Sweed *et al.*
The Egyptian Journal of Bronchology (2023) 17:75
https://doi.org/10.1186/s43168-023-00247-w

The Egyptian Journal of Bronchology

RESEARCH

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Impact of obstructive sleep apnea on cognition, mood, and fatigue: an MRI-based study

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Abstract

Background Obstructive sleep apnea disrupts the normal sleep cycle and is associated with many adverse consequences such as cardiovascular disease, DM, psychological problems, depression, decreased cognitive function, reduced quality of life, structural brain changes, and fatigue.

Purpose This work aimed to study the MRI structural brain changes and to assess the neurocognitive function, depression, and fatigue using multiple questionnaires (MoCA score, BDI-П, and FSS, respectively) in OSA patients.

Methods We enrolled 30 patients > 18 years with moderate (severity groups I), severe (severity groups П), very severe or extremely severe OSA (severity groups Ш), and 10 control subjects that were matched. All patients and control subjects underwent full-night PSG. Patients underwent neuropsychological tests including the Montreal Cognitive Assessment, Beck's Depression Inventory-II, and Fatigue Severity Scale (FSS) in addition to an MRI brain without contrast.

Results The mean AHI among patients (56.7% were females and 43.3% were males) was 39.97 ± 20.26 event/h. Severity groups I (40% of studied patients), П (46.7%), and Ш (13.3%). Abnormal MRI findings (WMCs) were detected in 18 patients (60%), versus 4 subjects (40%) in the control group, showing no statistically significant difference, $p = 0.300$. Among different severity groups, the prevalence of abnormal MRI findings was 4 (33.3%), 11 (78.6%), and 3 (75%) patients in severity groups I, П, and Ш, respectively. There was a statistically significant difference between patients and control regarding affection of subcortical and corpus callosal regions, $p = 0.007$ and 0.38, respectively, but not periventricular or deep white matter hyperintensities.

Montreal Cognitive Assessment, Beck's Depression Inventory-II score, and Fatigue Severity Scale, all showed statistically significant differences between patient and control groups. There was a significant negative correlation between AHI and MoCA score and a significant positive correlation between AHI and BDI-П, and also between AHI and FSS, $p = 0.005$, 0.016, and 0.008, respectively.

The Frontal lobe was the most affected lobe among our patients followed by the parietal lobe. The mean value of AHI in the group of patients with abnormal MRI findings was statistically significantly higher than that in the group with normal MRI findings (45.42 ± 19.29 versus 32.06 ± 19.82 event/h, respectively), $p = 0.010$. Comparing both groups showed: that the mean value of MoCA score in the group of patients with abnormal MRI findings was significantly lower than that in the group with normal MRI findings (17.89 ± 3.64 versus 24.08 ± 4.44, respectively), $p < 0.001$.

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Regarding both BDI-П and FSS, it was noted that the mean value in the group of patients with abnormal MRI findings was higher than that in the group with normal MRI findings (33.83 ± 7.94 versus 32 ± 7.39, and (58.39 ± 4.82 versus 55.17 ± 7.12 respectively), but this difference was not statistically significant, $p = 0.529$, $p = 1.000$, respectively.

Conclusion There was no significant difference between patients and the control group regarding WMCs in general, but there was a significant difference regarding the presence of subcortical and corpus callosal white matter hyperintensities. The Frontal lobe was the most affected. Neurocognitive function, depression, and fatigue were significantly affected in OSA patients in comparison to the control group. OSA patients with WMCs had a significantly higher AHI and a significantly lower MoCA score.

Keywords MRI, MoCA, FSS, Beck depression inventory, Cognition, Sleep apnea, AHI

Introduction

Obstructive sleep apnea (OSA), also referred to as obstructive sleep apnea-hypopnea syndrome (OSAHS) is the most common form of sleep-related breathing disorders (SRBDs) that is characterized by significant decrease or complete cessation of the airflow due to recurrent episodes of upper airway collapse during sleep but in the presence of breathing efforts [1]. These episodes are associated with recurrent arousals from sleep and oxyhemoglobin desaturations [2].

Estimates of the prevalence of OSA vary widely, depending on the methodology. The severity of OSA can be assessed using the apnea-hypopnea index (AHI) which is the number of complete (apneas) or incomplete (hypopneas) obstructive events per hour of sleep. When these apneas and hypopneas are combined with symptoms such as excessive daytime sleepiness (EDS), the term OSAHS is applied [3]. In the Wisconsin Sleep Cohort, OSA can be defined as AHI ≥ 5 events/h, the prevalence of OSA was reported as 24% in men and 9% in women aged 30–60 years [4, 5]. The prevalence of OSA with associated EDS (OSAHS) was approximately 3–7% in adult men and 2-5% in adult women [5, 6].

During non-REM sleep (80% of total sleep time), parasympathetic activity increases and sympathetic activity decreases leading to a lowering of blood pressure and heart rate [7, 8]. On the other hand, OSA disrupts the normal sleep cycle. Apneas and hypopneas, with the consequent compensatory hyperpneas, are usually associated with four main acute adverse consequences; Arterial blood gas abnormalities, in the form of IH and reoxygenation with fluctuations in $PaCO_2$ that lead to: organ dysfunction and oxidative stress and inflammation leading to endothelial dysfunction, excessive arousals, Increased sympathetic and decreased parasympathetic activity [8]. *And finally*, Large swings in the negative intrathoracic pressure (up to 80 cm H_2O) [7].

These adverse consequences are responsible for most of the complications that occur in OSA patients as [8–10] cardiovascular and cerebrovascular disease, Stroke, or Sudden cardiac death. DM and metabolic syndrome, psychological problems and depression, Decreased cognitive function, Reduced quality of life, Structural brain changes, and fatigue.

In this study, we were much more concerned with Structural brain changes and neuropsychological problems including cognitive function, depression, and fatigue.

Aim

This work aimed to study the MRI structural brain changes and to assess the neurocognitive function, depression, and fatigue using multiple questionnaires (MoCA score, BDI-П, and FSS, respectively) in OSA patients.

