

Sleep quality and frequency of comorbidities and its relation with chronic migraine related disability in patients with chronic migraine

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Abstract

Aim: Detecting quality of sleep and relation of comorbid situations that may effect sleep quality such as anxiety, depression, sleep apnea and excessive daytime sleepiness (EDS) with chronic migraine in patients with chronic migraine.

Material and Methods: 21 patients diagnosed with chronic migraine according to ICHD-3 Beta and 21 healthy volunteers as age and gender matched control group were included. Migraine type, duration, frequency of attacks in a month, Visual Analogue Scale (VAS), Migraine Disability Assessment Scale (MIDAS) scores of the migraine patient group were calculated. Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), Pittsburgh Sleep Quality Index (PSQI), Berlin Questionnaire (BQ), Epworth Sleepiness Scale (ESS) and Stanford Sleepiness Scale (SSS) were applied to every study participants. Scores of the chronic migraine patients from scales were compared to the ones of healthy controls. In addition, the relation between scores of the chronic migraine patients from scales and MIDAS score was studied.

Results: PSQI, ESS, HAM-A and BDI scores of the chronic migraine patients were detected to be significantly higher than of the healthy individuals ($p < 0.001$, 0.004 , < 0.001 , 0.021 subsequently). Chronic migraine patient group had a significantly higher risk of sleep apnea compared to healthy individuals according to BQ ($p = 0.015$). A positive significant correlation was detected between chronic migraine related disability and EDS of patients with chronic migraine ($p = 0.034$), ($r = 0.465$).

Conclusion: Sleep quality has been deteriorated due to headache in patients with chronic migraine. There is a strong relation between chronic migraine and comorbid conditions such as anxiety, depression, EDS, increased sleep apnea risk. Only EDS increases chronic migraine related disability.

Keywords: Chronic migraine; chronic migraine comorbidities; sleep quality; anxiety; depression; sleep apnea; chronic migraine related disability

INTRODUCTION

Migraine is the most frequent neurologic disease that creates disability in the general population (1). Chronic migraine is described as a subtype of migraine in which headache occurs for at least 15 days a month for 3 months by The International Classification of Headache Disorders-3 Beta (ICHD-3 Beta)(2). Chronic migraine is frequently seen together with psychiatric disorders such as depression and anxiety and comorbid situations such as sleep disorders. Sleep disorders are one of the comorbid situations of migraine that promote migraine disability and effect quality of life significantly (1).

Complaints about sleep and sleep disorders are frequent in patients with migraine. Ødegård et al. revealed in a study in 2010 that sleep disorders are 17 times more frequent in individuals with chronic headache compared to normal population and the patient group in which this relation is the strongest is patients with chronic migraine (3). The most common sleep complaints in patients with chronic migraine have been reported as difficulty falling asleep, difficulty maintaining sleep and EDS (4). Restless leg syndrome (RLS), parasomnias, increased EDS, bad sleep quality and insomnia are the most frequently reported sleep disorders (5).

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There is a complex and reciprocal relationship between migraine and sleep disorders.(5) Migraine attack can occur after a short period of morning sleep or during night sleep. Additionally, migraine attacks can be triggered with lack of sleep. The frequency of sleep disorders in patients with migraine can be explained by the biological involvement of the pathways involved both in migraine pathogenesis and sleep regulation. Some brain structures and neurotransmitter systems involved in sleep disorders may also be involved in primary headache disorders such as migraine. These structures and neurotransmitters contain monoamines, acetylcholine, GABAergic structures, orexin-hypocretin system, prostaglandins, cytokines (IL1) and adenosine (5). When the effect mechanism of sleep disorders in headaches are examined, former studies reveal that sleep deprivation increases the pain (6). Sleep deprivation may be causing a disorder in the descending pathways that inhibit the pain (7,8). It is suggested that disorder of serotonergic pathways that inhibit pain is related to migraine pathogenesis (9). When the effect of headache on sleep is considered, it was observed that chronic pain causes a change in the neural activity at raphe magnus that regulates sleep cycle. These types of changes can have an effect on sleep (10). Migraine pathophysiology includes cortical spreading depression, activation and sensitization of trigeminovascular system and dura, brain stem, cortex and excitatory and inhibitory balance of subcortical area (11-13). Additionally, hypothalamic-orexinergic system could play a role in the relation of migraine headache development and sleep (14). Neurons containing orexin in hypothalamus are ignited in case of wakefulness and disruption of orexinergic signals results in excessive sleepiness. Orexinergic cells affect not only monoaminergic activity during the sleep cycle, but also pain modulation. Orexin can also effect trigeminovascular tone. Migraine attacks are triggered by stress, exhaustion, sleep deprivation and bad sleeping habits and these simultaneously activate hypothalamus and orexin system. Low urinary melatonin and 6-sulfatoxymelatonin levels are associated with migraine (15,16). Melatonin levels not only play a role in the migraine pathophysiology but can also ease waking up from the REM sleep with headache related to low melatonin levels. With all these evidences put together, the relation between migraine and sleep and common pathophysiologic processes between migraine and sleep disorders are understood.

