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EXPLORING THE CRUCIAL ROLE OF PATTERN REVERSAL VISUAL EVOKED POTENTIALS (PRVEP) IN PATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA

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ABSTRACT

Primary open-angle glaucoma (POAG), one of the most prevalent forms of glaucoma in India, is characterized by optic degenerative neuropathy with multiple factors. It is often linked to elevated intraocular pressure, resulting in distinctive visual field defects and damage to the optic nerve head. Visual evoked potential (VEP) has proven to be sensitive to glaucomatous optic neuropathy, as it aligns with the functions of retinal ganglion cells. Our study was a prospective comparative study, that involved the examination of both eyes in 40 patients with confirmed primary open-angle glaucoma and 40 age-matched individuals without glaucoma. The findings revealed a similar occipitofrontal circumference in both the study group and controls (53.80±1.88cm vs. 53.54±1.77cm, respectively, p=0.526). The VEP results indicated a statistically significant prolongation in the latency of P100 (117.29±16.84ms vs. 102.22±7.04ms, p=0.000) and a notable reduction in P100 amplitude (6.03 ±2.15µv vs. 8.07±4.02 µv, p=0.014) in the study group and controls as assessed by a student's t-test. Therefore, Visual evoked potential emerges as a crucial electrophysiological tool for assessing visual field defects in primary open-angle glaucoma, providing an objective measure of optic nerve function.

KEYWORDS: Primary open-angle glaucoma, Optic nerve head, Visual evoked potential, Latency, Amplitude.

INTRODUCTION

Glaucoma is responsible for causing blindness in approximately 1.2 million individuals and accounts for 5.5% of total cases of blindness. Consequently, it stands as a primary cause of irreversible blindness in India.[1] Primary open-angle glaucoma is distinctively described as a multifactorial optic neuropathy that progresses chronically. It results in a characteristic acquired loss of optic nerve fibers. This loss occurs alongside open anterior chamber angles, distinctive visual field abnormalities, and elevated intraocular pressure that is detrimental to the eye's ongoing health. This condition becomes evident through the cupping and atrophy of the optic disc. It is crucial to comprehend the relationship between field loss and optic neuropathy, which displays a specific pattern of optic nerve head and visual field damage due to the loss of retinal ganglion cells, to accurately identify the disease's stage. Remarkably, as much as 20% to 30% of optic nerve fibers can sustain permanent damage before any detectable visual field loss occurs in glaucoma.[2,3] Previous research has emphasized that structural loss of retinal ganglion cells (RGC) precedes functional impairment in terms of visual field.[4,5] Additionally, it has been demonstrated that RGCs go through an extended period of dysfunction characterized by reduced neuronal sensitivity and degeneration before actual anatomical cell loss, while observable anatomical changes in the optic disc precede visual field defects.[6]

In recent years, there has been a growing fascination with electrophysiological testing in the context of glaucoma. This is primarily due to the widely accepted understanding that substantial damage to ganglion cells can take place before any functional impairments are detectable using static automated achromatic perimetry, which is considered the "gold standard" for identifying and tracking glaucomatous damage. Visual Evoked Potentials (VEP) are primarily employed to assess the functional integrity of the visual pathway, spanning from the retina through the optic nerves to the visual cortex. VEP has demonstrated sensitivity to detecting glaucomatous optic neuropathy because its responses align with the activities of retinal ganglion cells. The electrical impulses generated by ganglion cells travel to the cerebral cortex through a series of anatomical structures, including the optic nerve, optic tract, lateral geniculate nucleus, and optic radiations. Any disruption in the transmission of these electrical impulses can be monitored and recorded using VEP.[7] Elevated intraocular pressure is thought to exert pressure on the bundles of retinal nerve fibers as they traverse into the

optic nerve, leading to damage to retinal ganglion cells and axons. This pressure is associated with the deterioration of visual function, which subsequently alters the waveform of VEP.[8] VEP techniques hold the potential to serve as a valuable tool for the early detection of functional impairments in glaucoma and for assessing these changes over time. VEP measurements can objectively evaluate a patient's visual accuracy and align well with structural alterations in the retina and optic nerve head.

In the present study, various ophthalmic variables, risk factors for primary open-angle glaucoma, and visual evoked potentials were evaluated by comparing these factors between patients with primary open-angle glaucoma and a control group of normal, healthy individuals.

MATERIAL AND METHODS

The study was conducted in the Department of Physiology in collaboration with the Department of Ophthalmology, IGMC Shimla.

Study design: This was a prospective comparative study.

