·Clinical Research·

Correlation of pattern reversal visual evoked potential parameters with the pattern standard deviation in primary open angle glaucoma

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Received: 2013-04-10 Accepted: 2013-08-22

Abstract

• AIM: To evaluate whether glaucomatous visual field defect particularly the pattern standard deviation (PSD) of Humphrey visual field could be associated with visual evoked potential (VEP) parameters of patients having primary open angle glaucoma (POAG).

• METHODS: Visual field by Humphrey perimetry and simultaneous recordings of pattern reversal visual evoked potential (PRVEP) were assessed in 100 patients with POAG. The stimulus configuration for VEP recordings consisted of the transient pattern reversal method in which a black and white checker board pattern was generated (full field) and displayed on VEP monitor (colour 14") by an electronic pattern regenerator inbuilt in an evoked potential recorder (RMS EMG EP MARK II).

• RESULTS: The results of our study indicate that there is a highly significant (P<0.001) negative correlation of P100 amplitude and a statistically significant (P<0.05) positive correlation of N70 latency, P100 latency and N155 latency with the PSD of Humphrey visual field in the subjects of POAG in various age groups as evaluated by Student´s t-test.

• CONCLUSION: Prolongation of VEP latencies were mirrored by a corresponding increase of PSD values. Conversely, as PSD increases the magnitude of VEP excursions were found to be diminished.

• KEYWORDS: pattern reversal; pattern standard deviation; visual field; P100 latency

DOI:10.3980/j.issn.2222-3959.2014.02.24

Kothari R, Bokariya P, Singh R, Singh S, Narang P. Correlation of pattern reversal visual evoked potential parameters with the pattern standard deviation in primary open angle glaucoma. *Int J Ophthalmol* 2014;7(2):326-329

INTRODUCTION

Visual evoked response testing has been one of the most exciting clinical tools in glaucoma research in recent years. Transient pattern reversal visual evoked potential (PRVEP) generated in the cortical and sub-cortical visual areas when the retina is stimulated with pattern light is a very important, non-invasive, low-cost method and highly objective tool in detecting abnormalities of visual system.

Primary open angle glaucoma (POAG), one of the most prevalent types of glaucoma in India, is a disorder characterised by open iridocorneal angles and progressive optic disk cupping with resultant irreversible loss of vision. Ever since visually evoked cortical potentials were first used as a diagnostic aid, the important question has been whether they could predict the severity of visual field defects. Since PRVEP is known to be sensitive to glaucomatous neuropathy so it was thought pertinent to derive association, if any, between index of focal glaucomatous visual field damage namely pattern standard deviation (PSD) and PRVEP parameters in the POAG population in this part of the country. This perimetrical parameter is considered a more accurate index of localized defects in the visual field and visual evoked potential is the mass bioelectrical response of the visual cortex therefore localized damage of selectively vulnerable optic nerve fibers can probably be detected by visual cortical electrophysiological responses[1].

Therefore the purpose of the present study was to investigate the VEP responses in the selected primary open angle glaucomatous patients and to correlate them with pattern standard deviation of their Humphrey visual field.

SUBJECTS AND METHODS

Subjects The study was conducted in the Neurophysiology unit of the Department of Physiology in a medical college of Central India. The study included 100 patients diagnosed as having POAG by the ophthalmologist at the Glaucoma Clinic

of the Department of Ophthalmology and 200 healthy volunteers and normal subjects comprised the age matched controls after proper screening as per the inclusion and exclusion criteria. Both eyes of subjects were included in the study. Thus, Pattern Reversal VEP recordings from 600 eyes in total were obtained for the present study. This study was undertaken after prior approval by the Institutional Ethics Committee. The subjects were selected by random sampling method.

Detailed systemic and thorough ophthalmological examination was carried out for all the subjects. Informed consent was obtained prior to study commencement. Subjects were interviewed and the details regarding habits of tobacco, alcohol, smoking, occupation, medical history of systemic illness like hypertension, diabetes, tuberculosis, thyroid disorders and family history of glaucoma were entered in a standardized proforma. Glaucoma patients were either with or without treatment *i.e.* were recently diagnosed or already known cases on treatment. If the subject was already a known case of glaucoma then type of treatment and whether glaucoma was under control or not was also noted. Since primary open angle glaucoma characteristically is a bilateral and almost symmetrical disease, none of our cases had unilateral involvement.

