The Egyptian Journal of Bronchology

RESEARCH

Open Access

Evaluation of brain white matter changes on MRI in patients newly diagnosed with obstructive sleep apnea compared with the control group

Farzaneh Khoroushi[1], Yasmin Davoodi[1], Amirhossein Fathabadi[2], Reihane Bakhshi[3], Yasamin Sharifian[4], Maryam Salehi[1], Leila Ghofranyha[1], Ehsan Hassannejad[5] and Farnaz Kharaghani[3*]

Abstract

Background Obstructive sleep apnea (OSA) is nowadays introduced as a risk factor for white matter brain changes. Research on OSA and white matter changes provides contradictory evidence for the contextual link between the two conditions. This study aimed to determine the prevalence and severity of OSA and changes in the brain's white matter and the relationship between severity levels of both diseases.

Methods This was a cross-sectional study in which 40 patients with OSA and 40 patients without OSA underwent polysomnography to determine the severity of OSA and MRI for detecting white matter changes. The severity of white matter changes was classified according to the age-related white matter change (ARWMC) score, and the severity of OSA based on the apnea–hypopnea index (AHI). To evaluate the independent effect of OSA on white matter changes, a multivariate regression model, including the severity of OSA and risk factors, was used.

Results 76.5% of affected people did not show any changes, and from 13 (32.5%) patients with OSA who experienced white matter changes, 10% were mild, and 22.5% were moderate to severe changes. The white matter changes score increased with increasing OSA severity. The univariate analysis also showed a significant positive correlation between OSA severity and ARWMC score.

Conclusion Our major finding was that moderate to severe OSA was independently associated with the prevalence of white matter changes. We also observed a higher prevalence of moderate to severe OSA associated with increasing white matter changes, suggesting that the severity of the disease affects brain structural modification.

Keywords Obstructive sleep apnea, Stroke, White matter change, MRI, Blood pressure

*Correspondence:
Farnaz Kharaghani
farnaz_131269@yahoo.com
Full list of author information is available at the end of the article

Introduction

Obstructive sleep apnea (OSA) syndrome is a progressively prevalent condition characterized by repetitive obstruction of the upper airway while asleep, leading to compromised oxygen exchange and hypercapnia, ultimately disrupting sleep patterns [1]. According to population-based studies, the prevalence of symptomatic OSA among individuals over the age of 50 is estimated to be 4% for men and 2% for women [2, 3]. The prevalence of patients with OSA who do not have a clinical syndrome may be as high as 20–30% of the middle-aged population [2]. Obstructive sleep apnea syndrome correlates with significant medical, cognitive, and psychological side effects such as excessive daytime sleepiness, increased risk of motor vehicle accidents, depression, anxiety, obesity, insulin resistance, hypertension, diabetes, metabolic syndrome, heart failure, coronary artery disease, cardiac arrhythmias, stroke, and pulmonary hypertension [4, 5]. OSA causes systemic hypertension, which strongly predicts changes in the white matter of the brain. Thus, OSA may be a known risk factor for cerebral ischemia, in addition to age, hypertension, smoking, impaired lipids profile, diabetes, and vascular disease [5, 6]. One method of assessing early preclinical changes in OSA is magnetic resonance imaging (MRI). Changes in brain white matter are indicated by the presence of lesions in the subcortical and paraventricular areas of the brain, appearing as high-intensity lesions in T2 or FLAIR sequences of brain MRI [5].

In the past, white matter changes associated with OSA have been detected by various MRI methods. However, the independent effect of OSA on brain white matter changes remains contradictory. Some studies, such as the study by Kim. H et al. have shown that moderate to severe OSA is an independent risk factor for white matter changes (WMCs) in the middle-aged and elderly populations [5]. Eguchi et al. also observed that patients with hypoxia had a higher prevalence of non-symptomatic cerebrovascular disease than the group without hypoxia, suggesting that respiratory disorders during sleep contribute to the early phase of stroke [4]. Other studies by Minoguchi et al. and Nishibayashi et al. showed a significant correlation between subclinical cerebrovascular disease and moderate-to-severe OSA [7, 8]. Despite this, certain studies were unable to establish a connection between OSA and white matter lesions, although they did find some association with shared risk factors [6, 9–11].

