

Optic nerve functions and visual evoked potential after acute optic neuritis

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急性视神经炎后视神经功能与视觉诱发电位的研究

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摘要

目的:比较视神经炎患者和正常人的视神经功能与视觉诱发电位。

方法:本研究为2011年9月至2013年2月在马来西亚大学眼科医院进行的横断面研究。研究包含在检查前3mo至2y间发生特发性神经炎一次的视神经炎患者20例和10例正常人。眼科检查包括视力、色觉、视觉灵敏度、视野和视觉诱发电位。独立t检验用于比较视神经炎组与对照组视神经功能和VEP参数的差异。在参数非正态分布时, Mann-Whitney 试验用于比较两组间的中位数。

结果:视神经炎组的平均年龄为30.8岁。在视神经炎发作至评估期间的平均持续时间为6.6个月。视神经炎组视力较差, 平均LogMAR值(0.52)明显高于对照组($P=0.001$)。色觉下降, 视神经炎组的平均值为63% ($P=0.001$)。视神经炎患者的对比敏感度在四个空间频率上均有所下降[3CPD($P=0.029$), 6CPD($P=0.026$), 12CPD($P=0.002$), 18CPD($P=0.006$)]。视神经炎组的视野下降有统计学意义($P<0.001$)。与对照组相比, 视神经炎组的VEP P100潜伏期有轻微延长。但使用棋盘格模式1或

2时, VEP潜伏期的差异不显著。视神经炎患者的VEP振幅较高, 但两组差异无统计学意义。

结论:视神经炎急性发作, 平均6mo后视神经功能(即视力、色觉、对比敏感度和视野)显著下降。视神经炎组和对照组的VEP振幅和潜伏期无显著差异。VEP可能不是理想的诊断视神经炎既往发作史的试验, 尽管VEP参数在浮动后趋于正常。

关键词:视神经炎; 视觉诱发电位; 视神经功能

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Abstract

• **AIM:** To compare the optic nerve function and visual evoked potential (VEP) between optic neuritis patients and normal individuals.

• **METHODS:** A cross-sectional study was conducted at the Eye Clinic of Hospital Universiti Sains Malaysia (HUSM) between September 2011 and February 2013. We recruited twenty optic neuritis patients with a single episode of idiopathic optic neuritis occurring between 3mo and 2y prior to examination, and twenty control subjects. Ocular examination included visual acuity, colour vision, contrast sensitivity, visual field and pattern VEP. Independent *t*-test was conducted to compare the differences in the means of optic nerve function and VEP parameters between the optic neuritis group and control group. In parameters that were not normally distributed, Mann-Whitney test was used to compare the medians between the two groups.

• **RESULTS:** In the optic neuritis group, the mean age was 30.8y. The mean duration between the episode of optic neuritis and the time of evaluation was 6.6mo. The visual acuity was poorer in the group with optic neuritis, with the mean LogMAR score (0.52) being significantly higher in this group than in controls ($P=0.001$). Colour vision was likewise decreased, with a mean score of 63.0% in the optic neuritis group ($P=0.001$). Contrast sensitivity was reduced in all four spatial frequencies; 3CPD ($P=0.029$), 6CPD ($P=0.026$), 12CPD ($P=0.002$) and 18CPD ($P=0.006$) in patients with optic neuritis. There was also a statistically significant loss of visual field in this group ($P\leq 0.001$). Although subjects with optic neuritis had a slightly prolonged VEP P100 latency compared to normal subjects, this difference in VEP

latency was not significant using checkerboard pattern 1 or 2. Higher VEP amplitude was observed in optic neuritis subjects, but the difference between groups was not statistically significant.

• **CONCLUSION:** There were significant reductions in optic nerve functions (*i. e.* visual acuity, colour vision, contrast sensitivity and visual field) at a mean of 6mo after an acute attack of optic neuritis. However, no significant differences in VEP amplitude and latency were noted between patients with optic neuritis and the control group. VEP may not be the ideal test to diagnose a previous attack of optic neuritis, as VEP parameters tend to normalize after a variable interval.

