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Visual electrophysiological tests in obstructive sleep apnoea

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阻塞性睡眠窒息症视觉电生理检查

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摘要

目的:比较阻塞性睡眠窒息症(OSA)患者和正常人的图形视网膜电图(PERG)和图形视觉诱发电位(PVEP)。

方法:前瞻性横断面研究。研究包含马来西亚医科大学的40例OSA患者和31例正常人。随机选取眼部未发生病变并确诊OSA的患者参与研究。通过记录呼吸暂停低通气指数(AHI)以用于对OSA的严重程度分层。由马来西亚医科大学眼科电生理实验室内训练有素的技术人员对每位患者进行电生理检查(PVEP和PERG)。所得结果记录为中位数。使用IBM Statistics Version 21.0完成数据分析。

结果:在OSA患者中,与正常人相比,我们观察到PERG的P50振幅($P<0.001$)和PVEP的P100振幅($P<0.001$)显著降低。OSA患者PVEP的P100($P=0.003$)和N75的峰值时间($P=0.004$)均显著升高。然而在OSA患者和正常人之间的PERG的峰值时间检测无显著差异。在不同疾病严重程度的OSA患者中PVEP或PERG也无显着差异。

结论:OSA患者PVEP幅度和峰值时间及PERG幅度存在显著异常。这可能反映了OSA中的亚临床视神经功能障碍。需要进一步的研究来确定OSA的严重程度与视神经功能障碍程度之间的关系。

关键词:阻塞性睡眠窒息症;呼吸暂停低通气指数;图形视觉诱发电位;图形视网膜电图

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Abstract

• AIM: To compare the pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) between obstructive sleep apnoea (OSA) patients and controls.

• METHODS: This was a prospective cross-sectional study involving 40 OSA patients and 31 control subjects in Hospital Universiti Sains Malaysia. Patients with a confirmed diagnosis of OSA who had no ocular pathology were randomly selected to participate in the study. The apnoea-hypopnoea index (AHI) was obtained from their records and used for stratification of OSA severity. Electrophysiological tests (PVEP and PERG) were performed on each patient by a trained technician in the electrophysiology laboratory of the Department of Ophthalmology, USM. The results obtained were recorded as median values. Data analysis was done using IBM Statistics Version 21.0.

• RESULTS: Among OSA patients, we observed a significant reduction of the PERG amplitude P50 ($P<0.001$) and the PVEP amplitude P100 ($P<0.001$) compared to the control group. OSA patients also had a significant increase in PVEP time to peak P100 ($P=0.003$) and time to peak N75 ($P=0.004$). However, no significant differences were detected in PERG time to peak between OSA patients and controls. There were likewise no significant differences in PVEP or PERG between OSA patients with different disease severity.

• CONCLUSION: OSA patients have significant abnormalities in PVEP amplitude and time to peak, as well as PERG amplitude. This may reflect subclinical optic nerve dysfunction in OSA. Further research is needed to determine the association between the severity of OSA and the degree of optic nerve dysfunction.

• KEYWORDS: obstructive sleep apnoea; apnoea-hypopnoea index; pattern visual evoked potential; pattern electroretinogram

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INTRODUCTION

Obstructive sleep apnoea (OSA) is a life-threatening, sleep-related breathing disorder in which the throat muscles relax during sleep, causing soft tissue in the throat to collapse and block the upper airway. This leads to partial (hypopnoea) and complete pauses (apnoea) in breathing that last at least 10 seconds during sleep. As a consequence, the blood oxygen saturation may fall, with up to 40% decrease in oxygen levels in severe cases[1]. Chronic oxygen deprivation results in activation of the sympathetic pathway, vascular endothelial dysfunction, increased oxidative stress, and inflammation, which may contribute to the initiation and progression of vascular diseases[2]. OSA has been shown to be associated with an increased risk of systemic diseases including heart failure[3], diabetes mellitus[4], sexual dysfunction[5], cognitive decline[6]. In the eye, OSA has also been associated with various conditions, particularly retinal and optic-nerve related disorders[7-9].

