Received: 16 April 2021 | Revised: 9 September 2021 | Accepted: 9 October 2021

DOI: 10.1002/lio2.683

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

The evaluation of serum brain-derived neurotrophic factor and neurofilament light chain levels in patients with obstructive sleep apnea syndrome

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Abstract

Objectives: This study aimed to compare serum levels of brain-derived neurotrophic factor (BDNF) and neurofilament light (NfL) chain in normal individuals and patients with mild and moderate-severe obstructive sleep apnea syndrome (OSAS).

Methods: We enrolled 81 subjects referred to Otorhinolaryngology (Ear-Nose-Throat), Gazi University Faculty of Medicine, between 2017 and 2019. Based on the severity of OSAS, patients were divided into three groups: group 1 with mild OSAS (apnea-hypopnea index [AHI] 5-15; n = 26), group 2 with moderate-severe OSAS (AHI > 15; n = 32), and group 3 with normal individuals (AHI scores < 5; n = 23).

Results: Serum NfL and BDNF levels were evaluated together with the clinical data for all subjects. Significant differences were seen in the oxygen desaturation index (ODI), apnea index, hypopnea index, sleep efficiency, and NfL levels ($P < .05$) between the three groups. In the moderate-severe group, NfL levels showed a significant positive correlation with apnea index ($P < .05$, $r = .389$), hypopnea index ($P < .05$, $r = .455$), and ODI ($P = .04$; $r = .362$).

Conclusions: Our findings clarify the pathophysiology of OSAS in cases of repetitive hypoxia and chronic neuronal damage. Based on our results, we recommend that in addition to BDNF, NfL should also be evaluated in different and larger patient cohorts.

KEYWORDS
BDNF, biomarkers, NfL, OSAS

1 | INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common sleep-related breathing disorder characterized by hypoxemia and reoxygenation cycles caused due to repetitive and intermittent collapse in the upper respiratory tract.[1] These partial or total collapses result in chronic intermittent hypoxia, sleep fragmentation, hypercapnia, and sympathetic hyperactivity.[2] As a result, these patients experience excessive daytime sleepiness affecting their daytime quality of life.[3,4] Neuronal damage caused by chronic hypoxia increases the risk of cognitive impairment.[5] In addition, depression, stroke, and cardiovascular diseases are also common in these patients.[6] Any myopathy, neuropathy, or neurological condition that weakens the upper respiratory tract musculature predisposes to the development of OSAS. In population-based studies, OSAS is around 18% in men and 7% in women.[7]

Neurocognitive impairment is one of the important comorbidities associated with neurodegenerative diseases such as Alzheimer's and Parkinson's. It is also a major complication associated with OSAS.[8,9] Although sleep fragmentation may cause cognitive dysfunction owing to neuronal damage, it has been shown in experimental and clinical studies that chronic intermittent hypoxia causes some structural and functional brain changes. Experimental studies using mouse models of OSAS have shown decreased neuronal excitability in mouse hippocampal neurons[10] and increased apoptosis in the cortex.[11] Additionally, increased amyloid-beta levels (AB42) were detected in the cortex of mice exposed to chronic intermittent hypoxia. All these data support that the cascade of events induced by OSAS aggravates neuronal degeneration.[12]

Chronic intermittent hypoxia triggers systemic and neuronal inflammation. However, some adaptive mechanisms are initiated simultaneously to fix the damage.[5] Brain-derived neurotrophic factor (BDNF) is an essential neurotrophin that has a role in neuroplasticity, neurogenesis, neuronal development, and neuronal survival. This growth factor has been shown to play a role in mental illness, regulation of memory and sleep, and insomnia.[13-18] Serum BDNF levels increase in various conditions related to neuronal damage, indicative of its neuroprotective role in OSAS patients in response to intermittent hypoxia. The lack of BDNF during chronic intermittent hypoxia causes both the impairment of long-term synaptic plasticity and the inability to prevent neuronal damage.[19,20]

The neurofilament light chain (NfL) is the main intermediate filament in neurons that maintain axonal stability. Whatever the cause, any axonal damage causes increased NfL levels in the cerebrospinal fluid (CSF) and serum.[21] Chronic intermittent hypoxia may also cause neuronal degeneration and NfL release over time.

Since BDNF is a protective factor that comes into play in response to chronic intermittent hypoxia, its relationship with NfL, which indicates axonal damage, helps distinguish between mild and severe OSAS patients.

