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The potential role of interleukin-6 in the association between inflammation and cognitive performance in obstructive sleep apnea

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ABSTRACT

Background: Interleukin-6 (IL-6) represents one of the main molecules involved in inflammatory responses, which can be altered in either patients with cognitive impairment or obstructive sleep apnea (OSA). The present study aimed to evaluate serum IL-6 levels and cognitive performance in patients with severe OSA (Apnea-Hypopnea Index - AHI >30/h).

Methods: Thirty patients with severe OSA were compared to 15 controls similar in age, sex, and Body Mass Index. All patients underwent a sleep medicine interview, including the Epworth Sleepiness Scale (ESS), a polygraphic cardiorespiratory recording, the Montreal Cognitive Assessment (MoCA), and a blood sample for serum IL-6 assessment.

Results: OSA patients presented higher IL-6 serum levels (Md = 7.38) than controls (Md = 2.20, $p < 0.001$). Moreover, OSA patients showed lower MoCA (Md = 27.00) and higher ESS scores (Md = 8.00) than controls (Md = 30.00, $p < 0.001$; Md = 4.00, $p = 0.004$, respectively). Higher IL-6 serum levels were associated with lower oxygen saturation parameters and MoCA scores.

Conclusions: This study documented an association between inflammation, featured by higher IL-6 serum levels, and both nocturnal hypoxemia and cognitive impairment in OSA patients. Therefore, the increase in IL-6 levels may represent the result of vascular damage and neuroinflammation due to intermittent nocturnal hypoxia and further causing neurocognitive dysfunction in OSA.

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent sleep disorder with various known risk factors, including obesity, age, sex, and the consumption of tobacco and alcohol (Young et al., 2004). Among these, obesity is consistently recognized as one of the most significant risk factors of OSA and is highly comorbid with this sleep disorder (Tuomilehto et al., 2013). Additionally, OSA is frequently observed in patients with cognitive impairment and Alzheimer's Disease (AD) (Fernandes et al., 2021; Liguori et al., 2021b) and is considered a potential a risk factor for AD (Shi et al., 2018). Recent findings propose the involvement of inflammatory mediators in the origin of cognitive deterioration in OSA and/or obesity patients (Miller and Spencer, 2014). Consistently, neuroinflammation has been identified as a possible crucial mechanism in the pathophysiology of dementia disorders and AD (Calsolaro and Edison, 2016). Considering this hypothesis, several inflammatory mediators, such as interleukines, cytokines, chemokines, and adhesion molecules have been evaluated in patients with cognitive deterioration (Calsolaro and Edison, 2016). Interleukin-6 (IL-6) is a circulating cytokine secreted from a large number of cells, such as activated macrophages and lymphocytes (Yudkin et al., 2000). Inflammation is the main trigger of IL-6 secretion, however, other stimuli can promote the secretion of this interleukin, such as hypoxemia (Guilleminault et al., 2004). Therefore, IL-6 has been widely studied in

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patients with OSA (Nadeem et al., 2013; Zhong et al., 2016; Motamedi et al., 2018; Wali et al., 2021), and these studies documented higher IL-6 serum levels in these patients when compared to controls (Nadeem et al., 2013; Zhong et al., 2016; Motamedi et al., 2018; Wali et al., 2021).

Furthermore, IL-6 has been linked to the neurovascular contributions of cognitive decline and dementia (Custodero et al., 2022). Taking all these findings into account, a crucial role of IL-6 in linking OSA and peripheral metabolic alterations to cognitive impairment has been hypothesized (Lyra e Silva et al., 2021). Nevertheless, the aforementioned studies investigating IL-6 serum concentrations in OSA patients did not evaluate the correlation between cognitive performance and excessive daytime sleepiness (EDS). Therefore, this study aimed to evaluate the IL-6 serum levels in adults subjects affected by severe OSA in comparison to a population of controls similar in age, sex, and body mass index (BMI). As a secondary aim, it would explore the correlations between the IL-6 serum levels, cognitive performance, and EDS in OSA patients.