Considering the significance of the social burden caused by population aging, stroke, and dementia, it is essential to delve deeper into the understanding of the impact of OSA on the brain. In the event that OSA is determined to be connected with white matter alteration, the timely identification and treatment of OSA may mitigate the likelihood of developing dementia and stroke. Consequently, the aim of the present investigation was to analyze the potential association between the prevalence and severity of OSA and white matter lesions in a population of adults under the age of 50, who have no previous records of heart disease, neurological disorders, or hypertension.

Material and methods

Study population

The present study is a descriptive cross-sectional study conducted in collaboration with the Sleep Disorders Center and the MRI department of Imam Reza Hospital, affiliated with the Mashhad University of Medical Sciences (MUMS) during the years 2016 and 2017. It involved two groups of patients, one with OSA consisting of 40 patients, and another without OSA consisting of 40 patients. Patients exhibiting clinical indications of OSA, such as intermittent sleep apnea, snoring, daytime sleepiness, and daily dysfunction within the previous year, underwent polysomnography. Participants who were diagnosed with OSA were included in the study as the OSA group. Additionally, exclusion criteria involved the presence of a history of cardiovascular and neurological disease, along with the use of pharmacological and non-pharmacological treatments for OSA. The control group comprised patients who had MRI indications for any reason exhibited no clinical signs of OSA and had no confounding factors such as hypertension, stroke, or neurological disorders. The control group was matched with the OSA group based on age and gender. The research received approval from the ethics committee at Mashhad University of Medical Sciences (Code: IR.MUMS.fm.REC.1395.0325), and informed consent was obtained from each patient after a comprehensive explanation of the study design.

Demographic data

Demographic information, including age, sex, smoking status, family history, and medical data of the participants such as blood glucose, blood pressure, and body mass index (BMI), were collected from the patient's medical records.

Polysomnography recording

Nocturnal polysomnography was performed in the sleep laboratory of Imam Reza Hospital. Nocturnal laboratory-based polysomnography, which requires spending the night in a sleep laboratory under monitoring, was conducted using standard channels; then all polysomnography data were processed with software and scored by registered technologists. The definition of apnea involves

a decrease in airflow to 90% of the baseline for a minimum duration of 10 s. Hypopnea is defined as a decrease in airflow to 30% of the baseline for a minimum of 10 s, accompanied by a decrease in oxygen saturation index of more than 4% [12]. The apnea–hypopnea index (AHI) was determined as the mean number of occurrences of obstructive sleep apnea and hypopnea per hour of sleep. The severity of OSA was categorized into four levels according to AHI: individuals without OSA (AHI < 5), individuals with mild OSA (5 ≤ AHI < 15), individuals with moderate OSA (15 ≤ AHI < 30), and individuals with severe OSA (AHI ≥ 30).

MRI acquisition

For the purposes of this study, a Siemens MRI, Symphony model with a magnetic field strength of 1.5 Tesla was employed. The slice thickness was 5 mm, and T1, T2, and FLAIR sequences were measured. White matter changes on MRI were defined as lesions with a size of 5 mm or larger on T2 and FLAIR images. The lacunae were identified on MRI images as well-defined areas exhibiting signal characteristics akin to cerebrospinal fluid. Lesions demonstrating these characteristics, with a size of 2 mm or smaller, were designated as perivascular areas, with the exception of the areas surrounding the anterior commissure, where the perivascular spaces may be larger. The scoring of changes in the basal ganglia was done in a similar manner as that of the white matter, despite their location in the gray matter which contains a small quantity of white matter. This study used the age-related white matter change (ARWMC) scale proposed in 2001 by Wahlund et al. to assess age-related WMCs using MRI and CT scan imaging methods. In the ARWMC scale, WMC is assessed using a 4-point rating system across five specific regions of the right and left hemispheres [13] in our study five different regions in the right and left hemispheres were assessed separately. Frontal area: consisting of the anterior frontal lobe to the central groove.

Parieto-occipital area: consisting of parietal and occipital lobes together.

Temporal area: consisting of the temporal lobes (the boundary between the parietal and occipital lobes with the temporal lobe was described as a line from the back of the Sylvian fissure to the trigon of lateral ventricles).

Infratentorial area: consisting of the brainstem and cerebellum.

Basal ganglia: consisting of the striatum, globus pallidus, thalamus, insular cortex, internal, and external capsules.

A total of 10 areas were evaluated in two hemispheres, and a maximum score (30) which is the sum of the highest scores of 10 areas, was defined as the highest ARWMC score. Patients were then divided into four subgroups based on their ARWMC score based on the study done by Schulz et al. [9]. (Normal group with no WMCs (ARWMC = 0), mild WMCs (ARWMC = 1–2), moderate WMCs (ARWMC = 3–4), and severe WMCs (4 < ARWMC)). The number of lesions per person was also recorded.