This study aimed to compare serum levels of BDNF and NfL in patients with mild and moderate-severe OSAS with a group of normal controls. We also evaluated the relationship between these serum biomarkers and other clinical features such as the Epworth Sleepiness Score (ESS) and apnea-hypopnea index (AHI).

2 | MATERIAL AND METHODS

2.1 | Subjects

In this study, we enrolled 81 subjects referred to Otorhinolaryngology (Ear-Nose-Throat), Gazi University Faculty of Medicine, between 2017 and 2019. The patients were monitored by overnight in-laboratory polysomnography (PSG), and AHI scores were used to determine the presence and severity of OSAS. An AHI score of <5 per hour is normal, while 5-15 indicates mild, 15-30 moderate, and >30 severe OSAS. Subjects were divided into three groups: group 1 with mild OSAS (AHI scores 5-15; n = 26), group 2 with moderate-severe OSAS (AHI scores > 15; n = 32), and group 3 of normal individuals (AHI scores < 5; n = 23).

All patients were interviewed to collect information on sex, age, medical history, and record anthropometric characteristics, including weight, height, and body mass index (BMI).

The exclusion criteria were (1) brain trauma and neurological disorders with cognitive dysfunction; (2) dementia and neurodevelopmental disorders; (3) current and lifetime history of any psychiatric disorders; (4) severe physical diseases including cancer, rheumatism, stroke, and epilepsy, and other diseases involving thyroid, liver, kidney, lung, cardiovascular, endocrinal, and nervous system; (5) alcoholics and drug abusers; and (6) pregnant, menstrual and breastfeeding women.

2.2 | Serum sample collection and BDNF and NfL measurements

Fasting blood was collected between 07:00 and 07:30 A.M., the morning after PSG monitoring using a serum separator tube. Serum samples were prepared by centrifugation at 3200 × *g* for 10 minutes at 4°C and stored at −80°C until assaying. Serum BDNF and NfL levels were measured using an enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (Ray Bio Human BDNF ELISA Kit Cat: ELH-BDNF Lot: 0515200106, Abbexa abx258398 Human NfL ELISA Kit Lot: E2002668G). The absorbance was measured at 450 nm using a microplate reader to determine BDNF (ng/mL) and NfL (pg/mL) concentrations.

2.3 | Polysomnography (PSG)

All patients underwent full setup overnight PSG and were allocated to the different study groups based on their AHI scores. The sleep test was performed using the Nocturnal A1 System, version 2.0 (Nox Medical ehf Katrinartuni 2 IS-105 Reykjavik, Iceland). Every sleep study was reviewed and interpreted by a qualified sleep clinician. Apnea is defined as the absence of airflow for ≥10 seconds, and hypopnea is defined as a decrease in respiratory effort with ≥4% oxygen desaturation according to American Academy of Sleep Medicine (AASM) acceptable rule 1B criteria.[22] The severity of OSAS was quantified based on the AHI, and the scores were dichotomized for descriptive statistics using a <30/h cutoff. The following parameters were included in the statistical analysis: AHI, oxygen desaturation index (ODI) (1/h), apnea index (1/h), central apnea index (1/h), hypopnea index (1/h), and total sleep time with oxygen saturation below 90% (%) ($ST_{90,min}$).

2.4 | Ethics statement

Our study was approved by the Ethics Review Board of the Gazi University Faculty of Medicine Ethics Committee (Approval # 573-10.09.2018). All the participants gave written informed consent.

2.5 | Statistical analysis

Statistical tests were performed with SPSS software (IBM SPSS 18, statistical software). The distribution of the variables was validated by the normality test, and the differences between groups were evaluated using Kruskal-Wallis H to correct for multiple comparisons. The mean for the groups was compared using the one-way ANOVA test. Categorical variables were evaluated by the chi-square test. Correlation between clinical and biochemical data was assessed by Spearman rho correlation analysis. The relationships between age, gender, BMI, ODI, and levels of BDNF and NfL were examined using the Spearman correlation coefficient. All the tests were performed at a $P < .005$ significance level.

