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Vascular Impairment in Alzheimer's Disease: The Role of Obstructive Sleep Apnea

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Abstract. Epidemiological studies have suggested a pathophysiological link between obstructive sleep apnea syndrome (OSAS) and Alzheimer's disease (AD). The mechanism by which sleep disturbance can affect cognitive impairment is not clear. The aim of this study was to investigate whether AD patients with OSAS have an impairment in cerebrovascular disease markers. We included 69 patients without OSAS and 93 patients with OSAS. They underwent an ultrasonographic assessment of common carotid arteries intima-media thickness (IMT) and carotid plaque index. Cerebrovascular reactivity to hypercapnia in the middle cerebral arteries was calculated with the Breath-Holding Index (BHI). Pathological values of IMT and BHI were significantly associated with the presence of OSAS (IMT > 1.0 mm: OR 2.98, 95%CI: 1.37–6.46; $p < 0.05$; BHI < 0.69: OR 5.25, 95%CI: 2.35–11.74; $p < 0.05$, multivariate adjusted analysis). Furthermore, the extent of cerebrovascular impairment was correlated with the severity of OSAS. The finding of alterations of cerebral vessel functional and anatomic status in AD patients with OSAS suggests the potential for effective treatment for sleep-related disturbances in a subgroup of AD patients.

Keywords: Alzheimer's disease, carotid atherosclerosis, cerebral hemodynamics, obstructive sleep apnea, ultrasound

INTRODUCTION

Prevalence of sleep-disordered breathing and, in particular, obstructive sleep apnea syndrome (OSAS) is extremely high among patients with dementia [1]. Different studies have also suggested that the severity of dementia tends to be positively correlated with the severity of OSAS [2, 3]. Additionally, a longitudinal study has reported that elderly women with mild-moderate OSAS have a higher probability of developing mild cognitive impairment (MCI) or Alzheimer's disease (AD) than women without OSAS [4]. Further, preliminary findings suggest a positive effect of treatment of comorbid OSAS with continuous positive airway pressure (CPAP) in terms of slowing cognitive deterioration [5]. These findings show that OSAS often precedes dementia and therefore might contribute to its pathogenesis. On the other hand, the mechanism by which OSAS can affect cognition has still not been fully defined. The increasing amount of evidence regarding the possible involvement of vascular factors in sustaining cognitive deterioration in AD patients [6, 7] could suggest that OSAS negatively influences cognition through the promotion of brain hypoperfusion [8]. In this respect, OSAS is recognized as an independent risk factor for ischemic stroke [9], and different studies have demonstrated that cerebral arteries in patients with OSAS may suffer from anatomic [10] and functional [11, 12] pathological changes.

In the present study, we investigated the possibility that in AD patients, the presence of OSAS may be associated with vascular, structural, and functional damage at the level of cerebral arteries.