Statistical analysis

In this study, the Kolmogorov–Smirnov test was used to examine the natural distribution of the variables. Then, to compare the mean changes of the studied variables between the two groups, the independent sample *t*-test was used if the variables were normally distributed and the Mann–Whitney test when there was no normal distribution. To compare the mean values of each parameter between the ARWMC subgroups and the OSA severity subgroups, the ANOVA test was used when normally distributed and the Kruskal–Wallis test was performed in case of non-normal distribution. The Pearson test was used to examine the correlation between variables when normally distributed, and the Spearman correlation test was used when data were grouped (AHI) or not normally distributed. The chi-square test was used to compare the mean changes in the qualitative variables. All evaluations were performed using SPSS version 25. *p* values less than 0.05 were considered statistically meaningful.

Results

The study was conducted on a case group of 40 patients with OSA and a control group of 40 patients who had an MRI indication for any reason. The participant's characteristics are summarized in Table 1. The chi-square test did not show a significant difference between the two groups regarding gender and age ($p = 0.37$ and 0.576, respectively). Examination of the two groups by

Table 1 Baseline demographic data

Variables	Control group (mean ± SD)	Case group (mean ± SD)	*p* value*
Age (year)	39.12 ± 6.43	38.32 ± 6.28	0.576
BMI (kg/m^2)	27.18 ± 3.26	29.27 ± 3.54	0.008
FBS (mg/dl)	95.32 ± 9.96	99.15 ± 10.36	0.097
Systolic blood pressure (mm/Hg)	123.50 ± 5.79	125.45 ± 6.45	0.141
Diastolic blood pressure (mm/Hg)	79.62 ± 4.29	77.40 ± 3.68	0.006
ARWMC score	1.60 ± 0.89	4.23 ± 3.00	0.076
Number of lesions	1.60 ± 0.89	3.46 ± 1.56	0.024

Abbreviations: *BMI* body mass index, *FBS* fasting blood sugar, *ARWMC* age-related white matter change

* Independent *t*-test and Mann–Whitney *U* test were used; *p* value < 0.05 was considered significant

Kolmogorov–Smirnov test showed a significant difference in systolic and diastolic pressure. As expected, patients with OSA had a higher BMI than the control group.

The extent of the WMCs was measured using the ARWMC score. Thirteen patients (32.5%) in the case group and 5 patients (12.5%) in the control group showed changes in white matter, which was significantly different ($p=0.032$).

Participants were divided into four groups based on the ARWMC test score, and the average risk factors for WMCs were measured. The groups showed significant differences in mean age, BMI, fasting blood sugar (FBS), total white matter change score, and brain lesions (Table 2).

Table 3 shows the association between WMCs and OSA severity. No change in white matter was observed in 27 (67.5%) OSA patients, and only 10% of patients showed WMCs.

Also, the number and severity of white matter lesions in five brain regions of the right and left hemispheres were assessed in the case group (Table 4).

Participants were divided into four groups based on the severity of OSA measured by the AHI test, and the

Table 2 Comparison of the mean risk factors of different changes in brain white matter between different ARWMC subgroups

Variables	ARWMC = 0 *n* = 27 (mean ± SD)	ARWMC = 1–2 *n* = 4 (mean ± SD)	ARWMC = 3–4 *n* = 5 (mean ± SD)	ARWMC > 4 *n* = 4 (mean ± SD)	*p* value*
Age (year)	37.14 ± 6.07	43.87 ± 4.15	45.16 ± 2.31	46.25 ± 4.92	0.000
BMI (kg/m^2)	27.45 ± 2.96	29.31 ± 3.21	33.83 ± 4.62	29.62 ± 3.44	0.000
FBS (mg/dl)	95.61 ± 9.67	96.75 ± 12.02	108.17 ± 8.18	107.00 ± 3.55	0.006
Systolic blood pressure (mm/Hg)	123.63 ± 5.80	126.00 ± 4.24	130.00 ± 4.47	126.25 ± 12.50	0.065
Diastolic blood pressure (mm/Hg)	78.32 ± 4.19	80.00 ± 3.77	80.00 ± 3.16	76.25 ± 4.78	0.434
ARWMC score	0	1.37 ± 0.51	3.66 ± 0.51	7.5 ± 3.31	0.000
Number of lesions	0	1.37 ± 0.51	3.66 ± 0.51	5.00 ± 0.81	0.000