3 | RESULTS

After applying the inclusion and exclusion criteria, based on the OSAS severity, we had three groups of subjects: normal (n = 23), mild (n = 26), and moderate-severe (n = 32). None of the subjects

TABLE 1 Descriptive characteristics of normal group and OSAS patients

Variable of subjects	Normal group (n = 23)	Mild OSAS group (n = 26)	Moderate-severe OSAS group (n = 32)	*P*-value[a]
Female n (%)	12 (52.20)	10 (38.5)	9 (28.1)	.194[b]
Age (years)	44.17 ± 10.66	48.88 ± 11.30	49.75 ± 11.85	.178
BMI (kg/m^2)	28.05 ± 3.65	29.36 ± 3.87	30.03 ± 2.96	.120
AHI (/hrTST)	2.32 ± 1.47	9.78 ± 2.63	35.68 ± 22.59	.0003*
ESS	14.83 ± 9.19	14.27 ± 8.36	19.65 ± 8.71	.04*
ODI (/hrTST)	7.11 ± 15.39	15.43 ± 21.73	27.05 ± 28.85	.009*
Apnea index	2.63 ± 1.83	12.91 ± 12.62	32.03 ± 23.67	.0002*
Hypopnea index (1/h)	0.90 ± 1.12	5.27 ± 7.81	16.56 ± 20.41	.0001*
Sleep efficiency, %	75.21 ± 18.75	79.80 ± 16.07	80.62 ± 12.89	.0009*
Central apnea (1/h)	0.34 ± 0.70	1.24 ± 3.31	1.23 ± 2.65	.363
$ST_{90,min}$	7.04 ± 15.42	13.3 ± 20.34	28.43 ± 27.26	.0001*
BDNF (ng/mL)	42.40 ± 9.81	44.78 ± 8.24	49.69 ± 7.69	.007*
Nfl (pg/mL)	92.29 ± 18.50	95.29 ± 18.02	93.81 ± 17.90	.847

Abbreviations: AHI, apnea-hypopnea index; BDNF, brain derived neurotrophic factor; BMI, body mass index; ESS, Epworth Sleepiness Scale; hrTST, hour of total sleep time; Nfl, neurofilament light chain; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; sleep efficiency,% (in %, defined as the ratio between total sleep time and the time spent in bed), $ST_{90,min}$, sleep time with oxygen saturation below 90%, minutes.
[a]Kruskal-Wallis *H* test.
[b]Chi-square test.
*The statistical significance is marked with asterisks.

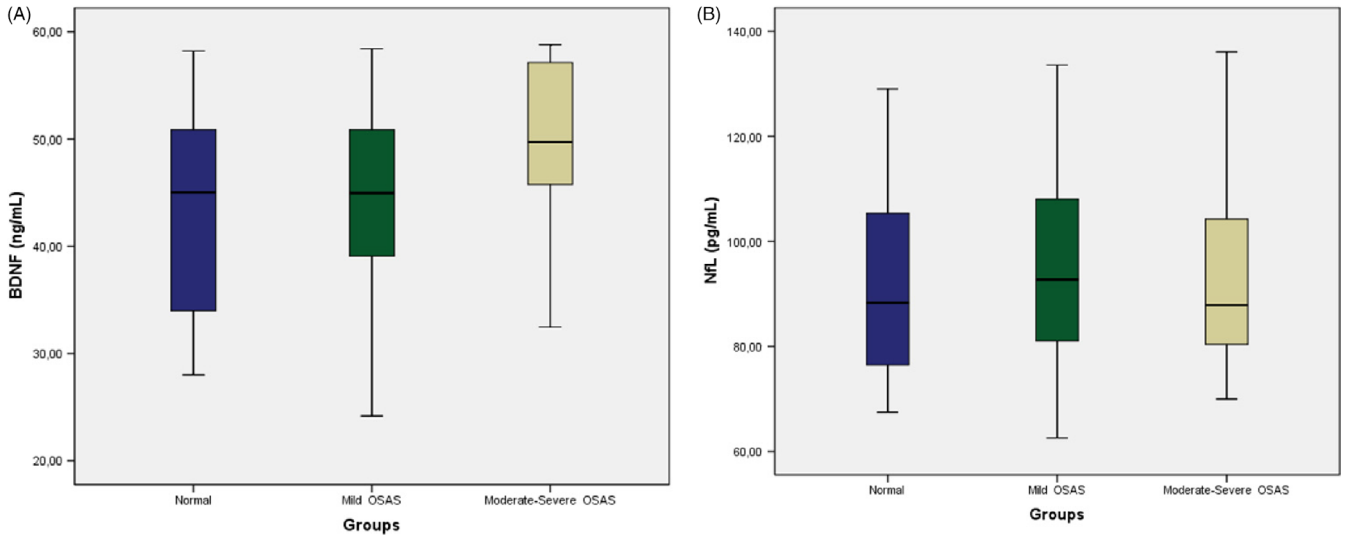

FIGURE 1 A, Mean ± SD of serum BDNF levels in normal and OSAS groups. Serum BDNF levels show a significant difference between the two groups ($P = .007$) (left). B, Mean ± SD of serum NfL levels in normal and OSAS groups. Serum NfL levels show no significant difference between the two groups ($P = .847$) (right)

