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Occurrence of "W" Pattern in visual evoked potentials of Primary Open Angle Glaucomatous patients.

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Abstract

The objective of the present study is to determine the occurrence of "W" morphology of P100 waveform in Pattern Reversal Visual Evoked Potential (PRVEP) recordings of a cohort of patients having Primary open angle glaucoma. This rural hospital based study was conducted in the Neurophysiology unit of the Department of Physiology, Mahatma Gandhi Institute of Medical Sciences, Sevagram. The study comprised of pattern reversal visual evoked potential (PRVEP) recordings from 176 eyes of 88 patients of primary open angle glaucoma (POAG) having age ≥40 years. The recordings were compared with those of 180 eyes of 90 age matched controls. VEP recordings were performed with the stimulus configuration consisting of the transient pattern reversal method in which a black and white checker board 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). All the recordings were investigated for the presence of "W" shaped complex (bifid pattern of P100) defined as having two peaks separated by a 10-50 msec interval. The appearance of peculiar "W" pattern obtained in our POAG patients was an aberrant response encountered in 19.31 % percent (34 eyes) of 176 open angle glaucomatous eyes. None of the previous studies have commented on the morphology of P100 waveform in POAG patients as far as the literature could be traced so it seems that ours is a preliminary attempt in this regard. We propose that it may carry the similar significance as a prolonged P100 latency since the latency magnitude of the bifid peaks were beyond the upper limit of normal latency of P100 potential. However, the validation of this proposition warrants further investigation on a larger sample of POAG population.

Keywords. Pattern reversal, P100 waveform, bifid pattern, glaucoma

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Introduction

Pattern reversal visual evoked potential (PRVEP) is known to be an objective method for assessing the visual function and has been shown to be sensitive to glaucomatous neuropathy. PRVEP is generated in the cortical and sub-cortical visual areas when the retina is stimulated with patterned light.

Primary open angle glaucoma (POAG) is described distinctly as a multi-factorial optic neuropathy that is chronic and progressive with a characteristic acquired loss of optic nerve fibers. Such loss develops in the presence of open anterior chamber angles, characteristic visual field abnormalities, and intra-ocular pressure (IOP) that is too high for the continued health of the eye. It is believed that elevation of intra ocular tension causes 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. [1,2]

Normal VEP waveform

Recently waveforms have begun to take on new importance in visual evoked response (VER) analysis. The normal waveform of Pattern Reversal Visual Evoked Potentials (PRVEPs) is characterized by an initial small negative (N70), followed by a major positive wave (P100) and then by a negative wave (N155). P100, the hallmark of full field VEPs, is the most consistent and

least variable peak compared with N70 and N155. Figure 1 (Panel a) represents the illustration of PRVEP waveform of a healthy visually normal subject.

The latency of P100 potential is universally accepted as the most useful measure for interpreting the pattern VEPs to full field stimulation in patients. It is usually recorded from the mid occipital region. P100 waveform recorded from inion is an algebraic sum of individual half field VEPs. The majority of P100 is generated by the lower half of the central field. The upper visual field may contribute as negative polarity and the lower as positive at inion. On moving the electrodes laterally or horizontally a point of polarity reversal i.e. transitional zone is found.

The visual evoked potential (VEP) to an alternating checkerboard stimulus is usually recorded from the occipital midline as an N-P-N complex with a major positive deflection at 100 ms (P100). Although difficult to characterize and seldom taken into account [3,4,5,6], abnormal or distorted VEP waveform, particularly in the time window of wave P100, is common and a wave form exhibiting a P-N-P or "W" morphology is occasionally encountered.

Shape abnormalities of P100 manifesting with such a “W” shaped complex (bifid pattern of P100) present with two peaks separated by a 10-50 msec interval. Its presence usually suggests abnormality [7]. Averaged pattern-VEPs are the result of distinct components that eventually combine in time and space accordingly, distorted VEPs are thought to reflect impaired or abnormally distributed activation of the contributing brain structures.

A mid occipital positivity peaking later than 130 msec after full field stimulation is definitely abnormal, since it is beyond upper limit of normal latency of P100 potential. Visual evoked responses (pattern VEPs) having abnormal waveform with P100 breaking up into two positive waves (superimposed quasi-sinusoidal sequences of negative/positive waves or with bifid wave P100) are reportedly common in diseases affecting the visual pathways for e.g. in multiple sclerosis (with an estimated incidence up to 45%), migraine, vascular disease, and other neurologic diseases [8-14]. It is also mentioned that there may be a “W” shaped VEP on full field stimulation in patients with central field defect as encountered in ocular diseases like glaucoma.