Abbreviations: *BMI* body mass index, *FBS*, fasting blood sugar, *ARWMC* age-related white matter change

* ANOVA and Kruskal–Wallis tests were used; *p* value < 0.05 was considered significant

Table 3 Prevalence of white matter changes in different groups of OSA severity

		Total population *n* = 80	ARWMC = 0 *n* = 62	ARWMC = 1–2 *n* = 8	ARWMC = 3–4 *n* = 6	ARWMC > 4 *n* = 4	*p* value*
OSA Severity	None	*n* = 40	35	4	1	0	0.000
	Mild	*n* = 27	24	3	0	0	
	Moderate	*n* = 10	3	1	3	3	
	Severe	*n* = 3	0	0	2	1	

Abbreviation: *OSA* obstructive sleep apnea

* Chi-square test was used; *p* value < 0.05 was considered significant

Table 4 Frequency and severity of white matter lesions in each of the 5 brain areas studied in the patient group

Area	Left lobe				Right lobe			
	OSA group		Total population		OSA group		Total population	
	Number of lesions (%)	Mean ARWMC score	Number of lesions (%)	Mean ARWMC score	Number of lesions (%)	Mean ARWMC score	Number of lesions (%)	Mean ARWMC score
Frontal	11 (27.5)	1.18 ± 0.4	12 (15)	1.16 ± 0.38	8 (20)	1.25 ± 0.46	9 (11.2)	1.22 ± 0.44
Parieto-occipital	8 (20)	1.25 ± 0.46	9 (11.2)	1.22 ± 0.44	8 (20)	1.25 ± 0.46	10 (12.5)	1.20 ± 0.42
Temporal	1 (2.5)	1.00 ± 0	1 (1.2)	1.00 ± 0	2 (5)	1.00 ± 0	2 (2.5)	1.00 ± 0
infratentorial	1 (2.5	1.00 ± 0	1 (1.2)	1.00 ± 0	0	0	0	0
Ganglia basal	3 (7.5)	1.33 ± 0.57	5 (6.2)	1.20 ± 0.45	2 (5)	1.50 ± 0.70	3 (3.8)	1.33 ± 0.57

Abbreviations: *OSA* obstructive sleep apnea, *ARWMC* age-related white matter change

Table 5 Comparison of the average risk factors of different changes in white matter in different subgroups of OSA

Variables	OSA severity	Non (mean ± SD)	Mild (mean ± SD)	Moderate (mean ± SD)	Sever (mean ± SD)	*p* value*
Age (year)		38.32 ± 6.28	36.82 ± 6.36	40.10 ± 5.32	45.00 ± 3.00	0.123
BMI (kg/m^2)		29.27 ± 3.54	28.31 ± 2.58	30.10 ± 3.47	35.16 ± 6.04	0.000
FBS (mg/dl)		99.15 ± 10.36	95.77 ± 10.16	105.40 ± 7.58	108.67 ± 3.2	0.006
Systolic blood pressure (mm/Hg)		125.45 ± 6.45	123.89 ± 5.60	128.30 ± 7.81	130.0 ± 5.0	0.031
Diastolic blood pressure (mm/Hg)		77.40 ± 3.68	76.70 ± 3.57	78.50 ± 3.37	80.00 ± 5.00	0.013
ARWMC score		4.23 ± 3.00	1.33 ± 0.57	4.42 ± 1.90	6.66 ± 4.61	0.018
Number of lesions		3.46 ± 1.56	2 ± 1.41	3.85 ± 1.06	5.00 ± 1.41	0.001

Abbreviations: *OSA* obstructive sleep apnea, *BMI* body mass index, *FBS* fasting blood sugar, *ARWMC* age-related white matter change

* Chi-square test was used; *p* value < 0.05 was considered significant

Table 6 Correlation between ARWMC score and OSA severity with their risk factors

Risk factors	Correlation with ARWMC		Correlation with AHI	
	R value	*p* value	*R* value	*p* value
Age	0.127	0.495	0.003	0.981
gender	0.343	0.164	0.087	0.445
BMI	0.227	0.364	0.334	0.002
Systolic blood pressure	0.262	0.293	0.250	0.025
Diastolic blood pressure	-0.150	0.552	-0.227	0.043
FBS	0.448	0.062	0.266	0.017
Number of lesions	0.862	0.000	0.781	0.000
ARWMC score	–	–	0.766	0.000
AHI score	0.766	0.000	–	–

