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RESEARCH

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Assessment of serum level of melatonin in migraine: a case control study

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Abstract

Background Migraine attacks are reported to be severe enough to affect daily living events and can affect different age groups including early childhood. Chronic migraine is usually associated with several comorbidities such as anxiety, depression, sleep disorders, fibromyalgia, and fatigue. The existence of a bidirectional relationship between sleep and migraine is documented. This study aims at assessing the relationship between serum melatonin, sleep quality, and both migraine and migraine severity. This case–control study was executed on 70 patients and 70 healthy controls. Serum melatonin was assessed in morning and evening blood samples. Patients underwent a thorough clinical examination, assessing migraine severity using the Migraine Disability Assessment Scale and the sleep quality of both groups was evaluated using the sleep quality scale.

Results Serum melatonin levels were significantly reduced among migraine patients in both morning and evening samples. Sleep quality was significantly impaired in migraine patients. There is a statistically significant negative correlation between melatonin in both samples and both of frequency of attack and migraine disability. Positive family history, presence of aura and chronic migraine had significantly lower melatonin in both samples compared to those without aura was associated with significantly lower melatonin. Sleep quality was negatively correlated with serum melatonin, and positively correlated with migraine severity and frequency.

Conclusion Serum melatonin is significantly reduced among migraineurs, and linked to migraine severity; they also had impaired sleep quality so melatonin administration may represent a chance for improving headache characteristics.

Keywords Migraine, Melatonin, Disability, Sleep quality scale

Background

Migraine is the primary headache disorder which is considered one of the most severe and devastating headaches. It affects at least 12–20% of the worldwide population [1] and is assumed to reach its highest peak in people aged 35–39, making it an important cause of disability in persons less than 50, especially in females affecting the quality of their life [2].

Numerous studies have shown that aberrant trigeminovascular system activation and sensitization play a significant part in migraine pathophysiology, despite the fact that the specific mechanism of migraine is still unknown [3]. Migraine clinical features may vary as reported by some patients who documented headache occurrence during a certain period of the day [4].

The "clock factor", melatonin is secreted from pineal gland pinealocytes. Hypothalamic suprachiasmatic nuclei organize melatonin production and release which are controlled by light signals transferred by retinal ganglion cells [5].

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Melatonin may have a biological function in the control of circadian rhythms, sleep, mood, and aging [6]. Melatonin and migraine are interconnected. Both have diurnal variations and receptors of melatonin have been distributed in the trigeminal nerve ganglia and nuclei, suggesting that melatonin declines trigeminovascular nociception [7].

Migraine is associated with a broad spectrum of sleep troubles and there is a bidirectional association between sleep and migraine. Migraineurs suffer from poor sleep quality more than others which has an impact on migraine chronicity [8]. So, finding the melatonin role in migraine pathophysiology is a vital issue to evaluate its possible usage in acute or prophylactic therapy and hence we assessed melatonin serum levels in migraine patients.

This study aimed to assess the relationship between serum melatonin, sleep quality, and both migraine and migraine disability.

Methods

Study design and population

This case–control study was performed at the neurology outpatient clinic for a period of 6 months from May 2022 to October 2022, on 70 patients (24 males and 46 females) with definite diagnosis of migraine in agreement with the rules of the international classification of headache disorders-third edition (ICHD-3) [9] with their ages range (20–45) years and a mean age of 34.03 ± 7.42 years and another 70 apparently healthy participants (25 male and 45 female) matched for age and sex as a control group with an age range of (21–45) years and a mean age of 34.06 ± 7.22 years.

The exclusion criteria were patients having active systemic diseases or organ failure, psychiatric disorders, or any other neurological disorders rather than migraine and migraine patients on prophylactic therapy.

Study tools

Baseline data assessment: A detailed history with special attention to educational level (illiterate, basic or high), age of onset, number of attacks rate per month, migraine features including duration of headache attack, severity, location of pain and if associated with aura or not and presence of family history for migraine was taken from all patients.

General and neurological examinations were done for all patients.

Migraine-related disability was evaluated using the Migraine Disability Assessment Scale (MIDAS) which is a questionnaire designed to measure the influence and burden of headaches on a patient's life and interpreted as the following: little or no disability (0–5), mild disability (6–10), moderate disability (11–20) and severe disability when scored more than 21 [10].

