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Clinical study

Pattern electroretinography and visual evoked potentials in optic nerve diseases

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Abstract

Background: To evaluate transient pattern electroretinography (PERG) and pattern visual evoked potential (VEP) for the diagnosis, differential diagnosis and follow-up of optic nerve diseases. *Methods:* Twenty-nine consecutive patients (14 female, 15 male) with the diagnosis of ischaemic optic neuropathy ($n = 14$) and optic neuritis ($n = 15$) were included in this study. Mean age of the patients with ischaemic optic neuropathy was 63.3 ± 3.3 (60–78) years and the mean age of the patients with optic neuritis was 28.3 ± 8.4 (19–43) years. In each patient ophthalmological examination and systemic evaluation were done and VEP and PERG were recorded. As a control group, VEP recordings of 35 healthy subjects were included. *Results:* In the ischaemic optic neuropathy group (group 1), mean VEP amplitude (±SD) (1.96 ± 0.95 μV) was found to be decreased significantly in the affected eyes in comparison to the control group and the unaffected eyes. The delay in latency (116.3 ± 20.14 msec in the affected eyes compared with 101.31 ± 6.19 msec in unaffected eyes) was statistically significant when compared with the healthy subjects. In the optic neuritis group (group 2), VEP amplitude was decreased (4.13 ± 4.04 μV vs 6.97 ± 3.35 μV and 6.97 ± 4.43 μV) and latency was increased (122.59 ± 20.09 msec vs 101.31 ± 6.19 msec and 108.76 ± 13.57 msec) in affected eyes significantly in comparison to the unaffected eyes and control group, respectively. Even though there were no significant differences for P50 latency and N95/P50 ratios between affected and unaffected eyes in both groups, N95 amplitude decreased significantly in the affected eyes of the ischaemic optic neuropathy patients and N95 latency was found to be decreased in optic neuritis patients. There was no correlation between VEP and PERG findings in both groups. *Conclusion:* VEP amplitude decreased significantly in ischaemic optic neuropathies while latency delay was more significant in patients with optic neuritis. PERG findings showed decreased N95 amplitude in ischemic optic neuropathy without associated latency changes.
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Keywords: Optic neuritis; Ischaemic Optic neuropathy; Visual evoked potential; Pattern Electroretinography

1. Introduction

The pattern visual evoked potential (VEP) is widely recognised as a sensitive measure of optic nerve pathologies, including demyelination and is a massed cortical response elicited by a change in retinal stimulation primarily driven by the fovea. It has been shown to be more sensitive for diagnosis of resolved optic neuritis than MRI, contrast sensitivity, Goldmann perimetry or visual acuity.[1–3] Previous studies in humans and animals show that the electroretinogram in response to pattern reversal stimuli is related to retinal ganglion cell layer activity and originates from more central cell types (ganglion cells) in comparison with the flash electroretinogram.[4,5] The pattern electroretinogram (PERG) can be considered as the precursor of the cortical VEP and gives valuable information regarding the pathways mediating central vision distal to the optic nerve. Optic nerve lesions can be expected eventually to result in retrograde degeneration to the retinal ganglion cells and PERG abnormalities could occur in relation to optic nerve dysfunction.[6] The most common

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optic nerve pathologies are ischaemic optic neuropathy and optic neuritis. They have similar signs and symptoms, so differential diagnosis is important to determine treatment, associated diseases and prognosis.[7,8]

The purpose of this study was to investigate the role of PERG in the differential diagnosis of optic nerve pathologies, particularly ischaemic optic neuropathy and optic neuritis and to compare it with VEP.

2. Materials and methods

The inclusion criteria were; patients with unilateral optic nerve pathologies (visual loss, decreased colour vision, afferent pupillary reaction in the affected eye). Exclusion criteria included history of other ophthalmologic disease or surgery or another neurological disease (other than multiple sclerosis (MS)). Informed consent was obtained from all subjects after explanation of the procedures.

The patients were subdivided into two groups: group 1 consisted of 14 patients with ischaemic optic neuropathy and group 2 consisted of 15 patients with optic neuritis. For comparison, the control group was formed of 35 subjects with a normal ophthalmological examination.

For electrophysiological recordings the same instrument was used under standardised conditions. For VEP; stimuli were checkerboard patterns with a check size of 73.2′ and temporal frequency of 1.02 rps. Mean luminance of the patterns was 99 cd/m^2 and contrast was 99%. Amplifier filter bandpass was set at 30 Hz to 1 Hz. Sweep duration was 300 msec. The VEP was recorded from three channels. The active electrode was applied to the occipital area, the reference electrode to the mediofrontal area and earlobe electrode was used as grounding. A total of 128 responses were recorded. All recordings were taken monocularly with appropriate eyeglasses.

