



## RESEARCH ARTICLE

## Evaluation of Retinal Nerve Fiber Layer and Optic Nerve Function in Patients with Obstructive Sleep Apnea Syndrome

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### Abstract

**Objective:** To evaluate retinal nerve fiber layer thickness (RNLF) with optical coherence tomography (OCT) and optic nerve function with visual evoked potential (VEP) in patients with obstructive sleep apnea syndrome (OSAS).

**Methods:** Fifty-one eyes of 30 newly diagnosed OSAS patients who received no treatment were included. The RNLF analysis with OCT and pattern VEP test (120', 30', 15', 7' pattern size) was performed to all patients.

**Results:** Of 30 patients, 20 were females and 10 were males. None of the patients were obese with a body mass index of (BMI) < 30 kg/m<sup>2</sup>. The mean Apnea Index of the patients was 42.5 ± 24.3. All patients had severe OSAS with an Apne Index of ≥ 30. Visual acuity was 20/20, intraocular pressure and optic disc were within natural limits in the all of the eyes included in the study. A statistically significant decrease (p < 0.05) was detected in the all parameters of p100 wave amplitude of VEP tests. Compared to the standard data of the healthy individuals at the same age, there was no significant difference in the p100 latency. Although there was thinning of the RNLF thickness, there was no statistically significant difference (p > 0.05).

**Conclusion:** In patients with OSAS, ischemia during deep sleep causes optic nerve dysfunction which can be detected by electrophysiological test, even in asymptomatic patients. In this study, the importance of early diagnosis and treatment is emphasized, and particularly early treatment may halt the progression of the optic nerve dysfunction. For a better understanding of these diseases and ocular manifestations, further long-term studies are needed.

### Keywords

Obstructive sleep apnea, Visual evoked potential, Optical coherence tomography, Electrophysiology

### Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, with an estimated prevalence of 2% for women and 4% for men in the middle-aged population [1]. It is characterized by the repetitive complete or partial collapse of the upper airway during sleep which causes the cessation (obstructive apnea) or significant reduction (obstructive hypopnea) of airflow. These respiratory events result in intermittent hypoxemia and hypercapnia, cortical arousals, and surges of sympathetic activity [2-4].

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of partial or complete upper airway obstruction which causes cessation of breath during sleep, and it is also a significant risk factor for the development of optic nerve ischemia [5,6]. The repeated apnea episodes cause optic nerve head vascular dysregulation secondary to impaired autoregulation of the optic nerve head blood flow. This dysregulation may be due to the imbalance between nitric oxide and endothelia. Further platelet activation may cause micro infarcts in the optic nerve. Also, direct optic nerve

damage can occur as a consequence of repetitive or prolonged hypoxia or increased intracranial pressure during the repetitive apnea [7-9].

In several studies, the relationship between OSAS and oculo-vascular health, particularly the association between OSAS and non-arteritic ischemic optic neuropathy, papilledema and optic nerve disorders, glaucoma, and floppy eyelid syndrome has been investigated [4,5]. At the beginning of the ocular vascular disease, electrophysiological and structural changes can be detected with the normal eyes which are asymptomatic and without pathological changes in the clinical examination.

OSAS may lead to changes in the optic nerve even if there is no complaint. In the present study, we aimed to investigate early changes in patients diagnosed with OSAS before the symptoms occur, and to emphasize the need for caution in terms of the affected ocular system.

## Materials and Methods

This prospective, comparative study included newly diagnosed OSAS patients at Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Department of Sleep who were referred to Ankara Numune Training and Research Hospital Eye Clinic Neuro-Ophthalmology Unit before their treatment started between January 2016 and May 2016. The study protocol was approved by the local Ethics Committee and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. An informed consent was obtained from each patient or legal guardian.

