Obstructive sleep apnea syndrome and Alzheimer’s disease pathology: may continuous positive airway pressure treatment delay cognitive deterioration?

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Claudio Liguori[1,2]
Riccardo Cremascoli[3]
Michelangelo Maestri[4]
Mariana Fernandes[1]
Francesca Izzi[1]
Gloria Tognoni[4]
Federica Scarpina[3] Gabriele Siciliano[4]
Nicola Biagio Mercuri[1,2,5]
Lorenzo Priano[3]
Enrica Bonanni[4]
Fabio Placidi[1,2]

[1] Sleep Medicine Centre, Department of Systems Medicine, University of Rome "Tor Vergata", Viale Oxford 81, 00133 Rome, Italy
[2] Neurology Unit, University Hospital of Rome "Tor Vergata", Rome, Italy
[3] Department of Neurology and Neurorehabilitation, IRCCS Istituto Auxologico Italiano, Piancavallo, Italy
[4] Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy
[5] IRCCS Fondazione Santa Lucia, Rome, Italy

Claudio Liguori dott.claudioliguori@yahoo.it

ABSTRACT

PURPOSE
The main aim of the present study was to identify the long-term effects of continuous positive airway pressure (CPAP) treatment in patients co-affected by obstructive sleep apnea syndrome (OSAS) and mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (ADD).

METHODS
This retrospective multicentre study included patients affected by MCI or ADD, diagnosed according to the core clinical and biomarkers criteria, and presenting comorbid OSAS. Only patients performing at least a 1-year visit during their follow-up to monitor cognitive deterioration and adherence with CPAP treatment were included. Both Mini-Mental State Examination (MMSE) and clinical dementia rating scale (CDR) were conducted during the baseline and the follow-up visits.

RESULTS
Twenty-four patients were included in the study and were distributed according to the diagnosis in MCI (*n* = 8) or ADD (*n* = 16). There were no significant differences in the variables analysed at baseline between the CPAP non-adherent and CPAP adherent patients. In the whole group, a significant decrease was found in MMSE scores, and a significant increase was found in CDR scores between baseline and follow-up. No longitudinal changes in ESS scores were statistically significant from baseline to follow-up. A significant difference was found for the mean score change of the CDR since CPAP non-adherent patients showed a higher mean change of CDR compared to CPAP adherent patients. No significant differences were found for the mean change of MMSE.

CONCLUSION
These findings highlight the clinical potential of treating OSAS with CPAP to delay cognitive deterioration in patients with MCI or ADD.

Keywords: Obstructive sleep apnea syndrome; Alzheimer's disease; Continuous positive airway pressure treatment; Mild cognitive impairment; Dementia.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is an increasingly prevalent sleep disorder in the adult-elderly population [1, 2]. It currently represents a risk factor for Alzheimer's disease (AD), and it is a common comorbidity in patients with mild cognitive impairment (MCI) and AD dementia (ADD), with very high prevalence rate (up to 40%) [3, 4]. Therefore, the detrimental role of OSAS on cognitive performances and neurodegenerative trajectories in cognitively intact subjects and patients with MCI or ADD has been widely established [5, 6]. The gold standard treatment for OSAS is continuous positive airway pressure (CPAP), which can reverse negative effects of OSAS [7]. Accordingly, several studies have recognized the beneficial effects of CPAP treatment on cognitive impairment, also examining the effects of CPAP on the core pathological biomarkers in AD patients [8,9,10,11]. In a randomized controlled study, composite neuropsychological outcomes indicated modest, but statistically significant improvements in cognitive functioning after 3 weeks of therapeutic CPAP in AD patients [12]. In retrospective clinical studies, CPAP treatment has been associated with a significant decrease in the longitudinal cognitive decline at a 3-year follow-up in mild to moderate AD patients co-affected by OSAS [13]. However, a recent study documented a non-significant role of comorbid OSAS on the longitudinal deterioration of cognitive subdomains or global cognition in a group of 144 AD patients [14]. These findings were in contrast with the majority of previous literature regarding the role of OSAS on ADD, which raises questions about the diagnosis and the treatment of OSAS in patients with MCI or ADD.
Considering the importance of reaching a general agreement about the role of OSAS on the longitudinal cognitive trajectories of patients with MCI due to AD or ADD, the present study aimed at identifying the long-term effects of CPAP treatment in patients co-affected by AD and OSAS through a retrospective multicentre analysis.