Gamma oscillatory response

Cortical mass responses in the form of stimulus-related oscillatory activity in the frequency range of above approximately 20 Hz upto 40 Hz (gamma band) with peak frequency centered around 25 to 30 Hz, are evoked in human visual cortex by contrast transient stimulation. They contribute to and can be separated with negligible filter distortion from conventional human VEPs to transient reversal contrast stimulation. The human gamma oscillatory responses mediating in cortical visual information processing is thought to reflect generating mechanisms independent of the VEPs. It can also contribute to VEP waveform distortion [15].

The recording of pattern reversal visual evoked potential (PRVEP) has been advocated as a novel, cost effective non-invasive approach to improve both the detection and monitoring of Chronic Simple Glaucoma [CSG], this provided the substantial ground to carry out this study in the POAG population.

Since the variable morphological pattern of P100 peak is a frequent problem in the interpretation of pattern VEPs especially among the patients of primary open angle glaucoma (POAG), the present study was conducted with a prime objective of determining the occurrence of “W” morphology of pattern reversal P100 waveform in a cohort of patients having POAG.

Material and Methods

The study was carried out in the Neurophysiology unit of the Department of Physiology of a rural medical college. The study included 176 eyes of 88 patients of primary open angle glaucoma (POAG) having age ≥40 years and 180 eyes of 90 age matched controls. Pattern Reversal VEP recordings were done in accordance to the standardized methodology of International Federation of Clinical Neurophysiology (IFCN) Committee Recommendations [16] and International Society for Clinical Electrophysiology of Vision (ISCEV) Guidelines [17] and montages were kept as per 10-20 International System of EEG Electrode placements [18].

Standard nomenclature has been adopted for describing the VEP waves and they are named by their polarity (P or N) and by their usual normal latency. The absolute latencies of the peaks of positive wave P100 and the negative waves N70 and N155 were noted. The amplitude of P100 was measured from the peak of N70 to the trough of P100 (N70 – P100).

The stimulus configuration was transient pattern reversal method in which a black and white checker board was generated (full field) on a VEP Monitor by an Evoked Potential Recorder (RMS EMG EP MARK II). Prior Ethics approval from the Institutional Ethics committee was obtained for the present study. Written Informed consent was taken from the patients before the study.

Statistical analysis

The statistical analysis of the data obtained in the above recordings was performed using statistical programme SPSS software and computer programs using Microsoft

excel software (Microsoft Corp, USA). Difference in latencies and amplitude duration between the controls and POAG eyes were compared by 1-way analysis of variance (ANOVA). Differences were said to be significant at $p < 0.05$ and highly significant if $p < 0.001$.

Results

In our study, the VEP waveform including the positive peak P100 as well as the negative peaks N70 and N155 were present in all the subjects. None of the subjects in our study failed to record a measurable response in any of the eyes. Also none of the control eyes showed a "W" pattern in their VEP waveform.

The mean ± SD value of P100 latency as per the normative data of our neurophysiology laboratory was 98.38 ± 3.74 msec whereas the same in those POAG with "W" pattern of VEP waveform was found to be 113.4 ± 6.59 msec. Similarly the mean ± SD value of P100 amplitude as per our norms was 7.78 ± 2.04 µV whereas the same in those POAG with "W" pattern of VEP waveform was found to be 1.86 ± 1.54 µV. Out of the 88 POAG patients, 17 patients were identified as exhibiting the "W" VEP. This represented 19.31 % percent (34 eyes) of 176 eyes. The latencies of the bifid peaks were outside the upper normal limits as determined by mean+ 3 SD of the normative data of our neurophysiology laboratory and their P100 amplitudes were less than mean – 3 SD of the norms. This difference of P100 latency in POAG eyes with "W" Pattern and control eyes was statistically significant ($p<0.001$). Similarly the difference of P100 amplitude in POAG eyes with "W" Pattern and control eyes was also statistically significant ($p<0.001$). The remaining POAG eyes showed normal pattern of VEP waveform although accompanied by other VEP abnormalities as prolonged N70, P100 and N155 latencies and diminished response in the form of reduced P100 amplitude. Prolonged N70 latency was observed in 11 (12.5%) eyes, prolonged N155 latency was seen in 18 (20.45%) POAG eyes.

