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The Potential Use of Pattern Reversal Visual Evoked Potential for Detecting and Monitoring Open Angle Glaucoma

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Abstract

Glaucoma is a widely prevalent eye disease characterized by an optic neuropathy, often associated with elevated intraocular pressure, leading to characteristic visual field defects and optic nerve head damage. Pattern- induced visual evoked potentials (VEPs) have been shown to be sensitive to glaucomatous neuropathy. The elevation of intraocular tension is believed to cause pressure on the retinal nerve fibers bundles as they course into the optic nerve and is associated with the loss of visual function; which alters the VEP waveforms. The present study was conducted to compare the pattern reversal visual evoked potentials (PREVPs) in patients with primary open angle glaucoma and in healthy controls to assess the utility of VEP in detecting early cases of primary open angle glaucoma. 90 primary open angle glaucoma (POAG patients) and 120 control subjects underwent VEP investigation in the Neurophysiology Unit of Dept. of Physiology, Mahatma Gandhi Institute of Medical Sciences, Sevagram on Recorders and Medicare Systems RMS Electromyograph (EMG) Evoked Potential (EP) Mark MKII. The latency and amplitude of first positive wave P100, and the latencies of the negative waves N70and N155 respectively in PR-VEP were recorded. Visual fields of all POAG patients were assessed by Humphrey field analyzer program 30-2 full threshold. The differences of PRVEP parameters among POAG and control groups were compared and it was found that P100 latency was prolonged in 172 eyes of 86 (88.89%) patients among the POAG group. P100-N70 amplitude was reduced in 160 eyes of 80 (88.89%) patients among the POAG group. None of the patients in our study failed to record a measurable response in either eye. The Mean Deviation (MD) values in the POAG patients were negatively correlated with the latency time of P100. No significant correlation was found between PSD and latency time or between PSD and amplitude of P100 among the POAG patients. Primary open angle glaucoma has been found to affect the PRVEP by causing both the reductions in P100 amplitude and increments in P100 latency when compared with that of the control group. Visual field index MD was found to be negatively correlated with the P100 latency. Our study advocates the use of PRVEP as an objective electrophysiological tool for monitoring patients with the progression of optic nerve pathology in POAG, because increase in latency times are significantly associated with progression of optic nerve damage

Keywords: primary open angle glaucoma, P100 latency, P100 amplitude, intra-ocular pressure, pattern reversal visual evoked potential

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Introduction

Recording the spontaneous electrical activity of the brain from electrodes placed on the scalp has been a clinical practice for many years now. The visual evoked potential (VEP) is one of several evoked potentials that can be recorded from scalp electrodes. It is well acknowledged that VEPs are useful for investigating the physiology and pathophysiology of the human visual system, including the visual pathways and visual cortex.

Pattern-induced VEPs are more sensitive to optic nerve lesions than flash-evoked responses [1] It serves as an objective method for assessing the visual function and has

been shown to be sensitive to glaucomatous neuropathy [2, 3, 4]. Glaucoma is fast emerging as a major cause of blindness in India second only to cataract [5]. It is a widely prevalent eye disease characterized by an optic neuropathy, often associated with elevated intraocular pressure, leading to characteristic visual field defects and optic nerve head damage. It is well established that damage to the ganglion cells and/or their axons produce these visual field defects [6].

The routine techniques recommended to detect damage resulting from glaucoma include intraocular pressure measurement, optic disc evaluation and visual field testing. New technologies such as confocal scanning laser ophthalmoscopy (CSLO) and optical coherence tomography (OCT) have become available that provide quantitative, reproducible and objective measurements of the optic nerve head and retinal nerve fibre layer thickness [7]. But high cost currently precludes their generalized use. Threshold perimetry is time consuming, fatiguing for the patient and shows a significant learning defect [8]. These short comings have led clinicians to seek alternative ways of detecting and monitoring glaucoma.

VEP has potential to be a useful tool in the early detection of functional deficits in glaucoma and its longitudinal assessment. The present study was conducted to compare the pattern reversal visual evoked potentials in patients with primary open angle glaucoma and in healthy controls to find assess the utility of VEP in detecting early cases of primary open angle glaucoma.

Material and Methods

Patients attending the Glaucoma clinic at Kasturba hospital in the Department of Ophthalmology in Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sevagram were recruited for the study. Both eyes were examined in 90 patients of an established POAG and in 120 controls without a diagnosis of glaucoma. Informed consent was taken from all the cases. The study was approved by our Institutional Ethics Committee. Detailed systemic and ophthalmological examination was performed on all the subjects.