Sleep health was evaluated using the Sleep Quality Scale (SQS) which is valid for ages 18–69 and includes 28 items for assessing the six parameters of sleep quality: daytime symptoms, restoration after sleep, problems initiating and maintaining sleep, difficulty waking, and sleep satisfaction. Scores can range from 0 to 84 with higher scores correlated with the severity of the sleep disorder. It is an effective and reliable apparatus for the detailed estimation of sleep quality (Cronbach's alpha coefficient 0.92). Arabic translation was done by forward–backward translation by an expert and was tested in a pilot study on 10% of samples (14 participants) with Cronbach's alpha of Arabic translation (0.81) [11].

Laboratory assessment

The measurement of the serum level of melatonin was done as follows: Blood was typically sampled through the use of intravenous catheters which were inserted at least 2 h before sampling to ensure that any increase in adrenaline levels during catheter insertion does not affect melatonin levels. The sample was drawn under low light, in the first half of the night, at about 10:00 pm and another sample was taken at 10 a.m. to ensure the circadian difference of melatonin, the sample was taken after 48 h of the last migraine attack [12]. 5 ml of venous blood was taken and then allowed to coagulate at room temperature for 10–20 min. Centrifuged for 20 min (at 2000–3000 RPM).The supernatants were collected with care. Melatonin levels were measured using competitive enzyme-linked immunosorbent assay (ELISA) kits.

The study was approved by our Institutional Ethics Committee (ZU-IRB #10012/23-10-2022). Written informed consent was obtained from all study participants after explaining the details and benefits as well as risks to them.

Statistical analysis

Data analysis was performed employing SPSS (Statistical Package for the Social Sciences) version 26 [13]. Quantitative parameters were defined by means and standard deviations or median and interquartile range based on the normality of distribution. Categorical data were represented using frequencies and percentages and then compared by the Chi-square test. Shapiro test was used to examine data normality. To compare quantitative data between cases and controls, an independent sample *t*-test (parametric test) and Mann–Whitney test (on-parametric test) were applied. The strength and direction of correlation between two continuous variables were assessed using Pearson and Spearman rank correlation

coefficients. The $p < 0.05$ and $p \leq 0.001$ were defined as significant and highly significant, respectively.

Results

A statistically non-significant difference between cases and controls regarding age, body mass index, sex, education, or smoking was reported (Table 1). While comparing melatonin in both the first and second samples, the patient group had significantly lower levels (14.8 ± 3.26, 4.94 ± 1.58 for patients versus 21.41 ± 4.1, 10.81 ± 3.75 for the control group). Concerning the sleep quality scale, patients reported significantly higher scores (median; IQR 46; 34–60) versus (median; IQR 16; 8–24) in the control group ($p < 0.001$).

The median duration of attack was 8 h (IQR; 6–18), the frequency of attack was 8 (IQR; 5–11.25), and the median age of onset was 17 (11–21.25).

Using the MIDAS scoring system to assess the disability caused by migraine in our patients revealed that 25.7% had little or no disability, 45.7% had mild disability, and 25.7% had moderate disability, while only 2.9% reported severe disability (Fig. 1).

Aura preceded migraine was reported in 20 patients whom had significantly lower melatonin in both samples compared to those without aura. Fifteen patients had chronic migraine with a significantly lower melatonin in both samples versus episodic migraine. There was a significant relationship between family history of migraine and melatonin (higher in those with a positive family history). Patients with unilateral migraine had a significantly higher melatonin while there was a

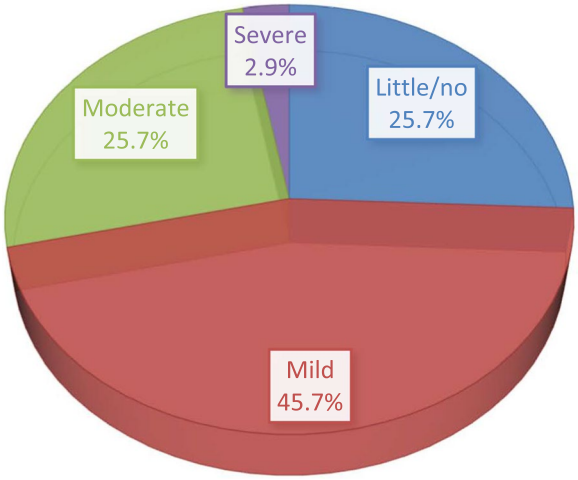

Fig. 1 Pie chart showing distribution of patients according to migraine disability

