.80 and specificity of 0.72. With permission of the original author, the Children's Sleep Habits Questionnaire was translated into Arabic and was used before in a previous study in our community.[13] Reliability analysis showed that Cronbach's alpha was 0.78 for the migraine group and 0.83 for the control group.

Measures of Migraine Disability

The Pediatric Migraine Disability Assessment Score was developed to assess migraine disability in pediatric and adolescent patients.[15] With permission of the original author, the Pediatric Migraine Disability Assessment Score was translated into Arabic by translation and back-translation and was used to assess migraine disability.

Determination of Urinary 6-Sulphatoxymelatonin

Parents of children with migraine and control children were asked to collect urine from their children between 8:00 PM and 8:00 AM the next day. Because of the possible suppression of melatonin secretion by light, children went to bed with the lights out, and none of them were exposed to light until their morning wake-up. Sample volumes were recorded, and 5-mL aliquots were stored frozen at –20° C until analysis. Urinary 6-sulphatoxymelatonin was measured by quantitative enzyme-linked immunosorbent assay (IBL International GMBH, Hamburg, Germany), according to the manufacturer's recommendations.

Statistical Analysis

Data were analyzed using the SPSS for Windows statistical package version 15 (SPSS Inc, Chicago, IL). Numerical data were expressed as means and standard deviations. Categorical data were expressed as frequencies and percentages. Chi-square tests were used to examine the relationship between qualitative variables. For quantitative data, comparisons between the 2 groups were completed using independent sample *t* tests or Mann-Whitney tests. Spearman's rho correlation was used to test the correlation between sleep and migraine disability. A P value <.05 was considered to be significant.

Results

Sample Characteristics

Of the total of 18 children with migraine, there were 12 (66.7%) boys and 6 (33.3%) girls, with a mean age of 10.56 years (standard deviation = 1.72). In this sample, 5.6% of fathers were illiterate, 77.8% had a high school education or less, and 16.7% had graduated from university. In this sample, as well, 16.7% of mothers were illiterate, and 83.3% had a high school education or less. The mean age of the control group was 9.69 ± 1.20; 7 (38.9%) were boys and 11 (61.1%) were girls. There were no significant differences between the migraine and the control groups with regard to age ($t = 1.739$, $P = .09$), sex ($P = .09$), fathers' levels of education ($P = .06$), and mothers' levels of education ($P = .13$).

Sleep/Wake Patterns

The mean (± standard deviation) night bedtime of the migraine group was 23:05 ± 1:20, mean morning wake-up time was 7:35 ± 2:01, and mean total sleep duration was 8.50 ± 1.21 hours. The mean (± standard deviation) night bedtime of control group was 21:54 ± 1:17, mean morning wake-up time was 7:11 ± 1:05, and mean total sleep duration was 9.28 ± 1.07 hours. There was a significant difference between the migraine and control groups with respect to bedtime ($t = 2.567$, $P = .02$). There were no significant differences in wake-up time ($t = 0.696$, $P = .49$) or total sleep duration ($t = –1.924$, $P = .06$).

Comparisons of the Children's Sleep Habits Questionnaire Scale Scores

Table 1 indicates that there were no significant differences in any of the Children's Sleep Habits Questionnaire subscales or the total scores between the migraine and the control groups ($P > .05$).

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Table 1. Comparisons of Children's Sleep Habits Questionnaire Scale Scores Between Migraine and Control Groups.

	Migraine Mean ± SD (n = 18)	Controls Mean ± SD (n = 18)	*P*
Bedtime resistance	10.22 ± 2.34	9.50 ± 2.81	.408
Sleep-onset delay	1.94 ± 0.94	1.89 ± 0.76	.893
Sleep duration	3.67 ± 1.68	3.44 ± 1.98	.493
Sleep anxiety	8.56 ± 2.71	6.94 ± 2.10	.054
Night wakings	5.50 ± 1.76	5.89 ± 1.75	.510
Parasomnias	11.00 ± 2.11	11.50 ± 2.38	.510
Sleep-disordered breathing	4.17 ± 1.42	3.61 ± 1.29	.118
Daytime sleepiness	17.50 ± 4.72	16.06 ± 4.05	.331
Total score	58.39 ± 8.95	55.44 ± 8.35	.315

Abbreviation: SD, standard deviation.

Table 2. Differences in Urinary 6-Sulphatoxymelatonin (ng/12 h) Between Migraine and Control Groups.

Migraine (n = 18) Mean ± SD	Controls (n = 18) Mean ± SD	*Z*	*P*
20 362 ± 16 716	26 359 ± 28 312	–0.127	.899

Abbreviation: SD, standard deviation.

Table 3. Correlations Between Children's Sleep Habits Questionnaire Scale Scores and Migraine Disability.

	r	*P*
Bedtime resistance	–0.480	.044
Sleep-onset delay	–0.095	.707
Sleep duration	–0.050	.844
Sleep anxiety	–0.201	.423
Night wakings	–0.062	.808
Parasomnias	0.506	.032
Sleep-disordered breathing	0.219	.383
Daytime sleepiness	0.031	.902
Total score	0.063	.805

Differences Between the Migraine and the Control Groups With Regards to Urinary 6-Sulphatoxymelatonin

The mean (± standard deviation) urinary 6-sulphatoxymelatonin in patients with migraine was 20 363 ± 16 717 (range = 510-51 448), and the mean (± standard deviation) in controls was 26 359 ± 28 312 (range = 1062-104 240). As shown in Table 2, there was no significant difference in 6-sulphatoxymelatonin between the migraine and the control groups ($Z = –0.127$, $P = .899$).

