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The Role of Pattern Visual Evoked Potential in Primary Open Angle Glaucoma

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ABSTRACT

Background: Primary open-angle glaucoma (POAG) is one of the leading causes of blindness worldwide. The death of retinal ganglion cells in POAG is reflected by increased cupping of the optic disc, loss of nerve fiber layer and functional visual field defect.

Objective: The aim of the work was to assess the role of Pattern Visual Evoked Potential (VEP) in diagnosis of primary open angel glaucoma.

Patients and methods: We studied 40 eyes of 21 subjects, the eyes were classified into 2 groups: Group I included 20 eyes of 11 patients with primary open angel glaucoma and Group II included 20 eyes of 10 normal control (age and sex) matched group. All eyes underwent a full field ophthalmic, OCT and pattern VEP.

Results: OCT results showed significant reduction of retinal nerve fiber layer (RNFL) thickness in glaucoma and glaucoma suspect eyes in the majority of quadrants as well as in the average RNFL thickness $p < 0.001$. The pattern VEP of glaucomatous patient when compared to normal control group reported affection of the VEP by causing both reductions in amplitude and increases in latency. And by statistically analysis of the results that there were highly statistically significant differences between both groups of the VEP measurements ($p < 0.001$).

Conclusion: The pattern visual evoked potential (VEP) has been shown to be sensitive to optic nerve lesions caused by ischemia and glaucoma has also been reported to affect the VEP by causing both reductions in amplitude and increases in latency.

Keywords: POAG, OCT, RNFL, VEP.

INTRODUCTION

Glaucoma is a multi-factorial optic neuropathy characterized by loss of the retinal ganglion cells axons, leading to progressive irreversible loss of vision, manifests by cupping and atrophy of the optic disc. Such loss develops retinal nerve fiber layer thinning and characteristic visual field abnormalities [(1)].

Primary open angle glaucoma (POAG) is a leading cause of irreversible world blindness. The onset is without symptoms and progression occurs silently until the advanced stages of the disease, when it affects vision. Diagnostic instruments providing quantitative analyses in glaucoma assess either structural or functional aspects of the disease [(2)].

A number of techniques have been developed to diagnose and monitor POAG. The search for ways of making an earlier diagnosis and hence improving the prognosis of the disease continues with varying degrees of success [(3)].

Visual field testing remains the main stay as a subjective test currently available for diagnosis and following patients with glaucoma [(4)].

Reliance on IOP, optic disc cupping changes, nerve fiber layer integrity and visual field changes may delay the treatment of glaucoma since irreversible changes may have already occurred at the time of diagnosis [(5)].

Imaging and quantitative analysis of retinal nerve fiber layer (RNFL) measurement can be accomplished with Optic Coherence Tomography (OCT) which is a non-invasive interferometric technique that provides cross-sectional images and measurements of the retinal nerve fiber layer thickness (RNFLT) with high resolution and good reproducibility[(6)].

Because glaucomatous damage can be controlled with medication and surgery , it is important to detect early signs of inner retinal damage. The pattern visual evoked potential (VEP) has been shown to be sensitive to optic nerve lesions caused by demyelination, ischemia, and compression of the anterior visual pathway. Glaucoma has also been reported to affect the VEP by causing both reductions in amplitude and increases in latency. Increased pattern VEP latency has been associated with optic disc cupping and the presence of visual field loss [(7)].

Visual field testing results are often unreliable with poor repeatability. The Ocular Hypertension Treatment Study (OHTS) found that nearly 86% of diagnosed visual field defects seen on standard visual field testing improve with subsequent testing. In the same vein as optical coherence tomography, the VEP is an objective way of evaluating functional vision loss versus depending on only subjective standard automated perimetry [(8)].

The aim of the current work was to assess the role of Pattern Visual Evoked Potential in diagnosis of primary open angel glaucoma.

