

SLEEP DISORDERED BREATHING

Optic Nerve Dysfunction in Obstructive Sleep Apnea: An Electrophysiological Study

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Study Objectives: The aim of this study was to evaluate the integrity of the visual system in patients affected by obstructive sleep apnea (OSA) by means of electroretinogram (ERG) and visual evoked potential (VEP).

Methods: We performed electrophysiological study of the visual system in a population of severe OSA (apnea-hypopnea events/time in bed ≥ 30 /h) patients without medical comorbidities compared to a group of healthy controls similar for age, sex, and body mass index. Patients and controls did not have visual impairment or systemic disorders with known influence on the visual system. ERG and VEP were elicited by a reversal pattern generated on a television monitor at low (55') and high (15') spatial frequencies stimulation. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) in both patients and controls.

Results: In comparison with healthy controls (n = 27), patients with OSA (n = 27) showed a significant latency delay coupled with a significant amplitude reduction of P100 wave of VEP at all spatial frequencies in both eyes. No significant differences between groups were detected as concerning ERG components. No correlations were found between polygraphic parameters, ESS scores, or VEP and ERG components in OSA patients.

Conclusions: This study documented that patients with OSA, without medical comorbidities, present VEP alteration as documented by lower amplitude and longer latency of the P100 component than healthy controls. These altered electrophysiological findings may be the expression of optic nerve dysfunction provoked by hypoxia, acidosis, hypercarbia and airway obstruction, frequently observed in patients with OSA. Hence, we hypothesize that OSA *per se* may impair optic nerve function.

Keywords: ERG, OSA, optic nerve, VEP, visual system

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Significance

Obstructive sleep apnea patients without medical comorbidities show alterations in visual evoked potentials consistent with subclinical optic nerve dysfunction, which may be provoked by hypoxia, acidosis, hypercarbia and airway obstruction. Since visual evoked potentials are considered sensitive instruments able to recognize early dysfunction of the optic nerve, we hypothesize that obstructive sleep apnea may directly impair optic nerve function before the appearance of other medical pathologies, which could additionally negatively involve optic nerve. Therefore, this report reinforces the importance of early identification and treatment of obstructive sleep apnea, which may prevent the occurrence or progression of optic nerve dysfunction.

INTRODUCTION

Obstructive sleep apnea (OSA) syndrome is a relatively common sleep disorder characterized by the occurrence of repetitive episodes of partial or complete obstruction of the upper airways associated with intermittent hypoxia.¹ OSA has been currently receiving significant attention given its numerous health consequences and widespread prevalence.²

Recently, a possible pathophysiological link between OSA and optic nerve pathology has been hypothesized.³ Epidemiological and clinical evidence for an association between OSA and glaucoma, nonarteritic anterior ischemic optic neuropathy, and papilledema supported this suggestion.³ Moreover, few studies have also investigated the retinal nerve fiber layer in patients with OSA, finding reduced retinal nerve fiber thickness.⁴

However, these previous studies investigating optic nerve involvement in patients with OSA have used in their analyses different study designs, methods, and apnea-hypopnea index cutoffs; moreover, patient populations counted numerous potentially confounding comorbidities that frequently occur in patients with OSA, including hypertension and diabetes.^{3,5–12}

The visual pathway can be accurately investigated by electrophysiological tests, such as electroretinogram (ERG) and visual evoked potential (VEP), because ERG provides information about the function of the retinal layers whereas

VEP measures the visual cortex response to the stimulation of the retina.¹³

Therefore, the aim of this study was to evaluate the integrity of the visual system by means of ERG and VEP in patients affected by OSA but without other comorbidities in comparison to a population of controls similar for age, sex, and body mass index (BMI).