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MATERIALS AND METHODS

Patients were selected from 211 consecutive subjects referred to our dementia outpatient service by general practitioners for progressive cognitive impairment. Inclusion criteria were a diagnosis of probable AD according to NINCDS–ADRDA criteria [13] and mild or moderate cognitive impairment defined as a Clinical Dementia Rating score of ≤ 2 [14]. The exclusion of subjects with a history of cerebrovascular disease, stepwise progression of cognitive impairment, and focal neurological signs left 168 patients diagnosed as having probable AD and mild to moderate cognitive impairment. Magnetic resonance (MR) scans were obtained using a 1.5 T magnet with the spin-echo technique, and T1- and T2-weighted and fluid-attenuated inversion-recovery sequences to detect possible white matter lesions that were graded according to Wahlund et al. [15]. Only patients without vascular lesions (grade 0) or those exhibiting small subcortical focal lesions, defined as areas with high signal intensity on T2 but isointense with normal brain parenchyma on T1 (classified as grade I), were included. Among 168 patients with probable AD, 6 were excluded for MR imaging evidence of cortical infarction or extensive white matter lesions. Finally, 162 patients were considered in the study. Clinical history with a structured interview (with caregivers' involvement) and hematochemical data were obtained from each patient with a focus on the major vascular risk factors (hypertension, diabetes, smoking habits, hyperlipidemia, obesity). Hypertension was defined as a history of high blood pressure, a systolic blood pressure $\geq$ 140 mm Hg, a diastolic blood pressure $\geq$ 90 mm Hg, or the use of an antihypertensive; dyslipidemia was defined as a history of dyslipidemia, a fasting serum total cholesterol $\geq$ 6.22 mmol/L (2.4 g/L) or triglycerides $\geq$ 2.26 mmol/L (2 g/L), or the use of a statin or fibrate; diabetes mellitus was defined as a history of diabetes mellitus, a fasting serum glucose $\geq$ 7.0 mmol/L (1.26 g/L), or the use of an oral antihyperglycemic or insulin; and smoking was defined as a history of active tobacco smoking [16]. Each patient was studied by means of a careful neurological examination and an extensive neuropsychological assessment of cognitive status. Moreover, an ultrasonographic morphological and functional evaluation of the neck and intracranial vessels was performed. Neck vessels were evaluated with continuous wave Doppler and Echo-Color Doppler using high resolution 7.5 MHz transducers (iU22 Philips ultrasound, Bothell, WA, USA). According to the Mannheim Consensus, carotid plaques were defined [17] as a focal structure protruding into the arterial lumen of at least 0.5 mm or 50% of the surrounding intima media thickness (IMT) value or showing a thickness > 1.5 mm measured from the media-adventitia interface to the intima-lumen interface. In each arterial segment, the plaque degree was quantified. Carotid plaques were defined as a thickening over 1.2 mm which does not include the whole vessel surface. In each arterial segment, the plaque degree was quantified as follows: 0, no plaque; 1, one small plaque < 30% of vessel diameter; 2, one medium plaque between 30% and 50% of vessel diameter or multiple small plaques; and 3, one large plaque > 50% of vessel diameter or multiple plaques with at least one medium plaque. The plaque index (PI) was calculated by adding the scores of the right and left carotid arteries [18]. The measurements of IMT were performed on the segment of 1.5 cm of the common carotid that precedes the carotid bifurcation in agreement with the method described by O'Leary et al. [19]. A longitudinal image of the distal segment of common carotid arteries was taken, and the measurement was obtained with an automatic system at the thickest point where there were no plaques on the proximal and distal wall. IMT was defined as the mean of the maximum thickness for proximal and distal wall of the common carotid of both sides. A semiautomatic software (QLAB version 8, Philips Medical Systems, Andover, MA) was used to improve measurement reliability and reproducibility [17, 20, 21].

Evaluation of intracranial circle was performed by means of transcranial Doppler (Multidop $\times$ DWL; Elektronische Systeme, GmbH, Germany). Cerebrovascular reactivity to the hypercapnia was measured with the Breath-Holding Index (BHI) [22]. This index is obtained by dividing the percentage increase in mean flow velocity (MFV), occurring during breath-holding, by the length of time (seconds) the subjects hold their breath after a normal inspiration. BHI = ([breath- holding MFV - basal MFV/basal MFV] $\times$ 100/seconds of breath-holding). Two transducers placed on the temporal bone window with a stable angle of insonation secured by a headframe were used to obtain a bilateral continuous measurement of flow velocity of middle cerebral arteries [23]. Subjects were requested to hold their breath for a period of 30 seconds. Breath-holding was monitored by a capnometer. For each patient, three recordings were obtained, and the BHI considered was the mean of all values obtained.

All-night polysomnography was performed using a 26-channel EBNeuro instrument (BE Micro–Holter EEG). The following parameters were recorded:

electroencephalography (derivations C3/A2 and C4/A1), electrocardiography, electrooculography, submental electromyography, airflow (using nasal pressure recording), snoring, finger pulse oximetry, body position, and thoracic and abdominal respiratory effort. Sleep events were scored manually by the same investigator according to the American Academy of Sleep Medicine criteria [24].

