Evaluation of Optic Nerve Parameters in Patients with Obstructive Sleep Apnea Syndrome

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ABSTRACT

Purpose: To evaluate the function of the optic nerve in patients with obstructive sleep apnea syndrome (OSAS) by visual evoked potential (VEP), computerized automatic perimetry and Farnsworth Munsell 100-Hue test.

Materials and Methods: To evaluate the optic nerve functions and following detailed eye examination in patients who were admitted to the Neurology outpatient clinic and diagnosed with OSAS, the following functional tests were performed (parameters evaluated): VEP (amplitude and latency of the P100 wave), Computerized Automated Perimetry (visual field indices=MD (Mean Defect), sLV (square root of Loss Variance), Farnsworth Munsell 100 Hue Test (TES total error score). These parameters were compared in patients according to their OSAS degrees and controls.

Results: The mean age of the controls was 49.3±13.1 years, mild OSAS group was 50.3±8.0 years, moderate OSAS group was 48.0±9.8 years, and the severe OSAS group was 49.6±7.2 years. There was no significant difference in age distribution between the groups ($p > 0.05$). The mean VEP p100 latency was significantly higher in the mild, moderate, and severe OSAS groups compared to controls ($p < 0.05$). The mean p100 Amp value did not differ significantly in the control group, and in the OSAS groups ($p > 0.05$). The mean HUE TES of the mild OSAS, moderate OSAS, and severe OSAS groups were significantly higher than the control group ($p < 0.05$).

Conclusion: The p100 latency of the VEP test and color discrimination are impaired in patients with OSAS.

Keywords: Obstructive Sleep Apnea Syndrome, Optic nerve, VEP (visually evoked potential), Computerized automatic perimetry, Farnsworth Munsell 100-Hue test.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder characterized by repeated episodes of complete or partial obstruction of upper airway during sleep, which is associated with oxygen desaturation.[1-3]

OSAS has been associated with several optic nerve pathology, including primary open-angle[4] and normotensive glaucoma[5], papilledema[6], decreased peripapillary nerve fiber layer thickness[7] and nonarteritic anterior ischemic optic neuropathy.[8] Despite recent studies, the pathophysiological mechanisms underlying OSAS still remain elusive.

The pathophysiology underlying OSAS is attributable to both anatomical (structural) and neuromuscular (nonstructural) elements.[9] Current understanding of the pathophysiologic basis of the disorder suggests that an interaction between unfavorable anatomic upper airway susceptibility and compensatory neuromuscular responses are important in maintaining upper airway patency during sleep.[10-11] However, the mechanisms linking sleep-related physiologic changes to upper airway obstruction in some individuals are not fully understood.

Recent studies reported that, OSAS patients showed alterations in visual evoked potential (VEP) consistent with early dysfunction of the optic nerve and VEP might be a sensitive diagnostic tool for detecting and monitoring subclinical optic nerve dysfunction in patients with OSAS.[5, 12]

Farnsworth-Munsell 100-Hue test is a noninvasive tool

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to diagnose color perception abnormalities and provide evaluation of optic nerve and macular disorders related to chromatic discrimination.[13-15]

The purpose of our study is to assess the function of the optic nerve and correlation with VEP, computerized automatic perimetry and Farnsworth Munsell 100-Hue test in patients with OSAS. To the best of our knowledge, this is the first study to assess the function of the optic nerve in OSAS patients with the ability of color discrimination by using the Farnsworth Munsell 100-Hue test.

MATERIALS AND METHODS

This is an observational, cross-sectional study including 46 eyes of 46 patients with a diagnosis of OSAS according to American Academy of Sleep Medicine (AASM) criteria[16] and 15 eyes of 15 healthy controls which was selected from healthy subjects without sleep-related breathing symptoms such as excessive snoring, obvious apnea, and daytime sleepiness using a self-administered questionnaire. Patients with any ophthalmologic pathology (i.e. glaucoma, optic neuropathy, chronic uveitis, retinal disorders, prior intraocular surgery or trauma) and any systemic disease other than diabetes and hypertension (i.e., chronic obstructive pulmonary disorders (COPD), bronchial asthma, and interstitial lung diseases) were excluded. The study was approved by the Institutional Review Board of Medical School of Erciyes University (No: 2018/446, date: October 3, 2018) and was conducted in adherence with the Declaration of Helsinki. Informed consent was obtained from all subjects included in the study.