MATERIALS AND METHODS

In this study we enrolled patients affected by severe OSA (apnea-hypopnea events/time in bed – A+H/TIB – ≥ 30 /h), undergoing nocturnal polygraphic cardiorespiratory monitoring, diagnosed according to American Academy of Sleep Medicine (AASM) criteria.¹⁴ The recording montage included: an oronasal pressure cannula to record airflow, snoring sound, piezoelectric belts to detect thoracic and abdominal respiratory effort, finger pulse oximetry, heart rate, and body position sensors. The following oxygen saturation (SaO₂) parameters were calculated: mean SaO₂, lowest SaO₂, time spent with SaO₂ < 90% (T < 90), and oxygen desaturation index (ODI) (number of oxygen desaturations ≥ 3 /h). A+H/TIB was defined as the sum of all apneas (> 90% reduction in airflow for > 10 sec) and all hypopneas (> 30% reduction in airflow > 10 sec) associated with $\geq 3\%$ O₂ desaturation per hour.¹⁵

As a control group we selected a population of healthy volunteers similar for age, sex, and BMI with patients with OSA. The inclusion criterion for controls was the absence of sleep disorders, evaluated by means of both a structured interview and a polygraphic cardiorespiratory monitoring (A+H/TIB < 5/h).

Exclusion criteria for patients and controls were the following: medical disorders; concomitant psychiatric or neurologic disorders; heavy smoking; bronchial asthma, chronic obstructive pulmonary disorders (COPD) and interstitial lung diseases; visual impairment or any condition affecting visual field such as intracranial or ocular mass lesions, uveitis, optic neuropathy, anterior ischemic optic neuropathy, optic disk disorders; vasospastic diseases; autoimmune disorders; malignancies; diabetes; hypertension and/or history of hypertensive crisis. In particular, patients have to show current systolic blood pressure < 140 mmHg, diastolic blood pressure < 85 mmHg, and fasting blood glucose < 100 mg/dL. Patients and controls were also requested to take no drugs. Finally, patients with systemic disorders with known influence on the function of the retina and optic nerve as well as with poor cooperation were excluded.

Patients and controls were seated in a semidark acoustically isolated room. Each subject was adapted to the ambient room light for 10 min. Stimulation was monocular. Visual stimuli were checkerboard patterns (contrast 100%) generated on a television monitor and reversed in contrast at the rate of two reversals per second. Simultaneously ERG and VEP recordings were performed at 120 cm distance with an optoelectronic stimulator Galileo Mizar Sirius (EBNeuro SpA, Florence, Italy), with high (15' checks) or low (55') spatial frequencies. For each eye and each recording session, responses to two blocks of 100 stimuli were recorded, under full refractive correction.

ERG responses were recorded by a DTL electrode (Bionen Sas, Florence, Italy) placed in the lower cantus of the eye, referred to an electroencephalogram (EEG) gold cup electrode placed over the ipsilateral temple. A ground electrode was placed on Fpz (10-20 International System). The interelectrode resistance was lower than 3 k Ω . The signal was amplified (gain 50,000), filtered (bandpass 1–30 Hz) and averaged with automatic rejection of artifacts (100 artifact-free events were averaged for every trial). The analysis time was 500 ms. The transient ERG response is characterized by a number of waves with three successive peaks of negative, positive, and negative polarity, namely N35, P50, and N95. P50 latency was determined from the visual stimulus onset to the maximal component peak, whereas the amplitude was calculated peak to peak (P50-to-N95).^{16,17}

VEP responses were recorded using gold-cup electrode located at Oz (active electrode), Fpz (reference electrode), and Cz (ground) (10-20 International System). The interelectrode resistance was kept lower than 3 k Ω . Biological signal was amplified (gain 20,000), filtered (high-pass 1Hz, low-pass 100 Hz) and 100 artifact-free signals were averaged separately for each eye. For transient VEP response, the following standard parameters were recorded: N75, P100 and N145. P100 latency was determined from the visual stimulus onset to the maximal component peak, whereas the amplitude was calculated peak-to-peak (P100-to-N145).^{16,17}

To control vigilance fluctuations during ERG and VEP sessions, participants' behavior was continuously checked by a coregistered EEG and by recording continuous reaction times in order to avoid dozing.