Depression and anxiety disorders are the most common comorbid situations in migraine. Frequency of depression is 63.8% while frequency of anxiety is 60.4% in patients with migraine (17). It is known that insomnia and excessive daytime sleepiness complaints related to both major depression and anxiety disorders are frequent. It is also detected that snoring and Obstructive sleep apnea syndrome (OSAS) are more frequent in patients with migraine compared to the ones with tension type headache or episodic headache (18). Increased CGRP levels, sympathetic activation, increased adiponectin

levels and orexin dysfunction were reported in etiology of OSAS related migraine frequency as well. Other than this, sleep quality of chronic migraine patients is effected by many other factors. Detecting and repairing factors effective in sleep quality of chronic migraine patients shall be favorable in making the results of the disease positive. For these reasons, we designed this case-control study to assess the frequency of comorbidities and the correlation between comorbidities and sleep quality in consecutively enrolled patients with chronic migraine, attending a tertiary-referral hospital and we tried to determine the most closely related conditions with migraine originated disability among these comorbidities.

MATERIAL and METHODS

The study has been planned as age and gender matched case-control study. 21 patients diagnosed with chronic migraine according to ICHD-3 Beta that presented to Ankara Atatürk Training and Research Hospital Neurology Outpatient Clinic between the dates of June-August 2018 and 21 healthy volunteers as control group were included in the study. Migraine type, duration, frequency of attacks in a month, VAS (19), MIDAS scores of the migraine patient group were calculated (20). BDI (21), PSQI (22), HAM-A (23), BQ (24), ESS (25) and SSS (26) were applied to every individual who participated in the study under the supervision of 3 specialist in neurology. Scores of the chronic migraine patients from scales were compared to the ones of healthy controls. In addition, the relation between scores of the chronic migraine patients from scales and MIDAS score was studied. Patients outside the 18-65 age bracket, pregnant women, those who have migraine prophylaxis in the last 1 month and patients with other accompanying headache syndromes were not included in the study. Approval of Ankara Atatürk Training and Research Hospital Ethics Committee was received before the study.

BDI: It is a scale used to determine the risk of an individual in terms of depression and to measure the level and severity of depressive symptoms. The scores between 0-13 are classified as normal, 14-19 as mild, 20-28 as medium and 29-63 as severe depression.

HAM-A: It is a 14-item scale used to determine the risk of an individual in terms of anxiety and to measure the level of anxiety symptoms and change in severity. It is scored between 0 and 56. Break point is taken as 6. Scores between 0-5 are considered as no anxiety, 6-14 are minor anxiety, 15-56 are major anxiety.

PSQI: Sleep habits (sleep time, wake-up time, time before falling asleep, total sleep time), the frequency of sleep problems during the night, sleep quality, use of sleep medication and having problems to stay awake in daily activities are the parameters evaluated by the test. The test measured the sleep quality in the last month, evaluated it on a total score of 21 and if the score was higher than 5, it indicated bad sleep quality.

BQ: Berlin Questionnaire is a three category scale that measures the risk of sleep apnea. It consists of a 10

questionnaire that includes information about the body mass index of the patient, snoring characteristics, sleep state and blood pressure. Each category is evaluated in itself and if 2 or more categories result in positive, it is considered as high risk of OSAS according to BQ.

SSS: It is a seven staged subjective test used to detect level of daytime sleepiness. Morning sleep state is graded as "1" being the lightest and "7" being the heaviest.

ESS: It is a test used to evaluate daytime sleepiness. It indicates the possibility of drowsing and falling asleep in various situations in the last month. It consists of 8 questions and each question is filled by the patient themselves by giving them points from 0 to 3. While the highest point is 24, if the total point is 10 and above, it indicates presence of EDS.