Table 1 Evaluation of the baseline data of studied groups

	Case group *N* = 70(%)	Control group *N* = 70(%)	Test	*p*
Age; mean ± SD	34.03 ± 7.42	34.06 ± 7.22	− 0.023[¥]	0.982
Sex				
Male	24 (34.3%)	25 (35.7%)	0.031	0.859
Female	46 (65.7%)	45 (64.3%)		
Education				
Illiterate	16 (22.9%)	7 (10%)	2.87	0.09
Basic	21 (30%)	24 (34.3%)		
High	33 (47.1%)	39 (55.7%)		
Smoking				
No	32 (45.7%)	34 (48.6%)	0.115	0.735
Yes	36 (54.3%)	36 (51.4%)		
BMI (kg/m^2); mean ± SD	25.58 ± 6.23	27.09 ± 5.88	− 1.471[¥]	0.144
Melatonin first sample; mean ± SD	14.8 ± 3.26	21.41 ± 4.1	− 10.555[¥]	< 0.001**
Melatonin second sample; mean ± SD	4.94 ± 1.58	10.81 ± 3.75	− 12.075[¥]	< 0.001**
SQS Median(IQR)	46 (34–60)	16 (8–24)	− 8.369[§]	< 0.001**
Duration of attack median(IQR)	8 (6–18)	NA		
Frequency of attack median(IQR)	8 (5–11.25)	NA		
Age of onset median(IQR)	17 (11–21.25)	NA		
Severity of attack median(IQR)	7 (4–13.25)	NA		

[§] Mann–Whitney test, IQR interquartile range, [¥]independent sample t test, **$p \leq 0.001$ is statistically highly significant, NA not applicable, SQS sleep quality scale

Table 2 Relation between melatonin and disease-specific data

	Melatonin first sample			Melatonin second sample		
	Mean ± SD	*t*	*p*	Mean ± SD	*t*	*p*
Aura						
Present (*n* = 20)	10.91 ± 2.48	− 9.672	< 0.001**	2.83 ± 1.25	− 10.118	< 0.001**
Absent (*n* = 50)	16.36 ± 1.98			5.79 ± 0.59		
Type						
Chronic (*n* = 15)	10.2 ± 2.48	− 9.155	< 0.001**	2.33 ± 1.03	− 11.759	< 0.001**
Episodic (*n* = 55)	16.05 ± 2.12			5.66 ± 0.71		
Family history						
Negative (*n* = 21)	12.8 ± 3.86	− 3.112	0.004*	3.76 ± 1.95	− 3.765	< 0.001**
Positive (*n* = 49)	15.66 ± 2.56			5.45 ± 1.06		
Status migrainosus						
Present (*n* = 10)	13.24 ± 5.11	− 1.099	0.298	4.24 ± 2.45	− 1.036	0.325
Absent (*n* = 60)	15.06 ± 2.82			5.06 ± 1.38		
Laterality						
Unilateral (*n* = 30)	15.99 ± 2.52	2.776	0.007*	5.51 ± 1	2.93	0.005*
Bilateral (*n* = 40)	13.91 ± 3.48			4.52 ± 1.8		

t independent sample t test, *$p < 0.05$ is statistically significant, **$p \leq 0.001$ is statistically highly significant

Table 3 Correlation between melatonin level and the studied parameters

	Melatonin first sample		Melatonin second sample	
	r	*p*	*r*	*p*
Age	0.129	0.289	− 0.018	0.884
Gender	− 0.032¥	0.792	− 0.107¥	0.38
Education	0.091¥	0.455	0.16¥	0.185
Smoking	− 0.022¥	0.857	− 0.028¥	0.816
BMI	− 0.083	0.496	0.083	0.492
Age of onset	0.041¥	0.736	0.058¥	0.633
Frequency of attack	− 0.963¥	< 0.001**	− 0.812¥	< 0.001**
Duration of attack	0.135¥	0.266	0.034¥	0.778
Migraine severity	− 0.842¥	< 0.001**	− 0.712¥	< 0.001**

r Pearson correlation coefficient ¥Spearman rank correlation coefficient, **$p \leq 0.001$ is statistically highly significant, BMI body mass index