Apnea was defined as a complete cessation of airflow for a minimum of 10 seconds. Hypopnea was defined as a > 30% decrease in the amplitude of airflow for 10 seconds or longer followed by 3% oxygen desaturation and/or arousal. The Apnea/Hypopnea index (AHI) was obtained by dividing the total number of apneas and hypopneas by the total hours of sleep time. Patients were diagnosed to have OSAS if the AHI was ≥ 5. Patients with an AHI between 5 and 14 were considered to have mild OSAS, patients with an AHI between 15 and 30 were considered to have moderate OSAS, and patients with an AHI greater than 30 had severe OSAS [25].

Neurosonology, polysomnography, and neuropsychological operators were blinded to all other data.

All the clinical, laboratory, and instrumental data were collected into a database and treated as continuous [age, Mini-Mental State Examination (MMSE) score, education (years), body mass index (BMI)] or dichotomous (gender, smoking attitude, hypertension, dyslipidemia, diabetes; use of antihypertensives, antidiabetics, statins and antiplatelet drugs). The main independent variable was coded in binary (presence/absence of OSAS of any degree) and categorical form (no OSAS, mild, moderate, and severe OSAS). BHI and IMT were treated as both continuous and as dichotomous factors, choosing a cutoff of 0.69 for pathological/normal BHI [22] and a cutoff value of 10 mm for normal/pathological IMT [20].

PI was analyzed as a single dichotomous variable (values of 0-1 and values ≥ 2) [26]. Mean difference of continuous variables was assessed first with *t*-test. Cross tabulation and chi-squared test were used to evaluate differences among groups of binary variables. All the significant mean differences of continuous variables were further evaluated in multivariate unadjusted and adjusted models, in order to estimate means including all the covariates and risk factors in the analysis. All the significant differences found in chi-squared tests were in-proof reviewed with adjusted logistic regression analysis models in order to re-evaluate the difference including all the covariates and risk factors. Oxygen desaturation index (ODI), AHI, average desaturation, lowest oxygen saturation, and percentage of time spent with $SaO2 \leq 90\%$ were treated as continuous variables. The possible correlation between nocturnal oxygen values and cerebrovascular data (IMT and BHI, treated as continuous), was evaluated with Pearson's two-tailed correlation coefficient.

All the models (multivariate and logistic regression analyses) turned out to be significant. The analysis was performed with SPSS 13.0 for Windows systems.

The study was approved by the ethics committee of the Marche Polytechnic University. All participants or caregivers gave their informed written consent according to the Declaration of Helsinki.

RESULTS

We did not observe any statistically significant difference between Group 1 (non OSAS patients) and Group 2 (OSAS patients) for age, MMSE, education, BMI, cardiovascular risk factors (gender, hypertension, diabetes, dyslipidemia, and smoking) and treatments (antihypertensives, antidiabetics, and

Table 1
Baseline characteristics (dichotomous variables)

	Non OSAS (%) $n = 69$	OSAS (%) $n = 93$	P (chi-squared)
Gender (Males)	33 (47.8%)	40 (43.0%)	0.632
Active Smokers	13 (18.8%)	12 (12.9%)	0.380
Hypertension	36 (52.2%)	51 (54.8%)	0.752
Diabetes	14 (20.3%)	14 (15.1%)	0.407
Dyslipidemia	13 (18.8%)	26 (28.0%)	0.198
Drugs			
Antihypertensives	32 (46.4%)	43 (46.2%)	0.999
Antidiabetics	12 (17.4%)	9 (9.7%)	0.653
Antiplatelets	11 (15.9%)	12 (12.9%)	0.652
Statins	3 (4.3%)	14 (15.1%)	<0.05
Factors			
Pathological BHI	12 (17.4%)	47 (50.5%)	<0.05
Pathological IMT	12 (17.4%)	36 (38.7%)	<0.05
PI ≥ 2	2 (2.9%)	8 (8.6%)	0.191

BHI, breath holding index; IMT, carotid intima media thickness; PI, plaque index.

