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Is NREM-predominant obstructive sleep apnea syndrome a different clinical entity?

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Background/aim: This study aimed to evaluate whether NREM-predominant obstructive sleep apnea syndrome (OSAS) patients (NREM AHI < REM AHI) have distinct clinical and polysomnographic features compared to REM-predominant OSAS patients (REM AHI > NREM AHI).

Materials and methods: A total of 342 patients (93 females and 249 males) who were admitted to the Sleep Disorders Unit at the Gazi University Faculty of Medicine and underwent polysomnography between January 2011 and April 2016 were retrospectively reviewed. Patient data, symptoms related to OSAS, Epworth Sleepiness Scale (ESS) scores, and polysomnographic findings were recorded. The patients were divided into two groups according to the apnea–hypopnea index (AHI) as patients with NREM-predominant OSAS and patients with REM-predominant OSAS.

Results: The total AHI in the NREM-predominant group was significantly higher than in the REM-predominant group ($P < 0.001$). The patients with severe OSAS constituted the majority in both groups, and the rate of patients with severe OSAS was significantly higher in the NREM-predominant group than in the REM-predominant group ($P < 0.001$). Arousal index and sleep time spent under 90% SaO_2 was higher in the NREM-predominant group ($P = 0.005$, $P = 0.001$), whereas nocturnal mean and minimum O_2 saturation values were lower in the NREM-predominant group compared to patients with REM-predominant OSAS ($P < 0.001$, $P = 0.013$). In evaluating systemic disorders, the prevalence of coronary artery disease was significantly higher in the NREM-predominant OSAS group ($P < 0.001$).

Conclusion: Our results showed that patients with NREM-predominant OSAS had a more severe course than patients with REM-predominant OSAS. However, we found no significant difference in sleep-specific symptoms, suggesting that the two groups represented distinct entities.

Key words: Obstructive sleep apnea, NREM sleep, REM sleep, apnea–hypopnea index, comorbidity

1. Introduction

OSAS affects about 2%–4% of the adult population (1), resulting in increased morbidity and mortality (2). It is a risk factor particularly for cardiovascular diseases, such as systemic arterial hypertension, ischemic heart disease, stroke, heart failure, and atrial fibrillation (3). As one of the main symptoms of OSAS, excessive daytime sleepiness is known to cause cognitive dysfunction, decreased quality of life, and traffic accidents (4).

Rapid eye movement (REM)-predominant OSAS is a phenotype of OSAS and its clinical and physiopathological basis is well understood. In addition, REM-predominant OSAS has been shown to be associated with female sex, increased age, and obesity (5). It is known that upper airway muscle tone decreases more remarkably during REM sleep compared to non-REM (NREM) sleep. Decreased muscle tone causes recurrent apnea/hypopnea and deep hypoxemia episodes at night (6). Several studies have shown longer apnea episodes, apnea-related desaturation, and deeper hypoxemia episodes occurring in patients with REM-predominant OSAS (7,8). Additionally, disturbed genioglossus reflex response to negative pressure and decreased chemosensitivity may worsen apnea episodes during REM sleep (9,10). Therefore, the damage caused by OSAS is considered to be more severe during REM sleep than NREM sleep. However, several studies have reported higher apnea–hypopnea index (AHI) scores during NREM sleep than during REM sleep. The studies by Liu et al., Siddiqui et al., and Muraki et al. reported higher AHI scores in patients with NREM-predominant OSAS compared to patients with REM-predominant OSAS (5,11,12). To date, no studies have demonstrated a

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commonly accepted clinical or polysomnographic finding or a pathological process that could explain the difference in patients with NREM-predominant OSAS. Based on the hypothesis that patients with NREM-predominant OSAS are a distinct patient group, in the present study, we aimed to evaluate whether NREM-predominant OSAS patients have distinct clinical and polysomnographic features compared to REM-predominant OSAS patients.

2. Materials and methods

2.1. Participants and procedures

We retrospectively reviewed the medical records of a total of 342 patients (93 females and 249 males) who were admitted to the Sleep Disorders Unit of the Gazi University Faculty of Medicine due to snoring, apnea, and excessive daytime sleepiness, who underwent polysomnography and were diagnosed with OSAS between January 2011 and April 2016. Patients with an AHI score of >5/s were diagnosed with OSAS; mild OSAS was defined as an AHI of 5/s–15/s, moderate OSAS was defined as an AHI of 15/s–30/s, and severe OSAS was defined as an AHI of higher than 30/s. The patients were administered the Epworth Sleepiness Scale (ESS) by the physicians and the symptoms of OSAS were inquired about; the results and demographic and clinical characteristics of the patients were recorded. The presence of systemic arterial hypertension, coronary artery disease, diabetes mellitus, or gastroesophageal reflux disease commonly occurring with OSAS was evaluated. Patients who were considered to have OSAS and those with an ESS score of higher than 10 points underwent polysomnography. Polysomnography was scored by a single operator to avoid biased results. During polysomnography, REM and NREM sleep times and rates, total sleep duration, AI, total AHI, REM AHI, NREM AHI, mean SaO_2, minimum SaO_2 measured at night, sleep time spent under 90% SaO_2, sleep induction time, and sleep times in supine and nonsupine positions were recorded.