Patients and methods

The current study was conducted at the sleep unit, Chest Diseases Department, in Alexandria Main University Hospital in the duration between October 2016 and September 2018. We enrolled 30 OSA patients and 10 control subjects that were matched with the patients regarding age, gender, BMI, smoking status, and associated comorbidities. Patients were divided into three groups according to severity of OSA as assessed by AHI and the fourth group involved the control subjects. Group 1 included patients with moderate OSA (15 ≤ AHI < 30), group 2 included patients with severe OSA (30 ≤ AHI < 60), group 3 included patients with very severe (60 ≤ AHI < 100) and extremely severe OSA (AHI ≥ 100) and group 4 included control subjects. We enrolled patients > 18 years of both sexes with moderate, severe, very severe, or extremely severe OSA. We excluded patients with known chronic lung disease, cerebrovascular disease or using psychoactive medications, patients who were previously treated with CPAP, patients with mild OSA or whose body weight > 120 kg or with a pacemaker (contraindications for MRI examination), and finally patients on tracheostomy or oxygen therapy.

Each subject underwent the following thorough history taking including an inquiry about symptoms relevant to underlying sleep-related breathing disorders such as

snoring, choking, or gasping attacks at night, witnessed apneas, EDS, fatigue [11, 12], and history of any comorbid illness. All patients underwent complete physical examination and routine laboratory investigations, lipid profile, arterial blood gases (ABGs), and Electrocardiogram (ECG). STOP-BANG Questionnaire [13] was applied, and patients were asked to rate their chance of dozing in each situation using the Epworth sleepiness scale: [14] The possible total score was 24. The normal upper limit, derived from two studies [15, 16] was generally considered to be 10 points.

Anthropometric data including body mass index (BMI) (Quetelet's index=weight (kg)/height (m) ^{2}) [17], neck circumference: measured at the level of laryngeal prominence [18], waist circumference [19], hip circumference: [20], and Neck circumference – Height ratio (NHR): NHR of 0.25 or greater is a helpful predictor for OSA [21].

All OSA patients and control subjects underwent full night PSG in our sleep unit using somnoscreen plus RC combi 39. According to the AASM Manual for Scoring of Sleep and Associated Events 2012, apnea events were defined, based on PSG, as a ≥ 90% drop of respiratory amplitude, lasting at least 10 s. Hypopneas were defined as > 30% drop of respiratory amplitude, lasting ≥ 10 s, associated with oxygen saturation drops of ≥ 3%. Time of oxygen saturation (SpO_2) below 90% (T90) during total sleep, average, and lowest nocturnal SpO_2 values were recorded [22].

Patients underwent a brief neuropsychological evaluation to evaluate most of their cognitive functions, depression, and fatigue. Tests included Montreal Cognitive Assessment (MoCA) [23]: It assesses several cognitive domains, and MoCA scores range between 0 and 30. A score of 26 or over is considered to be normal. Beck's Depression Inventory-II (BDI- II) :[24] BDI-II consists of 21 items. Each answer is scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The minimum score was 0 and the maximum score was 63 [25]. The standardized cutoffs used were 1–10: these ups and downs are considered normal. 11–16: mild mood disturbance. 17–20: borderline clinical depression. 21–30: moderate depression. 31–40: severe depression. Over 40: extreme depression [26]. Fatigue Severity Scale (FSS): [27] A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement. a total score of 36 or more suggests that the patient may be suffering from fatigue and needs further evaluation [28].

All OSA patients and control subjects underwent an MRI study of the brain without contrast. All scans were performed on a 1.5 Tesla MRI scanner (Philips Medical Systems, Nederland B.V.) with an eight-channel head coil. The protocols used to evaluate white matter in the brain were sagittal T1W/SE images and axial T1W, T2W and FLAIR images. WMCs on MRI were identified when there were hyperintensities > 5 mm on FLAIR images.

Statistical analysis of the data [29] Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp.) [30]. Qualitative data were described using numbers and percentages. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level. The used tests were Chi-square test: for categorical variables, to compare between different groups, Fisher's exact or Monte Carlo correction: correction for chi-square when more than 20% of the cells have expected count less than 5, Student's *t* test: for normally distributed quantitative variables, to compare between two studied groups, *F*-test (ANOVA): for normally distributed quantitative variables, to compare between more than two groups, and post hoc test (Tukey) for pairwise comparisons, Pearson coefficient: to correlate between two normally distributed quantitative variables, Mann-Whitney test: for abnormally distributed quantitative variables, to compare between two studied groups, Kruskal-Wallis test: for abnormally distributed quantitative variables, to compare between more than two studied groups and post hoc (Dunn's multiple comparisons test) for pairwise comparisons, Spearman coefficient: to correlate between two distributed abnormally quantitative variables.

Results

During the period from October 2016 to September 2018, we enrolled 39 patients with OSA of different severities (moderate, severe, very severe, and extremely severe OSA) and 10 control subjects in our study. Nine patients were excluded from our study due to a body weight of more than 120 kg and claustrophobia during performing MRI study. Both groups (patients and control) were matched regarding age, gender, smoking status, BMI, and associated comorbid conditions.

Among our studied patients, 17 (56.7%) were females and 13 (43.3%) were males. Their mean age was 58.17 ± 4.09 (mean ± SD) years (range 50–65 years). Regarding smoking status, 20 patients (66.7%) were nonsmokers, 6 patients (20%) were active smokers, 3 patients (10%) were passive smokers, and 1 patient (3.3%) was ex-smoker.

The distribution of the most common associated comorbidities was as follows: DM in 21 patients (70%), hypertension in 22 patients (73.3%), and hyperlipidemia in 22 patients (73.3). Other comorbidities such as atrial fibrillation, ischemic heart diseases, chronic kidney disease, and venous thromboembolism (DVT) were present

in 4 (13.3%), 7 (23.3%), 2 (6.7%), and 1 (3.3%), respectively and none of our patients showed impaired liver functions.

The most frequent presenting symptom was choking attacks at night which was reported by all studied patients (100%). This was followed in descending frequency by snoring, witnessed apneas, EDS, recurrent arousal at night, unrefreshing sleep, fatigue, dry mouth, nocturia, and morning headache in 28 (93.3%), 28 (93.3%), 26 (86.7%), 25 (83.3%), 25 (83.3%), 24 (80%), 23 (76.7%), 20 (66.7%), and 10 (33.3%) patients, respectively.

Among our studied patients, 17 (56.7%) had normal ABG, 12 (40%) suffered from hypoxemia and hypercapnia, and 1 patient (3.3%) suffered from hypoxemia only. Among different severity groups, all patients (100%) in severity group I (moderate OSA) showed normal ABG, in severity group II (severe OSA), 4 patients (28.6%) showed normal ABG, only 1 patient (7.1%) suffered from hypoxemia and the other 9 patients (64.3%) had associated hypoventilation. While in severity group III, only 1 patient (25%) showed normal ABG and the other 3 patients (75%) suffered from hypoventilation. There was a statistically significant difference between severity groups I and II and severity groups I and III, but there was no significant difference between severity groups II and III regarding hypoventilation.