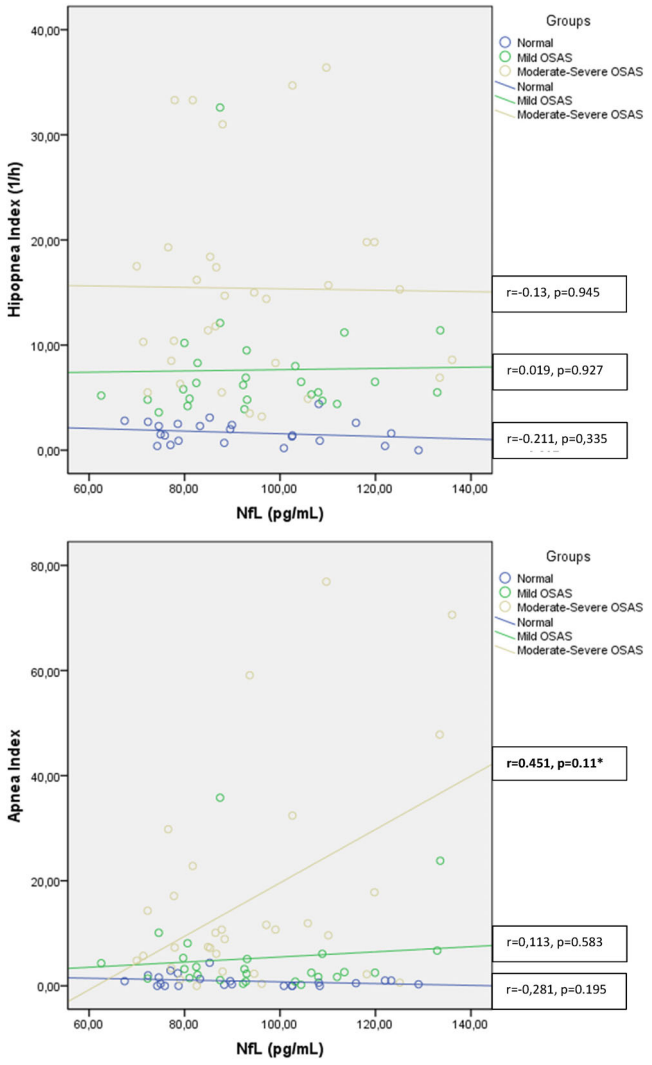

FIGURE 2 Correlation between serum BDNF and NfL levels and apnea and hypopnea indices. The values in bold and asterisk represent statistically significant correlations. Different colors indicate each group. The *r* and *P* values are indicated at the end of the line representing the relevant group

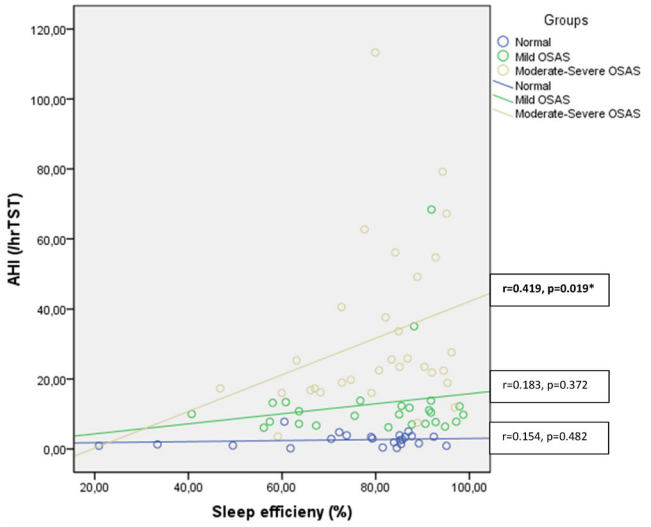

FIGURE 3 Scatter plot of sleep efficiency and AHI. The values in bold and asterisk represent statistically significant correlations. Different colors indicate each group. The *r* and *P* values are indicated at the end of the line representing the relevant group

received any treatment. The mean age of the control group was 44.17 ± 10.66, while those of the mild and moderate-severe groups were 48.88 ± 11.30 and 49.75 ± 11.85 years, respectively. The mean BMI of the normal group was 28.05 ± 3.65, while those of the mild and moderate-severe groups were 29.36 ± 3.87 and 30.03 ± 2.96, respectively. The baseline characteristics of the study population are summarized in Table 1. AHI, ESS, ODI, apnea index, hypopnea index, sleep efficiency, and central apnea data were collected for all three groups.