All participants underwent over-night polysomnography from 11:00 PM to 7:00 AM, using the Compu-medics Voyager Digital Imaging E-series system (Compu-medics®, Melbourne, Victoria, Australia) or Alice 5 system (Respironics, PA, USA). The polysomnography recordings included four-channel electroencephalography, two-channel electrooculography, one-channel submental electromyography, oxygen saturation via oximeter probe, respiratory movements via chest and abdominal belts, nasal pressure via pressure sensor, electrocardiography, and leg movements via tibial surface electrodes. A body position sensor attached to a thoracic belt was used to monitor body position. Sleep stages and respiratory parameters were scored according to the standard criteria of the American Academy of Sleep Medicine (AASM). Based on the guidelines of the AASM published in 2012, apnea was defined as  $\geq 90\%$  decrease in the airflow relative to the basal amplitude, persisting for at least 10 sec. Hypopnea was defined as  $\geq 50\%$  decrease in airflow amplitude relative to the baseline values with associated  $\geq 3\%$  oxygen desaturation or arousal, all sustained for at least 10 sec [10]. The Apnea-Hypopnea Index (AHI) was defined as the number of apneas and hypopneas divided by total sleep time. Obstructive sleep apnea was defined with an overall AHI

$\geq 5$ . The patients were categorized according to overall AHI: Patients were considered as mild OSAS with an AHI 5-15, as moderate OSAS with an AHI 15-30, as severe OSAS  $\geq 30$  [11,12].

Patients with diabetes, concomitant psychiatric, and neurological disorders, coronary artery disease, stroke, hematological diseases, autoimmune diseases, or any other condition reported to be associated with OSAS were excluded, with the exception of patients with well-controlled hypertension. In addition, any ocular disease and visual impairment or any condition affecting visual field and uveitis, optic neuropathy and optic nerve disorders; other than retinal vascular occlusion and conditions compromising the capability of patients to understand or participate in the study were considered exclusionary.

A total of 51 eyes of 30 OSAS patients (mean AHI  $42.5 \pm 24.3$ ) were included. All patients had a detailed neuro-ophthalmological examination. Nine eyes undergoing ocular surgery were not included in the study. The visual acuity, optic disc appearance, intraocular pressure, color vision and light reactions were recorded. The retinal nerve fiber layer thickness (RNFL) analysis with optical coherence tomography (OCT) and pattern visual evoked potential (pVEP) test (120', 30', 15', 7' pattern size) was performed to all patients. In accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards [13], the patients were tested by Metrovision brand MonPack model visual electrophysiology device for pVEP tests using simultaneous high-contrast (80%) checkerboard stimuli subtending the visual arc (min arc) 120', 30', 15', 7'. The RNFL parameters were measured with the Cirrus OCT, and the results were recorded. The results were compared with the standard data of the healthy individuals at the same age.

## Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed in mean  $\pm$  standard deviation (SD) and range (min-max) values. The Student's t-test and Mann-Whitney U test were used for statistical analysis. A *p* value of  $< 0.05$  was considered statistically significant.

## Results

This study included a total of 30 patients (20 males and 10 females). The mean age of patients was  $49.9 \pm 11.2$  years (range: 24 to 71 years). None of the patients were obese with a body mass index (BMI) of  $< 30$  kg/m<sup>2</sup>. The mean AHI was  $42.5 \pm 24.3$ . All patients had severe OSAS with an AHI of  $\geq 30$ .

Of 51 eyes included, intraocular pressure and optic disc views were within the normal limits and the visual acuity was 20/20.