• **KEYWORDS:** optic neuritis; visual evoked potential; optic nerve function

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INTRODUCTION

Optic neuritis (ON) is an inflammation of the optic nerve^[1]. In the absence of multiple sclerosis or other systemic disease, it is considered idiopathic^[2-3]. It usually affects patients 15–45y of age, with women predominantly involved^[1]. The most common pathologic basis for optic neuritis is inflammatory demyelination of the optic nerve, which has been postulated to be related to pro-inflammatory cytokines *e. g.* interleukin – 8, which may trigger myelin destruction, neural cell death and axonal degeneration^[4].

After an attack of ON, visual recovery may recover spontaneously, but there are often residual abnormalities, such as decreased contrast sensitivity, color vision, and visual field^[5-7]. Methods to quantify the impairment in optic nerve function include visual field testing and electrophysiological tests like visual evoked potentials (VEP)^[8]. VEPs measure the cortical activity in response to a flash or pattern stimulus. They are abnormal in the presence of any lesion along the anterior visual pathway. The purpose of this study was to compare the optic nerve functions and VEP between optic neuritis patients and normal individuals.

SUBJECTS AND METHODS

A cross-sectional study was conducted at Hospital Universiti Sains Malaysia (HUSM) Eye Clinic from September 2011 to February 2013. The study was approved by the Human Research Ethics Committee (HREC) USM and the conduct of the study followed the tenets of the Declaration of Helsinki. Twenty patients with a history of ON who fulfilled the inclusion and exclusion criteria were recruited, as well as twenty normal individuals to form the control group. The inclusion criteria was patients aged 12 to 55y old with a single episode of idiopathic ON occurring between 3mo and 2y prior to examination. Patients with glaucoma, optic neuropathies, dense ocular media, posterior segment pathologies, known

abnormalities of colour vision, demyelinating nerve disease and poor vision prior to the attack of ON were excluded from the study.

Ocular examination including visual acuity, colour vision, contrast sensitivity, visual field and pattern VEP was performed. Visual acuity was assessed using LogMAR visual acuity charts while colour vision was tested with the Ishihara colour vision plates. Contrast sensitivity was tested using vector vision CSV 1000E chart and visual field was performed with automated Humphrey's visual field analyzer using SITA Fast 30–2 analysis.

We performed pattern visual evoked potentials (PVEP) based on the standard ISCEV PVEP protocol 2009. The type of VEP device was Granzfield PVEP Roland–Consult, RETI–port 32, Germany. A standard silver–silver chloride skin electrode was used. The skin was cleaned and an adequate amount of gel (Nu – Prep) was used to ensure good, stable electrical connection. The placement of electrode was based on the “10–20 International System”. The electrode impedance was kept below 5 k Ω , measured between 10 and 100 Hz and was not more than 20% between electrode sites to reduce electrical interference. Patient was asked to sit at 1.5 m from the video monitor. PVEP was tested monocularly, in the affected eye, with appropriate refractive correction. The test was elicited by checkerboard stimuli with large 1° (*i. e.* 60min of arc) and small 0.25° (15min of arc) checks.

Independent *t*–test was conducted to compare the differences in the means of optic nerve function and VEP parameters between the optic neuritis group and control group. In parameters that were not normally distributed, Mann–Whitney test was used to compare the medians between the two groups. Independent *t*–test with welch correction for unequal variance was performed when parameters did not fulfill normality and equal variance. Simple linear regression was performed to screen potential variables that would be included and used in the multivariable model–building procedures at the multiple linear regression stage.

RESULTS

Twenty patients post–acute idiopathic ON and 20 subjects forming a control group were studied. In the ON group, the mean age was 30.8y (12–53y of age). Sixty five percent of patients were female. There was no significant difference of age or gender between the groups.