Study design
This was a prospective comparative study.

POAG patients exhibited
1. glaucomatous optic nerve changes including diffuse or focal neural rim thinning,
2. hemorrhage,
3. enlarged cupping,
4. nerve fiber layer defects with corresponding glaucomatous visual field loss,
5. best-corrected visual acuity <6/9
6. maximum IOP more than 21 mmHg using Non contact tonometer
7. Open angle at gonioscopy.

Control subjects *were defined as having a*
1. normal IOP <21 mmHg,
2. normal visual field with standard automated perimetry (SAP),
3. open angle at gonioscopy,
4. normal optic nerve head and retinal nerve fiber layer on clinical examination,
5. best-corrected visual acuity 6/6 and a
6. negative family history for glaucoma

Exclusion Criteria
Patients with secondary or angle closure glaucoma, hazy media (corneal or lenticular opacities), optic neuritis, diseases involving macula or retina, high myopia (>5 diopters), diabetes mellitus, previous intraocular surgery except for uncomplicated cataract extraction, multiple sclerosis and Parkinson's disease were excluded from the study.

Methodology
Pattern reversal VEP recording was carried out in air conditioned, quiet, sound proof darkened room in the Neurophysiology Unit of Dept. of Physiology, Mahatma Gandhi Institute of Medical Sciences, Sevagram on RMS EMG EP MKII.

Subject Preparation
Each subject was briefed previously about the procedure to alleviate any apprehension and to assure full relaxation during the test.

The subject was seated comfortably at a distance of 1 meter away from the screen of the VEP monitor so that accommodation of eye is relaxed. All the patients wore their optical corrections as necessary.

The only source of light was the stimulus itself. Standard disc EEG electrodes were placed on the scalp areas after preparing the skin by degreasing and abrading with a conducting jelly or electrode paste (RMS recording paste) rubbed lightly into the area with a cotton swab.

The standardized methodology as recommended by the International Federation of Clinical Neurophysiology (IFCN) Committee and International Society for Clinical Electrophysiology of Vision (ISCEV) was adhered to.

As per 10-20 International System of EEG placements, the reference electrode (Fz) was placed 12 cm above the nasion, the ground electrode (Cz) at the vertex and the active electrode (Oz) at approximately 2 cm above the inion.

The electrode impedance was kept below 5KΩ.

Procedure of VEP recordings

1. After controlling all factors that influence the VEP pattern, the subject was instructed to close one eye with his hand without any pressure on the eye and to fixate his other eye on a small red dot at the center of the screen of the VEP monitor, on which black and white checker board pattern is generated full field and reversed at a rate of 1/sec.
2. The recording was done monocularly for the left and right eyes separately.
3. At the viewing distance of 100 cm the check edges subtended 15 degree of visual angle.
4. The signals were fed into an amplifier with the low frequency cut-off filter set at 2.0 Hertz and the high frequency cut-off filter set at 100 Hertz.
5. The sensitivity was kept at 2μV. The luminance of the white areas was 80 cd /m^2 with a contrast of at least 75% compared to black squares.
6. The sweep duration was maintained at 300 ms. Responses to 200 stimuli were amplified and averaged for each eye, which were then analyzed by inline computer having automatic artifact rejection mechanism.
7. At least two trials for each eye were obtained and superimposed on one another to ensure replicability of the VEP pattern.
8. The absolute latencies of the peaks of positive wave P100 and the negative waves N70 and N155 were recorded.
9. The amplitude of P100 was measured from the preceding negative peak N70 to the peak of P100 and the latency is the time from stimulus onset to the peak of each component were considered in the study.

Visual fields of all POAG patients were assessed using the Humphrey field analyzer program 30-2 at full threshold. All patients had experienced the standard automated perimetry (SAP) examination at least two times and the second SAP visual fields were chosen for the present study.

Reliable visual field was defined as having

- a false positive error less than 33%,
- a false-negative error less than 33% and
- a fixation loss less than 20%.

Mean deviation (MD) i.e. index of global visual field damage and pattern standard deviation (PSD) i.e. index of localized visual field damage were considered in the study.

Visual field defects in SAP was considered significant when -

1. two or more contiguous points with a pattern deviation sensitivity loss of $P < 0.01$, or three or more contiguous points with sensitivity loss of $P < 0.05$ in the superior or inferior arcuate areas, or a 10-dB difference across the nasal horizontal midline at two or more adjacent locations and
2. An abnormal result in glaucoma hemifield test [9].

