

Correlation of optic nerve head changes in glaucoma patients with asymmetric pupillary light reflex, VEP and visual functions

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Abstract:

Background: Glaucoma is defined as a group of eye disease with multifactorial etiology, characterized by an acquired loss of retinal ganglion cells, progressive optic neuropathy with morphological abnormalities in the optic nerve head and, visual field defects, in which raised intraocular pressure(IOP) is modified risk factor. As glaucoma is a silent disease without much signs and symptoms, it is hard to diagnose the condition, especially in developing countries like India. Assessment of visual field defects is made by Perimetry. Asymmetric damage between eyes with glaucoma often results in creating relative afferent pupillary defect (RAPD). Colour vision assessment is done as red-green defects accompanied glaucomatous optic neuropathy. Due to raised IOP retinal nerve fibre bundle entering the optic nerve gets damaged leading to altered Visual evoked potential(VEP) waveforms.

Materials and Methods: In this case-control observational study, 100 eyes of 100 patients were included. 50 eyes of 50 patients of primary open angle glaucoma and 50 eyes of 50 patients of control cases were enrolled.

Results: The comparison of glaucoma staging system with optic disc changes, asymmetri pupillary light reflex, color vision defect and VEP were found to be clinically significant.

Conclusion: Since glaucoma is considered to be second most common cause of blindness in India but having an major advantage of being preventable by early diagnosis and prompt treatment, early diagnostic tools like RAPD, colour vision and VEP have proved to be assistive tool to perimetry and optic nerve head changes in primary open angle glaucoma.

Key Word: primary open angle glaucoma; RAPD; VEP; colour vision; perimetry.

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I. Introduction

Open angle glaucoma is referred to as “silent killer of sight” due to its progress without causing any obvious symptoms – or really any symptoms at all. Glaucoma is fast emerging as major cause of blindness in India second only to cataract.(1) According to WHO it is the second most common cause of blindness in the world after cataract.(2) Approximately 60.5 million people were having glaucoma in the year 2010 in the world.(3)Glaucoma is defined as a group of eye diseases with multifactorial etiology, characterized by an acquired loss of retinal ganglion cells, progressive optic neuropathy with morphological abnormalities in the optic nerve head and visual field defects, in which raised intraocular pressure is major risk factor. This damage to the ONH causes partial to full loss of the visual field, which is the portion of space in which objects are simultaneously visible in the steadily fixating eye (Harrington, 1976). Damage to visual field is irreversible, however, the loss can be transitory in the early stages of glaucoma. If the condition is untreated the damage to the affected visual field usually worsens and spread until eventually complete loss of vision occurs. The current study aims to correlate few parameters like symmetry of pupillary light reflex, VEP, colour vision defect and visual field defects with optic nerve head changes in glaucoma patients.

II. Material And Methods

This case control observational study was carried out on patients of Department of Ophthalmology at Acharya Vinoba Bhave Rural Hospital, Sawangi(Meghe), Wardha, Maharashtra from October 2013 to September 2015. A total 100 eyes of 100 patients (both male and females) were enrolled in this study.

Study Design: Cross sectional, comparative (case- control) and observational study

Study Location: This was a rural hospital based study done in Department of Ophthalmology, at Acharya Vinoba Bhave Rural Hospital, Sawangi(Meghe), Wardha, Maharashtra.

Study Duration: October 2013 to September 2015.

Sample size: 100 patients.

Subjects & selection method: The study population was drawn by random selection of primary open angle glaucoma patients who presented to Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe) from October 2013 to September 2015. Patients were divided into two groups (each group had 50 patients) as cases and controls :

Case (N=50 patients) – 50 eyes of 50 patients of primary open angle glaucoma

Controls (N=50 patients)- 50 eyes of 50 control subjects with normal eye

Inclusion criteria:

1. All patients above 40 years of age
2. Primary open angle glaucoma
3. Visual acuity 6/24 or better
4. Reliable visual fields
(fixation loss <20%, false negatives <33%, false positives <33%)

Exclusion criteria:

1. Closed anterior chamber angle
2. Patients with any other pathology for colour vision defects
3. Secondary and normal tension glaucoma
4. Hazy media occluding view of fundus.
5. Other ocular diseases affecting vision or visual field

Control subjects criteria:

1. Normal IOP <21 mm of Hg.
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 6/12 or better.
6. Negative family history for glaucoma.

Procedure methodology

A complete eye examination of each patient was performed after detailed history and written informed consent. Visual acuity testing was done using Snellen's chart. Anterior segment examination was done under diffuse torch light illumination. Swinging flash light test was done to visualize the symmetry of pupillary light reaction. Presence of RAPD in illuminated eye was indicated by any of three findings: a small initial momentary constriction followed by greater dilation, initially no apparent change followed by dilation, or initial immediate dilation. In cases where only one pupil was reactive, if the eye with the reactive pupil showed a marked, maintained contraction when the light was shone in it, but dilated when the light was shone in the eye with fixed pupil, this was considered to indicate an RAPD in the eye with the fixed pupil. RAPD grading was done using Bell et al(4) grading.