Transient PERG was recorded using silver loop electrodes (H–K loops). The loop electrodes were placed in the lower cul-de-sac without instillation of local anaesthetics. Stimuli were checkerboard patterns with a check size of 73.2′ and temporal frequency of 1.02 rps. The wire portion of the electrode was taped to the subject's cheek. The reference electrode was placed over the ipsilateral outer canthus ($\approx$ 1 cm away from the lateral canthus) and the ground electrode was attached to the earlobe. Conductive paste was used to place the electrodes. Recording was repeated twice (300 responses were recorded) in order to obtain a reliable average and sweep duration was 104 msec. Pupils were not dilated and the subjects wore their full spectacle correction without interfering with the electrodes. The high and low bandpass input filters were set at 1 and 30 Hz respectively, and the signal was averaged using a computer.

For analysis, P100 amplitude and latency in VEP and P50 and N95 amplitudes and latencies in PERG were measured and N95/P50 ratios were calculated. All data from VEP recordings were compared with those from a control group of normal subjects.

Differences between groups for discrete variables were evaluated using the chi-squared and Fisher's exact test, where applicable. When there was a failure of the parametric test assumptions, non-parametric tests were used. Continuous variables were evaluated using the Student's t-test and Mann-Whitney U-test, where applicable. Differences between three groups for VEP latency and amplitude variables were evaluated by Kruskal-Wallis analysis of variance. When the Kruskal-Wallis tests revealed a significant difference between groups, a multiple comparison test was used to differentiate the groups.[9]

3. Results

There were 14 patients in the ischaemic optic neuropathy group (group 1), 15 patients in the optic neuritis group (group 2) and 35 healthy volunteers as a control group. In group 1, there were four women (28.6%) and 10 men (71.4%). In group 2, there were 10 women (66.7%) and five men (33.3%). The higher female ratio in the second group was statistically significant (chi-square $p < 0.05$).

The difference between the mean ages ($\pm$SD) [in group 1; 63.3 ± 3.3 years (range: 60–78 years), and in group 2: 28.3 ± 8.4 years (range: 19–43 years)] was statistically significant (Student's t-test, $p < 0.001$).

In the ischaemic optic neuropathy group (group 1), mean VEP amplitude ($\pm$SD) was 1.96 ± 0.95 μV in the affected eyes and 5.16 ± 3.36 μV in the unaffected eyes and the difference was statistically significant (Wilcoxon signed rank test, $p < 0.01$). When we compared the VEP latencies, mean latency ($\pm$SD) was 116.37 ± 20.14 msec in the affected eyes and 106.34 ± 16.84 msec in the unaffected eyes (Table 1). Even though VEP latency was found to be prolonged in the affected eyes, the difference between the latencies was not statistically significant (paired t-test, $p > 0.05$). When we compared the affected and unaffected eyes for PERG evaluation, the mean P50 amplitude was 1.54 ± 1.14 μV in the affected eyes and 1.85 ± 0.65 μV in the unaffected eyes. The mean N95 amplitude was 2.35 ± 1.08 μV in the affected eyes and 3.09 ± 1.31 μV in

Table 1
Mean amplitude and latency values for visual evoked potential (VEP) recordings in ischemic optic neuropathy (ION), optic neuritis (ON) and normal controls

	Affected eyes		Unaffected eyes	
	Latency (msec)	Amplitude (μv)	Latency (msec)	Amplitude (μV)
ION ($n = 14$)	116.37 ± 20.14	1.96 ± 0.95	106.34 ± 16.84	5.16 ± 3.36
ON ($n = 15$)	122.59 ± 20.09	4.13 ± 4.04	108.76 ± 13.57	6.97 ± 4.43
Controls ($n = 35$)			101.31 ± 6.19	6.37 ± 3.35

Table 2
Mean amplitude and latency values for pattern electroretinogram (PERG) recordings in ischemic optic neuropathy (ION), optic neuritis (ON) in affected and unaffected eyes

	Affected eyes		Unaffected eyes	
	Latency (msec)	Amplitude (μv)	Latency (msec)	Amplitude (μV)
ION P50	51.79 ± 8.64	1.53 ± 1.14	54.01 ± 2.97	1.85 ± 0.65
ON P50	49.69 ± 8.59	2.30 ± 1.63	50.69 ± 7.65	3.10 ± 1.65
ION N95	89.42 ± 6.85	2.35 ± 1.08	90.11 ± 6.75	3.09 ± 1.31
ON N95	85.09 ± 15.46	3.99 ± 2.56	86.27 ± 15.66	4.70 ± 2.01
ION N95/P50	2.08 ± 1.51		1.75 ± 0.82	
ON N95/P50	2.22 ± 1.70		2.55 ± 2.95	

the unaffected eyes (Table 2). Even though there was no statistically significant difference between affected and unaffected eyes for P50 amplitude values (paired t-test, $p > 0.05$), the difference for N95 was statistically significant (paired t-test, $p < 0.05$). When we evaluated the latency values of P50 and N95, there were no significant difference between the affected and unaffected eyes (Wilcoxon signed ranks test $p > 0.05$) (Table 2). Also there was no statistically significant difference between the ratios of N95/P50 in the affected and unaffected eyes (Wilcoxon signed ranks test $p > 0.05$).