Finally, to guarantee the reliability of ERG and VEP results, the physicians involved in evoked potentials recordings (CO) as well as in data analysis (MGP; MP) were completely blinded to the study participants clinical status.

We also evaluated excessive daytime somnolence in patients with OSA and controls by means of the Epworth Sleepiness Scale (ESS).^{18,19}

Patients and controls provided informed consent to the study, which was approved by the Independent Ethical Committee of the University Hospital of Rome "Tor Vergata".

We used the Statistica 10.0 program (Statsoft Inc, Tulsa, OK, USA) for the statistical analysis. The Mann-Whitney *U* test was used to compare age, BMI, ESS scores, polygraphic cardiorespiratory data, and ERG and VEP latencies and amplitude between patients with OSA and controls.

Among the patients with OSA, correlations between all the serum data, BMI, ESS, and polygraphic scores were separately performed by utilizing the nonparametric Spearman rank order test. The significance level was set at $P < 0.05$ for all statistical analyses.

RESULTS

Demographic, Clinical, and Polygraphic Data of Patients and Controls

Three hundred sixty-eight consecutive patients with OSA were screened from September 2013 to August 2014. Among these patients, 341 presented some exclusion criteria for this study and thus they were excluded. In particular: 258 were affected by hypertension and/or diabetes, 23 had COPD, 44 had specific ocular pathologies, 5 had fasting blood glucose > 100 mg/dL, 11 were uncooperative with the study since the recording session was interrupted, complaining of difficulties in properly maintaining a good and accurate fixation throughout the examination. Therefore, 27 patients with severe OSA completely met the eligible criteria and thus were included in the study. The healthy control population consisted of 27 subjects of similar age, sex, and BMI with patients with OSA.

Demographic, clinical, and polygraphic features of patients with OSA and controls are summarized in Table 1.

VEP and ERG

Patients with OSA showed a significant latency delay of the P100 wave in both eyes at the high and low spatial frequencies compared to controls (see Table 2). Moreover, in comparison with healthy controls, patients with OSA showed a significant amplitude reduction of P100 wave of VEP at both spatial frequencies (see Table 2).

However, no significant differences between OSA and controls were detected concerning ERG amplitude and latency (see Table 3).

No correlations were found in patients with OSA and controls between polygraphic parameters, ESS scores, and VEP and ERG components.

DISCUSSION

This study has documented that patients with OSA show abnormal VEP without alteration of ERG components. In fact, our findings demonstrated that latencies and amplitudes of VEP responses were significantly altered in patients with OSA, whereas ERG components were preserved.

Clinical electrophysiology of vision is widely used in neurologic disorders. It consists of ERG and VEP that are considered sensitive objective measures of retinal and optic nerve pathologies. Concerning VEP responses, they provide a powerful indication of abnormal signal conduction within the visual pathway.^{20,21} 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.²⁰

Currently, OSA is being increasingly recognized as an important cause of medical morbidity and mortality. In fact, it is well documented that OSA may contribute to the development of systemic hypertension, cardiovascular and cerebrovascular diseases, and abnormalities in glucose metabolism, for example.^{22–26} OSA has been also recently associated with optic nerve pathology due to vascular and mechanical factors. In fact, it has been demonstrated that hypoxemia and consequent increase in vascular resistance may compromise optic nerve perfusion and oxygenation causing optic nerve vascular dysregulation.²⁷ Furthermore, elevated intracranial pressure during apneic events may contribute to optic nerve head damage, directly or by circulatory compression.²⁸ Therefore,

in patients with OSA both vascular and mechanical factors may play a significant role in causing optic nerve pathology, which includes glaucoma, nonarteritic anterior ischemic optic neuropathy, and optic disc derangement. However, the pathophysiological mechanism of optic neuropathy in patients with

Table 1—Demographic, clinical and polygraphic data of patients with obstructive sleep apnea and controls.