The visual evoked potential (VEP) is a measurement of the electrical signal recorded at the scalp over the occipital cortex in response to a stimulus, and reflects integrity of the afferent visual pathway. The electroretinogram (ERG) is a retinal biopotential evoked by a stimulus of constant mean luminance. In cases where the stimulus used is a checkerboard, the VEP is termed a pattern VEP (PVEP), and the ERG likewise (PERG). As the PERG is a local response from the area stimulated by the retinal image, it reflects the integrity of the optics, photo receptors, bipolar cells and retinal ganglion cells, and can be a subtle indicator of optic nerve dysfunction[10]. In OSA, optic neuropathy is postulated to occur due to various mechanisms, including increased intracranial pressure during apnoeic episodes, OSA-induced hypoxia and increased levels of cytokines like endothelin-1[11]. Thus, our study aims to evaluate optic nerve function by comparing PVEP&PERG changes between patients with OSA and the normal population.

SUBJECTS AND METHODS

This was a prospective cross-sectional study involving 40 obstructive sleep apnoea patients and 31 control subjects. It was conducted in the Eye Clinic of Hospital Universiti Sains Malaysia (USM) between Jul. 2015 and Sep. 2016. The conduct of the study followed the tenets of the declaration of Helsinki.

Patients with OSA confirmed by overnight in-laboratory polysomnography were randomly selected to participate in the study. The inclusion criteria was visual acuity better than 6/12 and normal anterior and posterior segment findings. Informed written consent was obtained from all patients. The apnoea-hypopnoea index (AHI), which represents the combined number of apnoeas and hypopnoeas that occur per hour of sleep, was obtained from patients' case notes and used for stratification of OSA severity (mild OSA having an AHI of 5-15, moderate 16-30, and severe >30).

Ocular examination using slit lamp biomicroscopy (Topcon Corp, Japan) was performed to rule out ocular pathology, which would have precluded participation in the study. Intraocular pressure was assessed with Goldmann applanation tonometry. Electrophysiological tests (PVEP and PERG) were performed on each patient by a trained technician in the electrophysiology laboratory of the Department of Ophthalmology, USM. The results obtained were recorded as median values. The technique of PVEP and PERG conformed to the International Society for Clinical Electrophysiology of Vision recommendations.

All data was analysed using IBM SPSS Statistics version 21.0. For data which followed a normal distribution, mean values were used for comparison, while in cases where the data was not normally distributed, median values were utilised. Statistical significance was taken as $P<0.05$.

RESULTS

A total of 71 age-matched subjects were included in this study. Of these, 40 had OSA (15 with mild, 9 with moderate and 16 with severe OSA) while the remainder were control subjects. Their other demographic and systemic features are shown in Table 1.

Among OSA patients, we observed a significant reduction of the PERG amplitude P50 ($P<0.001$, Table 2) and the PVEP amplitude P100 ($P<0.001$, Table 3) compared to the control group. OSA patients also had a significant increase in PVEP time to peak P100 ($P=0.003$) and time to peak N75 ($P=0.004$). However, no significant differences were detected in PERG time to peak between OSA patients and controls.

There were no significant differences in PVEP or PERG between OSA patients with different disease severity (Tables 4 and 5).

DISCUSSION

OSA is a sleep-related condition which has been associated with systemic and ocular pathology, especially involving the optic nerve[8,12-14]. Electrophysiological tests are useful to assess the functional integrity of the afferent visual pathway from the retina to the striate cortex[15-17]. To the best of our knowledge, this study is the first to demonstrate significant abnormalities in PVEP and PERG in OSA patients with no ocular comorbidities.