In the optic neuritis group (group 2), mean VEP amplitude in the affected eyes was 4.13 ± 4.04 μV and 6.97 ± 4.43 μv in the unaffected eyes, with a statistically significant difference (paired t-test, $p > 0.01$) (Table 1). Mean VEP latency was 122.59 ± 20.09 msec in the affected eyes and 108.76 ± 13.57 msec in the unaffected eyes and this difference was also statistically significant (paired t-test, $p > 0.01$). In this group, mean amplitude for the P50 component of PERG was found to be 3.1 ± 1.65 μv in the unaffected eyes and 2.30 ± 1.63 μv in the affected eyes. Mean N95 amplitude was found to be 3.99 ± 2.56 μv in the affected eyes and 4.70 ± 2.01 μv in the unaffected eyes (Table 2). Even though amplitudes were lower in the affected eyes in both groups, the differences between the affected and unaffected eyes for both P50 and N95 amplitudes were not statistically significant (paired t-test, $p > 0.05$ and $p > 0.05$ respectively). When we compared the latency values for P50 and N95, mean P50 latency for the affected eyes was 49.69 ± 8.59 msec and 50.69 ± 7.65 msec for the unaffected eyes and there was no statistically significant difference (Wilcoxon signed ranks test, $p < 0.05$). In the affected eyes mean N95 latency was 85.09 ± 15.46 msec and 86.27 ± 15.66 msec in the unaffected eyes. Even though the mean difference was only 1.18 msec, this difference was statistically significant (Wilcoxon signed ranks test, $p < 0.05$). There was no statistically significant difference between the affected and unaffected eyes for N95/P50 ratio (Wilcoxon signed ranks test, $p < 0.05$).

When we compared the groups by ANOVA test, VEP latency in the first and second groups were significantly delayed in comparison to the control group ($p < 0.05$ and $p < 0.001$ respectively). However, there was no significant difference for VEP delay between the first and second groups ($p > 0.05$). The VEP amplitude in the first group was statistically significantly lower than the control group and the second group ($p < 0.001$ and $p < 0.05$ respectively). Decreased amplitude in the second group was also statistically significant in comparison to the control group ($p < 0.05$).

In order to evaluate the performance of VEP recordings for diagnosis of optic nerve diseases and to determine any cut-off value for the diagnosis or risk of optic neuritis, we investigated the receiver operating characteristic (ROC). It was found that VEP latency has a cut-off value in terms of differential diagnosis for optic nerve diseases. When 107 msec was selected as the cut-off point, sensitivity and specificity were found to be 80% and 94.3% respectively for optic neuritis. However, there was no cut-off value for latency for the ischaemic optic neuropathy group with adequate sensitivity and specificity. On the other hand, when we compared the ischaemic optic neuropathy group with the control subjects, there was a cut-off value for VEP amplitude (3.0 μV) with a specificity of 91.4% and sensitivity of 92.9%. There was no correlation between VEP and PERG values.

4. Discussion

Visual evoked potential (VEP) is widely recognised as a sensitive measure of optic nerve demyelination and P100 latency has been reported to be significantly prolonged in approximately 90% of patients with a clinical history of optic neuritis, despite recovery of visual function to near normal levels in most patients.[1,3] When we compared the latency values and amplitudes of the affected and the unaffected eyes in the ischaemic optic neuropathy group, the difference between the latency values was insignificant; however the decreased amplitude in the affected eye was significant. Even though amplitude comparison between subjects is accepted as difficult, with ROC analysis VEP amplitude lower than 3.0 μV was shown to be a cut-off value for optic nerve ischaemia with a specificity of 91.4% and sensitivity of 92.9%. For the optic neuritis group, the latency values were significantly longer and the amplitudes were significantly lower in the affected eyes. According to our results; latency delay greater than 107 msec can be accepted as a sign of defect in optic nerve transmission with a sensitivity of 80% and specificity of 94.3%. This cut-off

value revealed the involvement of unaffected eyes in the optic neuritis group (mean VEP latency: 108.76 ± 13.57 msec). Even though signs and symptoms were detected only in one eye, the delayed VEP latency in the asymptomatic eyes indicated probable involvement. Latency delay can be accepted as a reliable sign of optic nerve demyelination, whereas amplitude decrease indicates damage related to ischaemia.

