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Original Article

A silent pre-stroke damage: obstructive sleep apnea syndrome

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Abstract: Objectives: We investigated the prevalence of silent cerebro-vascular lesions and atrophy in patients with obstructive sleep apnea syndrome (OSAS) and the correlation between OSAS severity and prevalence of silent cerebrovascular lesions in Turkish patients. Methods: Study subjects were 56.35 OSAS, polysomnography (PSG)-confirmed patients who visited the sleep disorders clinic in our university hospital. None had a history of cerebrovascular disease (CVD). The control group consisted of normal subjects who had no history of snorring, apnea, excessive daytime sleepiness and had under 10 score of epworth sleepiness score. We performed a cross-sectional study on OSAS severity and the prevalence of silent cerebrovascular lesions and atrophy detected by brain MRI analysis. Results: The control group included 21 subjects, the moderate OSAS (AHI 15 to < 30/h) group included 7 patients with a mean AHI of 22.0 ± 5.3/h while the severe OSAS (AHI ≥ 30/h) group included 28 patients with a mean AHI of 60.0 ± 27.4/h. A larger percentage of patients with severe OSAS had a higher BMI than those with moderate OSAS and control subjects ($P < 0.05$). Silent ischemic gliotic lesions was identified in 10 (38.2%) control subjects, 27 (61.8%) with moderate and severe OSAS. Among control subjects and the moderate, and severe OSA groups, 10 (38.2%), 6 (85.7%) and 21 (77.7%) respectively, had periventricular hyperintensity (PVH); most PVH was mild to moderate. Conclusion: Results indicate that patients with moderate to severe (AHI ≥ 15/h) OSAS have a higher prevalence of silent cerebrovascular lesion than those with no OSAS.

Keywords: Obstructive sleep apnea syndrome (OSAS), ischemic gliotic lesions, periventricular hyperintensity (PVH), polysomnography (PSG)

Introduction

There is growing evidence that obstructive sleep apnea syndrome (OSAS) is an independent risk factor for hypertension, other cardiovascular disease and cerebrovascular diseases (CVD) [1-5]. Sleep fragmentation associated with nocturnal respiratory events and hypoxia adversely affects various physiological functions such as those of the respiratory, cardiovascular, and endocrine systems as well as mental function. It is even less clear whether OSAS is a risk factor for stroke or whether stroke causes OSAS.

For many years, the relationship between OSAS and cerebrovascular diseases have been a discussion topic [6]. This subject was explained by the high frequency of these two different diseases occurring at the same age, and OSAS and CVD share the same risk factors (i.e. arterial hypertension).

There are several mechanisms by which OSA may increase the risk of stroke. One possibility is that cerebral blood flow velocity is decreased by the negative intrathoracic pressure that is typically generated during an obstructive apnea. Alternatively, cerebrovascular dilatory responses to hypoxia in patients with OSA may be decreased due to intermittent hypoxia, oxidant-mediated endothelial dysfunction, increased sympathetic activity, and impaired cerebral vasomotor response to carbon dioxide [7]. Recurrent reductions of cerebral blood flow velocity then precipitate ischemic changes in

patients with poor hemodynamic reserve (eg, intracranial arterial stenosis), particularly in border-zone areas and terminal artery territories [8]. In a study of simulated obstructed breaths with Muller maneuvers (high negative intrathoracic pressures against an obstruction), Andreas et al. demonstrated that during the obstructed effort a significant reduction in blood flow to the MCA occurred, an event that correlated with a fall in blood flow across the mitral and aortic valves. That study in awake humans predicts that blood flow might fall during an obstructive apnea or hypopnea during sleep [9].