Inclusion Criteria for Diagnosing Primary Open Angle Glaucoma Patients Open angle of normal appearance at gonioscopy, intraocular pressure (IOP) more than 21 mm Hg, characteristic glaucomatous optic nerve head changes, typical glaucomatous visual field defects, age >40y and (79y, best-corrected visual acuity (BCVA) -6/6 or better, IOP<21 mm Hg for patients under pharmacological (medical) treatment

Exclusion Criteria for Primary Open Angle Glaucoma Patients Patients with visual acuity (BCVA) <6/6, ptosis, strabismus, amblyopia, corneal or lenticular opacities, retinitis pigmentosa, multiple sclerosis (MS), albinism, diabetes mellitus, hereditary disorders, diseases involving macula, retina or visual pathway, optic neuritis, history of relevant neurological or heart disease or of drug abuse, past history of serious visual problems, recent eye medications (mydriatics or cycloplegics in the past 12h), miotic pupil, high myopia, hypermetropia or astigmatism >3 diopters, Parkinson's disease, previous intraocular surgery except for uncomplicated cataract extraction, secondary or angle closure glaucoma and any uncooperative subject or a subject with incomplete screening and examination was excluded from the study.

Ophthalmic Examination A single ophthalmologist conducted a complete ophthalmic examination of each subject which included visual acuity, anterior segment examination, posterior segment examination (fundoscopy), intra-ocular pressure and automated perimetry. All the subjects' visual fields were assessed by the static perimeter Humphrey visual field analyzer II; using Swedish Interactive Thresholding Algorithm (SITA) Standard protocol with stimulus size III, white object, (30-2 central with fovea-on).

Reliability indices for visual field assessment were- A) a false positive error less than 33%; B) a false-negative error less than 33%; C) a fixation loss less than 20%.

The main indices of the Humphrey perimetry are mean deviation (MD) and pattern standard deviation (PSD). MD represents an index of severity of global damage. It is a measure of overall field loss. As defined by the Hoddap-Parrish-Anderson's criteria, a MD in the range of 0 to <-6dB is considered to be mild glaucomatous defect, the one in the range of -6 to -12dB is moderate and >-12dB is severe glaucomatous defect. Table 1 represents the number of POAG eyes in each age group possessing the value of MD (as found in the automated perimetry) falling in each of the three grades of glaucomatous defects.

Another significant index of the Humphrey perimetry is the PSD. It is a measure of focal loss. It indicates the homogeneity of defect distribution in the visual field and therefore gives information about localized damage[2].

As per the minimal criteria for glaucomatous damage the visual field defects in automated perimetry were considered significant when 1) a cluster of three or more contiguous, non-edge points on the pattern deviation plot within Bjerrum's area have a probability of <5% of being seen in a normal population, one of which should have a probability of <1% or 2) PSD should have a probability of <5%, confirmed on two consecutive occasions; 3) Glaucoma hemifield test is abnormal or outside normal limits.

Methodology for Visual Evoked Potential VEP recordings were done in accordance to the standardized methodology of International Federation of Clinical Neurophysiology (IFCN) Committee Recommendations and International Society for Clinical Electrophysiology of Vision (ISCEV) Guidelines and montages were kept as per 10-20 International System of EEG Electrode placements [3,4]. Each subject was briefed previously about the procedure and was seated comfortably at a distance of 1 meter away from the screen of the VEP monitor.

Stimulus configuration 1) It consisted of the transient pattern reversal method in which a black and white 8 × 8 checker board pattern was generated (full field) and displayed on a VEP monitor (colour 14") by an electronic pattern regenerator inbuilt in an Evoked Potential Recorder (RMS EMG EP MARK II); 2) A fixation point (red square) was positioned at a corner of four checks which were located at the center of the field; 3) The rate of pattern reversal was 1Hz; 4) The recording sensitivity was kept at 2 μV. The electrode impedance was kept below 5KΩ; 5) The analysis time (sweep duration) was maintained at 300ms; 6)

Responses to 200 epochs were amplified and averaged for each eye and two trials for each eye were obtained; 7) The pattern stimulus luminance was 59 cd/sqm; 7) The contrast between black and white squares was kept as 80%; 8) The signals recorded were filtered by low cut and high cut frequency filter through a band spread of 2-100 Hz.