Correlations Between the Children's Sleep Habits Questionnaire Scale Scores and Migraine Disability

Table 3 shows that there was a significant negative correlation between the bedtime resistance subscale and migraine disability ($r = –0.480$, $P = .044$), whereas there was a significant positive correlation between the parasomnias subscale and migraine disability score ($r = 0.506$, $P = .032$).

Discussion

We conducted this study to examine differences in urinary 6-sulphatoxymelatonin levels between children with migraine and healthy controls, to describe their sleep patterns and problems, and to investigate potential relationships between sleep disturbances and migraine disability. Our results indicated that there was no significant difference in urinary 6-sulphatoxymelatonin levels between groups. There was a significant difference in bedtime. There were no significant differences in subscales of the Children's Sleep Habits Questionnaire or in total scores between children with migraine and healthy controls. In addition, our data suggested an association between sleep disorders and migraine disability. To the best of our knowledge, no previous study has examined urinary 6-sulphatoxymelatonin levels in children with migraine. In adults, Claustrat and colleagues were the first to demonstrate lower plasma melatonin levels among migraine patients.[16] In a study of 146 patients with migraine and 74 control subjects, Masruha et al[10] reported reductions in urinary 6-sulphatoxymelatonin during migraine attacks. However, patients with migraine that did not present with headache during the day of the urine sample collection did not have lower 6-sulphatoxymelatonin levels when compared with controls. Another recent study assessed 6-sulphatoxymelatonin levels in a large, consecutive series of patients with migraine and several co morbidities (chronic fatigue, fibromyalgia, insomnia, anxiety, and depression) and revealed strong correlations between concentrations of 6-sulphatoxymelatonin and chronic migraine. These researchers also determined an inverse relationship between 6-sulphatoxymelatonin levels and depression, anxiety, and fatigue.[11] Contrary to the adult studies, we did not find significant differences in 6-sulphatoxymelatonin levels in children with migraine compared with controls. Although the differences in melatonin levels were not significant, there was still a reduction in the migraine group relative to the control group. The reasons this difference did not reach significance are twofold. First, there was high variability in melatonin levels, as there was a wide range of melatonin in both patients and controls. Second, this study might be underpowered. However, our results are consistent with a recent study of melatonin levels in children with tension-type headache, which reported that children with frequent episodic tension-type headache do not exhibit different concentrations of melatonin when compared with healthy children.[17] We recognize that we did not collect data regarding the presence of migraine pain during the day of collection of urine, which has been previously reported in adults to affect the level of 6-sulphatoxymelatonin, as it is proposed that hypothalamic disturbance can occur only during attacks and that patients in the interictal period will not show a reduction in melatonin levels. Either all patients with migraine could show lower levels of 6-sulphatoxymelatonin or patients in the interictal phase show a compensatory increase in melatonin.[10]

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Previous studies have reported a high prevalence of sleep disorders among children with migraine.[18,19] The relationships between headache and sleep problems are evident even in a nonclinical population of children and adolescents, with the migraine group showing poorer sleep quality, sleepiness, and a tendency toward nocturnal behaviors.[18] Luc et al[20] found that children with migraine had a higher prevalence of excessive daytime sleepiness. A recent polysomnographic study indicated that sleep-disordered breathing was more frequent among children with migraine, and severe migraine and chronic migraine were associated with shorter sleep times, longer sleep latencies, and shorter rapid eye movement and slow-wave sleep.[21] Snoring, parasomnias, sweating during sleep, and daytime sleepiness were more common among children with migraine compared with children with other types of headache and control nonheadache groups in a community sample of school children.[22] A higher incidence of parasomnias has been documented in migraine patients compared with controls.[3] Contrary to previous studies, our study did not reveal significant differences in subscales of the Children's Sleep Habits Questionnaire or total scores between groups. However, this finding could be attributed to the small sample size. Further study with a larger sample size might reveal significant differences.

A recent study investigated the relationship between migraine and obstructive sleep apnea in the general population and reported that there was no significant relationship between migraine and the apnea hypopnea index.[23] Similarly, there was no significant difference in the sleep-disordered breathing subscale between the migraine and the control groups in our study.

Another important finding in our study is the significant positive correlation between the parasomnias subscale and migraine disability. As recommended by Barnes,[22] a treatment plan for migraine in children should focus on reducing headache frequency, severity, duration, and accompanying disability. Thus, screening for sleep disorders in children with migraine and treating them could decrease the degree of disability.

The main limitation of this study is that children's sleep was assessed by reports from parents and they were the only informants, which might lead to over- or underestimation of sleep disturbances. Another limitation is that children were recruited from a neurology clinic, which might attract severe cases of migraine, and the results cannot be generalized to community children with migraine.

In conclusion, we did not observe significant differences in 6-sulphatoxymelatonin levels between children with migraine and healthy controls. This study suggests an association between sleep disturbances and migraine disability.

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Author Contributions

MKA-K and NAK designed the study. NAK, OGS, and AH collected the data. MKA-K analyzed the data, wrote the first draft and the final manuscript, and all the authors approved it.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the Institutional Review Board (1R-2012) for Human Subject Research at National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt. Patients were recruited after their parents signed an informed consent form.

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