Sample size: Based on the three years of departmental statistics in the Department of Ophthalmology at Indira Gandhi Medical College Shimla, a sample size of 40 Primary open-angle glaucoma patients was selected over the period of one year. Both eyes were examined in 40 patients of established POAG and in 40 controls without the diagnosis of glaucoma.

Inclusion criteria

POAG Patients exhibiting best corrected visual acuity <6/9, Maximum IOP >21 mmHg using Goldmann applanation tonometer, Open-angle at gonioscopy, glaucomatous optic nerve changes including diffuse or focal neural rim thinning, hemorrhage, enlarged cupping, optic disc ratio >0.5, an asymmetry between the two optic nerve heads > 0.2 detected using TOPCON 3D Optical Coherence Tomography; Nerve fiber layer defects with corresponding glaucomatous visual field loss on automated perimetry.

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

Exclusion criteria

Patients with secondary or angle closure glaucoma, hazy media (Corneal, lenticular or vitreous opacities obstructing optic disc examination and visual field analysis), active ocular infection or inflammation, any pathological finding on ophthalmological examination, optic neuritis, diseases involving macula or retina, high myopia (>5 diopters), previous intraocular surgery except for uncomplicated cataract extraction, multiple sclerosis and Parkinson's disease were excluded.

METHODOLOGY

Detailed history focusing on presenting complaints with durations, their progressions, past history, family history, medical treatment, surgical treatment, and LASER treatment was taken. Detailed general physical examination, occipitofrontal circumference, and blood pressure were measured in both the POAG patients and controls. Ophthalmic variables were measured in all the subjects for the selection of the study group. Visual Acuity was assessed using Snellen's chart placed at a distance of 6 meters and best corrected visual acuity was documented. Slit lamp bio-microscopy with Haag Streit 9000 was done to evaluate the anterior segment. Pupil Examination was done by Torch light and Slit lamp. Relative afferent papillary defect checked with the help of Torchlight. Ocular motility was assessed to check any paralysis of ocular muscles. Intra-Ocular Pressure was measured using Goldman Applanation Tonometer mounted on Haag Streit - 900 slit lamp. Gonioscopy was done with a Goldman three-mirror lens to check the angle, to rule out narrow-angle glaucoma. Fundus examination was done after dilating the pupil with Tropicamide 0.8% and Phenylephrine 5%. The posterior segment and optic disc were evaluated by direct and indirect ophthalmoscopy and with a 78 D lens on a Slit lamp. Visual field analysis was done by using Octopus 900 Automated perimeter. Pattern reversal Visual Evoked Potential was done using the Neurosoft machine product of Neurosoft Ltd., Russia.

VEP recording

To alleviate any apprehension and ensure complete relaxation, each subject was thoroughly briefed about the procedure. After providing them with comprehensive and accurate information about the current study, each subject was asked to sign an informed consent form, indicating their willingness to participate in both the study and the interventional procedure during the test. All patients wore their necessary optical corrections. In a relaxed environment, the subjects were comfortably seated at a distance of 100cm from the 14-inch colored VEP monitor screen. This distance was chosen to promote relaxed eye accommodation. The only source of light in the room was the stimulus itself. To record the electrical activity of the brain, standard disc EEG electrodes were applied to specific scalp areas. Before electrode placement, the skin was prepared by degreasing and lightly abrading it. A conducting jelly or electrode paste was then gently applied to the area using a cotton swab. This standardized methodology adhered to the recommendations of the International Federation of Clinical Neurophysiology (IFCN) Committee. The study adhered to the guidelines set forth by the International Society for Clinical Electrophysiology of Vision (ISCEV).[9] In accordance with the 10-20 International System of EEG electrode placements,

specific electrode positions were established, the reference electrode (Fz) was situated 12 cm above the nasion, the ground electrode (Cz) was positioned at the vertex, and the active electrode (Oz) was placed approximately 2 cm above the inion. To ensure accurate recordings, electrode impedance was maintained at levels below 5KΩ.

After carefully controlling all the factors that could potentially affect the VEP pattern, subjects with one eye covered were given instructions to focus their uncovered eye on a small red dot located at the center of the VEP monitor screen. A checkerboard pattern composed of black and white squares, subtending a visual angle of 15 degrees, was presented with a reversal frequency of 1 Hz.

The white squares had a luminance of 80 cd/m^2 and exhibited a contrast of at least 75% when compared to the black squares. Sensitivity settings were maintained at 4μV. The recorded signals were directed into an amplifier with a low-frequency cut-off filter set at 2.0 Hz and a high-frequency cut-off filter set at 100 Hz. The duration of each sweep was fixed at 300 milliseconds. Separate recordings were conducted for the left and right eyes. Responses to 200 stimuli were amplified and then averaged for each eye. These averaged responses were subsequently analyzed using a computer equipped with an automatic artifact rejection mechanism.

