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Evaluation of comorbid diseases in obstructive sleep apnea syndrome

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SUMMARY

OBJECTIVE: It is known that obstructive sleep apnea syndrome affects many systems due to hypoxemia and hypercarbia. We aimed to demonstrate with the utilization of well-standardized questionnaire tools and electrophysiological tests that cognitive impairment, depression, autonomic dysfunction, and metabolic syndrome may occur in association with obstructive sleep apnea syndrome.

METHODS: The electrophysiological examination protocol of autonomic nervous system functions was performed with sympathetic skin response and R-R Interval. Patients were administered Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Montreal Cognitive Assessment, and Hamilton Depression Rating Scale by physicians in face-to-face interviews.

RESULTS: This study included 148 participants, consisting of 73 patients and 75 controls. There was a statistically significant difference between the patient group and control group with regard to sympathetic skin response, R-R Interval, post-hyperventilation R-R Interval, and R-R Interval variation ($p<0.001$). A statistically significant difference was observed between the patient group and control group in terms of median Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and Montreal Cognitive Assessment scores. It was observed that the control group achieved significantly better scores than the patient group in delayed recall ($p<0.001$) and language ($p<0.05$) categories.

CONCLUSION: Obstructive sleep apnea syndrome patients should be screened for diseases, especially in the cardiovascular system, that cause serious morbidity and impair functionality such as dementia and depression. We believe that many comorbid diseases encountered in obstructive sleep apnea syndrome patients can be prevented with early diagnosis and continuous positive airway pressure treatment.

KEYWORDS: Sleep apnea, obstructive. Cognitive dysfunction. Autonomic nervous system diseases.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and often a decrease in blood oxygen saturation[1,2]. Major symptoms include excessive daytime sleepiness, witnessed apnea, and loud snoring[3-5].

OSAS has been associated with many comorbid conditions such as hypertension, diabetes mellitus, coronary artery disease, metabolic syndrome, and cognitive impairment[6-8]. The effect of OSAS on the autonomic nervous system (ANS) plays an important role in the pathogenesis of complications of the cardiovascular system. As a result of recurrent apnea, hypoxemia and hypercarbia cause increased sympathetic activation via both peripheral and central chemoreceptors.

Studies have demonstrated that OSAS is associated with both neurocognitive dysfunction and mood disorders. The main complaints reported by OSAS patients include decreased stress sensitivity and a significant negative impact on job performance, driving safety, education, and daily household activities[9-11].

This study aimed to demonstrate with the utilization of well-standardized questionnaire tools and electrophysiological tests that cognitive impairment, depression, autonomic dysfunction, and metabolic syndrome may occur in association with OSAS.

METHODS

In this study, patients who applied to our center with complaints of snoring, excessive daytime sleepiness, and witnessed apnea, who were diagnosed with OSAS after PSG in the sleep laboratory, and who were staged as moderate or severe according to the American Academy of Sleep Medicine (AASM) international scoring were evaluated. Apnea-hypopnea index (AHI) ≥5 and less than 15 was classified as mild, ≥15 and less than 30 as moderate, and ≥30 as severe OSAS. Ethics approval was obtained from our university's clinical studies and ethics committee (approval no. 80558721/231). The study included 73 patients and 75 healthy individuals as the control group. Participants with factors that could affect ANS functions, such as diabetes,

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peripheral vascular disease, heart failure, chronic renal and liver failure, alcoholism, polyneuropathy, and drug use (anticholinergic, beta-blocker, etc.) were excluded. Consent was obtained from all study participants. The electrophysiological examination protocol of ANS functions was performed with SSR (sympathetic skin response) and RRIV (R-R Interval) calculated both at rest and during deep breathing. SSR was obtained from both upper extremities with a Medtronic brand EMG device. RRIV was performed according to the method described by Stalberg.

Patients were administered Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Montreal Cognitive Assessment (MoCA), and Hamilton Depression Rating Scale (HAM-D) by physicians in face-to-face interviews. Waist circumference, weight, height, and arterial blood pressure of the patients were measured. Body mass index (BMI) was calculated as weight/height (kg^2/m^2). For the evaluation of metabolic syndrome, blood samples were taken from the patients, and their fasting blood glucose, HDL, and triglyceride blood levels were assessed.

Statistical analysis

Statistical analyses were performed using the SPSS for Windows 21 package program. Descriptive statistics were expressed as percentages for qualitative variables and as mean ± standard deviation or median (interquartile range) for quantitative variables. A chi-square test was used to analyze the differences between groups in terms of categorical variables. For measurable variables, those with normal distribution were compared using the Independent samples t-test, and those without normal distribution were compared using the Mann-Whitney U test. $p<0.05$ was considered statistically significant for all analyses.

RESULTS

The study included 148 participants, consisting of 73 patients and 75 controls. Mean age was 50.3±12.1 years in the patient group and 43.6±11.9 years in the control group (p=0.063). In the patient group, 32 (44%) patients had moderate OSAS and 41 (56%) patients had severe OSAS. Mean AHI was 37.8±19.8 in the patient group.