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PATIENTS AND METHODS

This case control study included a total of 40 eyes of 21 subjects, the eyes were classified into 2 groups: Group I included 20 eyes of 11 patients with primary open angel glaucoma (POAG) and Group II included 20 eyes of 10 normal control (age and sex) matched group. All eyes underwent a full field ophthalmic, OCT and pattern VEP. In this study all subjects were examined in glaucoma clinic in private ophthalmic center. **Approval of the ethical committee and a written informed consent from all the subjects were obtained.** This study was conducted between June 2018 up to February 2019.

All cases examined as follow:

- Medical and family history.
- Visual acuity testing after correction.
- Intraocular pressure measurement with Goldman applanation tonometry.
- Slit lamp examination.
- Gonioscopy using three mirror lenses.
- Slit lamp biomiroscopy using 90 D lens.
- Indirect ophthalmoscopy.
- Humphrey 24-2 visual field testing.
- Optical coherence tomography (OCT) examination.
- Pattern Reverse Visual Evokred Potential (pRVEP) recording.

Inclusion Criteria:

- Glaucoma patient with primary open angel glaucoma.
- Best corrected visual acuity (BCVA) 0.8 or better.
- Glaucomatous early and moderate field defect.

Exclusion criteria:

- Patients with closed angle by gonioscopy.
- Patients with secondary open angel glaucoma.
- Patients with severe or advanced (POAG).
- Patients with retinopathy.
- Patients with neurological diseases or neurological field defect.
- Patients with a possible consistently unreliable visual fields (defined as a false negative > 33%, false positive > 33% and fixation losses > 20%) were excluded from the study.
- Patients with best corrected visual acuity (BCVA) less than 0.8.

Visual field examination:

- Central 24-2 full threshold automated static perimetry by Humphrey.
- A standard white stimulus was used in which its intensity can be varied from 0.007 to 10.000 asb, representing a range of over 6 log unit .The background illumination was 31.5 asb.
- Interpretation of the field test is dependent on the evaluation of the reliability indices .Good indices of fixation losses, false positive and negative errors (< 33%) were included.

OCT Assessment of the RNFL:

All scans were performed on Spectralis OCT software version 6.9.5, (Heidelberg engineering). Each eye was dilated with 1% tropicamide and 10% phenylephrine hydrochloride before recording the images. Internal fixation was used in all cases.

The device has a scanning speed of 40.000 A-scans/ second and an axial resolution of 7 μm which is responsible for improving the 3D image generated by the spectral domain OCT. A peripapillary circle scans with diameter of 3.5 micron are used to measure RNFL thickness in microns in each sector, compare it to a reference database. The measured average RNFL thicknesses are further classified in a color code and height profile.

Procedure for pattern reverse VEP recording:

1. The patient was seated comfortably at a distance of 1 meter away from the screen of the VEP monitor so that accommodation of eye is relaxed.
2. The source of light was stimulus. Standard disc EEG electrodes will be placed on the scalp areas after preparing the skin by spirit with a conducting jelly or electrode paste rubbed lightly into the area with a cotton swab.
3. 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.
4. 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 centre 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.

5. The recording was done monocularly for the left and right eyes separately.
6. At the viewing distance of 100 cm the check edges subtended 15 degree of visual angle.
7. Low frequency cut-off filter set was at 1-3 Hertz and the high frequency cut-off filter set at 100- 300 Hertz.
8. The sensitivity was kept at 2μV. The luminance of the white areas was 80 cd /m2 with a contrast of at least 75% compared to black squares.
9. The sweep duration was maintained between 250 ms to 500 ms. Responses to 200 stimuli were amplified and averaged for each eye, which were then analyzed by inline computer having automatic artifact rejection mechanism.
10. At least two trials for each eye were obtained and superimposed on one another to ensure replicability of the VEP pattern.
11. The absolute latencies of the peaks of positive wave P100 and the negative waves N75 were recorded.
12. The amplitude of P100 was measured from the preceding negative peak N75 to the peak of P100 and the latency is the time from stimulus onset to the peak of each component were considered in the test.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using ***Chi-square test.***

The comparison between two independent groups with quantitative data and parametric distribution were done by using ***Independent t-test*** while data with non parametric distribution were done by using ***Mann-Whitney test.***

Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

- P-value > 0.05: Non significant (NS)
- P-value < 0.05: Significant (S)
- P-value < 0.01: Highly significant (HS)

RESULTS

Table (1): Comparison between (control and patients) groups regarding demographic data, I.O.P, C/D ratio, and V/A.