Visual evoked potential waveform: (As shown in Fig.A) The PRVEP waveform consists of the initial negative peak (N70) followed by a large positive peak (P100) and followed by another negative peak (N145). In the present study, the absolute latency of the peak of P100 and N75-P100 amplitude were measured. At least two trials for each eye were obtained and superimposed on one another to ensure the replicability of the VEP pattern.

The data was transferred on an Excel spreadsheet and descriptive analysis was expressed as mean ± standard deviation. All calculations were accomplished by using Graph Pad InStat3 software.

The comparison of mean differences was done by a student's t-test. The difference was considered statistically significant with a P value <0.05.

RESULTS

Table 1: Comparison of the Socio-demographic profile of POAG Patients and The control group.

Variables	POAG patients (n=40)	Controls (n=40)
Age (years)	62.18±11.094	60.18±13.107
Gender (%) males	52.5%	47.5%
females	47.5%	52.5%
Education (%) illiterate	56%	40%
literate	44%	60%
Background (%) rural	55%	50%
urban	45%	50%

The socio-demographic profile was comparable with no statistically significant difference between the two groups.

Table 2: Comparison of General characteristics of POAG patients and the control group.

Characteristics	POAG patients	Controls	P value
Systolic bp (mmhg)	139.4±3.8	134.2±3.4	0.000
Diastolic bp (mmhg)	88.5±12.2	82.5±12.2	0.001
Occipito-frontal circumference (cm)	53.80 ± 1.88	53.54 ± 1.77	0.526

The comparison of general characteristics showed that both the systolic and diastolic blood pressures were significantly higher in the PAOG patients than in the controls. The mean value of Occipito-frontal was found to be similar in the two groups.

Table 3: Comparison of Risk profile of glaucoma in the POAG patients and the control group.

Risk factors	POAG patients	Controls	P value
Family history of glaucoma	20%	2.5%	0.04
Hypertension	50%	12.5%	0.00
Smoking	37.5%	12.5%	0.019
Diabetes	23%	2.5%	0.01

All the risk factors showed markedly increased percentages in the POAG patients with statistically significant differences between the two groups.

Table 4: Comparison of latency and amplitude of P100 between patients of POAG and controls.

Parameters	POAG patients	Controls	P Value
P100 Latency (MS)	117.29 ±16.84	102.22±4.81	0.000
P100amplitude (µV)	6.03±2.15	8.07±2.51	0.014

As compared to the controls, the mean P100 latency was significantly prolonged (as shown in Fig.B) and the mean P100 amplitude was significantly lower in the patients with Primary Open open-angle glaucoma. (as shown in Fig.C)

DISCUSSION

Primary open-angle glaucoma is a chronic condition characterized by the gradual deterioration of retinal ganglion cells (RGCs) and their axons. This deterioration can result from various factors, including elevated intraocular pressure (IOP), compromised vascular supply, or a combination of these factors. Notably, both mild and severe stages of the disease tend to selectively damage the larger ganglion cells located in the peripheral and foveal areas of the retina. This damage leads to a progressive loss of optic nerve fibers and subsequently a decline in the quality of vision. Understanding the early progression of glaucomatous optic neuropathy holds the potential to enhance our ability to combat the disease. This knowledge could enable more intensive treatment approaches for patients displaying signs of ongoing damage. In clinical practice, the follow-up and monitoring of patients with chronic open-angle glaucoma have traditionally relied on evaluating increased intraocular pressure, the presence of optic nerve head cupping, and the development of visual field defects. However, in addition to this classic assessment triad, modern techniques employing advanced methodologies offer the potential to track the progression of damage to retinal ganglion cells, their axons, and possibly the associated nerve fibers. It is widely recognized that Visual Evoked Potentials (VEPs) are valuable tools for investigating the physiology and pathophysiology of the human visual system, encompassing both the visual pathways and the visual cortex. Among VEPs, pattern reversal VEPs exhibit heightened sensitivity to optic nerve lesions when compared to flash-evoked responses.[10] They provide an objective means of assessing visual function and have demonstrated sensitivity in detecting glaucomatous neuropathy.[11]

The current study aimed to conduct a comparative analysis of visually evoked Potentials (VEPs) between patients diagnosed with primary open-angle glaucoma (POAG) and individuals without glaucoma. The primary objectives were to identify potential disparities in VEP latencies and amplitudes between these two groups and to evaluate the effectiveness of VEP as a diagnostic tool for detecting cases of glaucoma.