**Table 1:** VEP latency and amplitude values of OSAS patients.

| VEP pattern size | OSA (n: 51)            |                | HS (n: 51)   |                | P <sub>L</sub> | P <sub>A</sub> |
|------------------|------------------------|----------------|--------------|----------------|----------------|----------------|
|                  | VEP values (Mean ± SE) |                |              |                |                |                |
|                  | Latency (ms)           | Amplitude (µv) | Latency (ms) | Amplitude (µv) |                |                |
| VEP-120'         | 105.0 ± 11.9           | 9.4 ± 3.2      | 103.2 ± 4.9  | 11.34 ± 4.51   | P = 0.23       | P = 0.042      |
| VEP-30'          | 109.5 ± 8.6            | 7.4 ± 3.5      | 109.0 ± 5.9  | 9.5 ± 4.9      | P = 0.76       | P = 0.003      |
| VEP-15'          | 120.1 ± 8.6            | 7.2 ± 3.6      | 118.9 ± 8.9  | 8.9 ± 5.1      | P = 0.51       | P = 0.014      |
| VEP-7'           | 134.0 ± 15.3           | 3.2 ± 1.7      | 127.2 ± 22.6 | 4.5 ± 3.5      | P = 0.11       | P = 0.041      |

VEP: Visual Evoked Potential; OSA: Obstructive Sleep Apnea Syndrome; HS: Healthy Subjects; P<sub>L</sub>: Statistically Analysis of Amplitude Values; P<sub>A</sub>: Statistically Analysis of Latency Values.

At the pVEP tests, a reduction was detected on the all parameters (120', 30', 15', 7' pattern size) of the p100 wave amplitude ( $p < 0.05$ ). In the p100 wave latency, there was no statistically significant difference, compared to the control group ( $p > 0.05$ ) (Table 1).

The mean RNFL value was  $91.1 \pm 16.8$  in the patients with OSAS and  $95.0 \pm 9.6$  in the control group. Although thinning was detected, there was no statistically significant difference between the groups ( $p > 0.05$ ).

## Discussion

There have been reports that OSAS is also associated with ophthalmic disorders, including glaucoma and normal tension glaucoma, visual field changes, optic disk swelling, non-arteritic anterior ischemic optic neuropathy, central serous chorioretinopathy, and retinal vein occlusions [14-22].

Recently, OSAS has been increasingly recognized as an important cause of medical morbidity and mortality. Respiratory events caused by OSAS result in hypoxia, hypercapnia, and activation of the sympathetic nervous system [23]. Hypoxia-induced vasodilation of the central retinal artery may compress the adjacent central retinal vein and interfere with retinal blood flow. Hypercapnia-induced cerebral vasodilation may also increase the intracranial and cerebral spinal fluid pressure, inducing papilledema and elevated venous pressure in the optic nerve head. This vasodilation also has the effect of reducing the rate of retinal circulation. In addition, activated sympathetic tone can stimulate increases in the arterial blood pressure [5]. Thrombogenicity of sleep apnea patients is another probable mechanism for the promotion of vascular events in OSAS. Indirect optic nerve damage occurs due to hypoxia induced-increased intracranial pressure during the apnea episodes. Direct damage occurs by the circulatory compression on optic nerve which is hypoxia-induced vascular dysregulation in the optic nerve and retina [6,17,24,25]. Thus, in patients with OSAS, both vascular and mechanical factors may play a key role in causing optic nerve pathology, which includes glaucoma and non-arteritic anterior ischemic optic neuropathy. However, the pathophysiological mechanism of optic neuropathy in patients with OSAS is still unclear. It has been hypothesized that hypoxia, hypercarbia, acidosis, and altered vascular auto-regulation may contribute to the development of the

optic nerve pathology. All these factors contribute to the retina vascular dysregulation, leading to RNLF and optic nerve damages [5,17,23-25].

Electrophysiological tests enable the evaluation of the visual system, starting from the retinal pigment epithelium (RPE), to the occipital cortex. Pattern visual evoked potential is a sensitive indicator which shows the optic nerve function, and it measures the cortical cell response against the pattern stimuli. It is used for the evaluation of the patients with optic neuritis in the acute period of the disease, and it may also be used for long-term follow up of those patients, and for analysis of the optic nerve functions [6,25]. Concerning VEP responses, they provide a powerful indication of abnormal signal conduction within the visual pathway [6,26,27]. In this view, prolonged VEP latency is considered an index of optic nerve myelin damage, whereas changes in VEP amplitude may be expression of optic nerve axonal loss [6,26,27].