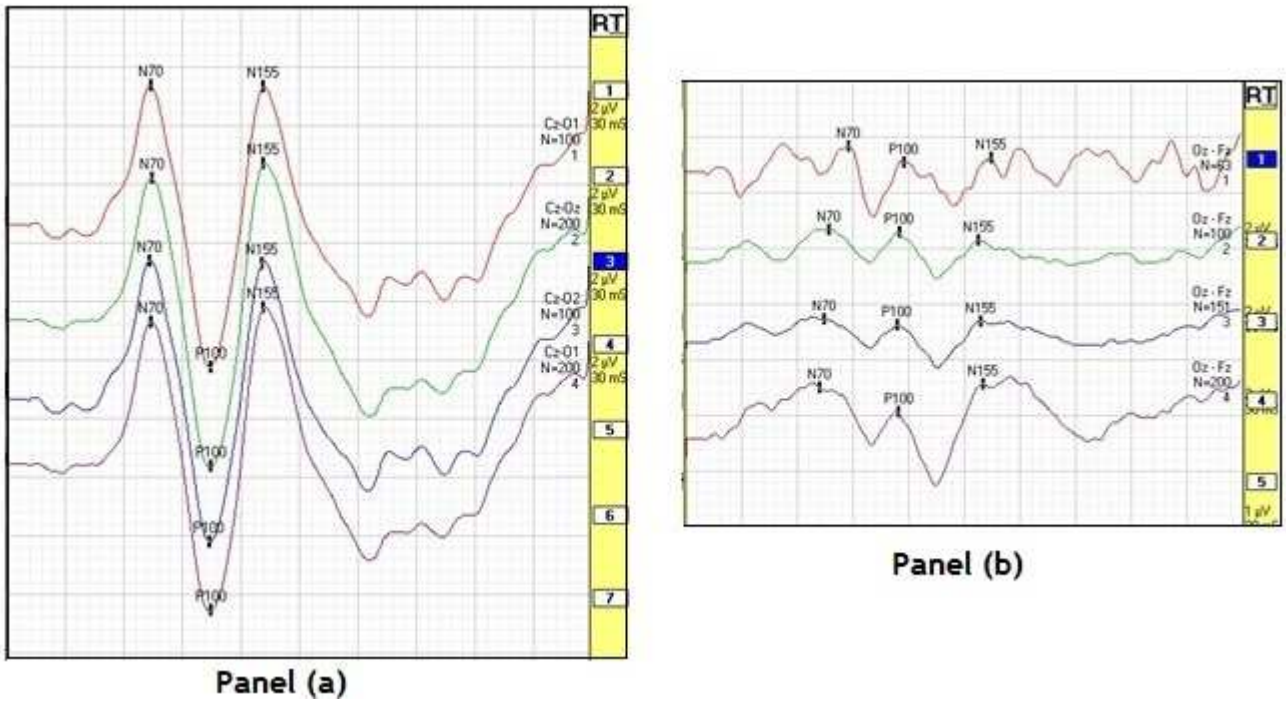

Figure 1.
Panel (a)*Normal VEP waveform showing P100 latency and amplitude within normal limits.*
Panel (b)*PRVEP Record of a 70 years male POAG patient showing "W" Pattern, prolonged P100 latency and Reduced P100 Amplitude & prolonged P100 Duration.*

Discussion

Much is now understood of the pathophysiology of the visual changes in primary open angle glaucoma (POAG) and the role of optic nerve damage in glaucomatous visual defects is well-documented. The P100 latency shows impairment of temporal characteristics of the visual system at low spatial frequencies, as could occur if glaucomatous optic nerve damage preferentially affected transient visual channels. Also there is enough evidence of prominent loss of ganglion cells axons in the optic nerve in POAG

and the large diameters nerve fibres are thought to be selectively lost in glaucoma [19].

It has been evidenced by the studies of monkey and human optic nerve that larger ganglion cells and their axons (presumably M cells) presumably originating from retinal ganglion cells with larger somatic size are lost as a result of chronic IOP elevation [20]. It is further supported by previous studies, one of which showed that rapid-phase axonal transport from the M-type ganglion cells to the magnocellular layers of the dorsal lateral geniculate nucleus was decreased selectively in chronic experimental glaucoma [21].

The other studies in support are the ones which demonstrated fewer remaining large ganglion cells in the damaged retinal areas in human eyes with glaucoma [20, 22]. The M ganglion cells may be lost more rapidly in chronic glaucoma because a higher proportion of their axons pass through the more susceptible parts of the lamina cribrosa. This loss eventually results in delayed visual evoked response and alteration in VEP waveforms which manifests as bifid peaking of P100 wave of pattern reversal VEP in patients of POAG.

The appearance of "W" pattern which we have observed in the POAG patients of our study, particularly in subjects of elderly age groups can substantially be explained in the light of the contentions put forth by the above mentioned earlier studies. The representative of altered PRVEP waveform obtained from our POAG population showing the peculiar "W" pattern is illustrated in Figure 1 (Panel (b).