Table 2
Baseline characteristics (continuous variables)

	Non OSAS (±SD) $n = 69$	OSAS (±SD) $n = 93$	*P* (*t*-test)
Covariates			
Age (years)	71.95 (±4.05)	72.83 (±4.28)	0.193
MMSE	17.74 (±1.43)	17.57 (±1.49)	0.470
Education (years)	9.98 (±3.16)	10.26 (±3.56)	0.600
BMI	26.05 (±3.22)	25.77 (±3.14)	0.574
Factors			
BHI	0.99 (±0.30)	0.74 (±0.32)	<0.05
IMT	0.87 (±0.16)	0.98 (±0.22)	<0.05

MMSE, Mini-Mental State Examination; BMI, body mass index; BHI, breath holding index; IMT, carotid intima media thickness.

Table 3
Polysomnographic characteristics of subjects with OSAS and control subjects

	Non OSAS	OSAS	*p*
Oxygen Desaturation Index	4.00 (± 2.06)	24.71 (± 12.60)	<0.05
Apnea/hypopnea index	3.30 (± 0.79)	19.44 (± 11.72)	<0.05
Average desaturation	90.85 (± 2.69)	88.39 (± 4.24)	<0.05
Lowest oxygen saturation	91.42 (± 3.02)	85.54 (± 7.63)	<0.05
Time spent with SaO2 < 90%, (%)	0.58 (± 0.79)	11.05 (± 15.59)	<0.05
Total Sleep Time (min)	388 (± 10.2)	375 (± 11.1)	<0.05
Sleep Efficiency (%)	79 (± 5.4)	74 (± 6.8)	<0.05
Sleep Onset (min)	9.5 (± 12.1)	7.8 (± 10.3)	0.174
REM sleep (%)	18.1 (± 3.2)	16.9 (± 2.7)	<0.05
Stage 2 (%)	61.3 (± 2.7)	60.6 (± 2.5)	0.09
Slow Wave Sleep (%)	7.7 (± 0.3)	3.1 (± 0.5)	<0.05
ArI	13.5 (± 3.2)	22.6 (± 2.8)	<0.05

ArI, total number of arousals per hour of sleep. Values are mean ± SD.

Table 4
Pearson's correlation between respiratory indices, BHI and IMT

		ODI	AHI	AVSO2	LOWSO2	TIMESO2	BHI	IMT
ODI	Pearson's	1	0.982	−0.611	−0.799	0.825	−0.480	0.394
	Sig. (2-tailed)		$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$
AHI	Pearson's	0.982	1	−0.644	−0.801	0.841	−0.499	0.401
	Sig. (2-tailed)	$p<0.05$		$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$
Av D	Pearson's	−0.611	−0.644	1	0.709	−0.726	0.395	−0.295
	Sig. (2-tailed)	$p<0.05$	$p<0.05$		$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$
LO2	Pearson's	−0.799	−0.801	0.709	1	−0.905	0.432	−0.291
	Sig. (2-tailed)	$p<0.05$	$p<0.05$	$p<0.05$		$p<0.05$	$p<0.05$	$p<0.05$
T<90%	Pearson's	0.825	0.841	−0.726	−0.905	1	−0.448	0.341
	Sig. (2-tailed)	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$		$p<0.05$	$p<0.05$
BHI	Pearson's	−0.480	−0.499	0.395	0.432	−0.448	1	−0.300
	Sig. (2-tailed)	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$		$p<0.05$
IMT	Pearson's	0.394	0.401	−0.295	−0.291	0.341	−0.300	1
	Sig. (2-tailed)	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	$p<0.05$	

ODI, oxygen desaturation index; AHI, apnea/hypopnea index; Av D, Average desaturation; LO2, lowest oxygen saturation; T < 90%, percentage of night time spent with SaO2 ≤ 90%; BHI, breath holding index; IMT, carotid intima media thickness.

antiplatelet drugs) with the exception of statins which were more represented in Group 2 (Tables 1 and 2). Table 3 shows mean and SD values of oxygen nocturnal and polysomnographic parameters. ODI, AHI, average desaturation, lowest oxygen saturation, percentage of time spent with SaO2 ≤ 90%, total sleep time, % sleep efficiency, % REM sleep, % slow wave sleep, and total number of arousals per hour of sleep were significantly different between OSAS and non OSAS groups ($p<0.05$).