Abbreviations: *OSA* obstructive sleep apnea, *BMI* body mass index, *FBS* fasting blood sugar, *ARWMC* age-related white matter change, *AHI* apnea–hypopnea index, *p* value < 0.05 was considered significant

Table 7 Linear regression analysis of variables related to ARWMC score

Risk factor	*B* value	*p* value
Age	0.410	0.075
FBS	.0.301	0.154
BMI	0.343	0.161
Systolic pressure	0.050	0.838
AHI	0.812	0.002

Abbreviations: *BMI* body mass index, *FBS* fasting blood sugar, *ARWMC* age-related white matter change, *AHI* apnea–hypopnea index, *p* value < 0.05 was considered significant

mean risk factors of WMCs were compared among them. The mean of all risk factors except age was significantly different between the groups. To perform the Bonferroni post hoc test and compare the two groups, due to the low number of severe OSA patients, we divided the moderate and severe OSA groups into one group and compared them with mild OSA and without OSA groups (Table 5).

Table 6 shows the correlation between ARWMC and AHI test scores and their risk factors. These results showed that WMCs increase with the increasing number of brain lesions and the severity of OSA.

In linear regression analysis, the cumulative effect of independent variables of age, BMI, FBS, systolic blood pressure, and OSA severity on the dependent variable, i.e., white matter changes (ARWMC test score), was investigated. There was still a significant correlation between the severity of OSA (measured by the AHI test score) and the ARWMC test score. It showed that this correlation was independent of risk factors for WMCs (age and high systolic blood pressure) (Table 7).

Discussion

The identification of a potential association between OSA and WMCs can contribute to the prevention of dementia and stroke within communities through the treatment of OSA. Numerous studies have been conducted in this field, but the results are contradictory [7–10]. In this study, we intend to elucidate the possible relationship between OSA and WMCs.

In the present study, 12.5% of patients without OSA, 11.12% of mild OSA patients, 70% of moderate OSA patients, and all patients with severe OSA showed WMCs in the brain. In the study by H. Kim et al. [5], 33.56% of people without OSA, 42.86% of mild OSA patients, and 62.26% of moderate to severe OSA patients showed changes in white matter.

In a study of the WMC severity in OSA people, 76.5% showed no change, 10% showed mild changes, and 22.5% showed moderate to severe changes. In the study of U.G. Schulz et al. [9], which was performed only in a population of people with the slightest symptoms of OSA, 26% had no WMC, and the other participants showed minor changes. In another study conducted by H. Kim et al.

[5], 52.37% of people with OSA did not show any difference in white matter, 38.78% of people showed moderate changes, and 15.42% of people showed severe changes. This discrepancy in the lower prevalence of WMCs in our study compared to other studies may be due to the lower mean age of participants in our study (38.32 ± 6.28) compared to U.G Schulz [9] (58 years) and H. Kim [5] (59.63 ± 7.48 years) studies. In the Rotterdam scan study [14], only 5% of people aged 60 to 90 showed no change in white matter. However, the prevalence of these changes was lower among people aged 60 to 70 years. (13% without subcortical lesions, 32% without periventricular lesions) [15].

Also, in the cardiovascular health study, approximately 30% of participants with a mean age of 75 years had no WMCs or showed slight changes. These studies demonstrate the effect of age as an important risk factor for WMCs [16].

In assessing the various risk factors between OSA and non-OSA people, only BMI was significantly higher in the OSA group. The difference in FBS was close to a significant level. Also, age and systolic blood pressure did not show a significant difference between the two groups due to participants' selection because people over the age of 50 with high blood pressure or a history of high blood pressure were not included in the study, and this conscious selection was due to that age and blood pressure were both common risk factors for OSA and WMCs.

To investigate the relationship between OSA severity and WMCs and other risk factors, these risk factors, total WMCs score, and the number of lesions were compared between 4 subgroups (normal people, mild, moderate, and severe OSA people). Mean BMI, FBS, systolic and diastolic blood pressure, number of brain lesions, and most importantly, the WMCs score increased significantly with increasing OSA severity. When this relationship was tested at the level of regression, age also showed a significant positive correlation with the severity of OSA and the mentioned parameters.