Statistical Analyses

The number and percentage values of group, sex, pain frequency, type and grouped scale values of the patient's included in the study were calculated. Chi-Squared test was used to determine whether PSQI, HAM-A, BDI, ESS and sex distribution showed a significant difference statistically based on patients with migraine and healthy individuals. Shapiro-Wilk test was used to determine the relevance of age, PSQI, HAM-A, BDI, ESS and SSS scores to normal distribution based on patients with migraine and healthy individuals. Mann-Whitney U non-parametric test was used to analyze whether PSQI, HAM-A, BDI and SSS values showed a significant difference statistically based on patients with migraine and healthy individuals. Independent Sample T test was used to analyze whether ESS scores showed a significant difference statistically based on patients with migraine and healthy individuals. MIDAS scores, average of VAS and disease duration, standard deviation, minimum, maximum values (definitive values) of chronic migraine patients were calculated. Correlation analysis was performed to detect relation between MIDAS scores and BDI, PSQI, HAM-A, BQ and ESS values of migraine patients and spearman rho relation coefficients were calculated. Shapiro-Wilk test was used to determine relevance of PSQI, HAM-A, BDI, ESS and SSS scores to normal distribution based on VAS of patients with migraine. One-Way ANOVA was used to test whether ESS scores showed a significant difference statistically or not based on pain frequency. Kruskal-Wallis non-parametric test was used to determine whether PSQI, HAM-A, BDI and SSS scores showed a significant difference statistically based on VAS. Bonferroni Correction Post-Hoc test was used to determine the origin group of parameters showing significance. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used for statistical analyzes and calculations. The statistical significance level was acknowledged as $p < 0.05$.

RESULTS

21 of the individuals participated in the study are patients with migraine, other 21 are in control group. Nine of the migraine patients had aura and 12 had not. There

was no difference between patients with migraine and control groups in terms of age and sex. The mean age of the migraine patients' group was 33.52 ± 10.10 while the mean age of individuals in the control group was calculated as 32.80 ± 7.23 . Age and sex values do not show a significant difference statistically based on patients and control groups ($p = 0.794, 0.956$). Average MIDAS score of the individuals in the patient group was calculated as 3.23 ± 1.17 , VAS average as 8.04 ± 1.28 and disease time as 6.28 ± 5.84 years.

Data on the scores of BDI, PSQI, HAM-A, BDI and ESS of patients with migraine and healthy individuals are indicated in Table 1. 11 of the patients with migraine were found to have low risk in terms of sleep apnea according to BDI, while 18 of the healthy individuals were found to have the same. BDI scores show a statistically significant difference between the two groups ($p = 0.015$). Majority of the low risk group were in the healthy group while majority of high risk group were in the group of patients with migraine (Table 1). When the PSQI scores of patients with migraine and healthy individuals were considered, 7 individuals who had good sleep quality were in the group of patients with migraine, 17 were in the control group and 14 individuals who had bad sleep quality were in the group of patients with migraine, 3 were in the control group. PSQI score distribution shows a statistically significant difference based on patient and control groups ($p = 0.001$) (Table 1). According to HAM-A, all of the individuals who did not have anxiety were in the healthy group, 5 individuals with minor anxiety were in the group of patients with migraine and 8 in the healthy group, 16 individuals with major anxiety were in the group of patients with migraine and 3 in the healthy group. HAM-A scores show a statistically significant difference based on patient and health groups ($p < 0.001$). When BDI scores are examined; 2 of the individuals in normal category were in the group of patients with migraine, 9 were in the control group, 13 of the individuals with mild depression were patients, 7 were healthy, 4 with moderate depression were patients, 4 were healthy and everyone ($n = 2$) who had severe depression were patients (Table 1). When the distribution of ESS scores are examined; 6 of the individuals in the normal category were in the group of patients with migraine, 11 in the control group, 7 of the individuals in normal but increased daytime sleepiness group were patients, 7 were in the control group, 5 of the individuals in increased but mild daytime sleepiness group were patients, 2 were in the control group, and every individual in increased but moderate daytime sleepiness and increased severe daytime sleepiness groups were patients. ESS score distribution does not show a statistically significant difference based on patient and control groups ($p = 0.220$) (Table 1).