ODI, AHI, average desaturation, lowest oxygen saturation, and percentage of time spent with SaO2 ≤ 90% resulted significantly correlated each other and with both BHI and IMT in the OSAS-affected group (Pearson's two-tailed correlation, $p<0.05$, for each pair, Table 4).

BHI, if treated as binary, showed a significantly higher ($p<0.05$) prevalence of pathological values among patients affected by OSAS (Table 1). Moreover, when we analyzed it as a continuous variable, mean BHI value turned out to be significantly lower among patients in Group 2 (Table 2).

Similarly, a higher rate of subjects with a pathological IMT was found among patients affected by OSAS (Table 1). In Group 2, mean IMT was significantly higher than that in Group 1 (Table 2). The distribution of carotid plaque severity, assessed by PI, was not different between groups (Table 1).

The observed differences in BHI and IMT between the two groups were confirmed in a multivariate adjusted model accounting for age, gender, smoking, hypertension, diabetes, dyslipidemia, MMSE, education, and BMI as covariates. Variables containing information about treatments were not added to the model because of the high collinearity of these data with the ones of the risk factors already present in the multivariate model (Table 5).

If treated as dichotomous values and analyzed in a logistic regression analysis including age, gender, smoking, hypertension, diabetes, dyslipidemia,

Table 5
Multivariate model results

	Multivariate unadjusted model			Multivariate adjusted model		
Estimated mean	OSAS	Non OSAS	p	OSAS	Non OSAS	p
BHI	0.752	1.00		0.759	0.993	
(95% CI)	(0.68–0.82)	(0.92–1.07)	$p<0.05$	(0.66–0.86)	(0.89–1.09)	<0.05
IMT	0.98			1.01	0.90	
(95% CI)	(0.94–1.02)	0.876 (0.83–0.92)	$p<0.05$	(0.94–1.07)	(0.84–0.97)	<0.05

BHI, breath holding index; IMT, carotid intima media thickness.

Table 6
Differences between mild and moderate/severe OSAS

	Mild OSAS (%) $n=50$	Moderate/Severe OSAS (%) $n=43$	P (chi-squared)
Gender (Males)	22 (44.0%)	18 (41.9%)	0.999
Active Smokers	6 (12.0%)	6 (14.0%)	0.999
Hypertension	29 (58.0%)	22 (51.2%)	0.537
Diabetes	7 (14.0%)	7 (16.3%)	0.779
Dyslipidemia	15 (30.0%)	11 (25.6%)	0.652
Factors			
Pathological BHI	10 (20.0%)	37 (86.0%)	<0.05
Pathological IMT	7 (14.0%)	29 (67.4%)	<0.05
PI ≥ 2	2 (4.0%)	6 (14.0%)	0.138

BHI, breath holding index; IMT, carotid intima media thickness; PI, plaque index.

Table 7
Differences between mild and moderate/severe OSAS

	Mild OSAS (±SD) $n=50$	Moderate/Severe OSAS (±SD) $n=43$	P (t-test)
Covariates			
Age (years)	72.10 (± 4.08)	73.67 (± 4.40)	0.08
MMSE	17.92 (± 1.27)	17.16 (± 1.64)	<0.05
Education (years)	10.40 (± 3.71)	10.11 (± 3.40)	0.704
BMI	25.46 (± 3.10)	26.14 (± 3.17)	0.300
Factors			
BHI	0.91 (± 0.30)	0.54 (± 0.21)	<0.05
IMT	0.86 (± 0.14)	1.12 (± 0.23)	<0.05

MMSE, Mini-Mental State Examination; BMI, body mass index; BHI, breath holding index; IMT, Carotid intima media thickness.