Results

The general characteristics indicating gender, age, diameter of pupil and occipito-frontal circumference of the POAG patients and control subjects are summarized in Table 1.

Table 1. *Characteristics of the study subjects*

Characteristics	POAG (n = 90 cases)	Controls (n = 120)
Age (years)	58.45 ± 11.27	52.07 ± 9.03
Gender (M/F)	50 (56%)/40 (44 %)	69 (57.5 %)/ 51 (42.5%)
IOP (mm Hg)	17.96 ± 5.76	13.03 ± 1.48
Diameter of pupil (mm)	2.67 ± 0.8	2.63 ± 0.64
Occipito-frontal Circumference (cm)	53.88 ±1.85	53.59 ±1.79

Table 2. *Comparison of PR-VEPs of Study Groups*

Parameters	POAG	Controls	p Value POAG vs. Controls
N70 latency (ms)	68.26 ± 8.86	66.96 ± 5.75	0.024 (<0.05)
P100 latency (ms)	105.42 ± 11.13	98.08 ± 3.99	0.0005 (<0.05)
N155 latency (ms)	141.95 ± 12.13	135.34 ± 8.50	2.84018E-12 (<0.001)
P100-N70 amplitude (μv)	4.79 ± 2.9	6.12 ± 2.22	1.49316E-08 (<0.001)
P100 Duration (ms)	73.64 ± 13.37	68.38 ± 10.32	7.38491E-07 (<0.001)

POAG = Primary open angle glaucoma, MD= mean deviation, PSD= pattern standard deviation

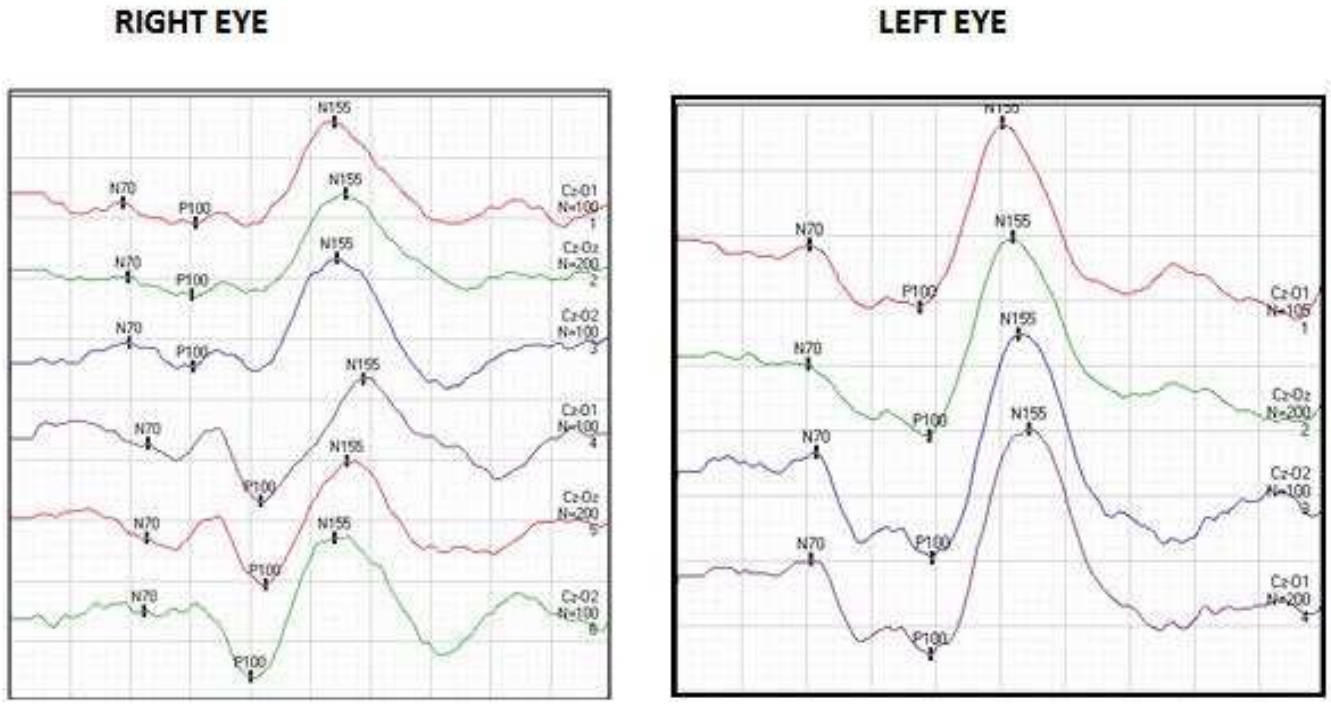

Figure 1. *PRVEP Waveform in a case of POAG (72 yrs, Male) showing prolonged P100 latency and "W" pattern*