2. Methods

The present study included adult patients, ranging from 18 to 80 years old, undergoing nocturnal polygraphic cardiorespiratory recording at the Sleep Medicine Centre of the University Hospital of Rome Tor Vergata between September 2019 and February 2020, and then diagnosed with severe OSA (Apnea-Hypopnea Index -AHI- $\geq$30 per hour of sleep) according to AASM criteria (Berry et al., 2012a; American Academy of Sleep Medicine, 2014). Polygraphic recordings were performed using a validated instrument (Embletta; Embla, Amsterdam, The Netherlands) and counted with the following set-up: an oronasal pressure cannula to record airflow, finger pulse oximetry, piezoelectric belts to detect thoracic and abdominal respiratory effort, heart rate, snoring sound, and body position sensors. The following parameters were registered: AHI, defined as the sum of all apneas (>90% reduction in airflow for >10 s) and all hypopneas (>30% reduction in airflow >10 s associated with $\geq$3% O2 desaturation) (Berry et al., 2012b); mean oxygen saturation (SaO2), lowest SaO2, time spent with SaO2 <90% (T < 90), and oxygen desaturation index (ODI) (number of oxygen desaturations $\geq$3% per hour).

Age-, sex- and BMI-matched controls were also recruited at the Sleep Medicine Centre of the University Hospital of Rome Tor Vergata. Controls underwent a standard sleep medicine visit for diagnostic purposes and did not show signs or symptoms on the screening questionnaires for OSA or other sleep disorders. Specifically, the health status of the control group was verified by employing a brief checklist to inquire about health issues encompassing medical, neurological, or psychiatric conditions. Additionally, controls participated in a sleep anamnestic interview to explore their sleep patterns and symptoms of sleep apnea. This assessment encompassed inquiries into the occurrence of snoring, chocking during sleep, or apneas as reported by their bed partner, awakening with a dry mouth, morning headache, and EDS, as screened through the Epworth Sleepiness Scale (ESS).

The exclusion criteria for both patients and controls included: concomitant psychiatric or neurologic disorders; chronic liver disease; heavy smoking; use of corticosteroids and any anti-inflammatory drugs in the four weeks preceding blood sample collection; recent infections; bronchial asthma, chronic obstructive pulmonary disorders, and interstitial lung diseases; autoimmune disorders; malignancies; diabetes; and any systemic disorders known to influence inflammatory markers. In particular, depression symptoms in OSA patients were assessed during the medical visit and clinical interview conducted by experienced healthcare professionals trained in sleep medicine and neurology. Additionally, cardiovascular diseases were also an exclusion criterion for controls.

All participants underwent a blood sample collection for IL-6 analysis after an onvernight fasting, a standard sleep medicine visit, including the assessment of EDS through the ESS (Johns, 1991; Vignatelli et al., 2003), and a cognitive performance evaluation through the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005; Pirani et al., 2022). Specifically, MoCA is a rapid screening instrument and has been validated in clinical settings to identify cognitive impairment in patients with OSA (Gagnon et al., 2018). MoCA assesses eight cognitive domains: Visuospatial/Executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall and Orientation. Finally, MoCA is scored in a range between 0 and 30, with a clinical cutoff score for cognitive impairment of 26. Quantitative measurements of IL-6 were analyzed by using enzyme-Linked Immunosorbent Assay (ELISA) (DRG Instruments Gmbh, Marburg, Germany).

The study procedures were approved by the Independent Ethical Committee of the University Hospital of Rome Tor Vergata (protocol code 189/21) and were conducted in accordance with the Declaration of Helsinki. All participants provided signed informed consent.

All descriptive and inferential statistical analyses were conducted with IBM SPSS software (version 25.0, IBM Corp., Armonk, NY, USA (IBM, 2020)). Categorical variables were summarized with counts and percentages with 95% confidence intervals and means and standard deviations or medians and interquartile ranges were obtained for numerical variables according to data distribution.