	OSA (n = 27)	Controls (n = 27)	P
Age (y)	44.75 ± 10.99	41.12 ± 11.24	NS
Sex (F/M)	6/21	10/17	NS
BMI	30.11 ± 6.52	30.61 ± 2.84	NS
ESS	12.42 ± 6.02	2.16 ± 1.55	< 0.01
A+H/TIB	50.47 ± 23.58	3.05 ± 1.39	< 0.001
ODI	46.87 ± 23.67	2.49 ± 1.23	< 0.001
Sat Mean	93.18 ± 2.70	96.91 ± 1.17	< 0.001
Sat Min	75.04 ± 11.51	91.37 ± 2.35	< 0.001
T < 90	12.25 ± 17.46	0.12 ± 0.19	< 0.001

Values are mean value ± standard deviation unless otherwise indicated. A+H/TIB, apnea-hypopnea events during time in bed; BMI, body mass index; ESS, Epworth Sleepiness Scale; F, female; M, male; NS, not significant; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SaO₂ mean, mean oxygen saturation; SaO₂ min, lowest oxygen saturation; SD, standard deviation; T < 90 (%), time spent with SaO₂ < 90%.

Table 2—Visual evoked potentials P100 latencies and amplitudes in patients and control groups.

	Eye	VEP 15'		VEP 55'	
		P100 Latency (ms)	P100-N145 Amplitude (μV)	P100 Latency (ms)	P100-N145 Amplitude (μV)
OSA (n = 27)	R	120.93 ± 8.55*	3.21 ± 0.56**	105.69 ± 6.07*	3.85 ± 0.24**
	L	120.13 ± 8.35*	3.01 ± 0.66**	106.59 ± 5.84*	4.33 ± 0.36**
Controls (n = 27)	R	106.03 ± 3.41	6.29 ± 0.83	99.83 ± 4.66	7.01 ± 0.69
	L	105.99 ± 3.44	6.32 ± 1.01	100.48 ± 4.69	7.13 ± 0.63

VEP amplitudes and latencies (mean value ± standard deviation). *P < 0.001, **P < 0.01. R, right eye; L, left eye; 15', stimulation at high spatial frequency (15' checks); 55', stimulation at low spatial frequency (55' checks); VEP P100-N145 15', P100 amplitude at stimulation at high spatial frequency (15' checks); VEP P100-N145 55', P100 amplitude at stimulation at low spatial frequency (55' checks); ms, milliseconds; OSA, obstructive sleep apnea; μV, microvolts; VEP, visual evoked potentials.

Table 3—Electroretinograms P50 latencies and amplitudes in patients and control groups.

	Eye	ERG 15'		ERG 55'	
		P50 Latency (ms)	P50-N95 Amplitude (μV)	P50 Latency (ms)	P50-N95 Amplitude (μV)
OSA (n = 27)	R	54.16 ± 3.05	1.66 ± 0.22	51.28 ± 2.59	1.96 ± 0.33
	L	53.96 ± 2.94	1.57 ± 0.18	50.87 ± 2.75	1.92 ± 0.31
Controls (n = 27)	R	53.92 ± 2.67	1.63 ± 0.19	52.08 ± 2.69	1.89 ± 0.34
	L	54.07 ± 2.84	1.59 ± 0.24	50.36 ± 2.99	1.88 ± 0.29

ERG amplitudes and latencies (mean value ± SD). R, right eye; L, left eye; 15', stimulation at high spatial frequency (15' checks); 55', stimulation at low spatial frequency (55' checks); ERG P50-N95 15', P50 amplitude at stimulation at high spatial frequency (15' checks); ERG P50-N95 55', P50 amplitude at stimulation at low spatial frequency (55' checks); ERG, electroretinogram, ms, milliseconds; OSA, obstructive sleep apnea; μV, microvolts.