METHODS

This retrospective multicentre study included patients affected by MCI due to AD or ADD, diagnosed according to the core clinical and biomarkers criteria, and presenting comorbid OSAS, who were followed at: i) the Neurology Unit of the University Hospital of Rome "Tor Vergata", ii) Neurology Unit of the University of Pisa, and iii) Neurology and Neurorehabilitation Unit of Istituto Auxologico Piancavallo. All patients underwent the diagnostic work-up for MCI or ADD and polygraphic cardiorespiratory monitoring for identifying OSAS. Therefore, CPAP treatment was started after OSAS diagnosis, and patients were followed in each centre according to local clinical practice. This study included only patients who performed at least a 1-year visit during their follow-up to monitor cognitive deterioration and adherence to CPAP treatment. CPAP treatment adherence was defined as a mean use ≥ 4 h per night for > 5 nights per week with a residual AHI < 5/h. Both Mini-Mental State Examination (MMSE) and clinical dementia rating scale (CDR) were conducted during the baseline and the follow-up visits. Therefore, the following data were collected and analysed using SPSS version 25 (IBM Corporation, Armonk, New York): age, sex, disease duration, education, body mass index, biomarkers for AD, Epworth Sleepiness Scale (ESS), follow-up duration, MMSE, CDR, and CPAP adherence. All data were collected from clinical records, and the need for informed consent was waived due to the retrospective nature of the present study, which was conducted according to the STROBE statement.

DATA ANALYSIS

Mann-Whitney, Chi-square, and Fisher's exact tests were used to compare patients who were adherent to CPAP treatment with patients who were non-adherent to CPAP treatment at the time of the follow-up. Delta change (D) score (mean change from baseline to follow-up measures) for MMSE and CDR outcome were calculated, and differences on these D scores were tested for the CPAP non-

adherent and CPAP adherent groups. Spearman correlation test was used to evaluate the correlation between baseline and follow-up characteristics and CPAP usage. A *p* value of 0.05 was considered statistically significant. Due to the small sample size, effect sizes were used to quantify differences in the measures considered.

RESULTS

Twenty-four patients diagnosed with OSAS were included and distributed based on the comorbid diagnosis in patients with MCI due to AD (*n* = 8) or ADD (*n* = 16). The majority of patients (67%) were men (*n* = 16), with a mean age of 74.8 years old (SD = 5.9), ranging from 65 to 84 years old. Patients' mean years of education was of 7.8 (SD = 4.2), ranging from 3 to 18 years of education. Patients were on average mildly overweight (M = 28.1, SD = 3.4), had mild cognitive deterioration (mean MMSE = 23.8, SD = 2.8, range = 16–27), and had a mean illness duration of 4.8 years (SD = 2.5). Regarding the sleep parameters, the mean ESS score was 11.7 (SD = 2.2), and the mean AHI was 33.7 (SD = 10.4). At baseline, the mean of ODI was 31.1 (SD = 12.4), and the mean of CDR was 0.81 (SD = 0.40). Patients at follow-up were distributed in two subgroups based on adherence with CPAP treatment: 12 patients were CPAP adherent (4 MCI and 8 ADD), and 12 patients were CPAP non-adherent (4 MCI and 8 ADD).
There were no significant differences in the variables analysed at baseline between the CPAP non-adherent patients and CPAP adherent patients (see Table 1), thus not allowing the hypothesis of identifiable markers to predict the compliance to CPAP treatment in patients with MCI or ADD. Considering the longitudinal analysis in the whole group (follow-up in years, M = 3.8; SD = 2.3), a significant decrease was found in MMSE scores ($p < 0.001$) between baseline (M = 23.8; SD = 2.8) and follow-up (M = 19.8; SD = 4.9), and a significant increase was found in CDR scores ($p = 0.002$) between baseline (M = 0.82; SD = 0.40) and follow-up (M = 1.69; SD = 0.85). No longitudinal changes in ESS scores were statistically significant from baseline (M = 11.7; SD = 2.2) and follow-up (M = 10.1; SD = 3.4). The mean change (D) between baseline and follow-up scores for MMSE and CDR demonstrated that CPAP non-adherent and CPAP adherent subgroups did not differ for MMSE ($U = 45.00$, $p = 0.19$), while a significant difference was found for CDR ($U = 5.50$, $p = 0.005$). Accordingly, CPAP non-adherent patients showed a higher mean change of CDR (M = 1.43; SD = 0.53) compared to CPAP adherent patients (M = 0.44; SD = 0.46).
Spearman correlation showed no significant correlations between the D scores of MMSE and any of the variables assessed at baseline. A significant positive correlation was found between D scores of CDR and p-tau (rho = 0.73, $p = 0.007$) and t-tau (rho = 0.68, $p = 0.02$), suggesting that higher p-tau and t-tau CSF levels at baseline are associated with a more severe cognitive deterioration.