In general, there was no statistically significant difference between hypoventilated and non-hypoventilated OSA patients regarding the presence of normal or abnormal MRI studies.

Despite this, there was a significant difference between both groups regarding the presence of corpus callosal hyperintensities, hyperintensities in corona radiate, hyperintensities along centrum semiovale (p value = 0.018)

Regarding ECG findings, there was a statistically significant difference between patients and the control group regarding the prevalence of tachyarrhythmia (AF), (4 out of 30 patients (13.3%) suffered from AF versus 1 out of 10 subjects (10%) of the control group, $p = 0.018$). Also, there was a statistically significant difference between patients and the control group regarding the prevalence of corpulmonale (13 out of 30 patients (43.3%) suffered from corpulmonale versus no one (0%) of the control group, $p = 0.018$).

Using the STOP-BANG Questionnaire, all our studied patients (100%) showed a high risk for OSA, whereas in the control group, only 2 subjects (20%) showed intermediate risk for OSA and the remaining 8 subjects (80%) showed a low risk for OSA. Among different severity groups, the mean values of ESS were 15.25 ± 2.49, 19.14 ± 2.66, and 23.25 ± 1.5 for severity groups I, II, and III, respectively. There was a statistically significant difference between severity groups I and II and severity groups I and III but no significant difference between severity groups II and III.

Our study showed a statistically significant positive correlation between AHI and the following: neck circumference, neck height ratio, STOP-BANG Questionnaire, and ESS, $p < 0.001$. The distribution of the studied patients according to the severity of OSA (AHI) is shown in Fig. 1. The mean value of AHI among our studied patients was 39.97 ± 20.26 event/h (range 18–92.40 event/h) versus 2.36 ± 1.02 event/h (range 1.2–4.3 event/h) among the control group, $p < 0.001$. The mean values were 22.76 ± 3.13, 42.57 ± 7.28, and 82.5 ± 8.53 event/h for severity groups I, II, and III, respectively. The mean value of T90 % among our studied patients was 25.83 ± 31.85 % (range 0.0-99.5 %) versus 1.01 ± 0.076 % (range 0.0–2.1%) among the control group showing a statistically significant difference between both groups, $p < 0.001$.

Abnormal MRI findings (WMCs) were detected in 18 patients (60%), versus 4 subjects (40%) in the control group. Among different severity groups, the prevalence of abnormal MRI findings was 4 (33.3%), 11 (78.6%), and 3 (75%) patients in severity groups I, II, and III, respectively (Table 1).

Regarding the presence of white matter hyperintensities in MRI, different regions such as periventricular, deep white matter, subcortical, corpus callosal, and cerebellar regions were assessed in our study. Figure 2 shows a comparison between patients and the control group regarding regions affected in the MRI study. There was no statistically significant difference between patients and the control group regarding the presence of periventricular or deep white matter hyperintensities, $p = 0.300$, but there was a statistically significant difference regarding affection of subcortical and corpus callosal regions, $p = 0.007$ and 0.38, respectively. Among severity groups, there was a statistically significant difference between severity groups I and II and severity groups I and III but no significant difference between severity groups II and

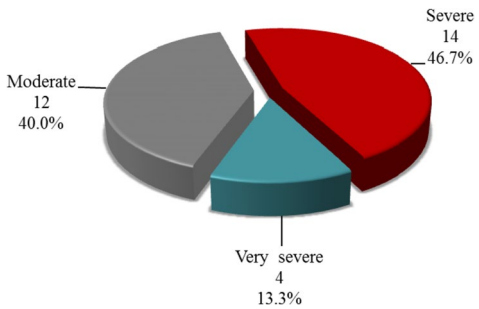

Fig. 1 Distribution of the studied patients according to the severity of OSA (AHI)

Table 1 Comparison between the different studied groups according to the presence of MRI abnormalities and regions showing white matter hyperintensities

Variables	Patients								Control ($n = 10$)		χ^2	^{MC}p	χ^2	$^{FE}p_0$
	Total ($n = 30$)		Moderate ($n = 12$)		Severe ($n = 14$)		Very severe ($n = 4$)							
	No.	%	No.	%	No.	%	No.	%	No.	%				
MRI findings														
Normal	12	40.0	8	66.7	3	21.4	1	25.0	6	60.0	6.789	0.070	1.21	0.300
Abnormal	18	60.0	4	33.3	11	78.6	3	75.0	4	40.0				
Regions showing white matter hyper intensities														
Periventricular hyper intensities	18	60.0	4	33.3	11	78.6	3	75.0	4	40.0	6.789	0.070	1.212	0.300
Deep white matter hyper intensities	18	60.0	4	33.3	11	78.6	3	75.0	4	40.0	6.789	0.070	1.212	0.300
Subcortical hyper intensities	14	46.7	2[a]	16.7	9[b]	64.3	3[b]	75.0	0[a]	0.0	15.184*	0.001*	7.179*	0.007*
Corpus callosal hyper intensities	11	36.7	0[a]	0.0	8[b]	57.1	3[b]	75.0	0[a]	0.0	18.535*	< 0.001*	5.057*	0.038*
Cerebellar hyper intensities	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–	–	–	–

In each row, different letters are significant (common letters are not significant)

χ^2 chi-square test, *MC* Monte Carlo, *FE* Fisher exact

p p value for comparing between the four groups

p_0 *p* value for comparing between total cases and control

*Statistically significant at $p \leq 0.05$

III regarding the presence of subcortical and corpus callosal hyperintensities.

Lobes affected in MRI are shown in Fig. 3. There was a statistically significant difference between patients and the control group regarding frontal lobe affection, $p = 0.003$ but not regarding other lobes affection. Severity group I showed affection for the frontal lobe only in 2 out of 12 patients (16.7%). In severity group II, the frontal lobe was affected in 11 out of 14 patients (78.6%), the parietal lobe was affected in 4 out of 14 patients (28.6%) and neither the occipital nor temporal lobe was affected. While in severity group III, frontal and parietal lobes were affected in 3 out of 4 patients (75%), but occipital and temporal lobes were not affected. A schematic representation of the studied patients and control group according to abnormal MRI findings and affected lobe is shown in Fig. 4.