The three groups showed statistically significant differences in the ODI, apnea index, hypopnea index, sleep efficiency, and NfL levels ($P < .05$). The mean AHI and ESS values for the mild group were 9.78 ± 2.63 and 14.27 ± 8.36, respectively, while those for the moderate-severe group were 35.68 ± 22.59 and 19.65 ± 8.71, respectively (Table 1). The mean $ST_{90,min}$ was highest in the moderate-severe OSAS group (28.43 ± 27.26, $P = .0001$) (Table 1).

The BDNF levels were significantly different between the three groups ($P = .007$) and were highest in the moderate-severe group (49.69 ± 7.69 ng/mL). The serum BDNF levels in men (45.47 ± 8.11 ng/mL) and women (46.39 ± 9.50 ng/mL) showed no significant difference ($P > .05$). However, when the female participants were divided into groups based on OSAS severity, a significant difference was found between the normal and moderate-severe groups ($P = .04$). No significant difference was seen in the NfL levels between the three groups ($P > .05$). The highest NfL levels were seen in the mild group (95.29 ± 18.02 pg/mL) (Figure 1).

In the moderate-severe group, apnea index and hypopnea index showed a significant positive correlation with the NfL ($P < .05$, $r = .389$ and $P < .05$, $r = .455$, respectively), but not with BDNF levels (Figure 2). All three groups showed a positive linear correlation between sleep efficiency and AHI ($P < .05$) (Figure 3).

The linear relationship between ESS and the serum levels of BDNF and NfL showed no statistical significance ($P > .05$) (Figure 4).

NfL levels compared on the basis of BDNF levels, showed significant differences in the mild, and moderate-severe groups when compared to the normal group (Figure 5). However, no significant relationship was seen between NfL and BDNF levels in the mild ($r = -.004$, $P = .986$), moderate-severe ($r = .176$, $P = .335$), and normal ($r = -.211$, $P = .334$) groups.

In the moderate-severe group, the ODI values showed a direct correlation with the serum NfL ($P = .04$; $r = .362$) (Figure 6), but not the BDNF levels. In addition, a significant positive correlation was seen between $ST_{90,min}$, and NfL values in the mild ($r = .450$, $P = .021$) and moderate-severe ($r = .378$, $P = .033$) groups (Table 2).

Based on the ODI, patients were divided into three groups: mild (5–14), moderate (15–29), and severe (≥30). Patients with an ODI < 5 were graded as having no oxygen disturbance, while those with an ODI > 15 were classified as moderate–severe. These three groups showed significant differences in the NfL ($P = .008$) but not the BDNF