The mean duration between the episode of ON and the time of evaluation was 6.6mo, while the median was 9.5mo. The mean logMAR visual acuity during an acute attack of ON was 0.78. There was a variable improvement in the visual acuity during the months following the attack, but the mean logMAR score was still significantly higher in the group with ON than the control group ($P=0.001$) (Table 1). Colour vision was likewise significantly decreased, with a mean score of 63.3% in the ON group ($P = 0.001$). Contrast sensitivity was reduced in all four spatial frequencies; 3CPD ($P=0.029$), 6CPD ($P=0.026$), 12CPD ($P=0.002$) and 18CPD ($P=$

Table 1 Comparison of optic nerve function between optic neuritis and controls

Optic nerve function	Mean (SD)		Mean difference (95% CI)	^a <i>P</i>
	Control (<i>n</i> =20)	ON (<i>n</i> =20)		
VA (LogMAR score)	0.04 (0.08)	0.52 (0.55)	0.48 (0.22,0.73)	0.001
Colour vision (%)	100 (0)	63.3 (43.3)	-36.7 (-56.3,-17.0)	0.001 ^b
Contrast sensitivity (CS)				
3CPD	1.71 (0.12)	1.45 (0.48)	-0.26 (-0.49,-0.03)	0.029
6CPD	2.03 (0.56)	1.72 (0.12)	-0.31 (-0.57,-0.04)	0.026
12CPD	1.71 (0.12)	1.45 (0.48)	-0.48 (-0.75,-0.21)	0.002
18CPD	2.03 (0.56)	1.72 (0.12)	-0.43 (-0.73,-0.14)	0.006

^aIndependent *t*-test with welch's correction for degree of freedom was applied; ^bIndependent *t*-test was applied; VA: Visual acuity; ON: Optic neuritis; SD: Standard deviation.

Table 2 Comparison of VEP latency and amplitude between optic neuritis and controls

VEP parameters	Mean (SD)		Mean difference ^a (95% CI)	<i>P</i>
	Control (<i>n</i> =20)	ON (<i>n</i> =20)		
VEP-P100C1	112.85 (3.68)	114.65 (11.39)	1.8 (-3.62,7.22)	0.508
VEP-P100C2	118.70 (4.22)	117.95 (12.45)	-0.75 (-0.67,5.20)	0.808
VEP-P100AC1	10.1 (6.5)	12.5 (6.5)	2.39 (-1.8,6.6)	0.254
VEP-P100AC2	9.7 (7.5)	14.1 (8.7)	4.42 (-0.77,9.61)	0.092

^aIndependent *t*-test was applied; VEP: Visual evoked potential; ON: Optic neuritis; SD: Standard deviation.

0.006) in patients with ON. There was also a statistically significant loss of visual field in this group (*P*<0.001).

Although subjects with ON had a slightly prolonged VEP P100 latency compared to normal subjects, this difference in VEP latency was not found to be significant using checkerboard pattern 1 or 2. Higher VEP amplitude was observed in ON subjects, but the difference between groups was not statistically significant (Table 2).

DISCUSSION

VEP is a non-invasive test to detect functional loss in the visual pathway from retina to the visual cortex^[9-10]. It is based on electrical potential differences recorded from the scalp in response to light or pattern stimulation to the eye^[11]. VEP waveforms are affected by physiologic (*e. g.* age, gender, pupil size, refractive error), non-physiologic (*e. g.* pattern size, pattern contrast, mean luminance) and pharmacologic factors (*e. g.* alcohol intake)^[11-18]. Pattern VEP was used to measure VEP parameters due to its relatively low variability of waveform and peak latency, not only intra-subject and inter-subject, but also in repeated measurements over time^[19-21]. The pattern reversal VEP has a prominent positive component at 100ms (P100), preceded and followed by negative components, N75 and N135^[22]. Patients with ON traditionally have prolonged P100 latency and reduced P100 amplitude^[23-25]. Prolonged latency on VEP is used as a proxy measure of demyelination, while the reduced amplitude has been attributed to axonal damage^[26].