Detailed anterior segment examination was done under high magnification of slit-lamp. Applanation tonometry was done in each patient to assess the intraocular pressure. Gonioscopy using 4 mirror gonioscopy was done for each patient in the study to confirm open anterior chamber angle in both the eyes. Fundus examination was done by slit lamp biomicroscopy using 78D/90D lens. Changes visualized in the optic nerve head i.e. changes in cup disc ratio vertically were clinically divided in three groups i.e. ≤ 0.5 , 0.6-0.7 and > 0.7 .

Color vision testing was done monocularly using Ishihara Chart test (38 plates) type unilaterally for both the eyes. The plates were held at a distance of 75 cm from the subject. The numerals which are seen on plates 1-25 are stated and each answer should be given without more than 3 seconds delay. If subject is unable to read numerals, plates 26-38 are used and the winding lines between two x's are traced. Each tracing should be completed within 10 seconds. Out of 21 if > 17 plates are read normally, the colour vision is regarded as normal and if < 13 it is labeled as deficient. Classification of color vision defect in Protan or Deutan is done according to the standard guidelines provided by Dr. Shinobu Ishihara.

Automated static perimetry was done using Humphrey Field Analyser (HFA II-1 series, Carl Zeiss Meditec). 30-2 was tested using the SITA strategy. Glaucoma staging system (GSS) was used in this study to classify field depression. Visual field depression was categorized as early, moderate, advanced and severe as per GSS. Pattern standard deviation plot is divided into 4 parts by horizontal and vertical meridian. 19 points on the temporal side and 18 on nasal side. Test points below $< 0.5\%$ significance level were also counted. Patients were divided into 6 groups depending upon the significance level of PSD value i.e. $< 0.5\%$, $< 1\%$, $< 2\%$, $< 5\%$, $< 10\%$ and $> 10\%$.

Mean deviation values obtained in db were used and divided into four groups i.e. ≤ 6 db, 6.01-12 db, 12.01-20db and ≥ 20 .01db

Visual evoked potential was done in all patients which was pattern reversal checkerboard method using RMS II polyrite D. Latency (P-100) and Amplitude (P-100-N75) were recorded. Total values of Latency (P-100) were added after testing of 50 controls and cases. The maximum value was obtained after addition of standard deviation to the mean value. It was found to be 102. POAG patients were divided into 2 groups on this basis i.e. >102 and <102 . Similarly amplitude (P-100-N75) values were obtained and added and mean was calculated. It was found to be 4.5. POAG cases were divided into 2 groups i.e. >4.5 and <4.5