The group differences between patients with OSA and controls for numerical variables were evaluated with Mann–Whitney *U* test, whereas the significance of the associations between categorical variables was examined with chi-square (χ2) tests. Additionally, OSA patients were divided into two subgroups: those with cognitive impairment (MoCA scores <26) and those without cognitive impairment (MoCA scores $\geq$26). Comparison analyses were then performed to examine differences in serum IL-6 levels between these two groups. Divided Kendall's tau-b (Tb) correlation coefficients (Abdi, 2007) were computed to explore the associations between IL6 serum levels and patients' demographic features, clinical data and polygraphic parameters. Kendall's tau-b was selected for this analysis since is generally considered to be a more conservative estimate compared to Spearman's correlation, which can be beneficial for minimizing the risk of Type I errors in small sample sizes (Abdi, 2007). Partial correlation was used to explore the relations between IL-6 serum levels and MoCA scores in each domain while controlling for AHI, BMI and age. For all the analyses performed, p-values below 0.05 were considered statistically significant.

3. Results

Thirty patients affected by OSA (76.7% male; mean age of 55.20 $\pm$ 12.49 years) and 15 controls (66.87% male; mean age of 53.60 $\pm$ 11.43 years) were included in the study. No significant differences in sex (χ2 = 0.128; p = 0.72), age (U = 225.0; p = 1.00) and BMI (U = 246.0, p = 0.61) were observed between patients with OSA and controls. Twelve patients (40%) reported EDS (ESS$\geq$10). Participants' demographic, clinical, and polygraphic features are shown in Table 1.

Patients with OSA showed significantly higher serum IL-6 levels (U = 391.0; p < 0.001) and ESS scores than controls (U = 0345.0; p = 0.004). Conversely, patients had significantly lower scores on MoCA than controls (U = 78.0; p < 0.001), specifically on the following domains: visuospatial abilities (U = 97.5, p < 0.001), language (U = 165.0; p = 0.30) and delayed recall (U = 77.5; p < 0.001).

Considering the OSA subgroups, patients with cognitive impairment (MoCA scores <26, n = 10) had significantly higher serum IL-6 levels (9.47 $\pm$ 1.80 vs. 5.73 $\pm$ 2.37) compared to those without cognitive impairment (MoCA scores $\geq$26; n = 20; U = 13.500, p < 0.01).

Correlation coefficients in OSA patients between IL-6 serum levels and age, BMI, EDS (ESS score), polygraphic measures (AHI, ODI, SaO2 and T < 90), and MoCA scores in each domain are reported in Table 2. Overall, in the OSA group, no correlations were observed between the serum levels of IL-6 and patients' demographic characteristics, or EDS assessed with the ESS. Conversely, the serum IL-6 levels were positively associated with BMI, AHI, ODI and T < 90. Further, serum IL-6 levels were negatively correlated with mean SaO2, MoCA total scores, and

Table 1
Participants' demographic, clinical, and polygraphic features.

	OSA Patients (n = 30)		Controls (n = 15)		Mann-Whitney test	
	Median	25–75th percentile	Median	25–75th percentile	U	p-value
Male, n. (%)	23 (76.7%)		10 (66.7%)		0.128	0.721
Age	55.00	45.00–62.25	55.00	44.00–59.00	132.50	1.000
BMI	30.15	28.20–31.78	29.40	25.00–32.00	246.00	0.613
ESS	8.00	5.00–11.25	4.00	3.00–7.00	345.00	0.004
MoCA	27.00	25.00–29.00	30.00	29.00–30.00	78.00	<0.001
Visuospatial	4.00	4.00–5.00	5.00	5.00–5.00	97.50	<0.001
Naming	3.00	3.00–3.00	3.00	3.00–3.00	225.00	1.000
Delayed Recall	3.00	2.00–4.00	5.00	4.00–5.00	77.50	<0.001
Attention	6.00	5.00–6.00	6.00	6.00–6.00	270.00	0.066
Language	3.00	2.00–3.00	3.00	3.00–3.00	165.00	0.030
Abstraction	2.00	2.00–2.00	2.00	2.00–2.00	210.00	0.312
Orientation	6.00	6.00–6.00	6.00	6.00–6.00	225.00	1.000
AHI	40.00	32.43–49.95				NA
ODI	36.35	29.15–44.95				NA
SaO2 Mean	93.05	92.00–94.00				NA
T < 90	8.00	7.00–11.23				NA
Serum IL-6 levels	7.38	4.51–8.93	2.20	1-40-4.50	77.50	<0.001