Comparing patient and control groups regarding different scores, the Montreal Cognitive Assessment (MoCA) was statistically significantly different regarding the value of the mean, $P < 0.001$ (Table 2). Among patients who showed abnormal MoCA scores (19 patients), abnormalities in Visual/executive skills, attention, concentration, working memory, and abstraction were reported by all patients. These were followed in descending order by abnormalities in delayed recall in 17 patients (89.5%), abnormalities in orientation in 16 patients (84.2%), abnormalities in language in 11 patients (57.9%), and abnormalities in naming in 8 patients (42.1%). Also, Beck's Depression Inventory-II (BDI-II) was statistically significantly different between both groups, $p < 0.001$, but there was no statistically significant difference between any of the 3 severity groups (Table 3). Regarding the Fatigue Severity Scale (FSS). The mean value for our patients was 57.10 ± 5.95 (range 43–68), and that for the control group was 39.80 ± 8.39 (range 25–52) showing a statistically significant difference between both groups as well, $p < 0.001$. Among different severity groups, all the patients in groups I, II, and III had fatigue with a mean of 53.08 ± 7.08, 59.14 ± 2.85, and 62 ± 2.71, respectively. There was a statistically significant difference only between severity group I and III but no significant difference between severity groups I and II or groups II and III, $p = 0.028$, 0.096, and 0.282, respectively.

Our study showed a significant negative correlation between AHI and MoCA score and a significant positive correlation between AHI and both BDI-II, and FSS, $p = 0.005$, 0.016, and 0.008, respectively as shown in Figs. 5, 6, and 7.

The mean value of AHI in the group of patients with abnormal MRI findings was statistically significantly higher than that in the group with normal MRI findings (45.42 ± 19.29 versus 32.06 ± 19.82 event/h, respectively), $p = 0.010$. Comparing both groups showed: that the mean value of MoCA score in the group of patients with abnormal MRI findings was significantly lower than that in the group with normal MRI findings, $p < 0.001$. Our study showed that the most affected brain lobe was the frontal lobe. It was affected in 16 (88.9%) of patients who showed abnormal MRI findings. The

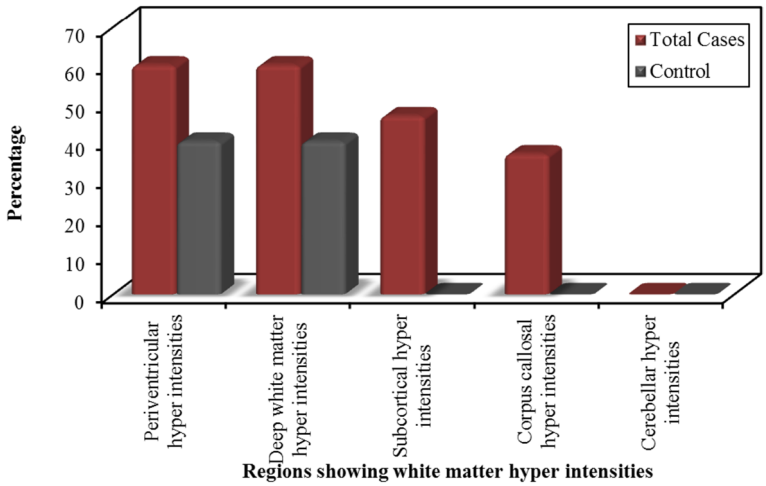

Fig. 2 Comparison between patients and control group regarding regions affected in MRI study

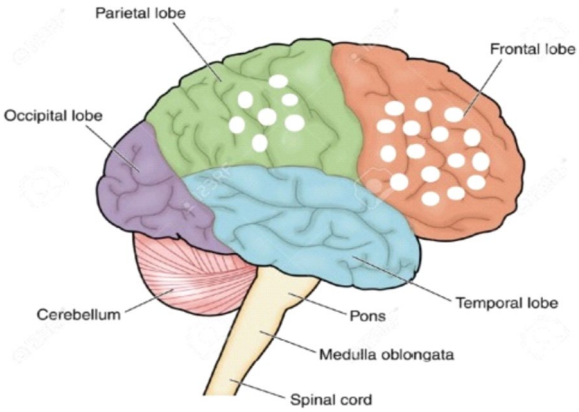

Fig. 3 Frontal and parietal lobes affection among patients with abnormal MRI findings. Each white circle stands for one patient (16 patients in the frontal lobe and 7 patients in the parietal lobe)

visuospatial skills, attention, and working memory. They were affected in 19 (100%) of patients who showed abnormal MOCA scores. Language was affected in 11 (57.9%) of patients who showed abnormal MOCA score (Table 3). Regarding both BDI-II and FSS, it was noted that the mean value in the group of patients with abnormal MRI findings was higher than that in the group with normal MRI findings, but the difference was not statistically significant, $p = 0.529$, $p = 1.000$, respectively (Table 4).

Discussion

The present work was designed to study the relationship between structural brain changes using structural MRI of the brain and neurocognitive function using multiple questionnaires in OSA patients with moderate, severe, and very severe degrees of OSA. Among the 30 studied

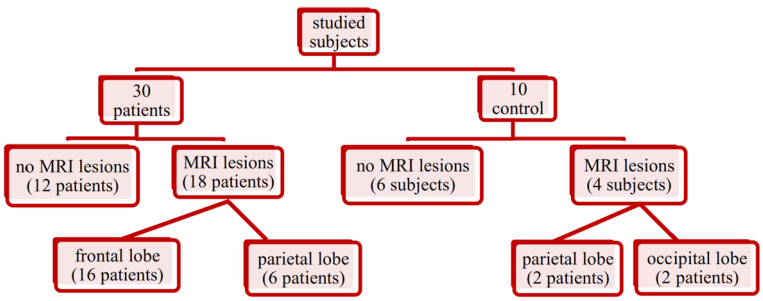

Fig. 4 Schematic representation of studied patients and control group according to abnormal MRI findings and affected lobe

frontal lobe is responsible for many domains of cognitive functions such as executive function, attention, memory, and language. Also, our results showed that the most affected cognitive domains were executive/

patients, only 43.3% were males and this male-to-female ratio does not match the known high prevalence of OSA in males as reported by the Wisconsin Sleep Cohort [5]. This ratio also doesn't reflect the prevalence of OSA in

Table 2 Comparison between the different studied groups according to cognitive function (MoCA score)