Visual Evoked Potential Waveform The PRVEP waveform consisted of the initial negative peak (N70) followed by a large positive peak (P100) and followed by another negative peak (N155). The analysis of all the three waves namely N70-P100-N155 has been attempted in the present study. Besides, the P100 duration (interpeak latency) is also included in the analysis.

Statistical Analysis The correlation of all the electrophysiological parameters with PSD of Humphrey visual field was evaluated by Pearson's correlation co-efficient (r) and its statistical significance was evaluated. P value <0.05 was considered to be statistically significant and P<0.001 was considered highly significant.

RESULTS

Characteristics of the Cohort of Subjects POAG patient group included 54 males and 46 females and the control group comprised of 124 males and 76 females recruited from the population in the age range of 40-79y.

The mean age of POAG patients was 57.94±11.14y and the mean age of controls was 56.08 ±10.87y. There was no statistically significant difference between the mean ages of both the groups. The P value for the paired difference between the glaucoma and control groups was found to be 0.63 (P>0.05). Hence the controls and the glaucoma subjects were statistically age matched.

There was a highly significant difference (P<0.001) in the mean PSD and the mean IOP of POAG patients as compared to that of control subjects.

The data compiled in Table 1 depicts that maximum proportion of the POAG population 118 (59%) out of 200 eyes had mild glaucomatous defect. Moderate glaucomatous defect was found in 47 (23.5%) eyes and severe glaucomatous defect was observed in 35 (17.5%) eyes.

Table 2 depicts the correlation of mean±SD values of PSD of 200 POAG eyes with mean VEP parameters in the glaucoma group. The data illustrates a highly significant negative correlation of P100 amplitude and a statistically significant positive correlation of N70 latency, P100 latency and N155 latency with the PSD.

Table 3 illustrates the statistical analysis of mean±SD values of PSD of 400 control eyes and their mean VEP parameters showing that no significant correlation was found between PSD and VEP latencies, as well as the amplitude and duration of P100.

Table 1 Agewise distribution of POAG eyes as per severity of glaucoma *n* (%)

Age (a)	Glaucomatous defects		
	Mild	Moderate	Severe
40-49 (*n*=54)	38 (70.37)	9 (16.67)	7 (12.96)
50-59 (*n*=60)	39 (65)	12 (20)	9 (15)
60-69 (*n*=40)	20 (50)	10 (25)	10 (25)
70-79 (*n*=46)	21(45.65)	16 (34.78)	9 (19.57)
Total (*n*=200)	118 (59)	47 (23.5)	35 (17.5)

Table 2 Correlation of PSD with VEP parameters of POAG eyes

Parameters	$\bar{x}$±SD (*n*=200)	*r*	*P*
PSD	5.21±3.69		
N70 latency (ms)	68.42±8.60	0.206	0.003
P100 latency (ms)	101.18±8.06	0.187	0.008
N155 latency (ms)	141.48±11.99	0.145	0.040
P100 amplitude (μV)	4.84±2.95	-0.357	0.000
P100 duration (ms)	73.06±13.16	-0.002	0.978

Table 3 Correlation of PSD with VEP parameters of control eyes

Parameters	$\bar{x}$±SD (*n*=400)	*r*	*P*
PSD	1.34±0.94		
N70 latency (ms)	66.63±5.6	0.078	0.119
P100 latency (ms)	96.95±4.24	0.045	0.369
N155 latency (ms)	135.45±8.32	0.094	0.060
P100 amplitude (μV)	5.90±2.16	-0.055	0.271
P100 duration (ms)	67.78±9.48	0.023	0.645

DISCUSSION

The follow-up observation of patients with chronic open angle glaucoma in clinical practice has so far been based on mainly on tonometry, optic disc analysis, and perimetry. It is well established that damage to the ganglion cells and/or their axons produce the characteristic visual field defects of glaucoma. In this regard, an electrophysiological method like the VEP could be a useful tool for monitoring of glaucomatous optic neuropathy and for measurement of visual field damage in perimetric glaucoma.