In the U.G. Schulz et al. study [9], participants were divided into different quartiles based on the median of oxygen saturation index (IQR) representing different intensities of OSA and having an oxygen saturation index greater than 7.5 was used to define the intensity of OSA (first quartile 3 (1.9–3.7), second quartile 7.4 (6–8), third quartile 12.9 (11.4–14.7), and fourth quartile 27 (21.2–41.1)). When the mean risk factors were compared between different severities of OSA, high blood pressure, mean systolic and diastolic blood pressure, BMI, waist-to-hip ratio, weight, neck circumference, and insulin level were significantly associated with OSA severity. Nonetheless, there was no correlation detected between diabetes status, lipid profile, smoking status, and, notably, ARWMC scores with OSA intensity. R.H. Mason et al. [6]. Reported similar results to the above study. One of the differences that caused this discrepancy in the results could be the lack of a control group in the above studies and conducting this study on OSA people with minimal symptoms, while our study had a control group and different OSA groups based on severity. The discrepancy may also stem from the index utilized in categorizing the severity of OSA in the aforementioned studies, namely the oxygen saturation index. In contrast, our study index was AHI, a very accurate index to define OSA severity.

In this study, the relationship between the severity of WMCs and OSA and its risk factors was also investigated. Participants in the study were divided into four subgroups (no change-slight change-moderate change-severe change) based on WMCs severity. Increasing age, BMI, and FBS were significantly associated with changes, and systolic blood pressure was also close to a significant level. Univariate analyses also showed a significant positive correlation between OSA severity and ARWMC score. To evaluate the independent effect of OSA on WMCs, a multivariate regression model including age, FBS, BMI, OSA severity, and systolic blood pressure was used. This association remained even stronger after the effect of potentially confounding factors had been eliminated. In addition, all subjects with moderate to severe WMCs had moderate to severe apnea (66.67% showed moderate apnea and 33.33% had severe apnea). This finding was noted as 87.5% of individuals without apnea and 88.89% of individuals with mild apnea showed no change. This difference in the distribution of OSA severity in different groups of WMCs was quite significant. In the H. Kim et al. study [5], the distribution of OSA severity in other groups of WMCs was compared, And severe changes (ARWMC > 5) are most common in moderate and severe OSA groups (6.58% of patients with severe OSA without change, 16.25% showed mild to moderate changes and 17.95% revealed severe changes in white matter). Also, most people without changes had no OSA. (66.43% compared to 48.13% in the group with ARWMC scores = 1–4 and 51.28% in the group with ARWMC > 5) This difference in the distribution of OSA severity in different groups of WMCs, similar to our study, was quite significant.

One of the crucial results of H. Kim et al. [5] study that was also confirmed in two studies by R.H. Mason [6] and U.G. Schulz [2] was that only moderate to severe—but not mild—OSA was associated with WMCs. They concluded that disease severity instead of the presence of OSA, might mediate the pathogenesis of WMCs. Similarly, in our study, people with moderate to severe OSA were compared with the normal group and the group with mild changes in pairs. The rate of change in white

matter in moderate to severe groups was significantly higher than in normal or mild groups, and there was no significant difference between normal and mild groups.

Some other studies in line with our studies showed an association between OSA and WMCs. Nishibayashi et al. [8] And Minoguchi et al. [7] show a significant correlation between subclinical cerebrovascular disease and moderate to severe OSA. However, some other studies, such as Davis et al. [11], and Kiernan et al. [10] did not find a connection between OSA and ARWMC. Davis et al. [11], Who qualitatively examined the severity of WMCs and embolic blood pressure in OSA people, reported that only blood pressure, and not the severity of WMCs, differed between OSA and non-OSA subjects. also In their study, the severity of OSA in patients with hypertension was not associated with WMCs defined as ARWMC ≤ 5 on the ARWMC scale.

One possible explanation for the results of studies such as U.G. Schulz et al. is the different temporal association of both diseases with hypertension. OSA may be present before hypertension occurs as an etiological agent, and WMCs arise afterward. Therefore, any effect of OSA on changes in the white matter of the brain may be delayed due to high blood pressure and may last for years. In the multivariate analysis of U.G Schulz's study, both current blood pressure and blood pressure history parameters were associated with WMCs, but after eliminating the effect of other variables, only blood pressure history was significantly associated. Therefore, the inability of some previous studies to show the relationship between OSA and WMC may be due to the disruptive effect of high blood pressure, which indicates the reason for long-term studies [9].