		Control group No. = 20	Patients group No. = 20	Test value	P-value	Sig.
Sex	Female Male	18 (90.0%) 2 (10.0%)	18 (90.0%) 2 (10.0%)	0.000*	1.000	NS
Age (years)	Mean ± SD Range	47.90 ± 5.38 41 – 58	49.80 ± 6.57 40 – 58	-1.001•	0.323	NS
I.O.P	Mean ± SD Range	15.00 ± 2.10 12 – 18	24.25 ± 1.25 22 – 26	-16.907•	0.000	HS
C/D ratio	Mean ± SD Range	0.16 ± 0.07 0.1 – 0.3	0.56 ± 0.05 0.5 – 0.6	-20.765•	0.000	HS
V/A	Mean ± SD Range	0.95 ± 0.05 0.9 – 1	0.84 ± 0.05 0.8 – 0.9	7.254•	0.000	HS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*:Chi-square test; •: Independent t-test

The Previous table shows that there was highly statistically significant difference found between two groups regarding I.O.P with (p-value=0.000), C/D ratio with (p-value = 0.000) and V/A with (p-value = 0.000). While there was no statistically significant difference found between two groups regarding Age and Sex.

Table (2): Comparison between (control and patients) groups regarding Visual Field.

Visual Field		Control group No. = 20	Patients group No. = 20	Test value ǂ	P-value	Sig.
MD	Mean ± SD Range	-1.00 ± 0.81 -1.9 – 0.25	-6.11 ± 1.21 -8.12 – -4.09	-5.416	0.000	HS
PSD	Mean ± SD Range	1.53 ± 0.26 1.14 – 1.99	3.79 ± 2.20 1.52 – 7.82	-4.818	0.000	HS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
ǂ: Mann Whitney test

The Previous table shows that there was highly statistically significant difference found between two groups regarding Visual Field: MD (P=0.000), PSD (P=0.000).

Table (3): Comparison between (control and patients) groups regarding RNFLT .

RNFLT		Control group No. = 20	Patients group No. = 20	Test value	P-value	Sig.
Average	Mean ± SD Range	106.90 ± 2.77 102 – 110	87.80 ± 11.11 73 – 108	7.457	0.000	HS
T I	Mean ± SD Range	154.30 ± 14.12 138 – 171	94.85 ± 29.72 38 – 135	8.079	0.000	HS
N I	Mean ± SD Range	134.80 ± 10.51 122 – 159	90.85 ± 24.77 51 – 128	7.305	0.000	HS
T S	Mean ± SD Range	126.00 ± 16.90 95 – 153	110.45 ± 18.57 64 – 130	2.769	0.009	HS
N S	Mean ± SD Range	127.10 ± 11.50 107 – 143	102.05 ± 23.39 51 – 140	4.299	0.000	HS
Nasal	Mean ± SD Range	96.90 ± 10.64 72 – 110	65.00 ± 14.91 41 – 90	7.790	0.000	HS
Temporal	Mean ± SD Range	68.50 ± 4.26 62 – 76	78.75 ± 22.48 53 – 130	-2.003	0.052	NS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

The Previous table shows that there was highly statistically significant difference found between two groups regarding RNFLT: Average (p=0.000), TI (P=0.000) ,NI (P=0.009), TS(P=0.000), NS (P=0.000) and Nasal (P=0.000) While there was no statistically significant difference found between two groups regarding: Temporal (P=0.052).

Table (4): Comparison between (control and patients) groups regarding VEP parameters.