Table 4 Correlation between sleep quality scale and the studied parameters

	SQS	
	r	*p*
Age	− 0.063	0.604
Gender	− 0.091	0.454
Smoking	− 0.082	0.501
Education	0.072	0.555
BMI	− 0.076	0.534
Age of onset	0.197	0.101
Frequency of attack	0.581	0.028*
Duration of attack	− 0.233	0.053
Melatonin first	− 0.613	< 0.001**
Melatonin second	− 0.462	< 0.001**
Migraine disability	0.533	< 0.001**

r Spearman rank correlation coefficient. *$p < 0.05$ is statistically significant **$p \leq 0.001$ is statistically highly significant BMI body mass index, SQS sleep quality scale

non-significant relation between melatonin and presence of history of status migrainosus Table 2.

There was a statistically significant negative correlation between melatonin in both samples and both of frequency of attack, and migraine disability. There was a non-significant correlation between melatonin and either age, body mass index, age of onset or duration of attack Table 3.

A statistically significant negative correlation between melatonin in both samples and sleep quality measured by SQS was observed and also a significant positive correlation between SQS and all of frequency and migraine severity Table 4.

Sleep disorders detected by SQS had a significant relation with classical and chronic migraine Table 5.

Discussion

Migraine is the most commonly studied headache disorder in its different aspects; including epidemiology, pathophysiology, and treatment options [14]. There are several ways to explain the link between melatonin

Table 5 Relation between sleep quality scale and disease-specific parameters

	SQS		
	Median (IQR)	***Z***	***p***
Aura			
Present ($n=20$)	62(54–75.5)	− 4.796	< 0.001**
Absent ($n=50$)	41 (30–46.5)		
Type			
Chronic ($n=15$)	64(50–76)	− 3.776	< 0.001**
Episodic ($n=55$)	42(32–54)		
Family history			
Negative ($n=21$)	46 (34–72)	− 0.738	0.461
Positive ($n=49$)	46 (34–56)		
Status migrainosus			
Present ($n=10$)	48(32–66)	− 0.353	0.724
Absent ($n=60$)	45(35–58)		
Laterality			
Unilateral ($n=30$)	43(32–56)	− 0.642	0.521
Bilateral ($n=40$)	46(37–60)		

SQS sleep quality scale Z Mann–Whitney test, ** $p \leq 0.001$ is statistically highly significant

and migraines. Several reports have demonstrated that melatonin possesses several antimigraine properties including inhibition of nitric oxide synthetase activity, decreases mRNA expression of Calcitonin gene-related peptide (CGRP) release and reducing the excitotoxicity promoted by glutamate [15]. In addition, melatonin owns different analgesic effects as it had a structure analogous to that of indomethacin and shares in the regulation of γ-aminobutyric acid receptors and β-endorphins release [16]. Despite having no serious side effects, melatonin has not yet found its place in migraine treatment up till now [17]. It is known that epilepsy and migraine are both episodic conditions and share multiple different characteristics [18]. Abnormalities in the melatonin cycle were found in epileptic patients especially, those with intractable epilepsy [19]. The anticonvulsant properties of melatonin could be attributed to different pathways including its antioxidant, antiexcitotoxic, and free radical scavenging activities which provide neuroprotection [20].

Our results showed that serum melatonin was significantly reduced among migraine patients, and these findings were in harmony with several previous studies [21, 22]. Starting early in 1989, Claustrat et al. found that serum melatonin level was lower in migraine patients and reaches its lowest level when depression co-occurred with migraine [23]. On the other hand, Zdunska et al. proved in their pilot study that melatonin levels were reduced among migraine patients when compared with controls but with a statistically non-significant difference [24].