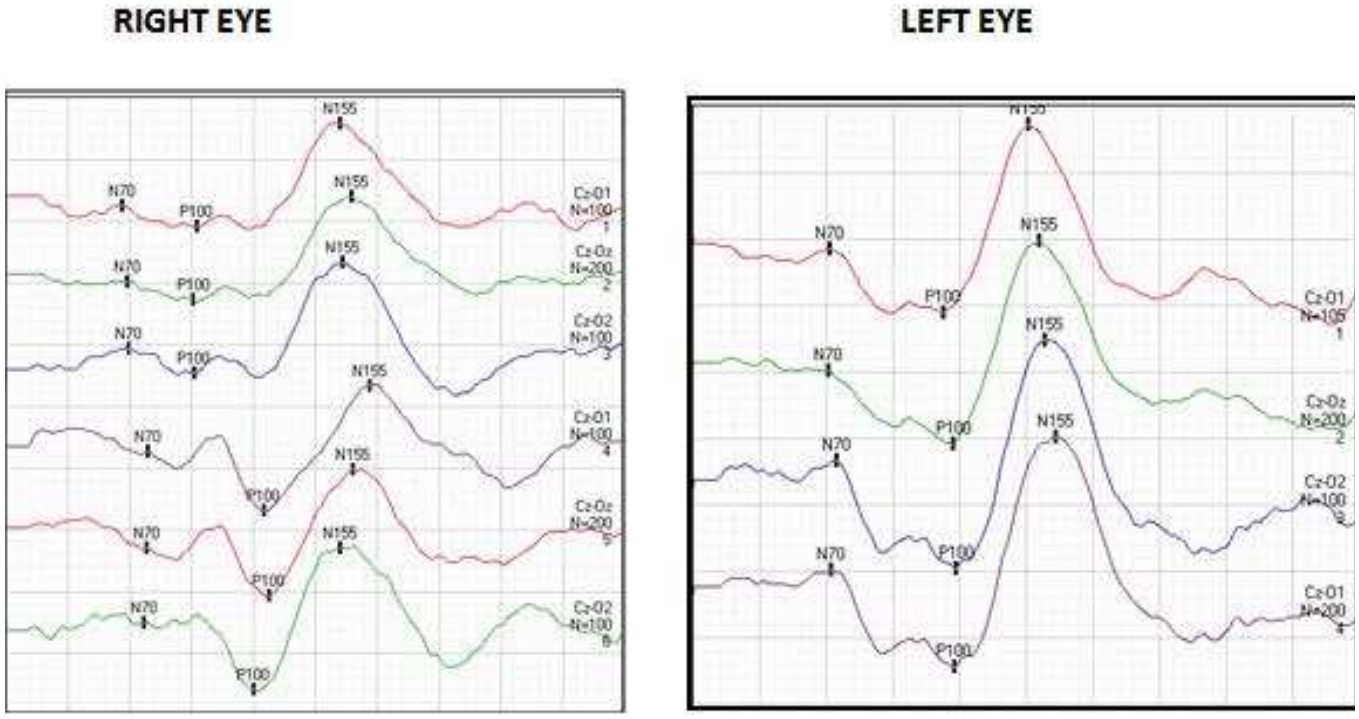

Figure 2- *PRVEP Waveform in a case of POAG (70 yrs/Male) showing prolonged P100 latency and reduced P100 amplitude*

P100 latency was found to be prolonged in 172 eyes of the 86 (88.89%) patients with POAG. P100-N70 amplitude was reduced in 160 eyes of 80 (88.89%) POAG patients. None of the patients in our study failed to record a

measurable response either eye. Waveforms of four patients were altered to either produce a "W" pattern or a distorted morphology. In summary, all 90 subjects (100%) in the POAG group exhibited an abnormal VEP response.

