

Relationship between Apnea-Hypopnea Index and Oxygen Desaturation in REM-Sleep Period and Morning Headache in Patients with Obstructive Sleep Apnea Syndrome

Obstruktif Uyku Apne Sendromlu Hastalarda REM Uyku Dönemindeki Apne-Hipopne İndeksi ve Oksijen Desaturasyonu ile Sabah Baş Ağrısı Arasındaki İlişki

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ABSTRACT

Introduction: In patients with morning headache, REM sleep period decreases though little is known about its physiopathology. We evaluate the polysomnographic records of obstructive sleep apnea syndrome (OSAS) patients with the hypothesis that oxygen desaturations may be a better determinant in patients with morning headache, especially those in REM sleep periods.

Methods: Patient group (group 1) with a total of 361 patients with OSAS and the controls (group 2) with 107 healthy individuals were evaluated. The presence of morning headache was compared between the groups, and sleep parameters were correlated with morning headache.

Results: In group 1, patients with OSAS and morning headache, apnea-hypopnea index in the REM sleep period (26.7/hour, min-max: 0–108.4/

hour) was higher than those in patients without morning headache (17.8/hour, min-max: 0–107.8/hour). The minimum oxygen saturation in REM sleep period and total sleep time (TST) was lower in patients with morning headache (REM sleep period: 82%, min-max: 50–94% ; TST: 79%, min-max: 50–97%) in compared to patients without morning headache (REM sleep period: 84%, min-max: 50–93% ; TST: 81%, min-max: 50–90%).

Conclusion: Here we demonstrated that higher apnea-hypopnea index and lower oxygen saturation in REM sleep period were associated with morning headache in patients with obstructive sleep apnea syndrome.

Keywords: Obstructive sleep apnea syndrome, morning headache, REM sleep period, apnea-hypopnea index, oxygen saturation

ÖZ

Amaç: Sabah baş ağrısı olan hastalarda, REM uyku periyodu azalmıştır, ancak fizyopatolojisi hakkında az bilgi mevcuttur. Oksijen desatürasyonunun, özellikle REM uyku dönemlerinde olmak üzere, sabah baş ağrısı olan hastalarda daha belirgin olabileceği hipotezi ile obstruktif uyku apne sendromlu hastaların polisomnografik kayıtları incelendi.

Yöntem: Toplam 365 hasta (Grup 1) ve kontrol grubu olarak 103 birey (Grup 2) değerlendirildi. Gruplar arasında sabah baş ağrısı varlığı karşılaştırıldı, sabah baş ağrısı olup olmamasına göre gruplar kendi içlerinde ayrılarak uyku parametreleri açısından ayrıca karşılaştırıldı.

Bulgular: Grup 1 içerisinde sabah baş ağrısı olan hastalarda REM dönemindeki apne-hipopne indeksi (26,7/saat, min-maks: 0–108,4/saat),

sabah baş ağrısı olmayan gruba göre (17,8/saat, min-maks: 0–107,8/saat) yüksek bulundu. REM dönemindeki ve toplam uyku zamanındaki minimum oksijen satürasyonu sabah baş ağrısı olan grupta (REM: %82, min-maks: %50–94; toplam: %79, min-maks: %50–97) sabah baş ağrısı olmayan gruba (REM: %84, min-maks: %50–93; toplam: %81, min-maks: %50–90) göre düşük bulundu.

Sonuç: Bu çalışmada obstruktif uyku apne sendromlu hastalarda REM uyku dönemindeki yüksek apne hipopne indeksi ve düşük oksijen satürasyonunun sabah baş ağrısı ile ilişkili olduğu bulundu.

Anahtar Kelimeler: Obstruktif uyku apne sendromu, sabah baş ağrısı, REM uyku dönemi, apne-hipopne indeksi, oksijen satürasyonu

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), a disorder that causes hypopnea and apnea due to partial or complete obstruction of the upper airways, is characterized by recurrent oxygen desaturation and

interrupted sleep (1). The criteria for OSAS are an apnea-hypopnea index (AHI) of at least 5 per hour (h), accompanied by symptoms such as daytime somnolence. It is a common disease in middle-aged adults

with an estimated prevalence of 4% in males and 2% in females (2, 3). When OSAS is defined only with an AHI $\geq 5/h$, the estimated prevalence in middle-aged adults is reported to be as high as 20% (4, 5).