Variables	Patients								Control ($n = 10$)		Test of sig.	*P*
	Total ($n = 30$)		Moderate ($n = 12$)		Severe ($n = 14$)		Very severe ($n = 4$)					
	No.	%	No.	%	No.	%	No.	%	No.	%		
MoCA score												
Normal ≥ 26	11	36.7	9[a]	75.0	2[b]	14.3	0[b]	0.0	7[a]	70.0	$\chi^2 = 15.076^*$	$^{MC}p = 0.001^*$
Abnormal < 26	19	63.3	3[a]	25.0	12[b]	85.7	4[b]	100.0	3[a]	30.0		
$\chi^2(^{FE}p_0)$	3.367(0.140)											
Min.–max.	12.0–27.0		19.0–27.0		13.0–27.0		12.0–14.0		23.0–30.0		$F = 30.094^*$	$< 0.001^*$
Mean ± SD	20.37 ± 4.98		24.50 ± 2.88		18.93 ± 3.67		13.0 ± 0.82		27.60 ± 2.76			
Sig. bet. Grps	$t(p_0) = 5.743^*(< 0.001^*)$		$p_1 < 0.001^*, p_2 < 0.001^*, p_3 = 0.008^*$									

t Student's *t* test, *F F* for ANOVA test, pairwise comparison bet. Each 2 groups was done using post hoc test (Tukey), *U* Mann-Whitney test, *H H* for Kruskal-Wallis test, pairwise comparison bet. each 2 groups was done using post hoc test (Dunn's for multiple comparisons test)

p p value for comparing between the different groups

p_0 *p* value for comparing between total cases and control

p_1 *p* value for comparing between moderate and severe

p_2 *p* value for comparing between moderate and very severe

p_3 *p* value for comparing between severe and very severe

*Statistically significant at $p \leq 0.05$

Table 3 Comparison between the different studied groups according to BDI-II

Variables	Patients								Control ($n = 10$)		Test of Sig.	*P*
	Total ($n = 30$)		Moderate ($n = 12$)		Severe ($n = 14$)		Very severe ($n = 4$)					
	No.	%	No.	%	No.	%	No.	%	No.	%		
BDI–II												
Normal (1–10)	0	0.0	0^{a}	0.0	0^{a}	0.0	0^{ab}	0.0	3^{b}	30.0	$\chi^2 = 34.856^{*}$	$< 0.001^{*}$
Mild mood disturbance (11–16)	0	0.0	0^{a}	0.0	0^{a}	0.0	0^{ab}	0.0	4^{b}	40.0		
Borderline clinical depression (17–20)	0	0.0	0^{a}	0.0	0^{a}	0.0	0^{ab}	0.0	3^{b}	30.0		
Moderate depression (21–30)	12	40.0	7^{a}	58.3	5^{ab}	35.7	0^{ab}	0.0	0^{c}	0.0		
Severe depression (31–40)	13	43.3	4^{a}	33.3	6^{a}	42.9	3^{a}	75.0	0^{b}	0.0		
Extreme depression (> 40)	5	16.7	1^{a}	8.3	3^{a}	21.4	1^{a}	25.0	0^{a}	0.0		
$\chi^{2(MC}p_0)$	33.743^{*} ($< 0.001^{*}$)											
Min.–max.	22.0–51.0		22.0–51.0		22.0–47.0		33.0–44.0		8.0 – 19.0		$F = 20.223^{*}$	$< 0.001^{*}$
Mean ± SD	33.10 ± 7.64		31.25 ± 7.72		33.71 ± 8.16		36.50 ± 5.20		13.50 ± 4.25			
Sig. bet. Grps	$t(p_0) = 7.678^{*}$ ($< 0.001^{*}$)		$p_1 = 0.808$, $p_2 = 0.570$, $p_3 = 0.896$									

χ^2 chi-square test, *MC* Monte Carlo, *t* Student's *t* test

F F for ANOVA test, Pairwise comparison bet. Every 2 groups were done using post hoc test (Tukey)

p *p* value for comparing between the four groups

p_0 *p* value for comparing between total cases and control

p_1 *p* value for comparing between moderate and severe

p_2 *p* value for comparing between moderate and very severe

p_3 *p* value for comparing between severe and very severe

*Statistically significant at $p \leq 0.05$

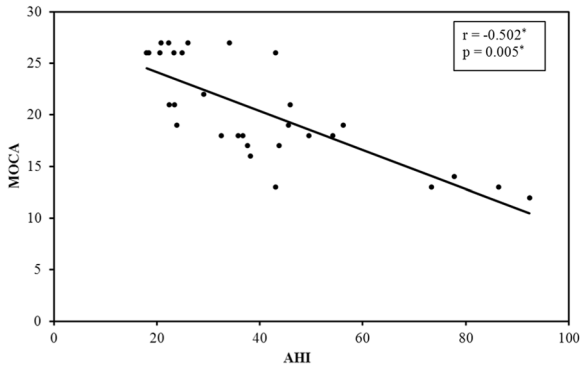

Fig. 5 Correlation between AHI and MoCA score in studied patients ($n = 30$)

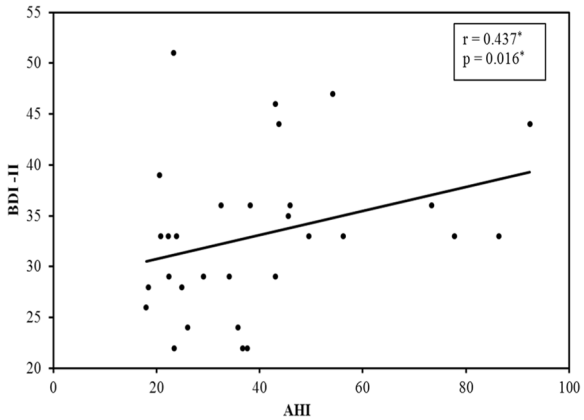

Fig. 6 Correlation between AHI and BDI–II in studied patients ($n = 30$)

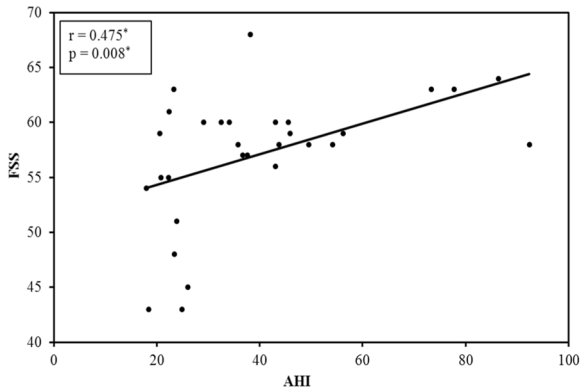

Fig. 7 Correlation between AHI and FSS in studied patients ($n = 30$)

our population as some patients were excluded from our study due to claustrophobia and weight > 120 kg during performing MRI study.