MMSE, education, and BMI as covariates, the presence of OSAS of any severity predicted the risk of developing a pathological IMT [Odds ratio (OR) 2.98; 95% Confidence Interval (CI): 1.37–6.46; $p<0.05$)] or a pathological BHI (OR 5.25; 95%CI: 2.35–11.74; $p<0.05$). PI, even corrected for all the covariates and risk factors, did not turn out to be significantly associated to the presence of OSAS.

Then, we also evaluated differences of BHI, IMT, and PI values inside Group 2.

Since the number of patients with severe OSAS was low (5 patients), we considered patients with moderate and severe OSAS as a single group. Then we compared them with patients with mild OSAS. Gender, diabetes, hypertension, smoking, dyslipidemia, age, BMI, and education turned out to be homogeneous among the two groups, while MMSE was significantly lower in the moderate/severe OSAS group (Tables 6 and 7). However, the difference, less than 1 point, cannot be considered clinically relevant.

Treating IMT and BHI as dichotomous variables, we observed a significantly higher prevalence of subjects showing pathological values of both indices in the moderate/severe OSAS group (Table 6). Moreover, the mean of IMT and BHI values turned out to be significantly different between mild and moderate/severe OSAS, with an increased IMT and a lower BHI observed in the moderate/severe OSAS group (Table 6). This result was confirmed by the multivariate model (Table 8).

The logistic regression model showed that patients affected by moderate/severe OSAS had an increased risk of having a pathological BHI (OR 125.54; 95%CI:16.93–930.69; $p<0.05$) or a pathological IMT (OR 14.14; 95%CI:4.49–44.51; $p<0.05$) with respect to subjects with mild OSAS, considering all the risk

Table 8
Differences between mild and moderate/severe OSAS at multivariate model

	Multivariate unadjusted model			Multivariate adjusted model		
Estimated mean	Severe OSAS	Mild-moderate OSAS	p	Severe OSAS	Mild-moderate OSAS	p
BHI	0.56	0.91	$p<0.05$	0.57	0.96	<0.05
(95% CI)	(0.47–0.64)	(0.84–0.99)		(0.44–0.69)	(0.85–1.08)	
IMT	1.12	0.87	$p<0.05$	1.12	0.89	<0.05
(95% CI)	(1.06–1.18)	(0.82–0.92)		(1.03–1.22)	(0.80–0.98)	

BHI, breath holding index; IMT, carotid intima media thickness.

factors and covariates. PI was not significantly different between mild and moderate/severe OSAS.

DISCUSSION

The major finding of this study is the presence of a significant association between OSAS and alteration of functional and anatomic markers of cerebrovascular impairment in AD patients. Furthermore, the extent of cerebrovascular impairment was correlated with the severity of OSAS. Accordingly, our data demonstrate a correlation between the severity of nocturnal oxygen desaturation and impairment of functional and anatomic characteristics of cerebral vessels. In the present study, as a measure of cerebrovascular involvement, we investigated ultrasonographic markers at the level of extra- and intra-cranial arteries. High carotid IMT and low BHI values have frequently been described in asymptomatic subjects as markers of individual susceptibility to the unfavorable effects of vascular risk factors [19, 27]. Carotid IMT is a surrogate of atherosclerosis that is able to characterize global vascular risk [20, 21] and, among the other markers including carotid plaques, is the only one related to having the predisposition for developing cognitive decline in normal subjects and AD or MCI patients [26, 28, 29]. BHI index, a standard method to measure cerebral vasomotor reactivity, defined as the capability of cerebral vessels to dilate in response to a vasodilatory stimulus, is a marker of cerebral hemodynamic health which is independently related to the risk of stroke in patients with carotid diseases [22, 30].