Pattern VEP		Control group No. = 20	Patients group No. = 20	Test value	P-value	Sig.
N75 latency	Mean ± SD Range	69.49 ± 4.81 60.5 – 74.5	76.81 ± 9.03 61.6 – 90.4	-3.200	0.003	HS
P100 latency	Mean ± SD Range	97.07 ± 4.76 90.1 – 104.2	109.07 ± 8.97 93.9 – 124.5	-5.283	0.000	HS
N75 -p100 mv	Mean ± SD Range	10.79 ± 1.12 9.4 – 12.6	7.34 ± 3.07 1.7 – 12.5	4.726	0.000	HS

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
•: Independent t-test

The Previous table shows that there was highly statistically significant difference found between two groups regarding VEP parameters: N75 latency (p=0.003), P100 latency (p=0.000) and N75-P100 mv (p=0.000).

Table (5): Correlation between Visual field (MD and PSD).

Visual Field	M D		P S D	
	r	P-value	r	P-value
Average RNFLT	**0.540***	**0.014**	**-0.610****	**0.004**
N75 latency	-0.356	0.124	**0.567****	**0.009**
P100 latency	-0.071	0.766	0.184	0.437
N75 -p100 mv	-0.019	0.936	-0.075	0.753
Age	**-0.530-***	**0.016**	0.277	0.237
I.O.P	**-0.447***	**0.048**	0.334	0.149
C/D ratio	-0.236	0.317	0.201	0.396
V/A	**0.592****	**0.006**	**-0.555***	**0.011**

The previous table shows that there was Positive correlation between MD and Average and V/A. While there was negative correlation between MD and Age and I.O. But there was Positive correlation between PSD and N75 latency. While there was negative correlation between PSD, Average RNFLT and V/A.

Table (6): Correlation between Average RNFLT.

	Average of NFLT	
	r	P-value
MD	**0.540***	**0.014**
PSD	**-0.610****	**0.004**
N75 latancy	-0.058	0.809
P100 latancy	-0.042	0.859
N75 -p100 mv	-0.078	0.744
Age	-0.152	0.523
I.O.P	-0.070	0.769
C/D ratio	0.333	0.152
V/A	0.237	0.314

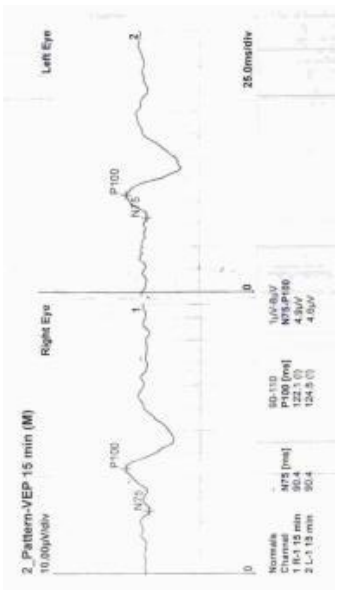
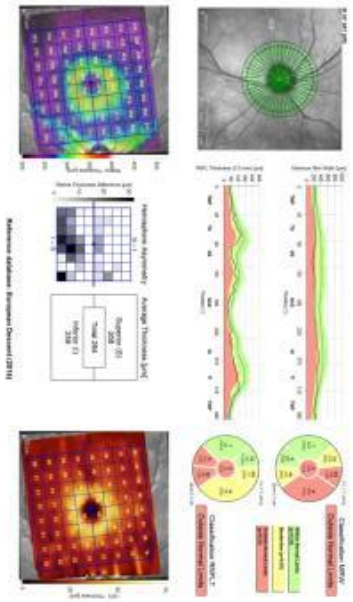
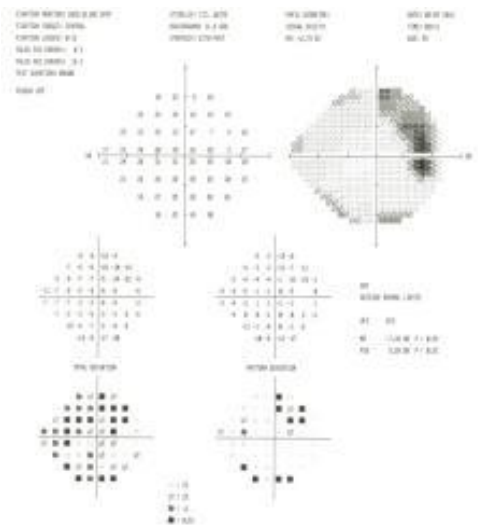
The previous table shows that there was Positive correlation between Average RNFLT and MD While there was negative correlation between Average RNFLT and PSD.