We found that OSA patients had significant reduction of their PVEP amplitude P100 and prolongation of time to peak P100 and time to peak N75. Our findings agree with those of previous studies conducted in other populations[18-20]. Abnormal VEP amplitude is suggestive of damage to optic nerve axons[21]. We postulate that these findings are due to

Table 1 Demographic and systemic features of OSA and control group

Electrophysiology	OSA patients (n=40)	Control group (n=31)	P
Mean age (SD)	45.4(12.2)	49.3(16.1)	0.250[a]
Mean BMI (kg/m^2) (SD)	33.77(6.62)	26.15(1.60)	0.001[a]
Gender, n(%)			
M	27(71.1)	11(28.9)	0.007[b]
Systemic disease (n,%)			
Hypertension	12 (66.7)	6(33.3)	0.306[b]
Diabetes	5 (83.3)	1(16.7)	0.222[c]
Hyperlipidaemia	12(66.7)	6(33.3)	0.306[b]
Smoker (n,%)	2(33.3)	4(66.7)	0.393[c]

OSA: Obstructive sleep apnoea; BMI: Body mass index; [a]Independent t-test; [b]Pearson Chi-square test; [c]Fisher's Exact Test.

Table 2 Comparison of mean PERG and PVEP between OSA and controls

Electrophysiology	OSA (n=40) Mean(SD)	Control (n=31) Mean(SD)	Mean diff(95% *CI*)	t-statistics (df)	[a]P
PERG amplitude N35 P50	2.9(1.02)	5.6(0.82)	−2.69(−3.14,−2.24)	−11.96(69)	0.000[a]
PERG amplitude N95 P50	4.7(1.86)	8.9(0.98)	−4.26(−4.94,−3.57)	−12.40(62)	0.000[a]
PERG time to peak N35	37.0(4.96)	37.1(3.05)	−0.98(−2.00,1.81)	−0.10(66)	0.919
PVEP time to peak P100	118.6(4.01)	115.6(4.32)	3.02(1.04,5.00)	3.04(69)	0.003[a]

OSA: Obstructive sleep apnoea; PERG: Pattern electroretinogram; PVEP: Pattern visual evoked potential. [a]Independent t-test.

Table 3 Comparison of median values of PERG and PVEP between OSA and controls

Electrophysiology	Median (IQR)		Z statistic	[a]P
	OSA (n=40)	Control (n=31)		
PERG time to peak P50	64.37(4.50)	64.00(3.00)	−0.691	0.490
PERG time to peak N95	104.50(9.69)	101.00(9.00)	−1.073	0.283
PVEP amplitude N75 P100	10.22(6.41)	18.80(6.28)	−6.168	<0.001
PVEP amplitude N135 P100	7.96(6.63)	17.90(4.60)	−5.965	<0.001
PVEP time to peak N75	84.12(10.25)	79.00(5.00)	−2.849	<0.001
PVEP time to peak N135	146.25(6.88)	147.00(9.00)	−1.367	0.172

OSA: Obstructive sleep apnoea; PERG: Pattern electroretinogram; PVEP: Pattern visual evoked potential; IQR: Interquartile range. [a]Mann-Whitney test.

hypoxic damage to the optic nerve secondary to repetitive apnoeic episodes in OSA patients, resulting in ischemia and damage to optic nerve axons.

Among OSA patients, we also observed a significant reduction of the PERG amplitude P50 compared with the control group. However, no significant differences in PERG time to peak were observed between controls and OSA patients. These findings differ from previous literature on this topic; Sergi *et al*[20] observed that both amplitude and time to peak of PERG were affected in OSA, while Liguori *et al*[19] found no significant changes in either of these PERG parameters in OSA. Moghimi *et al*[22] suggested that an abnormality in VEP despite a normal ERG may be attributed to an early pathological process that primarily affects the optic nerve, sparing the retinal function. It is interesting to note that the PERG has been found to be relatively normal in some conditions (*e. g.* demyelinating disease), while it may be markedly abnormal in others (*e. g.* ischaemic conditions). However, studies show that ischaemia tends to affect PERG amplitude more than time to peak, and vice versa for demyelination[10,15]. In our case, we believe that only the amplitude was abnormal because OSA is predominantly a condition of ischaemia.