All of the patients with OSAS were diagnosed by a board-certified neurologist specialized in sleep disorders (SI) with overnight polysomnography (Grass-Telefactor, West Warwick, Rhode Island, USA) recording. The Apnoea-Hypopnoea Index (AHI) was defined as 'total number of apnoeas and hypopnoeas×60/total sleep time (in minutes). Cases with an AHI>5 were regarded as having OSAS. OSAS was considered mild if the AHI was 5-15 events/h, moderate if 15-30 events/h, and severe if ≥30 events/h.

Healthy volunteered subjects of similar age and gender were enrolled as controls from the ophthalmology clinic for routine examination. All participants underwent complete ophthalmologic examination including best-corrected visual acuity, color vision assessment with Farnsworth-Munsell 100-hue test, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, fundus examination, 30-2 test pattern with dynamic strategy of Octopus 900 perimetry for VF examination, and VEP responses (Vision Monitor, Monpack 3, Metrovision, France) were performed. Visual fields with less than 7% the Reliability Factor (RF) values were included in the study. The mean deviation (MD) and square root of Loss Variance (sLV)) values were evaluated.

Pattern reversal VEP responses were recorded according to the ISCEV guidelines[17], using an optoelectronic stimulator at 120 cm distance with low or high spatial frequencies. N75, P100 and N135 amplitudes were recorded for standard parameters for VEP response. P100 latency was calculated from the visual stimulation onset to the maximum wave peak, while the P100 amplitude was determined peak- to-peak (P100-to-N135).

Color perception was evaluated using the Farnsworth-Munsell 100-hue test which involves color reference caps. Color perception abnormalities are recognised by the patient's ability to arrange the color caps in the correct order of hue.

Patients rested for 15 minutes before performing the FM 100- hue test.[13] The test was performed monocularly in participants according to the manufacturer's instruction. Subjects performed the whole test under photopic conditions with illumination of approximately 1000 lux (normal room lights, window curtains opened). The total error scores (TES) were calculated using the standard method and color defective patterns, if existed, were evaluated with using average of 2 trials.

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS 18.0, SPSS Inc., Chicago, IL). Descriptive statistics were performed for all parameters. Kolmogorov-Smirnov test was used for checking normal distribution of data. The correlation between the Apnoea-Hypopnoea Index (AHI) value, VEP responses, the mean HUE Total Error Score (TES), and automated perimetry parameters were evaluated by Spearman's correlation coefficient. p values < 0.05 were considered significant for statistical test.

RESULTS

A total of 46 OSAS patients were compared to 15 healthy controls. Demographic data of the OSAS patients and healthy controls are shown in Table 1. Fifteen (33%) of the patients were mild OSAS, 15 (33%) were moderate OSAS, and 16 (34%) were severe OSAS. There were no differences between subjects in the OSAS and control groups with respect to age or gender.

The mean Hue Total Error Scores were significantly higher in OSAS compared to those of controls (114.8±11.3, 125.7±32.9, 141.2±35.4 and 82.4±23.1 for mild, moderate, and severe OSAS, and controls, respectively) (p=0.0001).