Table (7): Correlation between VEP parameters.

	N75 latency		P100 latancy		N75 -p100 mv	
	r	P-value	r	P-value	r	P-value
M D	-0.356	0.124	-0.071	0.766	-0.019	0.936
P S D	**0.567****	**0.009**	0.184	0.437	-0.075	0.753
Average	-0.058	0.809	-0.042	0.859	-0.078	0.744
Age	0.268	0.253	0.172	0.468	**-0.575****	**0.008**
I.O.P	0.262	0.265	0.203	0.391	-0.106	0.656
C/D ratio	0.332	0.153	0.175	0.461	-0.218	0.355
V/A	-0.300	0.198	0.000	1.000	-0.155	0.514

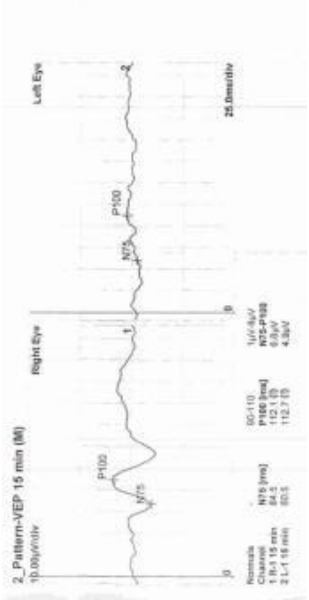
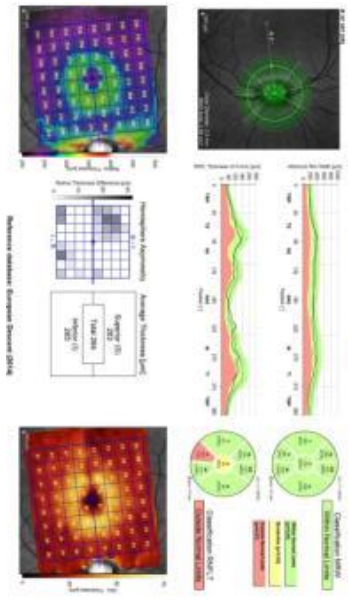
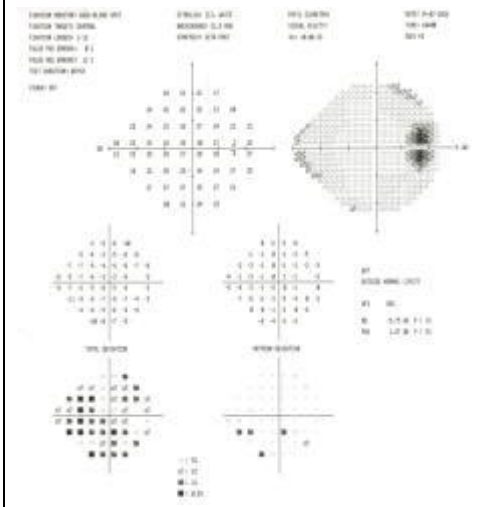
The previous table shows that there was Positive correlation between N75 latency and PSD While there was negative correlation between N75-P100 mv.

Figure (1): Case No. 1 Rt. Eye

VEP	OCT	Field
		

The previous figure example of moderate field defect of glaucoma patient: Vep shows delayed latency of P100 and reduction of amplitude of N75-P100mv when compared to control.

Figure (2): Case No. 2 Rt. Eye

VEP	OCT	Field
		

The previous figure example of mild field defect of glaucoma patient: Vep shows delayed latency of P100 and reduction of amplitude of N75-P100mv when compared to control.