Abbreviations: OSA, obstructive sleep apnea; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; IL-6, Interleukin-6; MoCA, Montreal Cognitive Assessment; AHI, apnoea-hypopnea index; ODI, oxygen desaturation index; SaO2, mean oxygen saturation; T < 90, time spent with SaO2 <90%; NA, non-applied.

Table 2
Correlations between IL-6 serum levels and age, BMI, excessive daytime somnolence, polygraphic measures and MoCA scores in OSA patients.

n = 30	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age	1													
2. BMI	.107	1												
3. ESS	.025	−.130	1											
4. Serum IL-6 levels	.097	.677[b]	−.026	1										
5. MoCA	−.034	−.563[b]	−.034	−.782[b]	1									
6. MoCA Visuospatial	−.087	−.419[b]	.079	−.479[b]	.432[b]	1								
7. MoCA Attention	−.152	.109	−.174	.051	0.000	.186	1							
8. MoCA Language	.303	−.341[a]	−.070	−.305[a]	.424[b]	.033	−.158	1						
9.MoCA Abstraction	−.026	−.334[a]	.027	−.334[a]	.363[a]	.186	−.071	.415[a]	1					
10. MoCA Delayed Recall	−.067	−.438[b]	−.024	−.651[b]	.861[b]	.281	−.063	.290	.196	1				
11. AHI	.091	.647[b]	−.058	.935[b]	−.776[b]	−.494[b]	−.019	−.298	−.312[a]	−.641[b]	1			
12. ODI	.093	.646[b]	−.063	.940[b]	−.774[b]	−.495[b]	−.013	−.292	−.309[a]	−.637[b]	.988[b]	1		
13. Mean SaO2	−.094	−.623[b]	.062	−.910[b]	.748[b]	.503[b]	−.089	.277	.295	.626[b]	−.871[b]	−.867[b]	1	
14. T < 90	.163	.625[b]	−.047	.820[b]	−.701[b]	−.346[a]	.106	−.303	−.356[a]	−.623[b]	.789[b]	.782[b]	−.791[b]	1

Note: Denomination and Orientation subcategories of MOCA were excluded from correlations since all patients had obtained the maximum score.
Abbreviations: OSA, obstructive sleep apnea; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; IL-6, Interleukin-6; MoCA, Montreal Cognitive Assessment; AHI, apnoea-hypopnea index; ODI, oxygen desaturation index; SaO2, oxygen saturation; T < 90, time spent with SaO2 <90%.
[a] $p < 0.05$.
[b] $p < 0.001$.

with the following MoCA domains: visuospatial, language, verbal abstraction, and delayed recall. Moreover, there is not a significant correlation between serum IL-6 and MoCA attention, language, abstraction, and delayed recall domains after accounting for age, BMI and AHI. Conversely, there was a negative partial correlation between serum IL-6 levels and both MoCA total score and MoCA visuospatial domain score, after controlling for age, BMI and AHI ($p = 0.003$; $p = 0.010$, respectively). Correlations between IL-6 and MoCA scores, controlling for age, BMI and AHI are presented in Table 3.

Table 3
Partial Correlations between IL-6 and MoCA scores, controlling for age, BMI and AHI.