OSA may exacerbate cerebrovascular abnormalities or other risk factors for stroke. Supporting this hypothesis, patients with OSA have an increased prevalence of systemic hypertension, heart disease, impaired vascular endothelial function, accelerated atherogenesis, diabetes, atrial fibrillation, prothrombotic coagulation shifts, proinflammatory states, and increased platelet aggregation [10]. Franklin et al. l suggested that transcranial doppler (TCD) studies assessing cerebral blood flow velocity (cbfv) of the middle cerebral artery during sleep have shown significant alterations in patients with OSAS [11]. According to the observations of Netzer et al., MCA middle serebral artery blood flow decreases during obstructive apneas and hypopneas rather than central apneas [12]. Cognitive impairments in patients with obstructive sleep apnea syndrome (OSAS) have been documented by a number of studies [13, 14]. Chronic nocturnal hypoxia and fragmented sleep are both thought to be causes of excessive daytime somnolence and cognitive deficits in OSAS patients [15]. Nevertheless, the mechanisms with respect to the relative role of nocturnal hypoxia and/or fragmented sleep in the pathophysiology of the cognitive deficits in OSAS patients are still unclear.

In this study, we examined the correlation between the prevalence of silent cerebrovascular ischemic lesions and brain atrophy determined by brain MRI and the severity of PSG-confirmed OSA in Turkish subjects.

Patients and methods

The study comprised 56 consecutive Turkish subjects with no past history of CVD. A sample of 35 subjects who had undergone polysomnography examination at the sleep laboratory of the Pulmonology Department of the Faculty of Medicine at Yuzuncu Yil University Hospital between June 2015 and September 2015 and brain MRI was conducted. The control group consisted of normal subjects who had no history of snorring, apnea, excessive daytime sleepiness and had under 10 score of epworth sleepiness score. All subjects were requested to fill out a questionnaire regarding their medical history, frequently used medications. The diagnosis of OSAS was established in accordance with the American Academy of Sleep Medicine (AASM). Patients were divided into two groups according to the apnea-hypopnea index (AHI). Group 1 comprised patients with moderate OSAS (AHI = 15-30, n = 7); and Group 2 comprised patients with severe OSAS (AHI > 30, n = 28). The study protocol had been approved by the local ethics committee and all patients had given their informed written consent.

Overnight polysomnography was performed using a 16 channel Embla (Medcare Inc., Iceland) with continuous monitoring by a sleep technician. The system consists of 4 channels of EEG (with electrode placements at C4-A1, C3-A2, O2-A1, and O1-A2) and 2 channels of EOG, recording submental EMG, oronasal air flow, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position, electrocardiogram readings, and tracheal sound. Apnea was defined as the complete cessation of airflow lasting more than 10 seconds. Hypopnea was defined as a greater than 30% reduction in airflow lasting more than 10 seconds accompanied by more than 4% desaturation and/or arousal. The average number of episodes of apnea and hypopnea per hour of sleep were measured as AHI. The OSAS diagnosis was made on the basis of an apnea/hypopnea index (AHI) greater than 5. Sleep stages were scored according to standard criteria with 30-second epochs and were reviewed and verified by a certified sleep physician.

A 1.5-T MRI system (Siemens Magnetom Symphony, Erlangen, Germany) with brain coil was used for examinations. The presence of a silent cerebrovascular lesion and cerebral atrophy was evaluated by MRI of the whole brain. The imaging protocol consisted of T1-weighted images (TR, 579 ms; TE, 15 ms), T2-weighted

Table 1. Characteristics of subjects with moderate, severe OSA and control subjects

	AHI 15 to < 30 (n = 7)	AHI ≥ 30 (n = 28)	Control (n = 21)	*P* value
Gender(men/women)	4/3	22/6	13/8	0.007
Age, years	50.14	48.84	49.05	0.982
BMI, kg/m²	31.54	31.39	30.49	0.872
AHI, /h	22.05	60.02	-	
Lowest saturation	82.14	69.71	-	
Time under 90% saturation	27.42	57.58	-	
Hypertension, n	1	6	2	0.650
Hyperglisemia, n	1	4	-	0.650
Impotans, n	-	1	-	0.650
Hipotiroidi, n	-	-	1	0.650
COPD, n	-	1	-	0.650

Table 2. The degree of atrophy of brain damage between patient and control groups