SSS score average of patients with migraine was calculated as 5.00 (IQR=3.50), control group's was 3.00 (IQR=4.009) and SSS scores do not show statistically significant difference based on patient and control groups

($p=0.0223$). PSQI score average of patients with migraine was calculated as 6.00 (IQR=6.00), control group's was 3.00 (IQR=2.00). PSQI values of migraine patients are higher compared to control group. PSQI scores show a statistically significant difference based on patient and control groups ($p<0.001$). ESS score average of patients with migraine was calculated as 8.47 ± 4.19 , individuals in the control group's was 4.85 ± 3.23 . ESS score values show a statistically significant difference based on patient and control groups ($p=0.004$). ESS scores of patients are higher compared to control group. BDI score average of patients with migraine was calculated as 13.00 (IQR=11.50), control group's was 8.50 (IQR=7.00). BDI score values of migraine patients are higher compared to control group. BDI scores show a statistically significant

difference based on patient and control groups ($p<0.021$). HAM-A score average of patients with migraine was calculated as 20.00 (IQR=13.50), control group's was 7.50 (IQR=5.00). HAM-A scores of migraine patients are higher compared to control group. HAM-A scores show a statistically significant difference based on patient and control groups ($p<0.001$) (Table 2).

There is a moderate, positive, linear and statistically significant relationship between the MIDAS and SSS scores of the individuals in the study ($p=0.034$) (Table 3). No significant relationship was detected between the MIDAS scores and PSQI, ESS, BQ, BDI and HAM-A scores of the individuals (respectively; $p=0.383$, $p=0.260$, $p=0.197$, $p=0.068$, $p=0.390$) (Table 3).

Table 1. Comparison of questionnaire, index, scale and inventory results based on patient and control groups

Variables	Group		Test Statistics	
	Chronic Migraine Patient Group n (%)	Healthy Control Group n (%)	χ^2	P
Sex				
Berlin Questionnaire				
Low risk	11 (37.9)	18 (62.1)	7.003	0.015
High risk	10 (83.3)	2 (16.7)		
Pittsburgh Sleep Quality Index				
Good sleep quality	7 (29.2)	17 (70.8)	11.267	0.001
Bad sleep quality	14 (82.4)	3 (17.6)		
Hamilton Anxiety Rating Scale				
No anxiety	0	9 (100.0)	18.574	<0.001
Minor Anxiety	5 (38.5)	8 (61.5)		
Major Anxiety	16 (84.2)	3 (15.8)		
Beck Depression Inventory				
Normal	2 (18.2)	9 (81.8)	8.235	0.041
Mild	13 (65.0)	7 (35.0)		
Moderate	4 (50.0)	4 (50.0)		
Severe	2 (100.0)	0		
Epworth Sleepiness Scale				
Normal	6 (35.3)	11 (64.7)	5.735	0.220
Normal but increased daytime sleepiness	7 (50.0)	7 (50.0)		
Increased but mild daytime sleepiness	5 (71.4)	2 (28.6)		
Increased but moderate daytime sleepiness	2 (100.0)	0		
Increased severe daytime sleepiness	1 (100.0)	0		

χ^2 : Chi-Square Comparison test

Table 2. Comparison of scale, inventory and index scores based on patient and control groups

Variables	Group		Test Statistics	
	Chronic Migraine Patient Group Avg \pm SD Median (IQR)	Healthy Control Group Avg \pm SD Median (IQR)	χ^2	P
Sex				
Stanford Sleepiness Scale	5.00 (3.50)	3.00 (4.00)	1.220	0.223
Pittsburgh Sleep Quality Index	6.00 (6.00)	3.00 (2.00)	3.642	<0.001
Epworth Sleepiness Scale	8.47 \pm 4.19	4.85 \pm 3.23	3.091	0.004
Beck Depression Inventory	13.00 (11.50)	8.50 (7.00)	2.301	0.021
Hamilton Anxiety Rating Scale	20.00 (13.50)	7.50 (5.00)	4.574	<0.001

t; Z: Mann-Whitney U non-parametric test, IQR: Interquartile Range

Table 3. Correlation analysis of relationship between MIDAS scores and scale scores of individuals in the patient group

Variables	Spearman Rho Relation Coefficient -r	P
MIDAS Score - Stanford Sleepiness Scale	0.465	0.034
MIDAS Score - Pittsburgh Sleep Quality Index	-0.201	0.383
MIDAS Score - Epworth Sleepiness Scale	-0.257	0.260
MIDAS Score - Berlin Questionnaire	-0.293	0.197
MIDAS Score - Beck Depression Inventory	0.405	0.068
MIDAS Score - Hamilton Anxiety Rating Scale	0.198	0.390
Beck Depression Inventory	13.00 (11.50)	8.50 (7.00)
Hamilton Anxiety Rating Scale	20.00 (13.50)	7.50 (5.00)