The mean MD (mean deviation) values of control group, mild OSAS, moderate OSAS, and severe OSAS

Table 1: *Characteristics and demographics of study subject.*

	Mild OSAS (n:15)	Moderate OSAS (n:15)	Severe OSAS (n:16)	Control (n:15)	P value*
Age (years)	50.3±8.0	48.0±9.8	49.6±7.2	49.3±13.1	0.25*
Sex **Male, n (%)** **Female, n (%)**	 12 (80.0%) 3 (20.0%)	 13 (86.7%) 2 (13.3%.)	 14 (87.5%) 2 (12.5%)	 12 (80.0%) 3 (20.0%)	0.32**
BMI	29.4±4.6	31.4±4.7	35.5±5.9	30.7±3.7	0.09*
DM	3/12	2/13	3/13	2/13	0.7**
HT	0/15	2/13	6/10	3/12	0.05**

BMI body mass index, OSAS obstructive sleep apnea syndrome, DM diabetes mellitus, HT hypertension,*Kruskal Wallis test, **Chi-squared test

were 2.21±1.1 db, 2.3±1.2db, 2.4±1.2 db, and 2.7±1.3 db respectively. There were no differences between participants in the OSAS and control groups (p=0.77). The mean sLV values of control group, mild OSAS, moderate OSAS, and severe OSAS were 2.6±1.1 db, 3.4±1.3 db, 3.0±1.2db, and 3.2±1.2 db respectively. There were no differences between participants in the OSAS and control groups (p=0.65).

The mean P100 latency was significantly higher in the mild, moderate, and severe OSAS groups than the control group (114.1±10.6, 114.2±11.1, 118.2±16.6, 97.3±8.8, respectively) (p=0.0001). In the, mild, moderate, and severe OSAS groups and the control group the mean P100 amplitude values (8.3±4.0, 7.6±4.0, 6.4±2.3, 9.2±4.1, respectively) did not differ significantly (p=0.32).

Spearman correlation analyses was performed to evaluate the association between AHI value, VEP responses (p100 latency and amplitude), the mean Hue Total Error Score (TES), and automated perimetry parameters (the mean MD (db) and PSD (db)). The mean Hue Total Error Score was positively correlated with AHI value (r=0.903; p=0.001). No significant correlations between AHI value and automated perimetry parameters (the mean MD (db) and PSD (db)), and p100 amplitude and latency were found (r=0.174; p=0.2, r=0.156; p=0.3, r=0.124; p=0.3, r=0.119; p=0.3, respectively).

Of the 46 patients with OSAS, 26 patients had weak score of (>100) Farnsworth 100-Hue testing. When midpoint cap was calculated for these patients, from average of 2 trials, all the patients with mild and moderate OSAS showed color defective pattern of blue-green to blue band (color caps 46 to 54), however patients with severe OSAS were not shown to choose a specific pattern.

DISCUSSION

Hypoxia, hypercarbia, acidosis and vascular autoregulation disruption associated with OSAS may disrupt the hemodynamics of the optic nerve and cause neurodegeneration. In addition, increased vascular resistance due to hypoxemia may impair the optic nerve

Table 2: *Comparison of optic nerve parameters between obstructive sleep apnea syndrome (OSAS) and control subjects.*

	Mild OSAS (n:15)	Moderate OSAS (n:15)	Severe OSAS (n:16)	Control (n:15)	P value*
VA (logMAR)	0.0±1.4	0.0±1.6	0.0±1.7	0.0±1.6	0.32
IOP (mmHg)	14.3±2.1	14.3±2.2	14.7±2.8	13.5±1.0	0.50
MD (dB)	2.3±1.2	2.4±1.2	2.7±1.3	2.21±1.1	0.77
sLV (dB)	3.4±1.3	3.0±1.2	3.2±1.2	2.6±1.1	0.65
P100 latency (ms)	114.1±10.6	114.2±11.1	118.2±16.6	97.3±8.8	0.0001
P100 amplitude (µv)	8.3±4.0	7.6±4.0	6.4±2.3	9.2±4.1	0.32
Hue TES	114.8±11.3	125.7±32.9	141.2±35.4	82.4±23.1	0.0001

VA visual acuity. IOP intraocular pressure. MD mean deviation, sLV square root of Loss Variance. TES total error scores.*Kruskal-Wallis test.

perfusion and cause functional changes of the optic nerve. Our study revealed prolonged latency and decreased amplitude of the VER test p100 wave, as well as color perception abnormalities. To the best of our knowledge, this is the first study assessing the function of the optic nerve in OSAS patients by using the Farnsworth Munsell 100-Hue test. Furthermore, we have found significant correlation between AHI value and the mean Hue TES.