Various authors have hypothesized that the underlying pathophysiology of OSA involves chronic oxygen deprivation, resulting in generalized sympathetic activation, vasculopathy, oxidative stress and metabolic dysregulation, thus leading to the increased risk of coronary artery disease, heart failure and stroke observed in these conditions[23-25]. Ocular conditions which have been attributed to this hypoxic theory in OSA include non-arteritic ischaemic optic neuropathy[26-28] and glaucoma[29-31].

A recent study among patients with nonarteritic ischemic optic neuropathy (NAION) found that the vast majority of them had OSA[7-8]. The postulated mechanisms include direct exposure of the optic nerve to OSA-induced hypoxia, hypoxia-induced cerebral vasodilatation causing impaired optic nerveautoregulation due to decreased cerebral perfusion pressure, and impaired autoregulation[11]. Hypoxia has been associated with imbalances in the vasoconstrictorendothelin-1 and vasodilator nitric oxide; the resulting vascular dysregulation disrupts the normal blood flow in the retina and

Table 4 Comparison of mean PERG & PVEP between OSA patients with different disease severity

Electrophysiology	OSA Severity by AHI	Mean difference (95% *CI*)	*F* statistic (df)	[a]*P*
PERG				
Time to peak N35 (ms)	Mild-moderate	-2.12 (-7.43, 3.19)	0.525 (2)	0.972
	Mild-severe	-0.43 (-4.96, 4.10)		1.000
	Moderate-severe	-1.69 (-3.56, 6.94)		1.000
PERG amplitude N35 P50 (μV)	Mild-moderate	0.16 (-0.92, 1.24)	0.859 (2)	1.000
	Mild-severe	0.48 (-0.45, 1.40)		0.611
	Moderate-severe	0.31 (-0.76, 1.38)		1.000
PERG amplitude N95 P50 (μV)	Mild-moderate	0.91 (-0.99, 2.82)	2.249 (2)	0.718
	Mild-severe	1.36 (-0.26, 2.99)		0.128
	Moderate-severe	0.45 (-1.43, 2.34)		1.000
PVEP				
Time to peak P100 (ms)	Mild-moderate	-1.88 (-6.12, 2.36)	1.019 (2)	0.822
	Mild-severe	-1.87 (-5.48, 1.75)		0.611
	Moderate-severe	0.01 (-4.18, 4.20)		1.000
PVEP time to peak N135 (ms)	Mild-moderate	-1.45 (-7.09, 4.19)	0.333 (2)	1.000
	Mild-severe	0.32 (-4.49, 5.12)		1.000
	Moderate-severe	1.77 (-3.80, 7.33)		1.000
PVEP amplitude N75 P100 (μV)	Mild-moderate	-2.10 (-8.33, 4.14)	0.385 (2)	1.000
	Mild-severe	-0.33 (-5.65, 4.98)		1.000
	Moderate-severe	1.76 (-4.40, 7.93)		1.000
PVEP amplitude N135 P100 (μV)	Mild-moderate	-1.16 (-7.48, 5.15)	0.113 (2)	1.000
	Mild-severe	-0.65 (-6.03, 4.73)		1.000
	Moderate-severe	0.51 (-5.72, 6.75)		1.000

OSA: Obstructive sleep apnoea; AHI: Apnoea-hypopnoea index; PERG: Pattern electroretinogram; PVEP: Pattern visual evoked potential. [a]One-Way ANOVA test.