Sleep stages and respiratory events were scored according to the standard criteria. Apnea was defined as the cessation of respiratory flow (≥90% drop in respiratory flow) for at least 10 s; hypopnea was defined as a ≥30% decrease in respiratory flow for at least 10 s, resulting in electroencephalographic arousal or 3% or higher decrease in oxygen saturation (13). Patients with a total sleep time of less than 240 min in polysomnography, patients with sleep efficiency of less than 40%, and patients in whom REM sleep duration was lower than 30 min were excluded. Patients with a pulmonary disease, central nervous system disorder, muscle disease, or neuropathy; pregnant women; patients on sedative drugs; and those who consumed alcohol were excluded from the study. The patients were divided into two groups according to the AHI as patients with NREM-predominant OSAS and patients with REM-predominant OSAS. Clinical characteristics and polysomnographic data were compared between the two groups.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). Numeric data were expressed as mean ± standard deviation (SD) or median (min–max), and categorical data were expressed as number and percentage. Parametric test assumptions (normality and homogeneity of variance) were tested before comparing numeric variables between the groups. When parametric test assumptions were met, two-way analysis of variance was used to investigate whether there were differences between patient groups and sexes in terms of numeric variables. The Mann–Whitney U test was used if parametric test assumptions were not met. The presence of a difference in categorical variables between the groups was investigated using the chi-square test or Fisher's exact test. A P-value of 0.05 was considered statistically significant.

3. Results

The patients with NREM-predominant OSAS constituted 45% of the whole study group (154 patients). Males were the predominant sex both in the REM-predominant (F = 70, M = 118) and NREM-predominant (F = 23, M = 131) OSAS groups. The mean age of women in the NREM-predominant group was significantly statistically higher than the mean age of women in the REM-predominant group (59.5 ± 9.6 years vs. 52.5 ± 9.3 years; P = 0.008. There was no statistically significant difference between the median ages of men in the NREM- and REM-predominant groups (48.6 ± 12.5 years vs. 47.7 ± 10.2 years; P = 0.539). There were no significant differences in terms of age, body mass index (BMI), neck circumference, number of cigarettes smoked per day, or ESS scores between the two groups. In evaluating systemic disorders, the prevalence of coronary artery disease was significantly higher in the NREM-predominant OSAS group (P < 0.001) (Table 1). The total AHI score in the NREM-predominant group was significantly higher than in the REM-predominant group (P < 0.001) (Table 2). Patients with severe OSAS constituted the majority of the patients in both NREM- and REM-predominant groups, and the rate of patients with severe OSAS was significantly higher in the NREM-predominant group than in the REM-predominant group (P < 0.001) (Figure). When polysomnographic data were evaluated, AI was higher in the NREM-predominant OSAS group (P = 0.005). Similarly, nocturnal mean and minimum SaO_2 values were lower in the NREM-predominant group, whereas sleep time spent under 90% SaO_2 was higher compared to patients with REM-predominant OSAS (P < 0.001, P = 0.013, P = 0.001) (Table 2).

Table 1. Clinical and baseline characteristics of NREM- and REM-predominant patients.

	NREM (n = 154)	REM (n = 188)	P-value
Age (years)	50.2 ± 12.7	49.5 ± 10.1	0.069
Smoking (pack years)	10 [0–90]	3 [0–70]	0.064
BMI (kg/m^2)	31.5 ± 6.0	31.8 ± 5.3	0.966
Neck circumference (cm)	43.0 ± 4.1	41.3 ± 3.8	0.409
ESS score	13.6 ± 5.4	12.6 ± 5.5	0.086
Hypertension, n (%)	54 (35.1%)	68 (36.2%)	0.832
Coronary artery disease, n (%)	27 (17.5%)	9 (4.8%)	<0.001
Diabetes mellitus, n (%)	31 (20.1%)	32 (17%)	0.461
Gastroesophageal reflux, n (%)	47 (30.5%)	65 (34.6%)	0.427

NREM: Nonrapid eye movement sleep; REM: rapid eye movement sleep; n: number of patients; BMI: body mass index; ESS: Epworth Sleepiness Scale.