The relationship between headache and sleep has been well-described, but the physiological mechanism is not fully understood (6–8). Headache, especially morning headache (MH), is a common clinical finding of OSAS (9). Furthermore, in the “International Classification of Headache Disorders (ICHD),” MH associated with OSAS is classified under the heading of “sleep apnea headache” (10). While the prevalence of a MH in OSAS patients was found to be 18%, only 5%–7% of the general population experiences this symptom (11–13). On the other hand, OSAS was detected in 12%–42% of people with nocturnal or MH (14). Previous epidemiological studies demonstrated a significant relationship between sleep apnea and headache and more detailed studies have shown that sleep apnea syndrome is associated with MH (11, 13, 15–17). However, other studies contradict these findings (18, 19). The relationship between MH and oxygenation problems is widely accepted, but its relationship with nighttime sleep is not fully known, and is likely associated with other sleep parameters (20).

The mechanism of obstructive sleep apnea causing MH is not clear. Previous work has suggested hypoxia, hypercapnia, impaired autoregulation of cerebral blood flow, transient increases in intracranial pressure, or fragmented sleep influences MH (21). Eliminating MH by OSAS treatment, with continuous positive airway pressure (CPAP), supports the association between OSAS and MH (22).

In sleep studies of patients with and without MH, it was revealed that patients with MH have significantly reduced REM sleep (20, 23). The purpose of our study was to evaluate the relationship between the REM period and MH in OSAS patients who have oxygen desaturation during REM sleep.

METHODS

Procedure

We recruited patients who presented with complaints of snoring and/or sleep respiratory problems between January 2014 and October 2015 at our sleep research center. All patients were clinically evaluated and had polysomnography studies, leading to OSAS pre-diagnosis.

Polysomnography was performed with the Grass Comet Plus AS40 device. Electroencephalography (EEG, F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1), electrooculography (EOG), submental electromyography (EMG), bilateral anterior tibialis electromyography, and electrocardiography (ECG) recordings were performed in accordance with the American Academy of Sleep Medicine (AASM) criteria. Respiratory inductive plethysmography belts recorded chest and abdominal movements. Airway flow was evaluated with a nasal airway and thermistor. Pulse rate and oxygen saturation were measured by a finger probe oximeter.

Sleep recording was performed between the period when the lights were switched off (when the patient fell asleep) and the lights were switched back on (normally between 06:30 and 07:00). In the morning, each patient filled in a questionnaire about any sleep apnea headache according to the ICHD-3 beta criteria.

Polysomnography was applied to all cases in the same protocol. The records were scored by an experienced sleep physician according to the standard AASM criteria, without knowing whether patients had MH (24). The AHI was determined by counting the number of apneas and hypopneas per hour during sleep. Patients with an AHI value $\geq 5/h$ were determined to have OSAS. OSAS severity was determined using four AHI

cut-off points: AHI $< 5/h$, AHI 5 to $< 15/h$, AHI 15 to $< 30/h$, and AHI $\geq 30/h$. Increased daytime sleepiness was evaluated by the Epworth Sleepiness Scale (25).

The study was approved by the Ethical Committee of Gulhane Medical Faculty. This study was conducted in accordance with the Declaration of Helsinki. As this is a retrospective study, the informed consent was not required.

Patients

The patients were divided into two groups based on PSG scoring: those with (Group 1) or without OSAS (Group 2), according to AHI values. Headache diagnosis was made according to the ICHD-3 beta criteria in our standard questionnaire. The primary criteria were headache associated with waking in the morning and recovery within four hours. Since the control group did not meet the criteria of AHI $\geq 5/h$, MH was used instead of sleep apnea headache terminologically. The presence of MH was compared between the groups, and the patients with and without MH in both groups were compared according to age, sex, body mass index, Epworth Sleepiness Scale, the presence of comorbidities, use of psychotropic drugs, and sleep and respiratory variables. Patients were further divided into subgroups according to OSAS severity level, and the same parameters were compared (AHI $< 5/h$: Control; $5 \leq$ AHI $< 15/h$: Mild OSAS; $15 \leq$ AHI $< 30/h$: Moderate OSAS; $30/h \leq$ AHI: Severe OSAS). The total sleep time, sleep effectiveness, percentage of stages 1, 2, 3, and REM sleep, oxygen saturation, the duration when oxygen saturation was under 90%, and oxygen desaturation index were assessed.

Statistical analysis

Statistical analyses were performed with SPSS 16.0 (IBM, Chicago, Illinois, USA). Fitness of data to a normal distribution was assessed by the Kolmogorov-Smirnov test. Normal distribution data were presented using the mean and standard deviation; data outside a normal distribution were presented using the median and minimum-maximum values. For independent groups, the normally distributed data were compared using Student's T-test, and abnormally distributed data were compared using the Mann-Whitney U test. For multiple comparisons, a Bonferroni correction was employed. Ratios were compared by the Chi-Square test. P-value below 0.05 was considered statistically significant.