Table 5 Comparison of median PERG & PVEP between OSA patients with different disease severity

Electrophysiology	OSA Severity by AHI	Median (IQR)	X^2(df)	[a]*P*
PERG time to peak P50 (ms)	Mild	64.75 (3.75)	0.42(2)	0.979
	Moderate	64.50 (4.00)		
	Severe	62.63 (6.63)		
PERG time to peak N95 (ms)	Mild	104.50 (4.00)	0.72(2)	0.697
	Moderate	104.25 (19.75)		
	Severe	104.88 (15.13)		
PERG time to peak N75 (ms)	Mild	87.00 (9.00)	6.620(2)	0.037
	Moderate	87.25 (8.38)		
	Severe	79.75 (15.81)		

OSA: Obstructive sleep apnoea; AHI: Apnoea-hypopnoea index; PERG: Pattern electroretinogram; PVEP: Pattern visual evoked potential; IQR: Interquartile range. [a]Kruskal-Wallis Test.

optic nerve head, thus potentially increasing the risk of NAION[32-33]. Aptel *et al*[8] also observed that patients with OSAS also had a higher risk of second eye involvement in NAION. As a result, these authors have suggested that polysomnography should be considered in patients with NAION, and that therapeutic measures for OSA be undertaken if polysomnography is diagnostic of OSA[8].

The prevalence of glaucoma in OSA varies between studies, from 5.7% to 27%[34]. OSA may cause glaucomatous optic neuropathy by creating transient hypoxemia and increasing vascular resistance, thus resulting in compromised optic nerve head perfusion and oxygenation. Kergoat *et al*[35] observed that retinal ganglion cells are sensitive to even transient episodes of hypoxia. Hypoxiais associated with an increase in oxidative stress, subsequently lead to retinal ganglion cell dysfunction[36]. Sergi *et al*[20] reported that the prevalence of NTG was higher in OSA patients compared with controls. Tsang *et al*[37] reported that moderate to severe OSA was associated with a higher incidence of visual field defects and glaucomatous changes in the optic nerve. Similarly, Moghimi *et al*[22] reported that OSA patients had a higher prevalence of glaucoma. Likewise, the prevalence of ocular hypertension has been observed to be greater in OSA patients than in controls[22].

The association between the AHI, which is a marker of the severity of hypoxic damage, and the degree of ocular damage objectively assessed by VEP and ERG, has been investigated in various studies. Sergi *et al*[20] observed that AHI was significantly greater in OSA patients with abnormal VEP and PERG, compared to controls. Likewise, Gutiérrez-Díaz *et al*[18] found that in OSA patients with glaucoma, multifocal VEP amplitude and latency were significantly correlated with the AHI ($P < 0.05$). However, Liguori *et al*[19] had conflicting results, as they failed to discover any correlation between polysomnographic parameters and VEP or ERG components in OSA patients. They explained their lack of significance by the fact that their study only included a subset of OSA patients, *i.e.* those with severe disease, who required continuous positive airway pressure therapy[19]. Although we stratified our patients' disease severity based on the AHI, our study did not demonstrate any significant association between either PVEP or PERG with the severity of OSA.

Our study builds on the pre-existing literature by highlighting PVEP and PERG abnormalities in asymptomatic patients with OSA. This adds strength to the hypoxic theory in OSA. Early identification and management of OSA may thus prevent ongoing optic nerve damage. The fact that these abnormalities were observed in patients with no ocular complaints suggests that patients with OSA may potentially have undiagnosed optic nerve dysfunction; if progressive, this subclinical damage may eventually manifest as various ocular conditions. One of the strengths of our study was that there were no significant differences between the groups in terms of their age and comorbidities. However, we concede that a limitation of our study was the unequal numbers of subjects in each disease severity group. Secondly, we were not able to perform the electrophysiological tests at the time of OSA diagnosis, which may explain the lack of significant association with disease severity stratification, as the latter was based on an AHI obtained at the time of diagnosis.

To conclude, OSA patients have significant abnormalities in PVEP amplitude and time to peak, as well as PERG amplitude. This may reflect subclinical optic nerve dysfunction in OSA. Further research is needed to determine the association between the severity of OSA and the degree of optic nerve dysfunction.

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