	Control	Patients	*P* value
Brain damage (n,%)	10 (38.2)	27 (6.8%)	P = 0.028
Atrophy (n,%)	3 (38.2%)	8 (61.8%)	P = 0.405

images (TR, 3800 ms; TE, 99 ms), and fluid-attenuated inversion recovery (FLAIR) images (TR, 9000 ms; TE, 105 ms) on 6-mm slices using a 1.5-T scanner for silent periventricular hyperintensity (PVH) and cerebral atrophy. The degree of PVH was classified into 4 categories based on FLAIR images: PVH 0, no PVH detected; PVH 1, PVH detected in the apex of the frontal or posterior horn; PVH 2, mild or middle PVH detected along the lateral ventricle; PVH 3, PVH strongly detected along the entire lateral ventricle. The images were transferred to a work station (Leonardo Syngo 2002B, Siemens Medical Solutions) in order to process the data and to measure silent cerebrovascular lesions. A single trained radiologist who was blinded to the patients' clinical details evaluated the existence, location, degree of PVH and cerebral atrophy on MR imaging.

Statistical analysis

Descriptive statistics for the continuous variables were presented as Mean, Standard deviation; minimum and maximum values while count and percentages for categorical variables. Student t test was used to compare group means. For determination linear relationships among the variables, Pearson correlation analysis was carried out. In addition, chi-square test was performed to determine the relationship between categorical variables. Statistical significance level was considered as 5% and SPSS (ver: 13) statistical program was used for all statistical computations.

Results

56 subjects were enrolled in the study. The 21 control subjects were; OSAS non-suspected because they had no snoring, excessive daytime sleepiness, apnea and had under 10 points from Epworth sleepiness score. 35 OSAS subjects, 7 of them were moderate (AHI 15 to < 30/h range) with a mean age of 50.14 and 28 of them were severe (AHI ≥ 30/h range) with a mean age of 48.84. **Table 1** shows characteristics of subjects with moderate, severe OSA as well as control subjects. The study population presented the following diseases; 7 subjects had HT, 5 subjects had diabetes mellitus, 1 subject had COPD, 1 subject had hypothyroidism and 1 had impotence. The 3 group did not differ with regard to BMI and age ratio. Ischemic gliotic lesions were identified 10 (47.6%) in normal subjects, 6 (85.7%) in moderate OSA patients, 22 (77.7%) in severe OSA patients (P = 0.001). Prevalence of silent ischemic gliotic lesions among subjects with moderate and severe OSA (AHI ≥ 15/h) was higher than among the control subjects (P = 0.028) (**Table 2**). Among the patients with moderate and severe OSA (AHI ≥ 15/h), the severity and number of ischemic lesions were higher than among control subjects.

In this study, we used the prevalence of silent Ischemic gliotic lesions or atrophy as a dependent variable and evaluated the order of inclusion in the model of the following independent variables: age, gender, BMI, hypertension, hyperglycemia and AHI. Among the 6 independent variables, age (P < 0.0001) and AHI (P = 0.013) were predictors of the prevalence of silent ischemic gliotic lesions in patients with OSA and control subjects. Cerebrovascular lesions were positive correlated with AHI, low-