Clinically, ON is recognized by a triad of unilateral loss of vision, impaired optic nerve function tests (especially colour vision), and periocular pain, all of which usually improve spontaneously in a few weeks, even in the absence of treatment^[27-29]. In our study, all optic nerve functions (visual

acuity, colour vision, contrast sensitivity and visual field) were poorer in the group with ON than the control group. Our study parallels the results of Brusa *et al*^[30], in which among thirty one patients who had an episode of ON, there was no significant improvement in optic nerve function, despite an improvement in VEP latency. The findings of Celesia *et al*^[31] differ, as among twenty patients with acute ON followed up for a year, visual function recovered completely in 65% of cases. The likelihood is that the recovery process, which may involve remyelination or ion channel reorganization, masks the concurrent insidious demyelination and/or axonal degeneration^[24,30].

We observed an insignificant trend towards prolongation of VEP P100 latency in our ON patients, compared to the control subjects. Likewise, there was no significant difference in the VEP P100 between ON patients and controls. In the acute stage of ON, VEP has been used to determine the degree of conduction block of the optic nerve fibers^[32-33]. The lack of statistical significance which we observed in the differences of VEP P100 amplitude and latency between the group with ON and the control is attributed to resolution of that conduction block^[3]. The relatively normal VEP P100 latency in our patients with ON may reflect the ongoing process of remyelination, which occurs for a variable time period after the acute attack^[23,30,34].

We found it interesting that despite similar VEP amplitude and latency among patients with ON and the control group, the optic nerve functions were still poorer in the group with ON. Trip *et al*^[35], who evaluated 25 patients with a history of ON, suggested that axonal loss contributes to optic nerve atrophy even after a single, unilateral attack. They found significant optic nerve atrophy, reduced retinal nerve fiber

layer thickness and macula volume loss in the affected eyes of these patients. They also observed that these aforementioned parameters were correlated with each other, as well as with visual acuity. This suggests that the reduced visual acuity, colour vision and contrast sensitivity observed in our ON group is likely due to a combination of optic atrophy, retinal nerve fiber layer thinning and macula volume loss. Keeping this in mind, optical coherence tomography may be a complementary tool in the evaluation of patients with ON, as the average RNFL thickness in these patients has been found to correlate well with visual function scores even in patients with an average Snellen visual acuity of 6/6 (logMAR 0)^[36].

A potential limitation of our study is related to the use of computer monitor stimulators. The sensitivity of VEP varies depending on the method used to display the checkerboard pattern; the original figures which attributed a sensitivity of approximately 90% to VEP in the diagnosis of ON were based on VEPs performed using fast optomechanical stimulators^[37]. Currently, the stimulators used are computer monitors, and although the difference in the speed of pattern reversal may appear negligible, its raster scan takes up to 18 ms to draw the checkerboard, resulting in a pattern reversal which is distributed in time. This produces a P100 with a variable latency.

The main limitation of our study was its cross-sectional nature, because our patients were sampled at varying time periods post their acute attack of ON. The use of VEP in ON, however, is restricted by the fact that both the amplitude and latency of VEP vary depending on the time after onset^[38]. Naturally, those sampled at 3mo post attack would have more prolonged P100 latency and reduced P100 amplitude than those sampled later, when remyelination is well in progress. A prospective approach would be ideal, with the initial VEP performed during the attack, and then again at 3, 6, 12 and 24mo post attack. We also omitted to measure the visual acuity at the point of performing VEP, which may be useful to demonstrate the correlation of VEP and clinical function. We are aware that performing VEP in both the normal and affected eyes will enable a greater comparison of the degree of impairment; these factors will be addressed in future studies. In conclusion, there were significant reductions in optic nerve functions (*i. e.* visual acuity, colour vision, contrast sensitivity and visual field) at a mean of 6mo after an acute attack of ON. However, no significant differences in VEP amplitude and latency were noted between patients with ON and the control group. VEP may not be the ideal test to diagnose a previous attack of ON, as VEP parameters tend to normalize after a variable interval. Clinical examination of optic nerve function tests is still invaluable in the diagnosis of a previous, subclinical attack of ON.

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