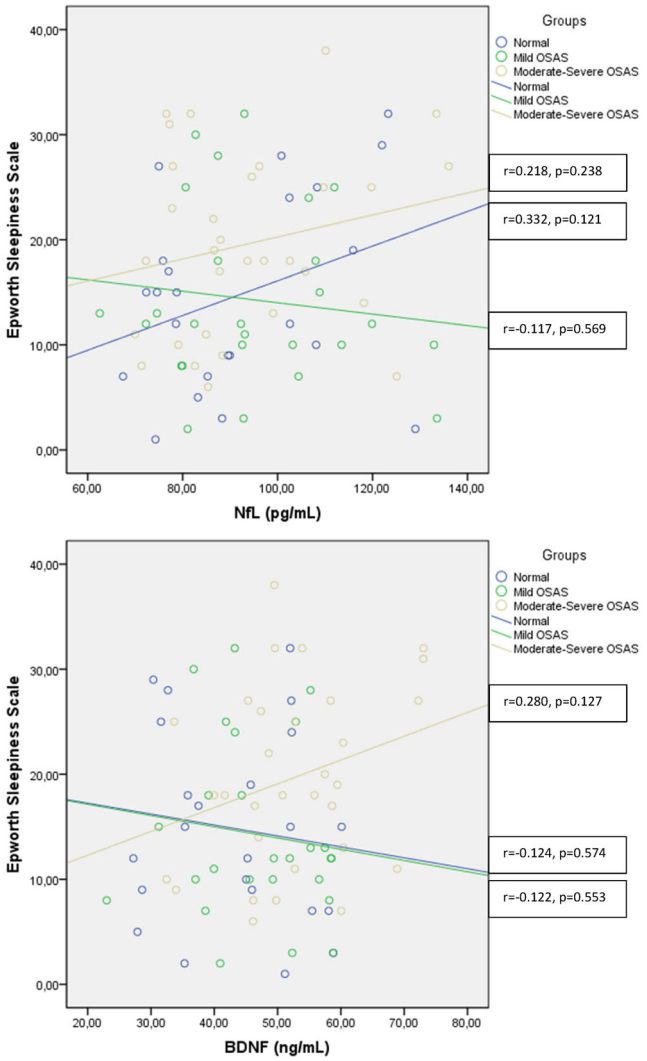

FIGURE 4 Scatter plot of Epworth Sleepiness Scale score and serum NfL and BDNF levels. The values in bold and asterisk represent statistically significant correlations. Different colors indicate each group. The *r* and *P* values are indicated at the end of the line representing the relevant group

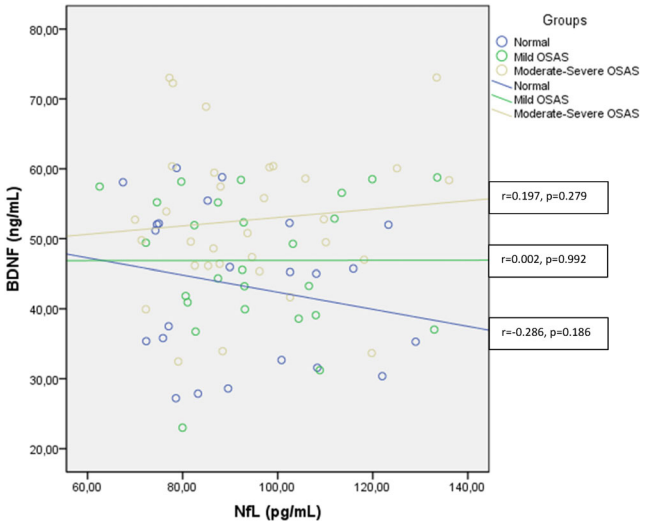

FIGURE 5 Correlation between serum levels of BDNF and NfL in normal and OSAS groups. The values in bold and asterisk represent statistically significant correlations. Different colors indicate each group. The *r* and *P* values are indicated at the end of the line representing the relevant group

values. The ODI showed a significant positive relationship with AHI in the moderate–severe group ($r = .446$, $P = .012$), and with NfL in both the mild ($r = .492$, $P = .011$) and moderate–severe ($r = .414$, $P = .021$) groups.

4 | DISCUSSION

Intermittent chronic hypoxemia is a risk factor for serious complications related to OSAS, such as neurocognitive deterioration.[23] It causes inflammation, oxidative stress, endothelial dysfunction, and increased sympathetic activation, contributing to multi-organ comorbidities.[24] Recurrent episodes of hypoxia-reoxygenation are associated with high levels of pro-inflammatory markers, including tryptophan and kynurenine. In addition, determining the kynurenine/tryptophan ratio can provide information about the course of chronic diseases.[25] OSAS patients diagnosed at a late stage are associated with neurocognitive impairment, a well-recognized public health concern.[26]

Chronic intermittent hypoxia results in neuronal and, finally, axonal damage, leading to the release of NfL first into the CSF and then blood. This is the first study to evaluate serum NfL levels in OSAS patients, opening the possibility of its use as a biomarker for cognitive deterioration in these patients. We also assessed the relationship between NfL and other parameters related to the clinical status, such as ESS, ODI, AHI index, and sleep efficiency, in OSAS patients. Our results will help us understand how OSAS patients lose their cognitive functions. Since NfL is a direct measure of axonal damage, an increase in its levels is a poor prognostic indicator. We found the highest NfL levels in the mild group, indicating that these patients are likely to develop additional cognitive problems in the future. Moreover, the NfL values were very close to each other in all groups. Although we excluded comorbid conditions, any undiagnosed neuronal deterioration could have caused this non-homogeneous distribution of NfL. Studies with a larger number of patients and more sensitive methods such as the single-molecule array can correct this problem.[27]

We found a significant positive correlation between NfL levels and $ST_{90,min}$ values in the mild and moderate-severe groups, indicating that axonal damage may be triggered with increasing exposure to hypoxia. NfL levels, therefore, might be used in addition to other parameters to grade the OSAS severity.