When the distribution of common symptoms in patients with NREM- and REM-predominant OSAS was compared, no statistically significant difference in the prevalence of individual symptoms between the two groups was found (Table 3).

4. Discussion

In our study, we found that the mean AHI score was significantly higher in the NREM-predominant OSAS group than in the REM-predominant OSAS group. Previous studies found no significant difference in the AHI values of REM and NREM sleep. Several studies reported no difference in AHI values between REM and NREM sleep (14,15), whereas other studies reported higher AHI values in NREM sleep (5,11,12), similar to our results.

We found the prevalence of REM-predominant OSAS to be 55% in our cohort, which is higher than previously published data. It was reported that REM-predominant OSAS varies between 10% and 45% in the OSAS population (16). We think the reason why the number varies over such a wide range is the different accepted definitions of REM-predominant OSAS in the studies. While most of the studies defined REM-predominant OSAS as an AHI-REM that was ≥2 times the AHI-NREM, we defined the REM-predominant group as patients with REM AHI > NREM AHI among the OSAS population.

Men were prevalent in both groups in our study, but the prevalence of women in the REM-predominant group was higher than in the NREM-predominant group, which was similar to the results of the study of Joosten et al. (17). While they could not explain the different ratios of women between the groups in their study, we assume that

Table 2. Polysomnographic data of NREM- and REM-predominant patients.

	NREM (n = 154)	REM (n = 188)	P-value
NREM1 % of TST	30.6 ± 18.5	16.5 ± 9.5	<0.001
NREM2 % of TST	38.9 ± 10.4	40.5 ± 7.4	0.004
NREM3 % of TST	15.3 ± 12.4	22.7 ± 9.2	<0.001
REM % of TST	15.8 ± 7.1	20.2 ± 6.5	<0.001
AI	33.3 ± 27.0	27.4 ± 16.5	0.005
AHI	41.9 [5.2–137.8]	21.8 [5.1–93.0]	<0.001
AHI REM	18.2 [0–108.3]	47.8 [7.6–100.0]	<0.001
AHI NREM	46.2 [5.3–140.2]	15.9 [0.6–92.6]	<0.001
Mean SaO_2 (%)	89.0 ± 5.8	91.1 ± 2.6	<0.001
Minimum SaO_2 (%)	75.1 ± 12.8	77.9 ± 9.6	0.013
SaO_2 <90% sleep time spent (min)	29.4 [0–100]	15.5 [0–100]	0.001
Sleep onset (min)	14.8 [1–169]	13.3 [1–100]	0.866
Sleep time in nonsupine position (min)	141.8 [19–311.5]	151.8 [0–346.5]	0.988
Sleep time in supine position (min)	164.3 [8–318.5]	178.8 [5–349.5]	0.048

NREM: Nonrapid eye movement sleep; REM: rapid eye movement sleep; n: number of patients; TST: total sleep time; AI: arousal index; AHI: apnea–hypopnea index; SaO_2: arterial oxygen saturation. Data are presented as mean ± standard deviation where values were normally distributed; otherwise, they are presented as median.

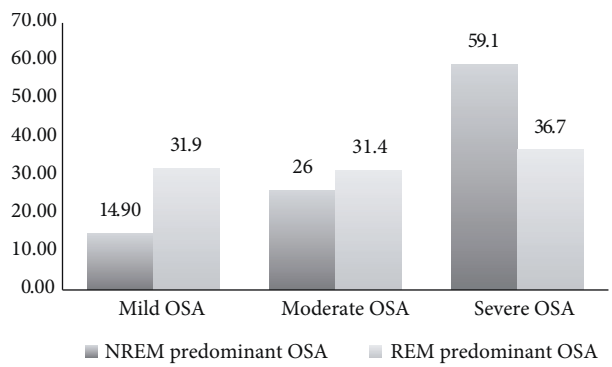

Figure. Distribution of NREM- and REM-predominant patients according to disease severity.

Table 3. Distribution of common symptoms seen in OSAS for NREM- and REM-predominant patients.