RESULTS

We recruited 652 patients, but excluded 179 who had an additional sleep disorder (except for snoring and OSAS), or used psychiatric or neurological drugs with known sleep effects. An additional five patients were excluded because the REM period could not be assessed, leaving 468 patients in the study. The PSG results indicated that 107 patients had AHI $< 5/h$ and were assigned to the control group. The remaining 361 patients had AHI $\geq 5/h$ and were assigned to the OSAS group (Figure 1). Patients in the OSAS group were significantly older than the control group, but there was no difference between the groups in terms of MH, male/female ratios, body mass index (BMI). Comorbid diseases were found to be higher in the OSAS group (Table 1).

No difference was detected between patients with and without MH in the OSAS group in terms of age and comorbid diseases. However, the female patient ratio and the Epworth Sleepiness Scale were higher in the group with MH (Table 2). The AHI in the REM period was higher in the group with MH (26.7/h, min-max: 0–108.4/h) than the group without MH (17.8/h, min-max: 0–107.8/h). The AHI in total time was not different between the group with MH (19.2/h, min-max: 5–128.8/h) and the group without MH (17.6/h, min-max: 5–94.6/h). The minimum oxygen saturation in the REM period was lower in the MH group (82%, min-max: 50–94%) than in the group without MH (84%, min-max: 50%–93%). The

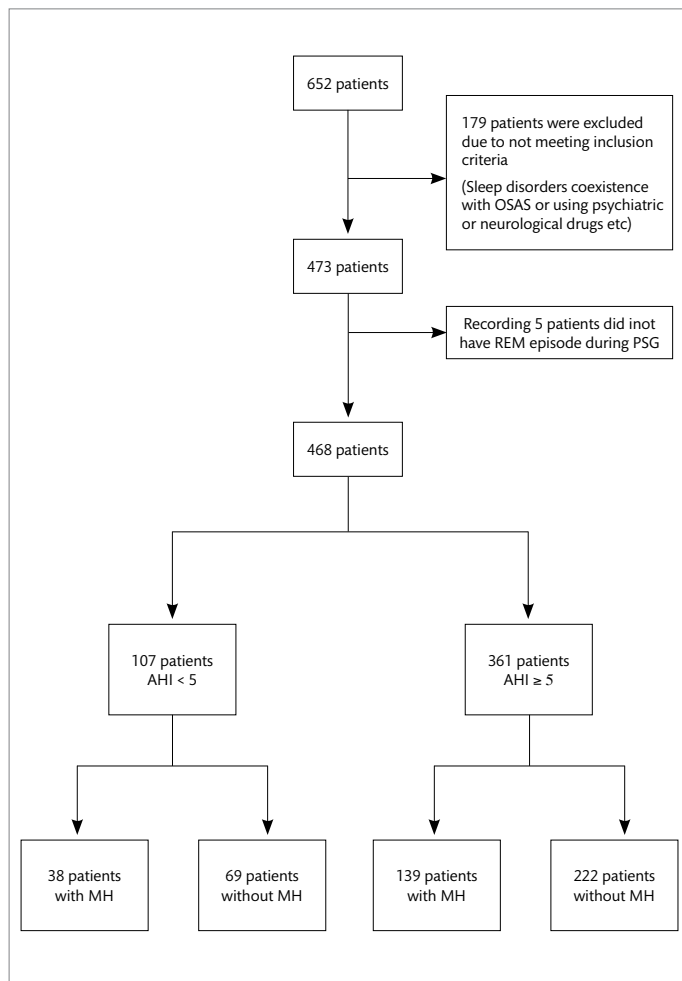


Figure 1. Patient selection phase.

minimum oxygen saturation in the total time was lower in the group with MH (79%, min-max: 50–97%) than in the group without MH (81%, min-max: 50%-90%). The oxygen desaturation index was higher in both the REM period and the total time in the group with MH than in the group without MH (REM 23.5/h, min-max: 0–101.4/h vs. 14.3/h, min-max: 0–120/h; total 14.6/h, min-max: 0–119.6/h vs. 11/h, min-max: 0.5–107.1/h) respectively. There was no difference between groups in terms of the other parameters (Table 3). MH was observed in 35.5% of the non-OSAS group, 36.1% in mild OSAS, 35.3% in moderate OSAS, and 44.3% in severe OSAS, but these differences were not statistically significant ($p>0.05$).