Group	Covariates			IL-6
OSA (n = 30)	Age & BMI & AHI	MoCA	Correlation	−.556
			p-value	**.003**
		MoCA Visuospatial	Correlation	−.486
			p-value	**.010**
		MoCA Attention	Correlation	−.044
			p-value	.828
		MoCA Language	Correlation	−.125
			p-value	.534
		MoCA Verbal Abstraction	Correlation	.083
			p-value	.681
		MoCA Delayed Recall	Correlation	−.320
			p-value	.103

In bold the significant values.
Note: Denomination and Orientation subcategories of MOCA were excluded from correlations since all patients had obtained the maximum score.
Abbreviations: OSA, obstructive sleep apnea; BMI, Body Mass Index; MoCA, Montreal Cognitive Assessment; AHI, apnoea-hypopnea index.

4. Discussion

In this report, a significant increase in serum IL-6 levels was documented in adults patients with severe OSA. This finding is in line with previous evidence that reported an increase in serum inflammatory markers in patients with OSA and is significantly associated with OSA severity (Ciftci et al., 2004; Nadeem et al., 2013) and BMI (Constantinidis et al., 2008). Further, in the current study, the higher IL-6 serum concentrations correlated with the alteration of oxygen saturation parameters, namely ODI, SaO2 Mean and T<90%. The alteration of these parameters reflects intermittent hypoxia, which is

present in patients with OSA, and usually leads to several brain and body health consequences (Drager et al., 2010). A key finding of this study is the correlation between higher serum IL-6 levels and poorer cognitive performance in OSA patients, even after controlling for confounding variables such as age, BMI, and AHI. Additionally, OSA patients with lower MoCA scores had higher serum IL-6 levels compared to those with normal MoCA scores. In this study, cognitive performance was evaluated through MoCA, which is more sensitive in detecting cognitive impairment in patients with OSA than the Mini-Mental State Examination (MMSE) (Gagnon et al., 2018), although the use of MMSE is still higher in sleep medicine settings. The higher discriminant validity of MoCA over the MMSE can be explained by the fact that MoCA covers more broadly different cognitive domains, which allows a greater identification of variations in attention and executive functions, as frequently reported in patients with OSA. In the current study, lower MoCA scores were found in patients with OSA when compared to controls, specifically showing worse performances in visuospatial, abstraction, delayed recall, and language domains, which are not fully explored by MMSE. Overall, severe OSA patients showed higher IL-6 serum levels and a worse cognitive profile, featuring reduced executive functioning, which may be due to chronic sleep fragmentation and intermittent hypoxia (Gagnon et al., 2014). It is important to highlight that these associations remain significant even after accounting for the effects of age, BMI, and AHI. This adjustment clarifies a specific relationship between IL-6 serum levels and cognitive outcomes, independent of age, BMI, and OSA severity.

Considering the findings of the present study, a link between the alteration of inflammatory mediators, in particular IL-6, and cognitive impairment and hypoxia in patients with OSA can be hypothesized. Consistently, recent evidence highlighted that systemic inflammatory responses, characterized by the proliferation of pro-inflammatory mediators throughout the body, can directly influence the CNS functioning and cause negative changes in cognition and behavior (Walker, 2019). Systemic inflammation can both trigger and sustain a pro-inflammatory cerebral response, inducing a state of neuroinflammation that promotes a high number of molecular changes, triggering neurodegenerative processes, synaptic dysfunction, and neuronal loss, clinically resulting in cognitive impairment (Sheng et al., 2003). Hence, IL-6 represents an important mediator of neuroinflammation (Erta et al., 2012; Gruol, 2015), and as an inflammatory cytokine. Consistently, its effects can be either detrimental to neurodegeneration (Heese, 2017) or neuroprotective via its effects on neurogenesis (Spittau et al., 2012; Meng et al., 2015). Therefore, the higher IL-6 blood levels documented in patients with OSA may reflect two distinct and possibly concomitant events. The first can be related to the negative effects of the excessive inflammatory response, triggered by intermittent hypoxia, both damaging brain health and activating the neurodegenerative processes. The second can reflect the attempt to counteract the neurodegenerative processes, triggered by OSA condition (Liguori et al., 2021a), possibly activating a cascade of events including IL-6-mediated neuroprotective effects. Nevertheless, these are speculative hypotheses that have to be confirmed by further clinical studies including the IL-6 cerebrospinal--fluid levels assessment, which can distinctly reflect the brain events occurring in OSA condition. Nonetheless, a recent study highlighted that patients with OSA with high IL-6 blood levels had a reduced likelihood of developing dementia (Baril et al., 2021).