Triglyceride, fasting blood glucose levels (p=0.004), waist circumference, and BMI were significantly higher, while HDL was significantly lower in the patient group compared to the control group (p<0.001). There was a statistically significant difference between the groups in terms of the presence of metabolic syndrome (p<0.001) (Table 1).

A statistically significant difference was observed in terms of median ESS, PSQI, and MoCA scores (p<0.001) (8 (5–12), 4 (2–6) for ESS; 5 (3–7), 3 (2–4) for PSQI; and 27 (25–28), 29 (27–30) for MoCA) (Table 1). In the analysis of MoCA subdomains (visuoconstructional skills, naming, attention, verbal fluency, abstraction, delayed recall, and orientation), it was observed that the control group achieved significantly better scores than the patient group in delayed recall (p<0.001) and verbal fluency (p<0.05) categories (Table 2).

There was a statistically significant difference between the patient group and control group with regard to SSR (p<0.05), RRIV, post-hyperventilation RRIV, and RRIV variation (p<0.001) (Table 3).

Table 1. Comparison of demographic characteristics and Epworth Sleepiness Scale, Pittsburgh Sleep Quality Scale, Hamilton Depression Scale, and MoCA of the patient group and the control group.

	OSAS (n=73)	Control (n=75)	p-value
Female/male	24/49	28/47	–
Age	50.3±12.1	43.6±11.9	0.63
BMI	29±5	25±4	**<0.001**
HDL	44±11.2	55±17.6	**<0.001**
Triglyceride	130±52	96±53	**<0.001**
Fasting blood sugar	95±11	89±11	**0.004**
Waist circumference	102±12	87±16	**<0.001**
Metabolic syndrome	26 (78.8%)	7 (21.2%)	**<0.001**
Epworth Sleepiness Scale	8 (5–12)	4 (2–6)	**<0.001**
Pittsburgh Sleep Quality Scale	5 (3–7)	3 (2–4)	**<0.001**
Hamilton Depression Scale	6 (4–14)	7 (3–11)	0.279
MoCA	27 (25–28)	29 (27–30)	**<0.001**

Bold indicates statistically significant p-values.

Table 2. Comparison of groups according to MoCA subdomains.

		OSAS (n=73)	Control (n=75)	Total	p-value
Language	**1.00**	1 (100%)	0 (0.0%)	1 (100%)	**<0.05**
	2.00	22 (68.7%)	10 (31.3%)	32 (100%)	
	3.00	50 (43.2%)	65 (56.8%)	115 (100%)	
Delayed recall	**0.00**	2 (100%)	0 (0.0%)	2 (100%)	**<0.001**
	1.00	5 (71.4%)	2 (28.6%)	7 (100%)	
	2.00	10 (100%)	0 (0.0%)	10 (100%)	
	3.00	23 (59.0%)	16 (41.0%)	39 (100%)	
	4.00	26 (43.3%)	34 (56.7%)	60 (100%)	
	5.00	7 (23.3%)	23 (76.7%)	30 (100%)	

Bold indicates statistically significant p-values.

Table 3. Comparison of SSR latency, SSR amplitude, RRIV, Post-hyperventilation RRIV, and RRIV variation.

	OSAS (n=73)	Control (n=75)	p-value
SSR latency (ms)	1,984 (1,635–2,210)	1,858 (1,568–2,184)	0.47
SSR amplitude (mV)	1.59 (0.9–2.9)	1.32 (0.6–2.3)	**<0.05**
RRIV (%)	35 (24–48)	24 (15–33)	**<0.001**
Post-hyperventilation RRIV (%)	66 (46–93)	45 (30.5–65)	**<0.001**
RRIV variation (%)	39 (25–53)	27 (17–37)	**<0.001**

Bold indicates statistically significant p-values.

DISCUSSION

Mean BMI was 25.3±4.5 in the control group and 29.4±5 in the patient group (p<0.01). Truncal obesity reduces chest compliance and functional residual capacity, leading to increased oxygen demand[12]. Obesity is a significant risk factor for the development and progression of OSAS[13]. Moreover, individuals with OSAS who lost 10% of their baseline weight had a sixfold reduction in OSAS progression and more than a 20% reduction in OSAS severity[12].

Lower HDL levels were detected in the patient group, and a highly significant difference was observed between the OSAS group and control group in terms of triglyceride, waist circumference, and total cholesterol values (p<0.001). This emphasizes the need for routine biochemical screening to detect treatable metabolic disorders in all OSAS patients.

In our study, metabolic syndrome was detected in 26 (35.6%) individuals in the OSAS group and 7 (9.3%) individuals in the control group (p<0.001) Considering that 20–30% of the adult world population is affected by metabolic syndrome and that it is one of the most important causes of mortality and morbidity worldwide[14], this should always be kept in mind by clinicians.