Several studies have demonstrated that moderate-to-severe OSAS has a greater effect on ocular perfusion, thus predisposing to normal tension glaucoma [6,26-28]. We believe that OSAS compromises circulation at the optic nerve head by causing hypoxia and vascular dysregulation in patients with normal-tension glaucoma. Thus, OSAS may be a treatable cause of circulatory deficiency in the optic nerve head. Besides optic neuropathy, it can lead to normotensive glaucoma, suggesting that the damage may remain stable and progression of the glaucoma may halt.

In previous studies, it has been well-established that VEP amplitude could be reduced by ischemic insults, whereas VEP latency becomes delayed in inflammatory conditions and which can damage optic nerve myelination [29,30]. In our study, we found amplitude reduction in the patients with OSAS, but not statistically significant latency delay of VEP. Consistent with previous literature findings, these findings may be explained by the repetitive insults related to intermittent hypoxia able to provoke reduced VEP amplitude. In our study, in contrast to previous reports, the absence of prolongation of latency suggests that inflammation of the optic nerve in the early period has not started, yet. This emphasizes the importance of early initiation of treatment in the patients with OSAS.

In our study, having been ruled out of the systemic diseases and other eye induced diseases provides a reliable assessment of the RNFL and optic nerve. Thus, optic nerve and retinal changes due to hypertension and diabetes mellitus has been ruled out. Therefore, we documented that VEP amplitude and latency were already affected in patients with OSAS before the appearance of other medical pathologies, which could additionally involve optic nerve. Similar VEP results were published in the many forms of hypoxia in chronic obstructive pulmonary disease [31]. In the present study, we consider that the important factor is the severity and duration of hypoxia and additional diseases. Our results may be different from the recent literature, due to the early period of disease and newly diagnosed of patients who had low p100 VEP amplitudes, and the lack of significant difference in latency.

Optical coherence tomography is a non-invasive, easy-to-use method. It enables *in vivo* cross-sectional imaging of retina using reflection of the light waves. Obtained high-resolution images enable visualization of anatomical structure of the retina and used for examination of optic nerve and peripapillary RNFL. It merely presents clinician the optic biopsy of the tissues. It has been currently used in diagnosis and follows up of macular diseases, glaucoma, and optic neuropathy [32]. Thinning of RNFL may be related to ageing or may accompany ocular disorders. Histopathological studies reported RNFL thinning in various systemic diseases [33].

In the literature, different RNFL findings of the OSAS patients were reported. The known mechanism is that acute ischemia first leads to edema in the neurons and to degeneration in the post-ischemic period. Degeneration after ischemia causes thinning of the RNFL. Adam, et al. [33] reported that RNFL thickness was not different between the control and OSAS groups. Moghimi, et al. [34] suggested that thinning of the RNFL has been associated with elevated intraocular pressure. Zengin, et al. [35] showed reduced mean RNFL thickness throughout follow-up period. In our study, although the thinning of RNFL thickness, there was no statistically significant difference, compared to the standard data of the healthy individuals at the same age. These different results may be the result of different stages of edema which was induced by hypoxia.

In conclusion, hypoxia leads to degenerative changes in the optic nerve and retina. In patients with OSAS, ischemia during deep sleep causes optic nerve dysfunction which can be detected by electrophysiological tests, even in asymptomatic patients. We emphasize the importance of identification and early treatment of OSAS which may, apart from its other benefits, prevent the occurrence or progression of optic nerve dysfunction and possible retinal changes. Further long-term follow-up studies in the similar groups of OSAS patients would shed light into these questions.

## Financial Disclosure

None of the authors have financial or proprietary interests in any material or methods mentioned.

## Conflict of Interest

Authors declare that they have no conflict of interest.

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- The study as approved by the local ethics committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki.
- Informed consent for the subject to participate in the research study was obtained from a parent or legal guardian.
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