In our study, using the 95th percentile of the normative data as a definition of abnormal, 19.31 % percent (34 eyes) of 176 eyes showed "W" VEP and had P100 latencies falling outside the range of the controls. This is a value far from that (100%) reported for the conventional VEP (cVEP) by Parisi et al [23] but it corroborates well with the findings of an Indian study by Sood et al [24] who have reported statistically significant delayed latency in 18.2% eyes without glaucomatous field defect when they used a check size of 16 and alternation rate of 1.88 cycles/sec. Our results are also better than those of Grippo et al [25] who showed that relatively few glaucomatous eyes (only 8% to 12.3% of the glaucoma eyes) had latencies that fell outside the range of control eyes.

The study by Grippo et al [25] was conducted on 75 eyes (47 patients), 75 eyes with suspected glaucoma (46 patients), and 41 control eyes (22 subjects) with the cVEP stimulus as a reversing checkerboard with checks of either 15 minutes or 60 minutes in width. In their glaucoma group, 12.3% (15 minutes cVEP), 8% (60 minutes cVEP) exceeded the normal range. Thus the glaucomatous eyes had, on an average, relatively small increases in latency, compared with the control or suspect groups.

Uncertainly understood as the result of synchronous, stimulus- related activation in the gamma range of neuronal assemblies responding to the visual properties of stimulus, the human 20–45 Hz (gamma) oscillatory mass response shares characteristics of conventional VEPs, such as the stimulus/response function for contrast and spatial frequency tuning, but does have differences, such as in time dynamics and source orientation in striate cortex.

In humans, the oscillatory gamma range response to contrast is peculiarly phase-locked to stimulus, has faster time dynamics and shorter latency than VEPs, and has different orientations of cortical sources. According to prevailing hypotheses, gamma activity originates in, and appears intrinsic to, structures with laminar organization such as the cortex, is enhanced during sensory information processing, and is modulated in part by oscillations in the synaptic input. It provides a frequency- and time-related coding system mediating (at some stage of visual information processing) in the synchronization of cortical neurons due to respond selectively to the stimulus physical properties [15].

Oscillatory responses at 20-40 Hz to contrast stimulation have been reported in the absence of the conventional broadband VEPs in patients with brain damage involving the visual system [13, 26]. Although anecdotal, this observation suggests pathophysiological conditions in which stimulus-related oscillations unaffected by pathologic brain conditions disorganizing the VEP response can account for abnormal VEP waveforms such as those described in neurologic diseases.

Oscillatory responses can thus mimic a degraded VEP waveform, which has clinical relevance. The observation of a predominant oscillatory response in unfiltered VEP recordings would indicate inadequate organization of the cortical response and therefore indicate functional impairment irrespective of the latencies of recognizable waves. The observation that oscillatory gamma activity originating in visual cortex can be evoked by contrast stimulation in the absence of conventional VEPs further indicates some independence among these electrophysiological events and supports an early functional role of gamma band activity in the stimulus-induced neuronal synchronization and in visual information processing.

Contributions of gamma activity to the distorted VEP waveform are possible if the mechanisms of generation are differentially affected by brain disorders. The extent to which VEP and oscillatory responses may mirror distinct parallel or consecutive phases/mechanisms of visual information processing remains speculative, yet a differential sensitivity to disorders of the visual system appears conceivable.

In a previous study [15], isolated or preponderant oscillatory responses were observed in unfiltered recordings in patients with either prechiasmatic or postchiasmatic damage, though with different incidences (60%–30.7%), and their occurrence does not appear related to any of the pathophysiological conditions considered or attributable to any single diagnosis or group of diagnoses.
However, the processes generating the low-frequency VEP and gamma oscillations are too complex to allow detailed hypotheses about selective pathophysiological interferences on these responses.

Conclusion

The shape of P100 waveform in pattern reversal VEP depends upon the surviving fastest conducting fibers i.e. Magnocellular (M) pathway fibers. Since these fibers are selectively lost in chronic glaucoma we propose that it may lead to appearance of "W" pattern which we have obtained in our POAG patients.

None of the previous studies mentioned in the literature have commented on the morphology of P100 waveform of POAG patients so it seems that ours is a preliminary attempt in this regard. As there was a statistically significant ($p<0.001$) difference in the magnitude of P100 latency and P100 amplitude of PRVEP waveforms of all the 19.31 % (34 of 176) open angle glaucomatous eyes so it can be construed that the "W" VEP response may carry the same significance as a prolonged P100 latency and reduced amplitude in the assessment of primary open angle glaucoma.

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