There are very few studies in the literature evaluating the use of VEP in OSAS. In a study recruited by Gutierrez-Diaz et al., they evaluated optic nerve dysfunction in patients with or without diagnosis of normal-tension glaucoma (NTG) using multifocal visual evoked potentials (mfVEP).[5] They found decreased mfVEP amplitudes and delayed mfVEP latencies in eyes of both non-glaucoma group and NTG patients. However, they did not show significant correlation between the mfVEP amplitude and latency and the standard perimetry and OCT variables. They interpreted these findings with the hypothesis that the mfVEP technique was able to reveal early dysfunction of the optic nerve in OSAS patients. In our study, all of the OSAS patients did not have glaucoma confirmed by Goldmann applanation tonometry, fundus examination, and perimetry. There were no differences between participants in the OSAS and control groups with respect to perimetry parameters. Our study revealed prolonged latency and decreased amplitude of the VEP test p100 wave.

The pathophysiological mechanisms underlying OSAS still remains elusive. Alterations in the optic nerve perfusion pressure is the key point of OSAS. Previous studies have claimed that recurrent hypoxia and reoxygenation episodes during sleep may contribute either a direct anoxic damage, or an indirect effect on the blood flow of optic nerve head.[18-20] Additionally, higher level of oxidative stress indicators and inflammatory cytokines were revealed in OSAS patients.[21-23]

Color discrimination is known to be impaired in various neurological disorders, however the underlying mechanism of whether peripheral (retinal) or central structural abnormalities is involved has not yet been clearly identified.[24] With previous reports it is shown that color vision disturbances may occur in patients with glaucoma before the development of visual field defects. Historically it was shown that, the risk for developing a visual field defect was shown to be higher amongst the patients with color vision defects in yellow-blue equation and green-blue equation but not with red-green equation in Hue-test.[25] Cones are categorized into three types by their pigments. Both the L- and M-cones, which are responsible for the color vision loss, are believed to be selectively harmed in experimental glaucoma models, so the impairment might differ with different colors.[26] S-cones compromise the least proportion of the cones and are highly susceptible to the damage and is correlated with the blue-yellow color vision. Color vision impairment due to S-cone deficiency is known to occur as the earliest color deterioration in glaucoma and retinal diseases before L- and M- cone involvement that are responsible for red and green color perception respectively.

In a very recent study recruited by Ouchi et al. the investigators revealed that Red VA and blue-green VA were significantly worse in the OAG eyes than in the normal eyes and were correlated with MD, whereas green-yellow VA and blue-purple VA were not significantly worse.[26] The limitation of our study is that, perimetry testing with blue-on yellow modality may have been more effective on putting out the perimetric results and correlate with the severity of the OSAS.

We believe OSAS may share a similar mechanism with glaucoma in retinal deterioration.

In OSAS various studies have shown the structural changes, such as the loss of macular thickness, decreased macular ganglion cell thickness and circumpapillary retinal nerve fiber layer thickness (cpRNFLT) with optical coherence tomography (OCT)[24], and retinal and choroidal thickness evaluation by OCT in adults with obstructive sleep apnea-hypopnea syndrome (OSAS).[27,28] Optic disc and retinal nerve fiber layer parameters as indicators of neurodegenerative brain changes in patients with obstructive sleep apnea syndrome.[28] Because of the possible difficulties of the measurements in cpRNFLT and other parameters in OCT, such as coexisting macular diseases, high myopia, tilted disc, disc atrophy, coexisting retinal changes due to comorbid diseases such as HT or DM, i.e., color vision testing is useful in complementing existing structural analyses. Besides it is also easy to test in non-ophthalmology clinics when compared to OCT. Our study had limitations in terms of a small subgroup sample size.

In conclusion, the results of this study suggest that measuring color vision may be a supplementing method for the detection of the severity of OSAS and may put a further insight into its possible central nervous system involvement.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical 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 Declaration of

Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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