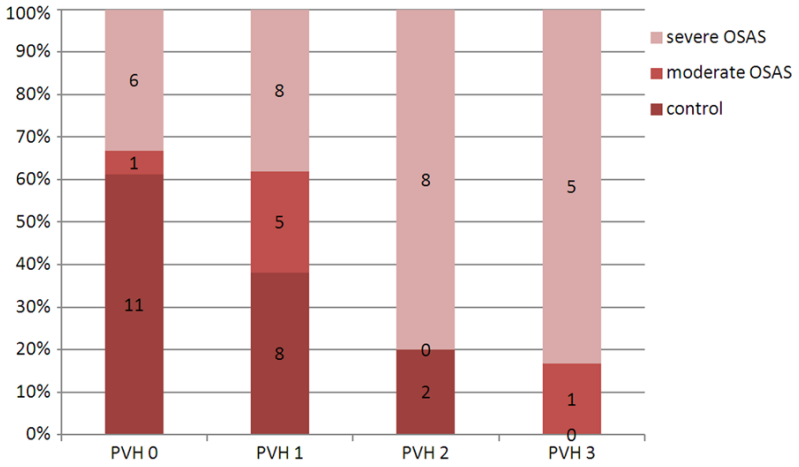

Figure 1. PVH distribution between groups. PVH 0: No PVH detected; PVH 1: PVH detected in the apex of the frontal or posterior horn; PVH 2: Mild or middle PVH detected along the lateral ventricle; PVH 3: PVH strongly detected along the entire lateral ventricle.

est desaturation ratio and desaturated time under 90% saturation. There was no significant statistical difference between atrophy in the controls and subjects with moderate and severe OSA (P = 0.405).

PVH was identified in 21 (38.2%) of the control subjects and in 34 (61.8%) of the OSA groups. (P = 0.028). The prevalence of PVH was significantly higher in the moderate and severe OSA (AHI ≥ 15/h) groups. Furthermore, the degree of PVH according to OSA severity was evaluated. Among the control subjects, 11 (61.1%) had no lesions, 8 (38.1%) had PVH 1, and 2 (20%) had PVH 2 and non had PVH 3. One (14.3%) of the patients in the moderate OSA group had no lesions, 5 (71.4%) had PVH 1, non had PVH 2 and 1 (14.3%) had PVH 3 respectively. Finally in the severe OSA group, 6 (22.2%) had no lesions, 8 (29.6%) had PVH 1, 8 (29.6%) had PVH 2, 5 (18.5%) had PVH 3 respectively (**Figures 1**, **2**).

Discussion

Our results indicate that moderate and severe OSA (AHI ≥ 15/h) are associated with a higher prevalence of silent ischemic gliotic lesions than control group and that severe OSA is a possible risk factor for silent cerebrovascular diseases, and there is no relationship between brain atrophy and OSAS.

Some authors suggest that the increase in obstructive apneas is due to loss in pharyngeal muscle tone in patients with stroke [16]. Thus the stroke itself becomes a cause of this type of respiratory episode. Nevertheless, the high clinical probability of OSAS before stroke and the larger number patients with stroke onset during the night (when cerebral gasometric and hemodynamic abnormalities are most pronounced) would point to prior obstructive OSAS.

The earlier observation by Partinen and Palomaki and later Koskenvuo et al. showed a strong epidemiological correlation between loud snoring and the risk of stroke development [17, 18]. For instance, in one study the unadjusted risk for stroke was 40 times higher in heavy snorers than in non-snorers [16]. Causality could not be clearly elucidated from these studies at that time; however, it seemed reasonable to the authors to assume a relation to effects of sleep-disordered breathing.

The prevalence of silent lacunar infarction increased with age, with no patient less than 50 years of age being affected. Takagi et al. performed brain MRI on 1,258 patients who had no history of CVD and found silent lacunar infarction in 9.5% of the male and in 5.9% of the female patients [19]. Here, we investigated OSA patients with no history of CVD, and the results revealed a distinctly high prevalence of silent ischemic gliotic lesions among those with OSA. Approximately 61% of the study patients with moderate and severe OSA were found to have silent ischemic gliotic lesions. With regard to the severity of PVH the prevalence and severity of PVH in OSA patients is higher than controls health screening of the brain.