The role of vascular impairment in AD pathogenesis and prognosis is a matter of an increasing and stimulating debate and is based on anatomic and clinical findings [31–35]. Although it was once thought that AD could be differentiated from vascular dementia by a lack of cerebrovascular disease, considerable evidence now shows that the blood supply to the brain is compromised in AD [36]. The decrease in flow rate is related to the presence of cerebrovascular disease. The presence of carotid atherosclerosis is a strong predictor of the rate of conversion to dementia in MCI patients [24, 35, 37] and of unfavorable outcome in AD patients [29, 38]. Furthermore, AD patients have a higher prevalence of intracranial artery atherosclerosis than normal subjects [39, 40]. Patients with severe carotid stenosis or occlusion and impairment of cerebral hemodynamics were reported to have poorer performance in cognitive domains related to the hemisphere ipsilateral to the stenosis [41–43]. Other prospective studies have confirmed the importance of altered cerebral hemodynamics in AD physiopathology [33]. Accordingly, the brains of AD patients are characterized by higher numbers of degenerated cerebral capillaries indicating that the pathogenesis of AD involves a dysfunction of cerebral microcirculation [44].

An interesting aspect of the present study is that the negative impact of alterations in the vasomotor reactivity and extent of atherosclerosis changes at the level of cerebral arteries were found to be independent from the presence and relevance of associated traditional vascular risk factors including hypertension, diabetes, dyslipidemia, smoking, and obesity. This suggests that vascular risk factors can produce different pathogenic effects on endothelial dysfunction and vessel atherosclerosis in OSAS patients that are probably more vulnerable to pathophysiological insults on cerebral vessels [45]. In this respect, during sleep, repeated hypoxic events might affect respiratory cholinergic mechanism, respiratory regulation, upper airway patency, and cerebral oxygenation. During daytime, hypo-oxygenation of the brain might be also due to chronic cerebrovascular and vasomotor deficits, provoked by a poor cholinergic tone. These alterations may cause amyloid-β deposition at extracellular level, as well as neurofibrillary cytopathology in cholinergic and other neurons at intracellular level [46, 47]. Experimental studies have shown a direct relationship between oxygen desaturation and degenerative changes in the arterial walls [48]. Cardiovascular instability leading to rapid and repeated changes in arterial blood pressure and the continuous changes in blood viscosity that have been described in patients with OSAS [49] probably constitute a further stimulation for pathological changes of the vessel walls [50]. Our

finding of a lack of significant differences in PI values between OSAS and non-OSAS AD patients can be explained by the low prevalence of carotid stenosis in our cohort consisting of subjects without any clinical and radiological sign of vascular disease.

In conclusion, the results of the present study suggest the possibility that in AD patients some less frequently considered risk factors like OSAS may play a prevalent and significant action in promoting cerebrovascular impairment. Currently, sleep-disordered breathing evaluation is not widely recommended in the routine assessment of patients with cognitive impairment. This approach, in consideration of the high prevalence of OSAS in AD patients [1–3], should be carefully revised. The finding of a relationship between OSAS severity and the extent of cerebrovascular impairment also suggests that a specific therapeutic approach could have a role in slowing the evolution of cognitive decline. Previous studies have demonstrated that untreated moderate-severe OSAS can cause brain injury and cognitive impairment, which cannot be fully reversed with CPAP treatment [51, 52]. For this reason, efforts should be made for detecting and treating OSAS before it becomes severe enough to cause irreversible effects. The association of CPAP and other specific interventions indicated for OSAS patients with an intensive use of pharmacological treatments which are able to improve cerebrovascular status [53] could be considered a promising approach in AD patients with OSAS. In this respect, the use of drugs like statins, antihypertensive drugs, antithrombotic agents, and treatments for insulin-resistance, which gave some demonstration of benefit on cognitive performance more than what was expected due to the effect on traditional vascular risk factors [54], deserves consideration for a comprehensive therapeutic strategy aimed at preventing the negative evolution of cognitive symptoms at least in the subgroups of AD patients.

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