In this study, we conducted a comparison between forty patients diagnosed with Primary Open Angle Glaucoma (POAG) and an equal number of non-glaucomatous controls, matched for age and sex. The mean age of the POAG patients was 62.18 years (± 11.094), while the mean age of the control group was 60.18 years (± 13.107). It's worth noting that the mean occipitofrontal circumference measurements were quite similar between the two groups, with values of 53.80 cm (± 1.88) for POAG patients and 53.54 cm (± 1.77) for non-glaucomatous subjects. The occipitofrontal circumference is relevant as it estimates the length of the optic nerve, which has an impact on VEP latencies.[12] Significantly higher values for both systolic and diastolic blood pressure were observed in the POAG patients compared to the controls (Systolic blood pressure 139.4 mm Hg ± 3.8 vs. 134.2 mm Hg ± 3.4, p=0.001 and Diastolic BP 88.5±12.2 vs 82.5±12.2, p=0.001 consistent with previous research findings by Tielsch JM, Katz J, Sommer A, et al.[13] This suggests that systemic hypertension may contribute to increased intraocular pressure (IOP) by elevating episcleral venous pressure, thus impeding the outflow of aqueous humor.[14]

Furthermore, the study group displayed a higher susceptibility to developing glaucoma due to increased exposure to risk factors such as smoking, diabetes, hypertension, and a family history of the condition, as compared to the control group. Any systemic disease related to the vascular system can potentially cause damage to the microvasculature network and disrupt the nutritional supply to retinal ganglion cell (RGC) axons, which can affect blood regulation in the optic nerve head area.[15]

A clear understanding of these risk factors is crucial for raising public and medical awareness regarding the prevention and early detection of this insidious disease. Additionally, managing POAG necessitates consideration of all potential risk factors, which may help halt the progression of glaucomatous field damage, even when intraocular pressure has been normalized.

Glaucoma is a medical condition characterized by increased intraocular pressure, which exerts pressure on the bundles of retinal nerve fibers as they pass into the optic nerve. This elevated pressure is associated with the loss of visual function and is known to alter visually evoked Potentials (VEP) waveforms.

In our study, we observed that Primary Open Angle Glaucoma (POAG) has a discernible impact on Pattern

Reversal VEPs (PRVEPs), as evidenced by statistically significant changes. Specifically, there was a marked prolongation of the P100 latency in POAG patients compared to the control group (117.29 ms ± 4.81 vs. 102.22 ms ± 4.81, p=0.000) and a reduction in the amplitude of P100 in POAG patients compared to the control group (6.03 µV ± 2.15 and 8.07 µV ± 2.51, respectively).

The absolute latency of the P100 peak reflects the time it takes for a signal to travel from the retina to the visual cortex, and this is typically indicative of the function of axons along the visual pathway. VEP latencies serve as a measure of early glaucomatous damage that occurs prior to the death of retinal ganglion cells. On the other hand, the N75-P100 amplitude signifies the number of functioning retinal ganglion cells responsible for activating an electrical signal. These findings mark the utility of VEP in detecting and monitoring glaucoma-related changes in visual function.

In conclusion, Visual Evoked Potentials (VEP) emerge as a crucial visual electrophysiological tool for assessing visual field defects in primary open-angle glaucoma (POAG). VEP offers distinct advantages as a more objective measure of optic nerve function because it is less susceptible to cognitive factors and the motor skills of the subject when compared to psychophysical tests.

Nonetheless, it's worth noting that further validation of the VEP test is warranted through longitudinal studies. Long-term investigations would help establish its reliability and effectiveness in monitoring the progression of glaucoma and evaluating the impact of treatment interventions over time.

Limitation

Fixation indeed presents a challenge in Visual Evoked Potentials (VEP) testing. While VEP is advantageous in not relying on subjects' responses or active participation to assess the visual field, issues such as subjects' inattentiveness, connectivity problems, and individual variability can lead to false negative errors.

One particular concern in VEP testing is the absence of a dedicated tool to objectively assess test reliability. To address this issue, it is suggested that a two-run VEP test could be employed. This approach could help assess intra-test variability. In theory, if the intra-test variability remains consistent, it would be possible to automatically identify and exclude widely variable values from certain segments of the test.

Implementing this software modification could potentially enhance the reliability of VEP testing by providing a more objective means of evaluating the consistency and accuracy of the results, thereby reducing the impact of fixation-related issues and other sources of variability.

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