OSA is still unclear. It has been hypothesized that hypoxia, hypercarbia, acidosis, and altered vascular autoregulation may contribute to the development of the optic nerve pathology.^{29,30} Congruously, it was demonstrated that moderate-severe OSA has a greater effect on ocular perfusion thus predisposing to normal tension glaucoma.^{31–33} In fact, recent studies performed in populations of patients with OSA, including subjects affected by normal tension glaucoma and medical comorbidities such as hypertension, showed that patients with OSA are affected by reduced retinal fiber layer thickness coupled with the alteration of amplitude and latency of multifocal VEP.^{4,31,32}

It is well accepted that VEP amplitude could be reduced by ischemic insults,³⁴ whereas VEP latency becomes delayed in inflammatory conditions.³⁵ We have found in patients with OSA, both amplitude reduction and latency delay of VEP. These findings may be explained by the repetitive insults related to intermittent hypoxia able to provoke reduced VEP amplitude, whereas the increased latency may be due to inflammatory conditions, well described in patients with OSA, which could damage optic nerve myelination.^{34,36}

The novel contribution of the present study lies in the observation that OSA pathology may *per se* affect optic nerve function and efficiency. Indeed, in our study we selected patients exclusively affected by OSA in order to avoid confounding factors represented by clinical comorbidities possibly damaging the visual system such as ocular pathologies, hypertension, or diabetes. Therefore, we documented that VEP amplitude and latency are already affected in patients with OSA before the appearance of other medical pathologies, which could additionally involve optic nerve.

Previously, electrophysiological studies in patients with COPD documented alteration of VEP similar to that reported in our study. In fact, prolonged latency and low amplitude of the P100 wave was reported in patients with COPD, representing axonal and demyelinating dysfunctions of the optic nerve. The finding that cranial optic neuropathy may be a common finding in patients with COPD was explained by the hypothesis that chronic hypoxemia, typical of COPD, is able to cause peripheral nerve damage by harming vasa nervorum.³⁷ Therefore, optic nerve involvement is relatively common in patients with COPD and related to acidosis, hypercarbia, and airway obstruction.³⁸

Taking into account that COPD and OSA share some common clinical consequences, such as hypoxia and hypercarbia, we could then suppose that the repetitive obstruction of the upper airways during sleep, which determines intermittent oxygen desaturation and hypercarbia, may cause an optic nerve dysfunction instrumentally detectable by electrophysiological studies, such as VEP.

Interestingly, in this study we did not find alteration of ERG in patients with OSA. ERG is commonly used to test the bioelectrical function of the retina. Therefore, the finding in patients with OSA of an alteration in VEP with unaffected ERG could be explained by an early pathological process that primarily affects optic nerve sparing the retinal function. This result seems to be in contrast to previous findings showing retina alterations in patients with OSA.^{4,31,32} However, these studies included patients affected by ocular pathologies such

as increased ocular pressure. In contrast, our findings draw strength from their strict inclusion and exclusion criteria: we endeavored to ensure our study only included patients affected by OSA without other comorbidities that could have altered ERG and VEP.

This study was focused exclusively on patients with severe OSA who are candidates for continuous positive airway pressure therapy. Therefore, the lack of correlations linking apnea-hypopnea and oxygen desaturation indices to the electrophysiological evaluations may be due to the fact that we did not evaluate the full spectrum of OSA disease. Moreover, we are aware that VEP responses are not specific enough to discriminate between inflammatory, mechanical or vascular causes of optic nerve damage. However, VEP is considered to be a sensitive instruments able to recognize early dysfunction of the optic nerve.²¹ Hence, taking into account that VEP is a useful tool to identify optic nerve pathology even in absence of clinical signs or symptoms,²¹ we suggest that changing in amplitude and latency of the VEP P100 wave in patients with OSA may be an early expression of optic nerve damage. However, the current data need to be confirmed in the near future in a larger clinically based cohort of patients with OSA ranging from mild to severe.

In conclusion, we emphasize the importance of identification and early treatment of OSA which may, apart from its other benefits, prevent the occurrence or progression of optic nerve dysfunction.

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