Upon separating and examining the cases with and without MH in the control group, no difference was determined in terms of age, sex, BMI, comorbid disease, Epworth Sleepiness Scale, or sleep parameters.

DISCUSSION

The present study main finding was that the AHI in the REM period was significantly higher in the group with MH than the group without MH in OSAS patients. There was no difference between groups in terms of AHI ratios in the total time. To the best of our knowledge, this is the first study reporting that the AHI in the REM period is higher in OSAS patients with MH than without MH. These results suggest that this likely due to increased respiratory events in the REM period in OSAS patients with MH. It is not known whether the OSAS-related MH mechanism is associated with hypoxia, hypercapnia, or sleep disorder. Furthermore, most patients with MH and sleep apnea do not meet the sleep apnea-related headache criteria (26). It was shown that hypoxemia plays a pathophysiological role in MH and patients with MH have significantly lower oxygen saturation during both REM and NREM periods. In this study, we observed the minimum oxygen saturation to be significantly lower in patients with MH in both REM and total sleep time, consistent with the literature (22). In the series of 116 OSAS patients, Greenough et al. found higher incidence of obstructive apnea in the group with a headache in the REM period; however, this difference was not significant,

Table 1. Characteristics of the Group 1 and Group 2

	Control group (n=107)	OSAS group (n=361)	P value
Age (year)	38.63±11.57	46.82±12.31	<0.001
Sex M/F (n)	69/38	241/120	0.663
Morning headache (%)	35.5%	38.5%	0.575
BMI (kg/m ²)	27.34 (19.10–58.27)	29.05 (18.67–60.41)	0.002
Comorbid disease	38.3%	50.4%	0.028

Significant findings ($p<0.05$) are shown in italics. Parametric data are shown as mean ± standart deviation, nonparametric data are shown as median (minimum-maximum). OSAS: obstructive sleep apnea syndrome, F: female, M: male, BMI: body mass index, Comorbid disease: Presence of cardiovascular disease, defined as a doctor diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Hypertension and diabetes were defined as a doctor diagnosis and treatment with medication.

Table 2. Comparison of gender, age, BMI and comorbid disease history in obstructive sleep apnoea syndrome groups with and without morning headache

	OSAS patients without MH (n=222)	OSAS patients with MH (n=139)	P value
Age (year)	46.70±11.65	47.02±13.34	0.811
Sex M/F	163/59	78/61	0.001
BMI (kg/m ²)	29.47±5.01	30.59±5.72	0.051
Comorbid disease	49.5%	51.8%	0.677
Epworth sleepiness scale	9.99±4.79	12.02±5.63	0.002
Excessive daytime sleepiness	35%	45.3%	0.002

Significant findings ($p<0.05$) are shown in italics. Parametric data are shown as mean ± standart deviation. OSAS: obstructive sleep apnea syndrome, MH: morning headache, F: female, M: male, BMI: body mass index, Comorbid disease: Presence of cardiovascular disease, defined as a doctor diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Hypertension and diabetes were defined as a doctor diagnosis and treatment with medication.

Table 3. Sleep parameters of obstructive sleep apnoea syndrome patients with and without morning headache

	OSAS patients without MH (n=222)	OSAS patients with MH (n=139)	P value
Sleep efficiency (%)	85.1 (38.4–98.4)	85.3 (28.7–98.8)	0.890
Total sleep time (minute)	386.2 (186.5–495.0)	388.5 (116.0–487.5)	0.841
Sleep stage 1 (%)	20.6 (0.8–89.3)	21.2 (0.4–86.1)	0.650
Sleep stage 2 (%)	50.4 (3.6–89.8)	50.4 (2.0–89.3)	0.800
Sleep stage 3 (%)	11.2 (0–36.7)	11.2 (0–44.4)	0.466
REM sleep (%)	13.5 (0.4–28.6)	14.1 (1.1–29.6)	0.887
AHI TST/h	17.6 (5.0–94.6)	19.2 (5.0–128.8)	0.481
AHI REM/h	17.8 (0–107.8)	26.7 (0–108.4)	0.035
Min total O₂ (%)	81 (50–90)	79 (50–97)	0.019
Min REM O₂ (%)	84 (50–93)	82 (50–94)	0.013
Ave total O₂ (%)	92.5 (71–96.5)	92.2 (68.5–97)	0.209
Ave REM O₂ (%)	92 (71.3–97.3)	91.4 (56.6–96.4)	0.151
Oxygen desaturation index total sleep time/h	11 (0.5–107.1)	14.6 (0–119.6)	0.008
Oxygen desaturation index REM/h	14.3 (0–120)	23.5 (0–101.4)	0.009

Significant findings ($p < 0.05$) are shown in italics. Nonparametric data are shown as median (minimum–maximum). OSAS: obstructive sleep apnea syndrome, MH: morning headache, REM: rapid eye movement, PLMI: periodic leg movement index, AHI: apnoea-hypopnoea index, TST: total sleep time, Min: minimum, Ave: average, O₂: oxygen.

likely because it was statistically underpowered. A significant difference might be obtained with a larger patient sample population (23). In fact, upon performing this evaluation with more subjects, respiratory events in the REM period were found to be significantly higher.