Pattern electroretinogram (PERG) is related to retinal ganglion cell layer activity, therefore the PERG will be affected by any process that either distorts the input to the ganglion cells, directly damages the ganglion cell bodies or compromises the optic nerve, leading to retrograde degeneration of the retinal ganglion cell axons.[10] Holder demonstrated that the PERG can usually distinguish between VEP delays due to optic nerve disease and those arising more distally.[11] The findings of increased latency and reduced amplitude of the main positive (P50) component of the PERG suggest dysfunction distal to the retinal ganglion cell layer and not those of optic nerve dysfunction. Holder analysed the PERG value at 95 msec and found it to be changed in optic nerve disease as opposed to the PERG value at 50 msec which was more affected in retinal and macular dysfunction.[12] Simultaneous recordings of PERG and VEP have been used to define the degree of optic nerve involvement in MS patients and to determine possible ganglion cell layer damage. It was suggested that retrograde degeneration of the ganglion cells can develop in MS patients affected by optic neuritis. The authors showed that PERG was reduced in amplitude in eyes affected by retrobulber neuritis and often absent in optic atrophy.[4] We studied 29 patients with the diagnosis of ischaemic optic neuropathy and optic neuritis and PERG findings revealed that P50 amplitude and latency showed no differences between affected and unaffected eyes of ischaemic optic neuropathy and optic neuritis patients. However, N95 amplitude was found to be significantly lower in affected eyes without a significant latency difference in ischaemic optic neuropathy patients. N95/P50 ratio was reported to be lower in optic nerve diseases; however in our study, in both groups N95/P50 ratios were higher than 1:1 and there was no significant difference between the groups and between the affected and unaffected eyes. In the optic neuritis group, there was no significant difference for P50 amplitude and latency; however in the affected eyes, N95 amplitudes were lower than the fellow unaffected eye, with a decreased latency of approximately 1 msec and this difference was statistically significant. Similar to the ischaemic optic neuropathy group, N95/P50 ratio was greater than 1:1 and there was no difference between affected and unaffected eyes. These findings supported previous studies that proposed that an abnormality confined to the negative component of the PERG was associated with optic nerve diseases such as optic nerve demyelination or compression or ischaemic optic neuropathy.[5,6,10] In addition to younger age and female preponderance, PERG findings are useful and complementary to VEP for the diagnosis and follow-up of optic neuritis patients.

Salzman et al reported absence of PERG response with normal flash ERG and delayed VEP latencies in patients with severe visual loss and poor acuity caused by optic neuritis, ischaemia or optic nerve compression, supporting the hypothesis of an inner retinal layer origin to the PERG.[13] However, Holder reported that extinction of PERG was not frequently seen in optic nerve diseases, but was frequently seen in patients with macular dysfunction.[6] Compressive optic nerve lesions may also give rise to PERG abnormalities.[6,14,15] In optic nerve demyelination, the greater the magnitude of VEP latency delay, the greater the incidence of PERG abnormality.[8] In our study, we could not demonstrate any significant PERG abnormality, except an unremarkable shortened N95 latency in the affected eyes of optic neuritis patients and decreased N95 amplitude in the affected eyes of ischaemic optic neuropathy patients, which suggested ganglion cell involvement. As we had VEP and PERG recordings mostly in the acute phase of the disease, long-term follow-up of patients may reveal more abnormalities.

Different studies were conducted to emphasise the role of PERG in optic nerve diseases and retinal pathologies.[16,17] In a study conducted by Prager et al, it was shown that a significant correlation between PERG amplitude and the duration of diabetes were found in diabetic patients with either no observable retinopathy or minimal background retinopathy. The amplitude of the PERG was reported to decrease with increasing retinopathy.[17] Trick and Nesher recorded the steady-state and transient PERG in primary optic neuropathy (open-angle glaucoma and Alzheimer's disease) and retinopathy (diabetic patients) cases and reported that mean amplitude of the P50 and N95 were decreased 18% and 33% respectively in glaucoma patients. The patients in the Alzheimer group exhibited PERG amplitude reductions similar to the pattern observed in glaucoma patients.[10] In our study, in the affected eyes P50 and N95 amplitudes were lower than the unaffected eyes in both groups; however, this difference was statistically insignificant.

In summary, the results of the present study indicate that simultaneous recording of the VEP and PERG can be used to estimate the place and degree of optic nerve involvement, and also to make differential diagnosis of optic nerve diseases. Both VEP and PERG are important in evaluating the functional integrity of the optic nerve and central retina. A delayed VEP should be accepted as a sign of optic nerve disease in correlation with PERG. As VEP parameters may be affected by other eye problems such as amblyopia, lens opacities or refractive errors, PERG can help in accurate interpretation in association with VEP.

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