Table 3. *Pearson Correlation Coefficient (r) of Various Parameters of PR-VEP In Relation To IOP of Study Groups*

Parameters	POAG (r)	Controls (r)
N70 latency (ms)	0.050	-0.141
P100 latency (ms)	0.426	0.046
N155 latency (ms)	0.068	+0.016
P100-N70 amplitude (μv)	-0.09	-0.117
P100 Duration (ms)	+0.03	+0.092

Table 4. *Correlations between the visual field indices and the latency time and amplitude of P100 in POAG patients*

	Latency time (r value)	Amplitude (r value)
POAG MD	-0.410	0.034
POAG PSD	0.215	0.126

Discussion

Primary open angle glaucoma (POAG) is perhaps the most common form of glaucoma in India, as reported in most of the prevalence studies in the country by Jacob et al [10], Das K et al [11], Dandona et al [12]. This has led to an increasing interest in electrophysiological testing in glaucoma here in the past few years. The disease is characterized by a triad of signs including increased intraocular pressure, visual field defects and cupping of the optic disc.

Glaucoma is a condition in which an elevation of intra ocular tension is believed to cause pressure on the retinal nerve fibers bundles as they course into the optic nerve and is associated with the loss of visual function; this is known to produce an alteration of the VEP waveforms. The waveform alteration can be in the form of "W" pattern as shown in Figure 1 in the recording of a 72 yrs old male POAG patient.

PR-VEP provides an objective and sensitive readout of the function of retinal ganglion cells (RGCs), and the latency of P100 can be used as a measure of early glaucomatous damage before RGCs death (13). The present study found that the latency of P100 was delayed and the amplitude of P100 was reduced in POAG patients when compared with that of control subjects, which is consistent with previous investigations reported in glaucoma patients in the past by Parisi et al (3), Bach (4), Horn (5), Grippo et al (14), Tong (15), Vaegan and Hollows (16). Figure 2 shows the waveform of a 70 year male POAG patient of our study where the prolonged P100 latency and reduced P100 amplitude are quite evident.

For the neurologist as well as for the ophthalmologist it is important to consider causes other than demyelinization in the evaluation of latency increments. Compression of visual pathway and glaucomatous atrophy may give VEP results identical to those obtained in multiple sclerosis. (16).

Allison et al (17) found that P100 showed large changes after the age of 60; probably as a neural substrate of this potential is affected more by degenerative changes in visual system that occur after 60 years of age.
The identification of glaucoma patients with abnormal latencies could open the possibility of neuroprotection of unhealthy retinal ganglion cells. Furthermore, Rejdak et al [13] have used the latency of P100 in P-VEP as a marker of reversible ganglion cell damage in trials of neuroprotective agents for the treatment of glaucoma.

In our study POAG has been found to affect PRVEPs by reducing amplitude, corroborating the results of Abe and Iwata [18] and Ermers et al [19], and by increasing latency, as reported by Cappin and Nissim [20], Huber and Wagner, Schwartz and Sonty [21] and Sokol et al [22].

Furthermore, we found the MD values in the POAG patients were negatively correlated with the latency time of P100, which is in agreement with previous studies by Horn, Bergua, Jünemann and Korth [5]. Increased pattern VEP latency was also significantly correlated with both the severity and location of visual field defects and the degree of cupping and pallor of the optic disc by Towle et al [23].

Parisi [24] has also reported significantly delayed P100 latency in POAG eyes when compared with controls and correlated with mean deviation (index of global visual field damage, MD). In his study P100 amplitudes were also significantly lower in POAG eyes than in control eyes and correlated with MD.

To summarize, the transient pattern reversal VEP is a straightforward investigation which takes 10-15 minutes in total to perform and requires the patient to fixate for only about 30-60 seconds at any one time. It thus requires lesser co-operation than conventional kinetic or computerised static perimetry and therefore has distinct advantages with regard to that group of patients who have difficulty in performing a field investigation. It positively establishes optic nerve function in patients with subjective complaint of visual loss.

Conclusion

PRVEP can be an objective electrophysiological tool for monitoring patients with the progression of optic nerve pathology in POAG, because increase in latency times are significantly associated with progression of optic nerve damage. Our findings suggest that VEP is a valuable tool in glaucoma research and may be used as an adjunct in glaucoma diagnosis or follow up, especially for patients for whom it is difficult to obtain reliable standard automated perimetry results; or where unavailability of equipment or high cost precludes the use of newer imaging technology. However, longitudinal studies are required to further validate the test.

Declaration of Interest

None of the authors has a financial or proprietary in any material or method mentioned. The authors alone are responsible for the content of the paper. It was a self financed project.

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