DISCUSSION

In our study RNFL thickness was highly significantly thinner in patients group than in control group in all quadrants (superior, nasal and inferior) as well as in the average RNFL thickness (P =0.000) .except temporal quadrant which was non-significant (P=0.052).

Another study done by **Shiota *et al.*** [9] in the study of diagnostic capability of OCT in evaluating the degree of glaucomatous retinal nerve fiber change. They studied the average RNFL thickness in normal subjects, early glaucoma, moderate glaucoma and blind glaucoma. Their results was 102.30 ± 10.34 , 77.68 ± 15.7 , 66.07 ± 14.2 and 44.93 ± 4.93 um respectively there were significant difference in all RNFL thickness parameters between normal and all glaucoma subgroups p< 0.001.Their study included 160 eyes of 160 healthy subjects & 134 eyes 0f 134 patients with POAG. Peripapillary RNFL thickness was measured on OCT using the fast RNFL thickness protocol. The RNFL thickness parameters used for evaluation included average RNFL thickness and inferior, superior, nasal and temporal RNFL thickness.

Harewerth *et al.* [10] had decided that standard automated perimetry (SAP) measures of visual field defects and OCT measures of RNFL defects are correlated measures of glaucomatous neuropathy. The normal inter subject's variability and the dynamic ranges of the measurement suggest that RNFL thickness may be a more sensitive measurement for early stages and perimetry is a better measure to moderate to advanced stages of glaucoma **[10].**

Paunescue *et al.* [11] had provided that OCT provides a more reliable ONH analysis because of its consistent location of the reference plane and automated determination of the ONH based on fixed anatomic landmark, the retinal pigment epithelium (RPE). OCT is able to position the disc margin automatically at locations where the RPE ends**.**

Leung *et al.* [12] has studied a comparison of the optic disc and retinal nerve fiber layer in detecting glaucomatous damage. They compared the relationship between optic nerve structural measures and visual function as well as diagnostic sensitivity for glaucoma detection between RNFL and neuroretinal rim measurements. In their study populations at 90% specificity, the diagnostic sensitivities for detecting glaucomatous damage were 82.7% , 67.3% % and 52.6% for RNFL, rim area, rim/disc area and rim volume respectively. The RNFL showed a stronger structural function association and a higher diagnostic sensitivity for glaucoma detection than did the neuroretinal rim.

In study done by **Harewerth *et al.*** [10] to detect the relationship between RNFL and Perimetry measurements. They investigated the relationship between SAP results of RGCs and OCT measures of ganglion cell axons. They suggested that RNFL thickness may be a more sensitive measurement for early stages and perimetry is a better measure for moderate to advanced stage of glaucoma.

For RNFL thickness, in contrast to ONH parameters numerous reports have arrived at the consistent conclusion that it is a useful surrogate market for assessment of structural damage in glaucoma **[13].**

The results in this study coincides with the results of the study done by **Anton *et al.*** [14], to assess Stratus OCT, original parameters for identifying glaucomatous damage and to evaluate differences among glaucomatous, ocular hypertensive and normal eyes. The study was done at two centers. The study included 55 normal individuals, 95 patients with ocular hypertension (OHT) and 79 patients with glaucoma. RNFL and ONH protocols were used to evaluate all study participants. Measurements taken were RNFL thickness, RNFL asymmetry between both eyes, rim volume, rim width, disc area, cup area, rim area, cup disc ratio horizontal and vertical. The main outcome measures were the differences in OCT parameters among groups, and the area under receiver operating characteristic curves .They found that the mean RNFL thickness around the disc and superior and inferior RNFL thickness were significantly thinner in glaucomatous eyes than in OHT or normal eyes p< 0.001.Rim parameters were significantly smaller in glaucomatous eyes than in normal and OHT p<0.001. They concluded that almost all RNFL and disc parameters showed significant differences and discriminated between glaucomatous and normal eyes.