Interestingly, our study did not find a correlation between IL-6 serum levels and ESS scores in severe OSA patients. This lack of correlation might be attributed to the subjective nature of the ESS compared to more objective measures of daytime sleepiness, such as the Multiple Sleep Latency Test. The subjective assessment of EDS may not always align with objective measures or with inflammatory markers like IL-6. This discrepancy is further supported by research indicating that while IL-6 levels have been associated with EDS in some studies (Vgontzas et al., 1999; 2004), the role of IL-6 in the physiological regulation of sleep is not as well understood as other cytokines. For instance, IL-6 levels have been shown to increase in response to total or partial sleep loss (; 2004) and in patients with OSA (Bravo et al., 2007). However, plasma levels of IL-6 did not consistently correlate with EDS in all studies, potentially due to differing definitions and measures of EDS (Bravo et al., 2007). This underscores the need for further research using both subjective and objective assessments of sleepiness to better understand the relationships between inflammation and cognitive impairment.

The present study has some limitations that need to be acknowledged. First, IL-6 was the only cytokine measured, which does not allow to investigate the whole inflammatory response. Future studies should include inflammatory or anti-inflammatory markers that may be implicated in the link between OSA and cognitive performance. Second, the sample size is relatively small, which limits the analysis. Third, while our study controlled for age, sex, and BMI, the absence of data on socioeconomic status and the exclusion of controls with cardiovascular diseases are limitations that may affect the generalizability of our findings; this limitation underscores the need for future studies to include a broader range of demographic and health-related variables. Another limitation of our study is the reliance on clinical interviews for diagnosing depressive comorbidity, rather than structured diagnostic interviews or validated questionnaires, which could impact the precision and objectivity of the assessment. Finally, the effect of continuous positive airway pressure (CPAP) treatment was not measured, which requires further studies to explore it. Future longitudinal studies are needed to explore the role of IL-6 in the prediction of cognitive decline in OSA, and how CPAP may play a role in counteracting these effects.

While our findings underscore IL-6 as a key marker of inflammation associated with cognitive decline, translating these insights into clinical practice demands careful consideration. Targeting IL-6 may hold promise for mitigating cognitive impairments in OSA patients by addressing the underlying inflammation. However, establishing a definitive causal relationship between IL-6 and cognitive decline and evaluating the effectiveness of anti-inflammatory treatments are crucial next steps. Future research should focus on whether targeting IL-6 or other inflammatory pathways can lead to significant improvements in cognitive function and overall management of OSA patients. In summary, this study emphasizes the importance of inflammatory responses in patients with severe OSA, and their potential role in the cognitive impairment. However, the dual role of IL-6, with both beneficial and detrimental effects on cognition and brain health, needs further exploration.

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Data availability statement

The data that support the results reported in this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Mariana Fernandes: Writing – original draft, Formal analysis, Data curation. **Matteo Spanetta:** Writing – original draft, Investigation. **Giorgio Vetrugno:** Investigation. **Marzia Nuccetelli:** Investigation. **Fabio Placidi:** Methodology. **Alessandro Castelli:** Investigation. **Natalia Manfredi:** Investigation. **Francesca Izzi:** Methodology. **Giuseppina Laganà:** Writing – review & editing. **Sergio Bernardini:** Supervision. **Nicola Biagio Mercuri:** Supervision. **Claudio Liguori:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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