		NREM (n = 154)	REM (n = 188)	P-value
Habitual snoring, n (%)		152 (98.7%)	188 (100%)	0.202
Witnessed apnea, n (%)		136 (88.3%)	159 (84.6%)	0.400
Daytime sleepiness, n (%)		126 (81.8%)	145 (77.1%)	0.287
Morning headaches, n (%)		66 (42.9%)	99 (52.7%)	0.071
Experiencing behavioral changes, n (%)		45 (29.2%)	56 (29.8%)	0.909
Difficulty adapting to environmental changes, n (%)		33 (21.4%)	49 (26.1%)	0.318
Decrease in decision ability, n (%)		66 (42.9%)	88 (46.8%)	0.465
Having diagnosis of anxiety or depressive disorders, n (%)		34 (22.1%)	44 (23.4%)	0.771
Nocturia, n (%)		94 (61%)	115 (61.2%)	0.980
Diminished libido, n (%)		64 (41.6%)	62 (33%)	0.102
Suffering sleepiness despite adequate night sleep, n (%)		66 (48.5%)	62 (37.6%)	0.056
Motor vehicle accident due to falling asleep, n (%)		28 (20.6%)	29 (17.6%)	0.507
Probability of falling asleep during at least 1 h of motor vehicle travel, n (%)	Never	20 (13%)	34 (18.1%)	0.394
	Rarely	38 (24.7%)	51 (27.1%)	
	Moderate	60 (39%)	59 (31.4%)	
	Frequently	36 (23.4%)	44 (23.4%)	
Probability of falling asleep when stuck in traffic jam for a few minutes	Never	54 (35.1%)	86 (45.7%)	0.253
	Rarely	64 (41.6%)	66 (35.1%)	
	Moderate	26 (16.9%)	27 (14.4%)	
	Frequently	10 (6.5%)	9 (4.8%)	

NREM: Nonrapid eye movement sleep; REM: rapid eye movement sleep; n: number of patients.

this difference might be because of hormonal changes, as women in the NREM-predominant group were more likely to be menopausal.

When the factors affecting disease severity were investigated, factors that were found to affect disease severity in previous studies (5) such as age, BMI, neck circumference, REM duration, and sleep times in supine/nonsupine positions did not differ significantly between the two groups. There were significant differences between the two groups in terms of nocturnal minimum and mean SaO_2, sleep time spent under 90% SaO_2, and AI, which could affect disease severity. The findings of significantly lower nocturnal mean and minimum SaO_2 and longer sleep time spent under 90% SaO_2 in the NREM-predominant OSAS group when compared to the REM-predominant OSAS group are consistent with the reports by Liu et al. and Siddiqui et al. (5,11). Siddiqui et al. attributed lower nocturnal oxygen saturation values in NREM sleep to longer sleep apnea times (5). The finding of higher AI in the NREM-predominant group was consistent with the findings of Verginis et al., who reported on older children with OSAS (18). Yamauchi et al. similarly found a higher AI in patients with NREM-predominant OSAS; they considered this as another factor contributing to disease severity (19). They suggested that irregular respiratory patterns caused by arousal in patients who possibly have low arousal thresholds might have resulted in more dynamic changes in $PaCO_2$ due to high loop gain; this may have in turn caused recurrent apnea and hypopnea episodes (19). In support of this hypothesis, Terrill et al. concluded that patients with NREM-predominant OSAS have higher loop gain (20). The authors of the present study also suggest that this could be the reason for more severe disease in the NREM-predominant OSAS group.

The present study also found higher prevalence of coronary artery disease in patients with NREM-predominant OSAS. We were unable to locate any literature data supporting our findings on patients with NREM-predominant OSAS. The increased arousal index found in NREM sleep causes intermittent hypoxia. Previous studies have suggested that increased sympathetic activity caused by intermittent hypoxia increases the risk of

developing coronary artery disease by causing arousal-related tachycardia and increased left ventricular afterload, endothelial dysfunction, and systemic inflammation (3). In the present study, it was suggested that increased prevalence of coronary artery disease in patients with NREM-predominant OSAS may be caused by increased AI.

Although the present study found significant differences between REM- and NREM-predominant OSAS groups in terms of disease severity and polysomnographic features, there was no significant difference in terms of sleep-related symptoms and ESS scores. The ESS is a simple and easily applied test used in disease screening; however, its inability to measure disease severity due to its lower sensitivity and specificity may be the reason for not finding any significant difference in ESS scores between the groups (21). The differences in terms of sleep-related symptoms could be more accurately evaluated using detailed and objective sleep, quality of life, and depression scales and tests. The inability of the present study to find a significant difference in terms of clinical symptoms may be caused by the fact that we did not use detailed tests and scales; this is one of the limitations of the present study. Another limitation of this study is that we did not include duration of apnea episodes during NREM and REM sleep, which were suggested to affect disease severity in previous studies.

In conclusion, the disease has a more severe course in patients with NREM-predominant OSAS. Higher AI and lower SaO_2 values in the present study seem to be related to more severe disease in patients with NREM-predominant OSAS. The lack of difference between the two groups in terms of sleep-specific symptoms precludes us from determining that NREM-predominant OSAS is a distinct clinical entity from REM-predominant OSAS. More detailed studies on the subgroups of OSAS must be designed in the future that consider the factors in detail that cause more severe disease and that measure sleep, depression, and quality of life using tests and scales.

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