Targo et al have shown an association between higher cerebrospinal fluid NfL levels and decrease in sleep depth in patients with Alzheimer's disease. However, no association was seen with sleep

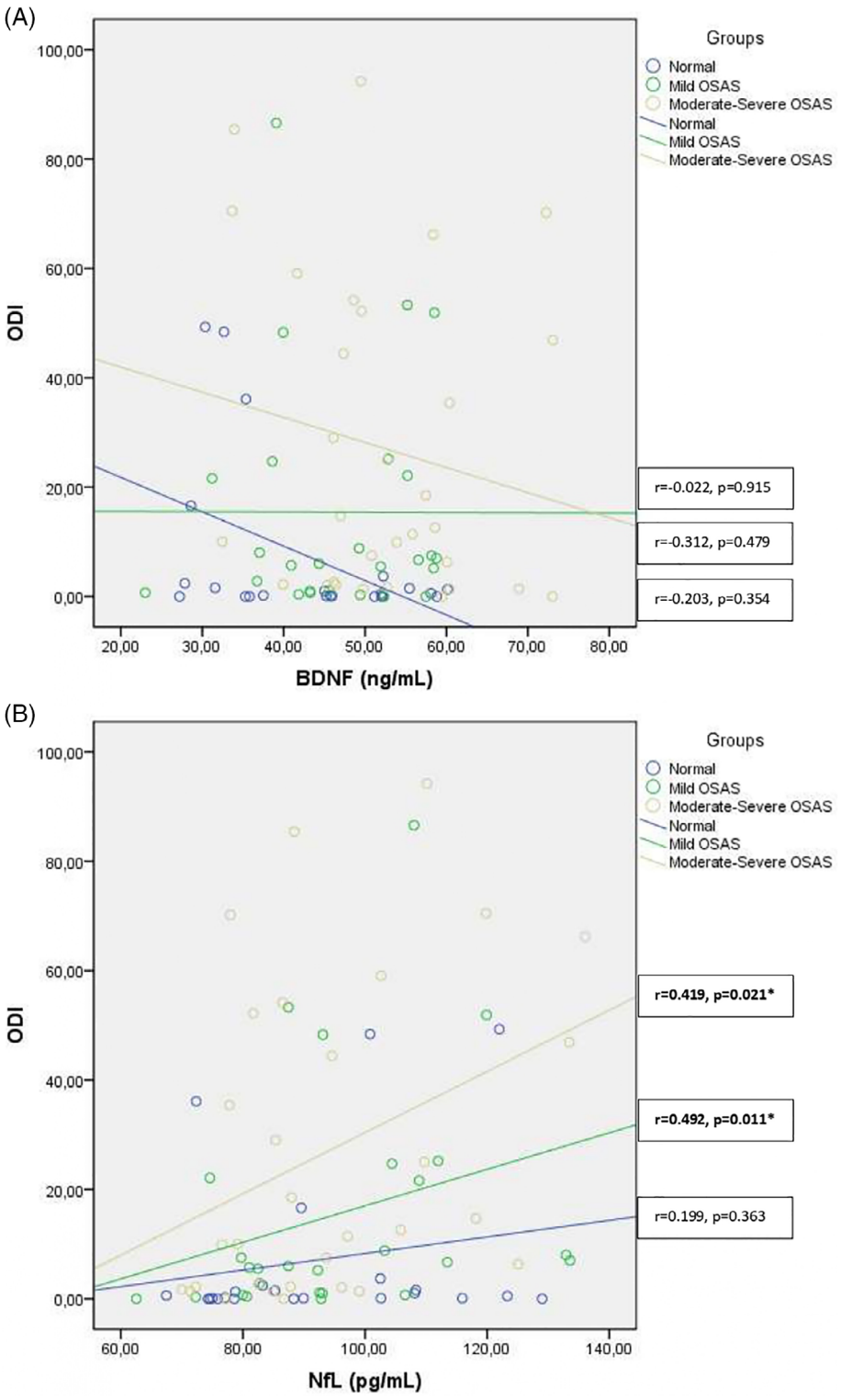

FIGURE 6 A, Correlation between ODI and serum levels of BDNF in normal and OSAS groups. B, Correlation between ODI and serum levels of NfL in normal and OSAS groups. The values in bold and asterisk represent statistically significant correlations. Different colors indicate each group. The *r* and *P* values are indicated at the end of the line representing the relevant group

efficacy.[28] In line with these findings, we found no significant association between sleep efficiency and NfL. However, we could not evaluate the relationship between sleep depth and NfL levels. In addition, the NfL levels in the CSF were higher than the serum levels measured in our study.