r: correlation coefficient

DISCUSSION

A two-way relationship between migraine and sleep has been emphasized by many previous studies. (27,28). Disruption of sleep or insomnia are the most known triggers of migraine. In addition to this, amount of sleep decreases in patients with migraine related to the intensity of the headache. In view of this relationship between migraine and sleep, it is obvious that migraine disrupts sleep quality. Recent studies stated that, similar to the results of our study, disorder of sleep quality is higher in patients with migraine compared to healthy controls. Seidel et al. declared that especially migraine patients who have 8 or more attacks in a month have worse sleep quality than the individuals in healthy control group (29). Lin et al. detected that PSQI scores of patients who report high migraine frequency are higher than the healthy controls, similar to the result of our study (28). All these studies support that sleep quality is poorer in chronic migraine, the migraine subtype with the highest frequency of migraine by definition.

While anxiety disorder and depression are important comorbidities of chronic migraine, it is known from the previous studies that they also increase migraine frequency (30). Anxiety disorder and mild depression was detected to be significantly higher in patients with chronic migraine compared to healthy individuals in our study as well and they are consistent with the previous literature information. Especially Zhu et al. commented that association of history of migraine and anxiety and/or depression comorbidities are indicators of bad sleep quality, similar to the results that we detected in our study (31). It is stated that there is a two-way relationship between migraine and anxiety and/or depression similar to relationship between migraine and sleep quality (32). This relationship is based on headache characteristics, primarily frequency of pain. Increased frequency of

headaches strongly effect quality of life as well as anxiety and depression (33). In our study, while a significant relationship between chronic migraine and major anxiety was detected as expected, the statistically significant relationship detected between mild depression and chronic migraine was not detected between severe depression and chronic migraine. We think that it is especially because the number of patients included in the chronic migraine group was not adequate and this relationship will result as expected in studies that will be conducted in the future with a broader participation.

Morning headache is the most frequently reported type of headache in OSAS and the relationship between migraine and OSAS is not clear (34). It has been reported in a recent composition that migraine and tension type headaches in the society do not have a relationship with OSAS. However, the amount of articles stating this relationship is not that few (35,36). It was in reported cross-section CaMEO study that frequency of sleep apnea and bad sleep quality are higher in patients with chronic migraine (36). We detected that patients with chronic migraine had significantly higher risk of sleep apnea compared to the healthy control group in BQ that we applied in our study. As a result of this relationship, we concluded that the presence of high sleep apnea may increase nighttime sleep disruption and poor sleep quality originating from this may increase the frequency of migraine in patients.

EDS is another one of those comorbid condition that can be detected in migraine (37). It is reported 3 times more in patients with migraine compared to the healthy controls (38). It is reported that frequency of EDS prominently increases as the frequency of migraine increases (29). A study conducted revealed that the rate of EDS prevalence is a high 39.8% in individuals with chronic migraine (39). ESS scores of patients with chronic migraine were also statistically significantly higher than healthy controls in favor of higher EDS rate in our study. The etiology of EDS in chronic migraine is thought to be due to disease-related poor sleep quality (40), rather than disease-related direct hypothalamic involvement (39). In addition to this, although not certain, another hypothesis is the fact that EDS increases migraine attacks (5). The statistically significant and positive correlation that we detected in our study between MIDAS score that indicates attack frequency related disability in migraine and SSS that indicates EDS, supported this hypothesis.

There were some limitations in our study. The number of patients and healthy volunteers included was relatively low. It was our fault to not give sleep schedules to patients with chronic migraine to evaluate characteristic features of headache and especially sleep related changes. Another important limitation was the failure to take into account the effect of sedative drugs used for other reasons by the individuals who participated in the study in order to more accurately evaluate presence and frequency of EDS, presence of anxiety and/or depression and sleep quality. Lastly, we could receive more reliable information by evaluating with polysomnography in order to more

objectively indicate sleep quality and changes in the sleep architecture of patients with chronic patients.

CONCLUSION

In conclusion, we have detected in our study that quality of sleep was deteriorated due to migraine in patients with chronic migraine and chronic migraine is highly related with comorbid situations such as anxiety, depression, EDS and increased sleep apnea risk. However, we have found that only EDS among them increased chronic migraine related disability. The fact that EDS might aggravate migraine attacks and migraine related disability was a novel finding in our study. Future studies focusing on the relation between EDS and migraine attacks and migraine related disability might reveal the pathophysiology beneath it, which might help chronic migraine related disability and worse quality of life while treating EDS.

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