The trials to discover the bond between melatonin and migraine had extended to involve different clinical trials. Peres et al. announced that use of 3 mg of melatonin was effective in migraine prevention as it caused clinical improvement in 78.1% of patients; this improvement included a reduction in headache attacks, intensity and duration [25]. In the same context, Miano et al. studied the role of melatonin in migraine prevention in children and reported that those children experienced a reduction in their headache frequency by more than 50% [26].

On comparing levels of melatonin among different migraine subtypes, lower levels were obtained in those with chronic migraine and those possessing a positive family history of migraine. In the same line, Masruha et al. informed that the urinary levels of sulfatoxymelatonin (melatonin metabolite) were significantly reduced in chronic migraine patients [16], also Ong et al. informed that the salivary melatonin levels measured at dim light were markedly reduced among chronic migraineurs [27]. In contrast, Zdunska et al. [24] found that there were non-significant differences in melatonin concentrations among migraineurs with aura when compared with those without aura.

It is known that migraine headaches are closely related to sleep alterations, as sleep deprivation and excess sleep cause alterations in headache frequency and sleep disorders are considered the main precipitating factors for migraine attacks and the pain improves with sleep [28]. This was supported by our study, as there is a significant difference between patients and controls regarding the sleep quality measured by SQS, the same was observed by previous studies [29, 30]. In the same way, Peres et al. [31] documented that the change in patient sleep schedule is associated with increased headache frequency.

In the current work, a significant correlation between sleep quality and the frequency of migraine attacks was obtained and higher SQS values were reported in chronic migraine. This is in accordance with Lin et al., who concluded that sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI) is strongly correlated with the number of migraine attacks whether preceded by an aura or not and the highest scores were recorded for patients with chronic migraine [32]. Regular sleep is claimed to reduce migraine attacks and improve chronic migraine [33].

We also noted a strong correlation between poor sleep and migraine with aura but different results were obtained in a previous study conducted by Iliopoulos et al. Who described that over 50% of migraine patients had a lack of sleep while oversleeping was four folds more likely in migraine with aura than in migraine

without aura [34]. This also agreed with Duan et al., who stated that poor sleep quality was significantly independently associated with an increased risk of developing migraine and the migraine-related burden [8].

Because the main function of melatonin is to control the sleep–wake cycle, it is accepted that migraine patients with sleep disorders would have the lowest melatonin levels. Also, Peres et al. proved that low melatonin concentrations have been reported in migraineurs with insomnia [35].

In the current study, advanced migraine disability measured by MIDAS was observed in association with lower melatonin levels and this finding was supported by Ebrahimi-Monfared study, which concluded that melatonin administration in migraine is associated with a reduction in migraine frequency, intensity and improvement in the disability [36].

Conclusion

Migraine patients tend to have a significantly lower melatonin levels especially, in the presence of aura and occurrence of chronic migraine. Bad sleep quality prevailed in patients with migraine and was strongly correlated with migraine disability. So we recommended a multicenter clinical trial to evaluate the role of exogenous melatonin for migraine prophylaxis as melatonin may represent a hope for improving this annoying headache. Screening for sleep quality and official diagnosis of sleep problems are important integral parts of patient care to improve overall patient outcome.

Abbreviations

ICHD-3	International classification of headache disorders-third edition
MIDAS	Migraine Disability Assessment Scale
SQS	Sleep quality scale
IQR	Interquartile range
mRNA	Messenger ribonucleic acid
CGRP	Calcitonin gene-related peptide
PSQI	Pittsburgh Sleep Quality Index

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Author contributions

SF, AA and RH carried out this work. AA designed the study and had done the statistical analysis. SF, and RH collected the patients, gathered clinical data and wrote the manuscript. All authors were involved in drafting the article or revising it critically for important. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials supporting the results of this article are included within the article [and its additional file(s)].

Declarations

Ethics approval and consent to participate

The study was approved from the Institutional Ethics Committee of the Faculty of Medicine, Zagazig University (ZU-IRB #10012/23-10-2022). Written informed consent was obtained from all study participants after explaining the details and benefits as well as risks to them. Surrogate consent from the patient's legal guardian or designated health proxy was permitted in cases where the patient did not have decision-making capacity.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no conflicts of interest with respect to the authorship and/or publication of this article.

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