Regarding associated comorbidities, in our study, we reported prevalence of hypertension, hyperlipidemia, DM, IHD, AF, CKD, and DVT in 73.3%, 73.3%, 70%, 23.3%, 13.3%, 6.7%, and 3.3%, respectively in descending order and none of the patients showed any evidence of liver disease. We tried to avoid enrolling OSA patients with comorbidities such as DM and hypertension but this was not possible due to the very high prevalence of these comorbidities among OSA patients with moderate and severe degrees. This very high prevalence of hypertension, DM, and hyperlipidemia was reported by previous studies as well [31–33]. The association between these comorbidities and OSA is mainly due to IH. It promotes increased sympathetic nervous activity, oxidative stress, endothelial cell dysfunction, inflammation, platelet aggregation, and accelerated atherosclerosis [34]. Choking attacks at night were the most common presenting complaint, they were reported by all patients. This matched with a systematic review which reported that the most useful finding to identify patients with OSA was choking or gasping attacks [35]. Regarding anthropometric data, there was a strong positive correlation between AHI and both neck circumference and NHR, $p < 0.001$. Our results matched those of Wysocki J. et al. [36] who proved that the neck circumference was a significant predictor of the AHI value in males with OSA. Another study by Hoffstein V. et al. [37] revealed that obese patients with OSA have fatter necks than similarly obese non-apneic snorers and that neck circumference was a more useful predictor of OSA than general obesity.

The main aim of our study was to assess structural brain changes and cognitive function in OSA. Many studies addressed this question but no clear data reported if OSA can be an independent factor for WMCs or cognitive dysfunction [38–40]. We found no statistically significant difference between patients and the control group regarding abnormal MRI findings (WMCs) in general, $p = 0.300$. We can explain this non-significant difference between both groups regarding WMCs to the small sample size of both groups (patients and controls). However, there was a significant difference between both groups regarding the presence of subcortical and corpus callosal white matter hyperintensities (Table 1). In agreement with our results, Davies C. W. et al. [39] revealed that there was no apparent increase in MRI abnormalities in OSA patients over their matched control subjects. On the other hand, Ho B. L. et al. [38] conducted a systematic review and meta-analysis and reported a strong bidirectional relationship between OSA and WMCs. They concluded that OSA patients had a higher prevalence of WMCs more than their control group and that patients with WMCs had associated moderate to severe OSA. Similarly, Kim H. et al. [41] provided strong

evidence for the relationship between WMCs and OSA. Also, Macey P. M. et al. [40] revealed extensive affection of white matter in OSA patients.

We also found that the percentage of patients that showed WMCs increased with the increase in OSA severity from moderate to severe OSA (33.3% and 78.6% in moderate and severe OSA groups, respectively) (Table 1). This is in agreement with Kim H. et al. [41] who concluded that the severity of OSA contributed to the pathogenesis of WMCs rather than OSA by itself as WMCs were present in moderate to severe OSA not mild OSA. Also, Nishibayashi M. et al. [42] and Kenji M. et al. [43] proved that deep white matter and periventricular hyperintensities were more prevalent in patients with moderate to severe OSA than those with less severe OSA. On the other hand, Kiernan, T. J. et al. [44] reported no association between the severity of OSA and WMCs but they attributed this result to the small sample size and that all patients were hypertensives.

Moreover, when we compared the 2 groups having normal and abnormal MRI findings, we found that the mean AHI was significantly higher in the group with abnormal MRI findings than in the group with normal MRI findings, $p = 0.010$ (Fig. 7). This was proved also by Kim H. et al. [41] who revealed that the prevalence of OSA and the mean AHI were higher in groups with WMCs, even after adjustment for all covariates and this suggested that OSA contribute by additional mechanism to the pathogenesis of WMCs. On the other hand, Ding et al. [45] reported that there was no significant difference in the level of AHI between subjects with and without WMCs.

Regarding regions affected by MRI, our study reported the detection of periventricular, deep white matter, subcortical, and corpus callosal hyperintensities in 60%, 60%, 46%, and 36% of patients, respectively as shown in Table 1. Similarly, Nishibayashi M. et al. [42] Hamilton G. S. et al. [46], and Kenji M. et al. [43] reported that WMCs occur typically in periventricular and deep white matter

Table 4 Comparison between the group of patients showing normal and abnormal MRI findings regarding MoCA score, BDI-II, and FSS

Patients ($n = 30$)	**MRI**				**Test of sig.**	***P***
	Normal ($n = 12$)		**Abnormal ($n = 18$)**			
MoCA score						
Normal ≥ 26	9	75.0	2	11.1	$\chi^2 = 12.656$	$^{FE}p = 0.001^*$
Abnormal < 26	3	25.0	16	88.9		
Min.–max.	13.0–27.0		12.0–27.0		$t = 4.180^*$	$< 0.001^*$
Mean±SD	24.08 ± 4.44		17.89 ± 3.64			
Median	26.0		18.0			
BDI–II						
Normal (1–10)	0	0.0	0	0.0	$\chi^2 = 1.275$	$^{MC}p = 0.555$
Mild mood disturbance (11–16)	0	0.0	0	0.0		
Borderline clinical depression (17–20)	0	0.0	0	0.0		
Moderate depression (21–30)	6	50.0	6	33.3		
Severe depression (31–40)	5	41.7	8	44.4		
Extreme depression (> 40)	1	8.3	4	22.2		
Min.–max.	22.0–51.0		22.0–47.0		$t = 0.637$	0.529
Mean ± SD	32.0 ± 7.39		33.83 ± 7.94			
Median	31.0		34.0			
FSS						
Normal (< 36)	0	0.0	0	0.0	–	–
Fatigue (≥ 36)	12	100.0	18	100.0		
Min.–max.	43.0–64.0		45.0–68.0			
Mean ± SD.	55.17 ± 7.12		58.39 ± 4.82		$U = 108.0$	1.000
Median	56.50		58.50			

χ^2 chi-square test, *FE* Fisher exact, *U* Mann-Whitney test, *t* Student's *t* test, *p p* value for comparing between the two categories

*Statistically significant at $p \leq 0.05$

regions in their study. We reported no statistically significant difference between patients and the control group regarding affection of periventricular and deep white matter regions (p = 0.300 for both), but there was a statistically significant difference between patients and the control group regarding affection of subcortical and corpus callosum regions, p = 0.007, 0.038, respectively.