Regarding the relationship between MH and OSAS, while Loh et al. and Goksan et al. found a relationship between the MH presence and OSAS level, Olson et al. found no relationship between the OSAS level and other PSG variables and headache presence (13, 22, 27). In our study, we did not find a relationship between the OSAS level and MH presence. Unspecified MH was detected at a ratio of 36–58% in OSAS patients, and headache may be the reason for patient admission (21). However, headache prevalence in the group with snoring and without OSAS was found to be the same as the group with OSAS (21). In this study, the MH presence was found to be 35.5% in the non-OSAS group presented with snoring complaints and 38.5% in the OSAS group but was not significantly different.

While Greenough et al. observed that patients with a headache spend less time in REM sleep, other studies have shown no effect on sleep effectiveness or REM and NREM sleep percentages consistent with our study (19, 22, 23). We found no difference in sleep effectiveness and the stages of sleep in patients with and without MH. The presence of MH does not change the structure, effectiveness, or duration of sleep in OSAS patients. A migraine, cluster headache (CH), chronic paroxysmal hemicrania (CPH), and hypnic headache, among primary headaches, frequently occur in specific stages of sleep, suggesting a pathophysiological relationship with sleep. While a migraine occurs during stage 3, and in the REM sleep period, CPH and CH usually occur in sleep and in the REM period of sleep, particularly in OSAS patients (21, 28–30). The effect of the REM period is apparent in these primary headaches, and we showed an association of MH with the REM period supported by a high AHI was high in the REM period in the group with MH. Although these headaches usually occur during sleep, they have minimal effects on sleep quality, and we did not find any difference between groups in terms of sleep quality.

Patients with chronic hypoxemia complain about a diurnal headache, and those with nocturnal respiratory failure often have MH. Sufficient nocturnal oxygenation by CPAP usually terminates these complaints (22). In this study, the desaturation index in both the REM period and total sleep time was significantly higher in the group with MH and showed a

relationship between MH and hypoxemia. In the literature, the headache pathogenesis in OSAS patients is assessed to determine cerebral and physiological effects of hypoxia and hypercapnia, rather than the deterioration of sleep physiology. The current study findings support this opinion (21).

Since headache is more frequently observed in females than males in general, MH is observed more frequently in female OSAS patients than male patients (22). The female ratio in patients with MH in the OSAS group was significantly higher compared to the ratio of females without MH, consistent with the literature (31). The findings of the present study also revealed that MH is more common in female patients. The frequency of excessive daytime sleepiness was 34.9% in patients with an AHI $\geq 5/h$ in the study by Krisitansen et al., compared to 47.5% in the present study (32). There are studies in the literature that did not find a difference in the Epworth Sleepiness Scale between groups with and without MH (23, 33). We found increased daytime sleepiness in the group with MH to be significantly higher than non-MH, likely due to MH increasing daytime sleepiness.

There are a few limitations to discuss. This study was retrospective and not designed to identify headache subtypes. Also, we did not follow-up with patients to see if CPAP treatment decreased headache. However, the aim of this study is not to determine treatment effectiveness. In a study conducted with a small number of patients, Greenough et al. drew attention to the effect of the REM period, and determined that MH and the minimum oxygen saturation in the REM period were lower and AHI higher upon repeating a study with a higher number of patients (23).

To the best of our knowledge, this is the first study revealing the effect of the REM period in patients with OSAS and MH. We consider that MH observed in patients is closely related to increased respiratory events in the REM period. The remarkable increased AHI in the REM period in MH patients with OSAS strengthened the opinion that the pathogenesis of a headache depends on the cerebral physiological effects of apnea in the REM sleep period. The results obtained contribute to MH identification associated with the REM sleep physiology. There is a need for a multi-centered, randomized, double-blind, and extensive series of studies to completely demonstrate the relationship of high AHI in the REM period with MH and different types of headaches.

Ethics Committee Approval: The study was approved by the Ethical Committee of Gulhane Medical Faculty. This study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: As this is a retrospective study, the informed consent was not required.

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