DISCUSSION

The current retrospective multicentre study shows that CPAP treatment performed with adherence may delay cognitive deterioration in patients with MCI due to AD or ADD. This finding supports those of previous studies, suggesting that OSAS may accelerate cognitive decline and advance the transition from MCI to ADD; conversely, CPAP treatment, in particular when used in the early stages of dementia, may slow the progression to dementia [11,12,13]. Although the evidence regarding the role of OSAS (treated and untreated) in patients with AD significantly supports the importance of recognising and treating this sleep disorder in patients with cognitive impairment, a recent longitudinal study reported divergent findings, namely, a non-significant role of comorbid OSAS on the longitudinal deterioration of cognition in AD patients [14]. In addition, a study performed in patients with MCI (not biomarker-based) documented that CPAP use in moderate OSAS was not associated with a delay in progression to dementia or cognitive decline [15]. Considering these antithetical results, it becomes important to analyse the differences between the present findings and the most recent literature [14, 15]. We are aware of the difference in the study design

(retrospective vs prospective), but the present study results are consistent with findings reported by previous prospective studies in which CPAP treatment in MCI and AD patients was associated with slower cognitive decline [7, 12, 13, 16, 17]. Nonetheless, it is important to note that retrospective collection of data has a higher risk for bias, namely, the different degree of cognitive impairment or dementia and unavailability to continue the recommended follow-up assessments. Accordingly, patients with a more significant cognitive impairment can be more easily lost at follow-up than MCI patients. Another major limitation that needs to be addressed is the small sample size, especially of the MCI group. The different distribution of patients in MCI and AD groups may affect the cognitive data, since AD patients may have diluted the effects of potential longitudinal beneficial effects of CPAP treatment on MMSE scores. Future studies with a larger sample are needed in order to further explore this aspect, possibly focusing on the cognitive trajectories of MCI patients co-affected by OSAS and treated with CPAP. A third limitation of the present study is that cognitive impairment was measured using only two brief instruments. However, the use of further and broader tools for assessing cognition in patients with OSAS is important to understand which aspects of cognitive decline can be improved by CPAP in MCI and AD patients. Finally, although the standard for adequate CPAP treatment in OSAS patients is widely accepted ("mean use ≥ 4 h per night for > 5 nights per week with a residual AHI < 5 events per h"), the need of further studies aimed at identifying the sufficient CPAP treatment regimen for improving cognition in patients with OSAS showing AD neurodegeneration has emerged.

Considering the findings of previous prospective studies as well as the current research, one can argue that the importance of recognising and treating OSAS in patients with cognitive impairment has currently become more important than longitudinally observing patients with MCI or ADD to monitor the effects of comorbid OSAS on cognitive trajectories. In keeping with this need, the present multicentre study also suggested a lower mean change of CDR in patients adherent to CPAP treatment than in those who were not adherent. These results highlight the implication not only of starting CPAP treatment in patients with OSAS comorbid to MCI or AD but also of improving the follow-up of those patients to monitor adherence to therapy. Hence, this evidence reinforces the importance of having multidisciplinary teams caring for patients with MCI or ADD and of assisting the care of different aspects of the disease, focusing particularly on sleep disorders.

DECLARATIONS

Ethics approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: informed consent was waived due to the retrospective nature of the present study

Conflict of interest: the authors declare no competing interests.

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Table 1. Participants baseline characteristics in the two subgroups

	CPAP non-adherent (n = 12) Mean ± SD	CPAP adherent (n = 12) Mean ± SD	Differences test	Effect size d
Male, n	8	8		
Age, years	74.4 ± 6.9	75.2 ± 4.	U = 66.00, p = 0.73	0.14
Education, years	8.4 ± 4.7	7.2 ± 3.8	U = 61.00, p = 0.51	0.26
Illness duration, years	3.8 ± 2.0	5.7 ± 2.8	U = 40.00, p = 0.06	0.81
Body mass index	27.9 ± 4.3	28.2 ± 3.0	U = 39.50, p = 0.83	0.83
Biomarkers				
No	1 (9%)	4 (33%)	χ^2 = 0.814; p = 0.32	0.37
Yes	10 (91%)	8 (67%)		
$A\beta_{42}$, pg/mL	604.3 ± 217.8	574.9 ± 244.0	U = 37.00, p = 0.56	0.91
p-tau, pg/mL	90.5 ± 46.9	59.5 ± 36.0	U = 25.00, p = 0.12	1.33
t-tau, pg/mL	473.6 ± 230.7	391.5 ± 306.2	U = 33.00, p = 0.36	1.04
MMSE	23.7 ± 3.2	23.9 ± 2.4	U = 68.50, p = 0.84	0.08
CDR	0.86 ± 0.56	0.78 ± 0.26	U = 30.00, p = 0.86	1.14
ESS	11.0 ± 2.4	12.1 ± 2.1	U = 11.50, p = 0.33	2.03
AHI	35.1 ± 11.6	32.6 ± 9.6	U = 54.50, p = 0.72	0.42
ODI	34.6 ± 12.4	28.0 ± 12.2	U = 30.00, p = 0.24	1.14

SD standard deviation, *CPAP* continuous positive airway pressure, *Aβ₄₂* β-amyloid$_{42}$, *p-tau* phosphorylated tau, *t-tau* total tau, *MMSE* Mini-Mental State Examination, *CDR* clinical dementia rating, *ESS* Epworth Sleepiness Scale, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index