The combination of obstructive sleep apnea and metabolic syndrome is referred to as "Syndrome Z"[15]. Although there is no clear consensus, changes in the hypothalamic-pituitary axis, recurrent hypoxia, inflammation, and generation of reactive oxygen species caused by adipokines are thought to be responsible for the changes seen at the cellular level in OSAS and metabolic syndrome[16]. In a cohort study by Marshall et al., while the prevalence of diabetes was 4.7% in the nonapnea group, this rate was 17.7% in the severe apnea group. The calculated odds ratio for severe apnea was 4.37. In a 4-year period, the incidence of diabetes was 2.2% in those without apnea and 20% in those with severe apnea[17]. Comparison between the groups demonstrated that fasting blood glucose was significantly increased in the OSAS group compared to the control group (p<0.01). Accordingly, the presence of undiagnosed diabetes should be kept in mind and screened in patients with OSAS or suspected OSAS, and it may be unregulated despite the diagnosis.

While there was no statistically significant difference between the groups in terms of HAM-D scores, there were 16 participants in the OSAS group and 7 participants in the control group who scored between 16 and 28. It is known that hypoxemia and sleep disruptions have direct effects such as excessive daytime sleepiness, fatigue, and irritability; it is assumed that these symptoms are similar to depressive-somatic symptoms, but do not cause depression alone[18].

In our study, the total MoCA score of the OSAS group was significantly lower than the control group [27 (25–28) vs. 29 (27–30), respectively] (p<0.001). One study indicated that cognitive impairment caused by OSAS resulted from neuronal apoptosis due to chronic exposure to hypoxia[19]. This finding is consistent with animal studies demonstrating that exposure to intermittent hypoxia is associated with increased apoptosis in the hippocampus in rodents[20]. Furthermore, hypoxemia with voxel-based morphometry revealed gray matter volume reduction in brain regions that are responsible for memory and executive functions (e.g., frontal, parietal, and temporal regions and the hippocampus)[21]. These findings suggest that intermittent hypoxia in OSAS may play an important role in cognitive dysfunction and gray matter volume reduction, which may contribute to the development of dementia. Second, mice exposed to hypoxic conditions have shown increased cerebral amyloid plaque formation and tau phosphorylation[22,23]. β-Amyloid accumulation and tau phosphorylation in the brain are common features of Alzheimer's disease that may contribute to the link between OSAS and dementia.

In our study, MoCA subscores in the language and delayed recall domains were significantly lower in OSAS patients than in the control group (p<0.05 and p<0.001, respectively). The frontal lobe is responsible for the motor function of speech, while the temporal lobe performs the function of understanding and naming speech. Previous studies suggest that intermittent hypoxia particularly affects the frontal white matter and temporal lobe[21]. Recent studies have shown that cognitive dysfunction can improve with the application of at least 4 weeks of continuous positive airway pressure (CPAP) therapy[24]. According to the results of our study, we believe that OSAS patients should be evaluated in a multidisciplinary approach; the temporal, frontal, and hippocampal regions in particular are more sensitive to hypoxia and these symptoms may regress with CPAP treatment.

There are few EMG studies in the literature evaluating autonomic dysfunction in OSAS. Ito et al. conducted a study using RRIV, corrected QT interval, and heart rate variability to demonstrate the relationship between OSAS and ANS, as well as treatment response, and the reported findings indicating that OSAS had an impact on the ANS that regressed with treatment[25]. According to the results of our study, RRIV at rest and post-hyperventilation RRIV values were significantly lower in the OSAS group compared to the control group ($p<0.001$). While there was no significant difference between the groups in terms of SSR latency, SSR amplitude was found to be significantly higher in the OSAS group ($p<0.05$). Sympathetic hyperactivity has been demonstrated in OSAS patients. As a result, the increase in sympathetic activity increases the resting heart rate and decreases RRIV variation of ECG. Since comorbid diseases such as increased sympathetic activity, susceptibility to arrhythmias, hypertension, and coronary artery disease can determine mortality in OSAS, it is important to follow-up patients in this regard.

CONCLUSION

Recurrent apnea in OSAS can lead to oxygen desaturation and sleep disruptions, resulting in significant neurobehavioral and cardiac consequences. These consequences can affect all systems in the body at a cellular level, and we recommend that OSAS patients should be screened for diseases, especially in the cardiovascular system, that cause serious morbidity and impair functionality such as dementia and depression. We believe that many comorbid diseases encountered in OSAS patients can be prevented with early diagnosis and CPAP treatment.

AUTHORS' CONTRIBUTIONS

FGA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology ,Project administration, Resources, Writing – original draft, Writing – review & editing. **DIA:** Conceptualization, Data curation, Formal Analysis, Software. **OOE:** Conceptualization, Data curation, Formal Analysis, Supervision, Validation, Writing – original draft, Writing – review & editing.

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