BDNF has a critical role in neuroprotection and neuronal plasticity in the central and peripheral nervous systems.[19] De novo synthesis of BDNF increases because of repetitive hypoxic stimulation, as well as increased circulating levels of BDNF in patients with acute ischemic stroke.[29-30] However, whether serum BDNF levels in OSAS patients are due to intermittent pathological hypoxia or other triggers remains controversial.

Chronic intermittent hypoxia leads to an increase in reactive oxygen species. Various transcription factors such as c-Fos, C-Jun, NFkB, HIF-

TABLE 2 Correlations between sleep time with oxygen saturation below 90% and serum biomarkers

Groups	Biomarkers	$ST_{90,min}$ Rho
Normal	NfL	0.208
	BDNF	−0.281
Mild OSAS	NfL	**0.450***
	BDNF	−0.182
Moderate-severe OSAS	NfL	**0.378***
	BDNF	−0.017

Note: Spearman correlations between sleep time with oxygen saturation below 90% and serum biomarkers. The values in bold represent statistically significant correlations.
Abbreviations: BDNF, brain derived neurotrophic factor; NfL, neurofilament light chain; $ST_{90,min}$, sleep time with oxygen saturation below 90%, minutes.
*$P < 05$

1a, and Nrf2 are upregulated in response to increased oxidative stress. An increase in the oxidation state of the cell leads to upregulation of cellular elements responsible for the secretion of inflammatory cytokines, and as hypoxia continues, inflammation increases, inevitably resulting in cellular apoptosis and necrosis.[31-34] When occurring in the neuron, these events lead to neuronal damage, which increases as the exposure to chronic intermittent hypoxia increases. As a result, the expression of BDNF, one of the most important elements of the adaptive neuroprotective response expression, is increased.[20] In our study, since the moderate-severe group was the most exposed to a hypoxic state, it also had higher BDNF levels than the other groups.

A few studies on serum BDNF levels in OSAS patients show that it acts as a neuroprotective neurotrophin. In addition, high serum BDNF levels have been reported in naive newly diagnosed OSAS patients. In a study on neurocognitive impairment in OSAS patients, a negative relationship was seen between serum BDNF levels and the Montreal Cognitive Assessment (MoCA).[5] We did not use any questionnaire to measure the neurocognitive status of OSAS patients in this study. Instead, we assessed the serum NfL levels which reflect neuronal damage. Though the absence of a questionnaire may be the limitation of our study, we believe NfL is a good biomarker for neuronal damage. Moreover, we categorized patients into three groups based on the OSAS severity and measured the serum levels of BDNF and NfL in them. Our findings demonstrate the highest BDNF levels in the moderate-severe group.

Consistent with our findings, Flores et al have previously shown that OSAS patients have higher serum BDNF levels compared to healthy controls.[5] In contrast, studies by Panaree et al,[35] Wang et al,[36] and Staats et al[37] did not find differences in the serum and plasma BDNF levels between OSAS patients and healthy controls. Results and patients were not evaluated in terms of ODI in these studies, which could explain the discrepancy in the results.

Several studies have suggested the role of BDNF and NfL in the pathogenesis of neurodegenerative diseases such as Alzheimer's and Huntington's.[38,28] These reports and our present findings demonstrate that increased BDNF levels in response to chronic hypoxia and sleep interruption may have a role in preventing the progression of neuronal damage. We also show that NfL levels may indicate neuronal damage in these patients and are, therefore, inversely related to BDNF levels. In our study, the moderate-severe OSAS group had the highest AHI, BMI, ESS, and ODI. Interestingly, this group also showed a positive correlation between the NfL levels and apnea and hypopnea indices. Our results, therefore, suggest that repetitive chronic episodes of intermittent hypoxia can cause more neuronal damage.

5 | CONCLUSIONS

Our findings show that BDNF and NfL are promising biomarkers that reflect the clinical condition of OSAS patients. They also clarify the pathophysiology of OSAS in cases of repeated hypoxia and chronic neuronal damage. Hence, in addition to BDNF, NfL should also be evaluated in different and larger patient cohorts.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Burak Arslan analyzed the data, contributed to the design of the current study, and wrote the manuscript. Rabia Şemsi analyzed the data and wrote the manuscript. Aylin Sepici Dinçel analyzed the data and drafted the manuscript. Ayşe İriz designed the cohort collection and drafted the manuscript.

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How to cite this article: Arslan B, Şemsi R, İriz A, Sepici Dinçel A. The evaluation of serum brain-derived neurotrophic factor and neurofilament light chain levels in patients with obstructive sleep apnea syndrome. *Laryngoscope Investigative Otolaryngology*. 2021;6(6):1466-1473. doi:10.1002/lio2.683