The association between ischemic gliotic lesions and OSA severity is considered to be due to various biological reactions occurring during hypoxia, hypercapnia, and arousal associated with respiratory events [20]. The first biological reactions probably include an inflammatory response, oxidative stress, and relevant atherosclerotic changes due to abnormal hemostasis. Minoguchi et al. [21] reported that

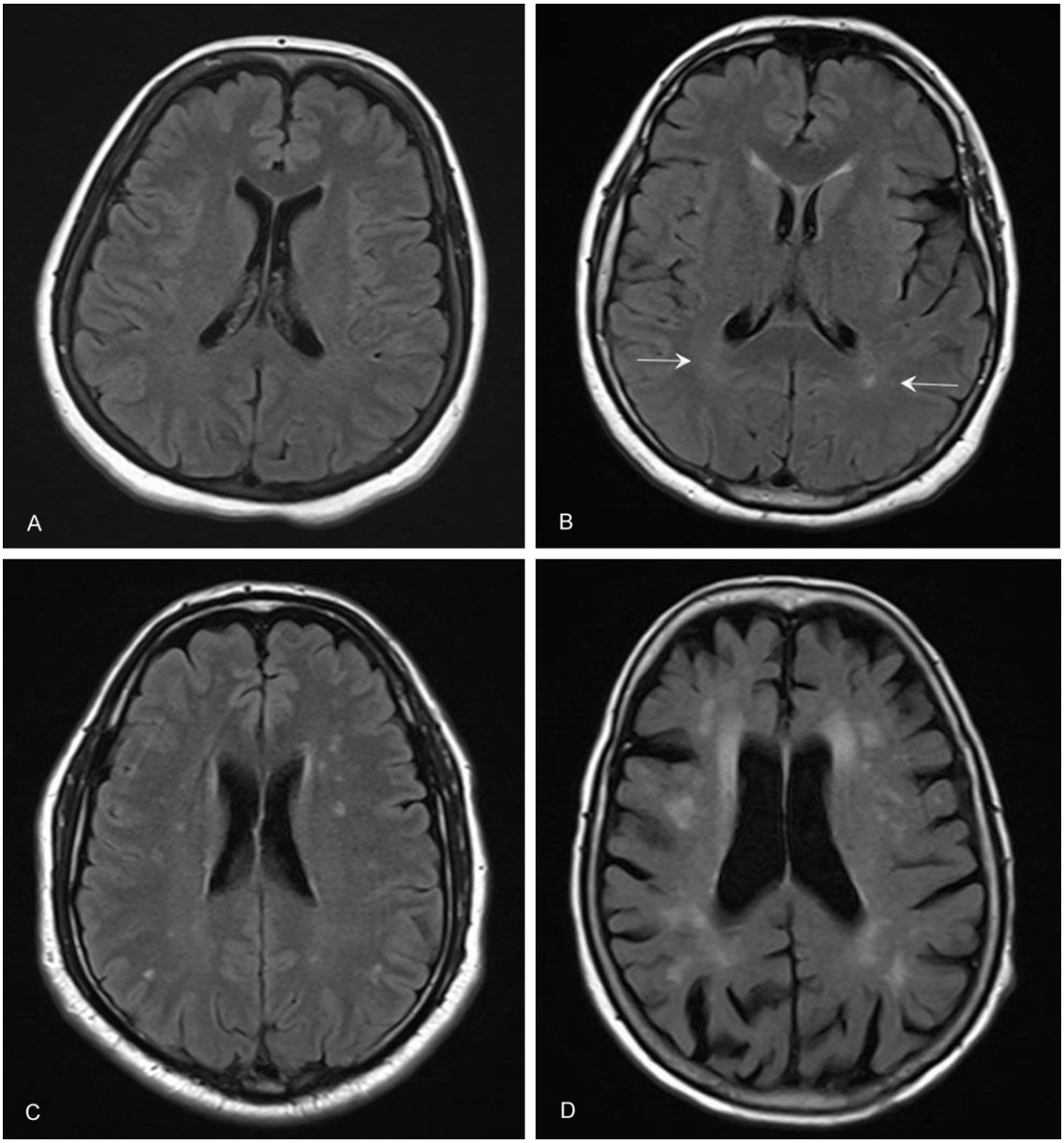

Figure 2. Examples of images from this study population. PVH 0: no PVH detected (A). PVH 1: PVH detected in posterior horn (arrow) on FLAİR images (B). PVH 2: mild-middle PVH detected along the lateral ventricle on on FLAİR images (C). PVH 3: PVH strongly detected along the entire lateral ventricle on FLAİR images (D).