Regarding the distribution of WMCs according to lobes affected. Our study revealed that the frontal lobe was the most affected (in 53.3% of the total patients) followed by the parietal lobe (in 23.3% of the total patients) and neither the occipital nor temporal lobe was affected (Fig. 3). Similarly, Hamilton G. S. et al. [46] reported that WMCs most commonly affected the frontal lobe, less commonly parietal and occipital lobes, and rarely brainstem or basal ganglia. Also, Kim et al. [41] revealed that WMCs occurred predominantly in the frontal lobe. In our study, frontal lobe affection was more common among the group with severe OSA than that with moderate OSA (78.6% and 16.7%, respectively), and similarly, Kim et al. [41] reported that there was an increasing trend for the frontal WMCs across OSA severity groups, $P < 0.0001$.

The debate about the relationship between OSA and WMCs can be attributed to the fact that many of the associated comorbidities with OSA can cause WMCs perse as DM and hypertension. Also, age, gender, and obesity may contribute to the occurrence of WMCs. In our study to avoid this, we matched patients and a control group regarding age, gender, BMI, DM, and hypertension. This association of WMCs and different comorbidities was addressed in several studies; Perros P. et al. [47] and Novak V. et al. [48] revealed that type I and II DM, respectively were associated with white matter hyperintensities mainly in the periventricular region. Another study by Dejgaard A. et al. [49] reported subcortical or brain stem abnormalities in type I DM. Ferguson S. C [50, 51]. concluded that chronic hyperglycemia may affect brain function and structure in the form of white matter hyperintensities affecting basal ganglia. On the other hand, other studies [52–55] found no evidence of white matter hyperintensities on MRI in diabetic patients. Regarding hypertension, several studies [56–58] reported that high blood pressure was associated with an increased risk of more severe WMCs. Concerning age and gender, Takagi et al. [59] reported that in their study, the prevalence of WMCs increased with age and that none of the patients aged less than 50 years were affected. Another study by Ewoud J. V. et al. [60] reported that higher age and female sex were associated with a high prevalence of WMCs. On the other hand, Robbins J. et al. [61] revealed that gender and higher age were not associated with WMCs. Stanek, K. M. et al. [62] suggested that there is an association between obesity and white matter affection in the fornix and corpus callosum. In our study, 29 out of the 30 patients had BMI ≥ 30, but we matched between patients and control group regarding BMI and the affection of corpus callosum was significantly higher among our studied patients, p = 0.038. From the previous studies, it is evident that WMCs are not specific for OSA due to many common risk factors between OSA and WMCs but we think that OSA may contribute to WMCs. Other studies that support this theory reported improvement in WMCs with CPAP treatment of OSA [63, 64]. This may suggest that OSA itself exerts an effect on white matter.

Cognitive deficits were more common in OSA patients using the MoCA score in our study. There was a statistically significant difference between patients and the control group regarding its mean value, $p < 0.001$. Also, the percentage of cases that showed abnormal scores increased with the increase in OSA severity from moderate to severe to very severe OSA (25%, 85.7%, and 100% respectively), (Table 2). Moreover, there was a significant negative correlation between OSA severity (AHI) and MoCA score, p = 0.005 as shown in Fig. 6. Regarding different cognitive domains, we found that all domains were affected with a significant difference between patients and the control group regarding all of them except abstraction. The most commonly affected domains in our study were visuospatial/executive skills, attention, concentration, working memory, and abstraction (in 100% of patients with abnormal scores). Olaithe M. et al. [65] conducted a systematic review and meta-analysis and concluded that cognitive deficits occurred in patients with OSA. Also, Fulda S. et al. [66] conducted a systematic review and meta-analysis and proved that patients with OSA had more pronounced cognitive and behavioral impairment, especially across tasks assessing attention and driving ability. Another meta-analysis [67] found that general intelligence and language were typically not affected by OSA, but attention was markedly affected. Similar results were reported by other studies [68–70]. Variable results of the studies may be due to different tests used to assess cognitive domains, different IQ, education levels, and different ages and sex of the subjects involved in different studies. Cognitive dysfunction in OSA patients may occur due to multiple mechanisms but the evidence for these mechanisms is equivocal [71]. Hypoxia, hypercapnia, and sleep disruption are the main mechanisms involved [72, 73]. As the frontal subcortical region is concerned with executive function, attention, and cognitive processing speed and it is affected in most of the patients in our study, we conclude that many cognitive domains are mostly affected in patients with OSA by different mechanisms and may deteriorate with increasing severity of OSA.

Moreover, studies that reported improvement in cognitive impairment with CPAP treatment also support that OSA may have an independent role in cognitive dysfunction [64, 74].

Depression was another item assessed in our study by using BDI-Π. There was a statistically significant difference between patients and the control group regarding the value of the mean, $p < 0.001$, (Table 3). Moreover, there was a significant positive correlation between AHI and BDI-Π, $p = 0.016$ as shown in Fig. 6, in agreement with Millman R. P. et al. [75] who reported that the score for depression increased with an increase in AHI. Khawaja I. S. et al. [76] revealed a high prevalence of depression in OSA patients and that OSA may be responsible for the failure of treatment in cases with resistant depression. Many other studies revealed increased prevalence of depression in OSA with variable percent of depression among patients with OSA (from 17.6 to 63%) [77–80]. On the other hand, Phillips B. A. et al. [81], Pillar G. et al. [82], and Asghari A. M. et al. [83] found no association between depression and OSA. These variations are mostly due to different scores used to assess depression, different study designs, and different patient characteristics. Depression and OSA share many factors and comorbid clinical conditions such as age, sex, obesity, DM, hypertension, and systemic inflammation [84]. In our study, we matched between groups regarding the confounding factors, so we suggest that there may be an association between depression and OSA and that depression scores may increase with increased severity of OSA.

In the present study, fatigue was assessed using FSS. There was a statistically significant difference between patients and the control group regarding the value of the mean, $p < 0.001$. Also, we found a significant positive correlation between AHI and FSS, $p = 0.008$ as presented in Fig. 6. Similarly, Stepnowsky C. J. et al. [85] and Jackson M. L. et al. [86] reported an association of fatigue with OSA. Others [87, 88] revealed that fatigue is associated with OSA but not related to the severity of OSA.