Therefore, in the present study, people who did not have high blood pressure in the past and present and did not receive any medication were selected. Although there was a correlation between hypertension and OSA among different subgroups of OSA severity and a positive correlation between OSA severity and hypertension was confirmed, there was no association between OSA and systolic blood pressure in univariate or multivariate analyses. Also, with the addition of systolic blood pressure in multivariate analyses, the correlation between OSA severity and ARWMC was still maintained, which indicates the independent effect of OSA on WMCs, apart from the mediating effect of blood pressure.

Several pathological mechanisms can be identified for the association between OSA and changes in the brain's white matter. One mechanism is based on recurrent hypoxia and hypercapnia during recurrent episodes of apnea in people with OSA. This condition activates a chemical stimulation and reflux that increases the traffic of sympathetic vasoconstrictors to peripheral blood vessels. A wide range of autonomic, neuroendocrine, and hemodynamic changes occur during reflux responses and resumption of respiration. Increased cardiac output with vasoconstriction leads to a sharp rise in blood pressure, followed by a rapid and sudden drop in blood pressure. Changes in cerebral blood flow and velocity are associated with massive blood pressure fluctuations that induce cerebrovascular shear stress episodes [5].

Previous blood pressure studies and studies measuring brain hemodynamics in sleep apnea have shown a direct effect of sleep-related respiratory events on blood pressure and cerebral blood flow. This appears to be an interaction between respiratory effort and the period of nocturnal hypopnea and their association with increased cardiac preload, decreased cardiac overload, activation of carotid body baroreceptors, and vasodilation through both increased arterial carbon dioxide and reduced oxygen saturation, all of which can affect the reduction of cerebral blood flow [5].

The ischemic effects of nocturnal apnea can be exacerbated by oxidative stress from intermittent episodes of hypoxia and re-oxygenation, which together cause cerebrovascular endothelial dysfunction and self-regulation that preferably damage small cerebral arteries. Increased white matter intensity on MRI scans are ischemic tissues caused by recurrent episodes of cerebrovascular shear stress and the inflammatory process, and atherosclerosis [5].

Increased risk of WMCs may also occur through pathophysiological mechanisms that are not specific to cerebral blood flow. As in previous studies, increased expression of sensitive systemic markers, such as tumor necrosis factor, CRP, and platelet activity, was reported in patients; OSA may induce general atherosclerosis through the effect of intermittent hypoxia, which will stimulate the activity of multiple inflammatory and oxidative processes. Therefore, changes in white matter in younger people may be independent of blood pressure and inflammatory and oxidative processes [5].

For the first time in a study by Chen et al. [14], a correlation between changes in the integrity of white matter fibers and peripheral inflammatory markers in patients with severe OSA was found. They noted that elevated plasma levels of leukocyte superoxide, CRP, and soluble adhesion molecules indicate the presence of chronic inflammation in patients with OSA. Accumulation and adhesion of circulating leukocytes to the vascular endothelium lead to vascular inflammation and the progression of atherosclerosis, and reduced nitric oxide access leads to endothelial dysfunction, which increases the risk of intracranial vascular disease. Vascular endothelial inflammation and exacerbation of oxidative stress may partly explain the exacerbation of intracranial

atherosclerosis and subsequent white matter injury in untreated OSA patients.

Obstructive sleep apnea is associated with mood, cognitive, and autonomic nervous system changes that indicate changes in the central nervous system in the areas of the brain that mediate these behaviors. These changes are mainly seen in the regions that regulate memory (e.g., anterior cingulate, hippocampus, and frontal cortex) and in underlying areas of autonomic flow regulation (e.g., anterior cingulate, cerebellum, and brainstem areas). When the frequency of lesions in each part of the brain was examined, the highest frequency was related to the frontal cortex, followed by the parieto-occipital cortex and the basal ganglia; As H. Kim et al. [5] study that major WMCs were observed in the frontal region (89.4% of the total WMCs). Paul M. Macey et al. [17] showed that WMCs in patients with OSA include axons of major structures within the limbic system, brain bridge, frontal cortex, temporal cortex, and peritoneal cortex.

As the present study, in the H. Kim et al. study, the mean AHI scores increased significantly with increasing intensity. In addition, in H. Kim et al. study, the mean age, people over 65 years, people with high blood pressure, mean cholesterol, and triglycerides also increased with severity of changes [5].

Conclusion

The present study provides evidence for an association between OSA and WMCs in the brain. Our main finding was that moderate to severe but not mild OSA is independently associated with the prevalence of WMCs. It was also observed that a higher prevalence of moderate to severe OSA is associated with increased severity of changes, which indicates the effect of disease severity on structural changes in the brain.