the presence of silent brain infarction was increased in patients with OSA and was associated with an elevation in markers of platelet activation, such as soluble CD40L and soluble P-selectin, and systemic inflammation (CRP). In a recent study of us demonstrated a relationship between severity of OSAS and red blood cell distribution width (RDW) [22]. RDW is a numerical measure of the size variability of circulating erythrocytes. RDW has been reported as an independent predictor of adverse outcomes in the general population and is believed to be associated with cardiovascular morbidity and mortality in patients with a previous myocardial infarction [23, 24]. We also found a negative association of RDW with average minimum oxygen saturation and desaturation time under 90% during sleep, which could be explained by the effect of hypoxia on RDW. Intermittent hypoxia is a trigger for the cardio-

vascular and metabolic modifications associated with OSAS [25]. A positive relationship between RDW and the oxygen desaturation index may also indicate the severity of OSAS. Also we found a positive correlation between pulmonary artery pressure and RDW, and a relationship between OSAS severity and pulmonary hypertension. These reports reveal that OSA tends to result in atherosclerotic changes.

The second biological reaction in OSA is the hemodynamic change associated with respiratory events. Abnormal cerebrovascular hemodynamics have been reported to be associated with increased intracranial pressure followed by decreased cerebral perfusion pressure related to apnea [26]. The cerebrovascular system is generally controlled by an autoregulation mechanism that can protect blood flow to a certain extent if the cerebral perfusion pressure decreases. However, hemodynamic changes may still occur since this autoregulation mechanism is inadequate to protect the brain from the rapid fluctuations in pressure that are associated with apnea [27]. Hypercapnia associated with apnea and the concomitant changes in cerebral blood flow velocity and vessel wall tension that are associated with both these conditions were reported to result in long-term damage of cerebral blood vessels [28].

A possible explanation for the development of CVD in OSA patients may be that recurrent respiratory events occurring during the night cause frequent arousal accompanied by hypertension due to sympathetic hyperactivity, and that this hypertension continues until morning.

Munoz et al. reported that severe OSA with an AHI of 30/h is a risk factor for CVD in elderly people aged over 70 years [29]. We found that subjects with moderate and severe OSA (AHI ≥ 15/h) had a high prevalence of silent cerebrovascular lesion. Subsequent studies examining nocturnal blood pressure in sleep apnea patients, 2-4 as well as Netzer et al. suggested that a significant decline in blood flow occurred in 76% (169/223) of obstructive hypopneas and in 80% (98/123) of obstructive apneas, compared with only 14% (13/96) of central apneas ($P < 0001$). Obstructive apneas and hypopneas compared with central apneas lead much more frequently to a reduction in cerebral blood flow, as assessed by the qualitative method of MCA Doppler ultrasonography, during NREM sleep. Their observation that a reduction in blood flow of the MCA occurred more often with a longer duration of hypopnea suggests that there is an interaction between respiratory efforts and the duration of the event in regard to their impact on cerebral blood flow and on systemic blood pressure [30]. An explanation for the relationship between partial airway obstruction and decreased perfusion of the MCA might be provided by the observation of Andreas et al., who were able to demonstrate reduced blood flow during Muller maneuvers [31].

All of these studies support the relationship between OSAS and CVD.

There are several limitations to this study. First, the sample size was small. Secondly, we did not have information regarding the length of time that patients had experienced OSAS.

In conclusion, results presented here suggest that the presence of silent cerebrovascular lesions in OSA patients is an important part of a preconditioning phase of symptomatic CVD. Therefore, from the viewpoint of stroke prevention, early diagnosis and treatment is required in patients with moderate and severe OSA.

Disclosure of conflict of interest

None.

Authors' contribution

HG, MDB carried out the Manuscript preparation. BS, SE carried out the review of manuscript. AY, AB carried out the literature search. ET carried out the data collection.

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