The assessment of visual field defects with VEP is a hard task. Earlier workers have been interested in correlating VEP findings with perimetric defects. As the VEP, which primarily reflects the macular function, gets altered only when the central visual field was disturbed, it was considered not very useful in detecting early glaucoma by Ermers *et al* [5]. Muller *et al* [6,7] and Cappin and Nissim [8] have tried to demonstrate field defects with VEP using localized retinal stimulation. They also conducted VEP recordings with patient fixating center of the 22 (screen (full field), the central 8 (only and also the center of the screen when the central 8 (was occluded (peripheral). These tests did not show significant phase changes except in four cases with large field defects. The amplitude of the response from the eyes with moderate and severe defects was markedly reduced by comparison with that of the normal eye.

In recent years multifocal visual evoked potential (mfVEP) has generated considerable interest as a method for objective assessment of visual field and the extent of glaucomatous damage. It has been shown over the past decades that this method may detect glaucomatous visual field defects with high sensitivity and specificity, and it can have a role in the detection and monitoring of glaucomatous progression based on good repeatability but this tool that has yet to find its place within accepted clinical practice[9].

In the present study, the POAG patients showed different degrees of visual field impairment detected by an increase in PSD. The correlation of mean ±SD values of PSD is represented in Table 1. Overall the data illustrates a highly significant negative correlation of P100 amplitude and a statistically significant positive correlation of N70 latency, P100 latency and N155 latency with the PSD.

These observations of the present study are in contrast with Parisi [10] who assessed visual field by Humphrey perimeter (central 24-2 threshold test) and simultaneously recorded visual evoked potential (VEP) in 21 subjects with open angle glaucoma (POAG) to evaluate whether glaucomatous visual field defects could be related to an impaired retinal function, to a delayed neural conduction in post-retinal visual pathways, or both. VEP in POAG eyes of their study showed no significant correlations (P >0.05) between electrophysiological parameters and corrected pattern standard deviation (CPSD) of 24-2 Humphrey perimetry.

However, our result of correlation of P100 latency and PSD are in accord with significant correlation (r=0.434, P<0.01) of CPSD and VEP P100 implicit time observed in a subsequent study by Parisi *et al*[11]. On the contrary Mokbel and Ghanem [12] observed no significant correlation between PSD and latency time, PSD and amplitude of P100 in their POAG patients.

As per the minimal criteria for glaucomatous damage, visual field defects in Standard Automated Perimetry are considered significant when glaucoma hemifield test (GHT) is abnormal or outside normal limits. This test compares the sensitivity of five clusters of points above and below the horizontal midline which resemble nerve fiber bundle patterns. This type of loss common in glaucoma is usually asymmetrical about the horizontal meridian.

The analysis is defined as abnormal if one or more of the five regions demonstrate asymmetry across the horizontal midline which is beyond 1% probability level for normal population values. It is regarded as borderline if the asymmetry is within 1% probability level for all five regions but beyond 3% probability level for one or more regions.

Evaluating the proportion of eyes having GHT values in the arbitrary range of 1-3 where 1 means within normal limits, 2 is outside normal limits and 3 stands for borderline, it was found that 49.5 % (99 out of 200) eyes had GHT outside normal limits, 14.5 % (29 out of 200) had borderline GHTs and 36% eyes (72 out of 200) had GHT within normal limits.

In conclusion, since an increased PSD is a more specific indicator of glaucomatous damage therefore our result of prolongation of latencies mirrored by a corresponding increase of PSD values is a positive finding of our study. Conversely, as PSD increases, the magnitude of VEP excursions (P100 amplitude) were found to be diminished because with the increase of glaucomatous damage, there is loss of retinal ganglion cells and a corresponding decrease in proportion of healthier neurons. To conclude, the correlation of PSD with abnormal VEP responses therefore emphasizes that localized damage of selectively vulnerable optic nerve fibers could be successfully monitored by visual evoked responses especially in patients with unreliable or questionable Humphrey visual fields or where unavailability of equipment or high cost particularly in a low resource rural setting as in this study, precludes the use of newer imaging technology.

ACKNOWLEDGEMENTS

Conflicts of Interest: Kothari R, None; **Bokariya P,** None; **Singh R,** None; **Singh S,** None; **Narang P,** None.

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