In our study, we tried to find the relation between structural brain changes (WMCs) and cognitive impairment (MoCA score). Concerning the association between MRI abnormal findings (WMCs) and MoCA score, we compared the 2 groups having normal and abnormal MRI findings and found that the mean value of MoCA score was significantly lower in the group with abnormal MRI findings than in the group with normal MRI findings ($p < 0.001$), (Table 4) (lower MoCA score means more deterioration in cognitive function). Bracco L. et al. [89] and Ewoud J. V. et al. [60] reported that there was a significant association between periventricular WMCs and the performance of executive function skills. Also, Xiong Y. et al. [90], and Brickman A. M. et al. [91] found that WMCs were associated with both global function and executive function deficits. Jokinen H. et al. [92] revealed that WMCs were related to progressive impairment of cognitive function. Zimmerman M. E. et al. [93] reviewed many papers on neuroimaging in OSA. They found evidence for hippocampal atrophy, and neurochemical data indicative of white matter affection in the frontal lobes, plus a lack of activation within dorsolateral prefrontal cortices (this is associated with executive functions). More differences in neural function have been found in patients with OSA in cortices, they are involved in sensory, motor, and autonomic activity. These regions of structural brain damage are in line with deficits in executive function, memory, and psychomotor functions in patients with OSA. On the other hand, Wahlund L. O. et al. [94], and Schmidt R. et al. [95] reported a lack of association between progressive WMCs and a decrease in cognitive function.

Regarding the association between MRI abnormal findings (WMCs) and BDI-Π, the difference between the 2 groups was not statistically significant, $p = 0.529$, Table 4. Contrary to our study, previous studies [96–99] reported that WMCs (especially deep white matter and periventricular) were associated with depression. Also, Alexopoulos G. S [100]. reported that the limbic system and frontostriatal circuits were functionally related to depression and that these were affected in OSA. These differences may be related to different questionnaires used in the assessment of depression and to the different types of neuroimaging used between studies (regions affected may appear in one type of MRI and not in the other type).

Regarding the association between MRI abnormal findings (WMCs) and FSS, the mean value of FSS was higher in the group with abnormal MRI findings but the difference was not statistically significant, $p = 0.529$ as shown in Table 4. Similarly, Schwartz R. B. et al. [101] reported a nonsignificant presence of foci of white matter hyperintensities in subcortical, periventricular, and centrum semi-ovale regions by MRI scans in patients with chronic fatigue. Also, Cope H. et al. [102] and Greco A. et al. [103] revealed no associated abnormalities on MRI scans in patients with chronic fatigue. On the other hand, Lange G. et al. [104] and Natelson B. H. et al. [105] reported the presence of a significantly large number of brain abnormalities in the form of small foci of subcortical white matter hyperintensities predominantly in the frontal lobe in patients with chronic fatigue.

Like many previous studies, we found in our study that despite the association between increased AHI and WMCs, decreased MoCA score, increased BDI-Π score, and increased FSS in OSA patients, we could not confirm the causal relationship between OSA and WMCs,

cognitive dysfunction, depression, and fatigue due to many associated risk factors between all of them [44].

Nevertheless, our study had points of strength. We used full-night PSG for the diagnosis of OSA in our patients which is the gold standard method for OSA diagnosis. Furthermore, we matched patients with the control group regarding age, gender, smoking status, BMI, and associated comorbidities to avoid any bias in our results as much as possible. On the other hand, our study had some limitations. The first one is concerned with the cross-sectional design of our study which does not allow us to confirm any causal relationship between WMCs, cognitive dysfunction, depression, and fatigue in OSA. The second one is that our study was performed on a small number of patients and a control group. Another limitation was the several comorbidities our patients suffered from as DM, hypertension, and hyperlipidemia which act as confounding factors for WMCS, cognitive dysfunction, depression, and fatigue. These factors could not be avoided due to the inclusion of patients with moderate, severe, and very severe OSA only in our study and these severity groups usually suffer from these comorbidities. We concluded that there was no statistically significant difference between patients and the control group regarding WMCs in general, but there was a significant difference regarding the presence of subcortical and corpus callosal white matter hyperintensities. The frontal lobe was the most affected. There was a statistically significant difference between patients and the control group regarding abnormality in MoCA score as well as BDI-Π and FSS. A strong negative correlation was between AHI and MoCA score and a strong positive correlation between AHI and BDI-Π and FSS. The group of patients with WMCs had a significantly higher AHI and a significantly lower MoCA score. Despite the association between increased AHI and WMCs, decreased MoCA score, increased BDI-Π score, and increased FSS in OSA patients, we could not confirm the causal relationship between OSA and WMCs, cognitive dysfunction, depression, and fatigue due to many associated risk factors between all of them. Further studies on a larger scale of patients are recommended. Studies that enroll OSA patients free from any other comorbidities could yield a better result. In addition, Studies that assess the effect of CPAP treatment on the reversal of WMCs, and cognitive impairment in OSA patients could better confirm the causal relationship between OSA and the studied parameters.

Abbreviations

AASM	American Academy of Sleep Medicine
ABGs	Arterial Blood Gases
AHI	Apnea-hypopnea index
BDI-II	Beck's Depression Inventory-II
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
OSAHS	Obstructive sleep apnea-hypopnea syndrome
PSG	Polysomnogram
SRBDs	Sleep-related breathing disorders
T90	Time of oxygen saturation below 90%
WMCs	White matter changes

Authors' contributions

Rania Ahmed Sweed directed the practical part of the research, presenting the results and writing the manuscript. Rana Alsaeed Rizk Abd Elghany performed the practical part, statistics, and data collection. Anwar Ahmed Elganady decided on the main idea of the research and the methodology and revised the whole manuscript. Enas Elsayed Mohamed directed the research methodology and revised the manuscript. Jaidaa Farouk Mekky directed the part related to depression, cognition, and fatigue assessment and questionnaires and revised the manuscript. Mohamed Mahmoud Elshafei revised the MRI brain wrote detailed reports and revised the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received for this research.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

All subjects enrolled in the study signed an informed consent before participation. The study was accepted by the local ethical committee of Alexandria Faculty of Medicine (available from www.med.alexu.edu.eg/wp-content/uploads/2012/04/ethics-guide.pdf).

Informed consent was obtained from all individual participants included in the study.

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Received: 22 April 2023 Accepted: 24 October 2023
Published online: 13 December 2023

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