Abbreviations

AHI	Apnea-hypopnea index
ARWMC	Age-related white matter change
BMI	Body mass index
CT	Computed tomography
FBS	Fasting blood sugar
OSA	Obstructive sleep apnea
MRI	Magnetic resonance imaging
MUMS	Mashhad University of Medical Sciences
WMC	White matter change

Acknowledgements

Not applicable.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Farzaneh Khoroushi, Yasmin Davoodi, Farnaz Kharghani, and Ehsan Hassannejad The first draft of the manuscript was written by Amirhossein Fathabadi, Maryam Salehi, and Yasmin Sharifan. and all authors commented on previous versions of the manuscript. All authors read carefully and approved the final manuscript.

Funding

None.

Availability of data and materials

The data and materials that support the findings of this study are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate

The study design followed the Declaration of Helsinki and was approved by the Ethics Committee of Mashhad University of Medical Sciences. (Ethics code: IR.MUMS.fn.REC.1396.121.). Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors participating in this research agree on publication and want it.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Central Khorasan, Iran. [2]School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Department of Radiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [4]School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [5]Department of Radiology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.

Received: 1 November 2023 Accepted: 13 January 2024
Published online: 01 February 2024

References

1. Patil SP, Schneider H, Schwartz AR, Smith PL (2007) Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest 132(1):325–337
2. Mannarino MR, Di Filippo F, Pirro M (2012) Obstructive sleep apnea syndrome. Eur J Intern Med 23(7):586–593
3. Zimmerman ME, Aloia MS (2006) A review of neuroimaging in obstructive sleep apnea. J Clin Sleep Med 2(04):461–471
4. Eguchi K, Kario K, Hoshide S, Ishikawa J, Morinari M, Shimada K (2005) Nocturnal hypoxia is associated with silent cerebrovascular disease in a high-risk Japanese community-dwelling population. Am J Hypertens 18(11):1489–1495
5. Kim H, Yun C-H, Thomas RJ, Lee SH, Seo HS, Cho ER et al (2013) Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep 36(5):709–715
6. Mason RH, Craig SE, Schultz U, Howard S, Nicoll D, Rothwell P, Davies RJ, Stradling JR. Prevalence Of Age-related Brain White Matter Changes In 159 Patients With Mild-moderate, Minimally Symptomatic, Obstructive Sleep Apnoea (OSA). InB72. CONSEQUENCES OF SLEEP DISORDERED BREATHING: CLINICAL ASPECTS. American Thoracic Society. 2010. p. A3666–A3666.
7. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Oda N, Tanaka A et al (2007) Silent brain infarction and platelet activation in obstructive sleep apnea. Am J Respir Crit Care Med 175(6):612–617
8. Nishibayashi M, Miyamoto M, Miyamoto T, Suzuki K, Hirata K (2008) Correlation between severity of obstructive sleep apnea and prevalence of silent cerebrovascular lesions. J Clin Sleep Med 4(3):242–247
9. Schulz UG, Mason RH, Craig SE, Howard S, Nicoll DJ, Kohler M et al (2013) Leukoaraiosis on MRI in patients with minimally symptomatic obstructive sleep apnoea. Cerebrovasc Dis 35(4):363–369
10. Kiernan T-EJ, Capampangan DJ, Hickey MG, Pearce LA, Aguilar MI (2011) Sleep apnea and white matter disease in hypertensive patients: a case series. The neurologist 17(5):289–91
11. Davies CW, Crosby JH, Mullins RL, Traill ZC, Anslow P, Davies RJ et al (2001) Case control study of cerebrovascular damage defined by magnetic

resonance imaging in patients with OSA and normal matched control subjects. Sleep 24(6):715–720
12. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK et al (2012) Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med 8(5):597–619
13. Wahlund L-O, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M et al (2001) A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 32(6):1318–1322
14. Chen H-L, Lu C-H, Lin H-C, Chen P-C, Chou K-H, Lin W-M et al (2015) White matter damage and systemic inflammation in obstructive sleep apnea. Sleep 38(3):361–370
15. De Leeuw F, de Groot JC, Achten E, Oudkerk M, Ramos L, Heijboer R et al (2001) Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. Journal of Neurology, Neurosurgery & Psychiatry 70(1):9–14
16. Kuller LH, Longstreth W Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr (2004) White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 35(8):1821–1825
17. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM (2008) Brain structural changes in obstructive sleep apnea. Sleep 31(7):967–977

Publisher's Note