Pillai *et al.* [15] reported that the SD-tVEPs can discriminate between healthy and glaucomatous eyes. Low-contrast latency showed the highest accuracy in discriminating among patients with mild, moderate, and severe glaucoma versus controls **[15].**

In our study we studied the pattern VEP of early and moderate glaucomatous patient reported affection of the N75 and P100 by causing both reductions in amplitude and increases in latency when compared to control (age and sex) matched group.

That coincided with study done by **Goyal *et al.*** [16] reported that transient VEP amplitude drop was observed in response to elevated IOP. They reported an increase in latency of the positive wave (P-100) in glaucoma patients and ocular hypertensives as compared to normal .They also

found that the latency in glaucomatous eyes was increased as compared to ocular hypertensives.

And by statistically analysis of the our results, there were highly statistically significant differences between the VEP measurements of the glaucoma group than control group ($p<0.01$). This conclusion supported from the study done by **Taksande and Rawekar** [17], to assess the comparative evaluation between RNFLT and PRVEP in early diagnosis of primary open angel glaucoma. Results show In POAG eyes, mean p100 latency of 108.39±3.66 and in control group it was 101.05±1.29 which was significantly prolonged when compared with those of controls (*T value= 16.90, p=0.0001*) and mean N75 p100 amplitude of 3.33±1.13 and in control group it was 5.65±0.62 which was significantly reduced when compared with those of controls (*t-value=16.07, p=0.0001*).

Another study done by **Mukesh *et al.*** [18] to compare visual evoked potentials (VEPs) in primary open angle glaucoma (POAG) patients and controls so as to find any evidence of differences in VEP latencies and amplitudes .the results showed The pattern reversal latency N75 and P100 of cases was longer than the control and All the pattern reversal VEP amplitudes (N75 and p100) were significantly lesser in cases.

In our study, there was non- significant correlations between RNFLT and any of VEP measurements ($p>0.05$). That coincide with the study done by

Vincenzo *et al.* [19] to assess the Correlation between Optical Coherence Tomography, Pattern Electroretinogram, and Visual Evoked Potentials in Open-angle Glaucoma Patients. The results showed PERG and VEP parameters showed a significant (P <0.01) delay in implicit time and a reduction in peak-to-peak amplitude. In OAG eyes, the NFL overall and NFL temporal values were significantly correlated ($P < 0.01$) with the PERG P50 implicit time and P50-95 peak-to-peak amplitude. No correlations ($P > 0.01$) between NFL values and VEP parameters were found. The lack of correlation between average RNFL thickness and PRVEP responses could also be explained by considering that PRVEP responses depend on the magnitude and timing of afferent inputs to the visual cortex and result from both retinal activity and neural conduction along the post retinal visual pathways [19].

Another study done by **Grippo** [20], who found that there is not much change in latency of P-100 in glaucoma or ocular hypertension. Further the increase in latency could not correlate with the perimetric field loss. Thus they came to the conclusion that VEP is an indicator of retinal ganglion cell death rather than damage. Hence it is of little use in detecting early nerve dysfunction.

Horn *et al.* [1] suggested that VEP with blue on yellow pattern stimulation may be useful in detecting early glaucomatous damage. This is based on the assumption that the short wavelength sensitive nerve pathway or the blue wave sensitive pathway is the earliest to be affected in glaucoma. Hence this S-cone VEP may pick up early changes not evident on conventional VEP [1].

CONCLUSION AND RECOMMENDATION

The pattern visual evoked potential (VEP) has been shown to be sensitive to optic nerve lesions caused by ischemia. Glaucoma has also been reported to affect the VEP by causing both reductions in amplitude and increases in latency. By studying the pattern VEP of glaucomatous patient when compared with (age and sex) matched control group reported affection of the VEP by causing both reductions in amplitude and increases in latency. The results show that there were highly statistically significant differences between cases and control groups of the VEP measurements **(P-value< 0.01).**

Thus the present study reveals deficit in optic pathway conduction. Thereby, VEP can be used as a noninvasive objective test to detect optic nerve damage at the earlier stage in Glaucoma subjects to prevent or delay the progression to irreversible stage.

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