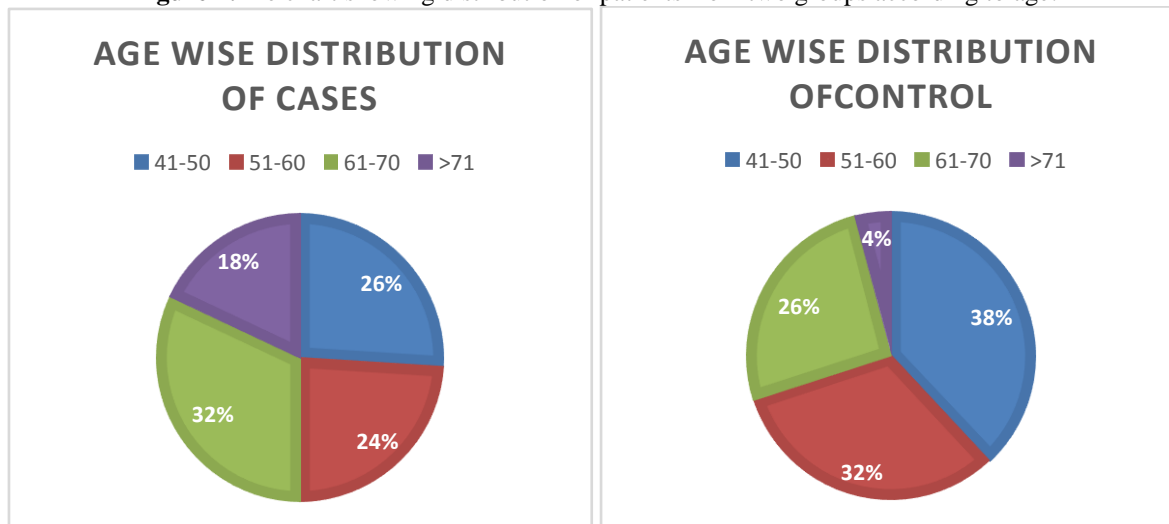
Statistical analysis

The data on demographic parameters like age and gender was expressed in terms of frequencies. Also, the descriptive statistics like mean, standard deviation and median were obtained for age in both the study groups. The mean IOP between 2 groups was compared for statistical significance using t-test for independent samples. Frequency distribution of patients was obtained for optic nerve head changes, color vision defects and affected percentage in each quadrant for both the groups. Distribution was also obtained for perimetry in each group and compared using Fishers’ exact test. The mean VEP between two groups compared using t-test for independent samples. The significance of association between glaucoma staging and C:D ratio, RAPD grade, VEP latency, VEP amplitude, color vision was obtained using Fisher’s exact test. Further, the association of C:D ratio with RAPD grading, color vision, VEP latency and VEP amplitude, mean deviation were tested for statistical significance using Fisher’s exact test. All the analyses were performed in R-3.0.0 programming language and the statistical significance was evaluated at 5% level.

III. Result

Age wise distribution of study groups is shown in figure 1. In case group, there were 16 (32%) patients in the age group 61-70 years, followed by 13(26%) patients in the age group 41-50 years, while 12(24%) patients in 51-60 years. The mean age of patients in this group was 60.36 ± 10.09 years with a median of 61.5 years. In control group, there were 19(38%) individuals in the range 41-50 years, 16(32%) in 51-60 years and 13(26%) in 61-70 years. Mean age was 55.61 ± 9.88 years with median of 55 years.

Figure 1: Pie chart showing distribution of patients from two groups according to age.



In our study, case group included 33 males and 17 females whereas there were 19 males and 31 females in control group.

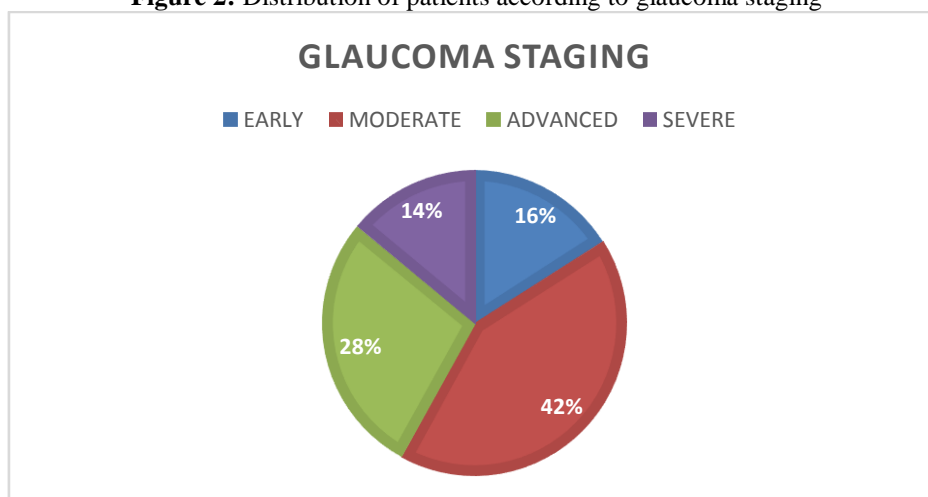
Table 1: Distribution of patients gender wise in two groups

Gender [No.(%)]	Number and Percentage	
	Case(n=50)	Control(n=50)
Male	33(66%)	19(39%)
Female	17(34%)	31(62%)

In this study, mean IOP of patients in case groups was found to be 22.36 mm of Hg and standard deviation was 2.25 mm of Hg while in control group mean IOP was 14.08 mm of Hg and standard deviation was 2.25 mm of Hg. The difference in the mean IOP in two groups was statistically significant(p -value < 0.0001)

Distribution of patients according to glaucoma staging was found as 8 in early stage, 21 in moderate, 14 in advanced and 7 in severe stage.

Figure 2: Distribution of patients according to glaucoma staging



In our study we have studied association of glaucoma staging with CD ratio in patients from case group. Observations are shown in table no. 2.

Table 2: Association between glaucoma staging and CD ratio in patients from case group

Glaucoma staging	CD Ratio (V) [No.(%)]			Total
	≤ 0.5	0.6-0.7	>0.7	
Early	4(50%)	4(50%)	0	8
Moderate	5(23.8%)	11(52.4%)	5(23.8%)	21
Advanced	1(7.01%)	8(57.1%)	5(35.2%)	14
Severe	0	1(14.3%)	6(85.7%)	7
Total	10(20%)	24(42%)	16(32%)	50

Association of glaucoma staging with RAPD was studied in this study. Out of 21 moderate cases, 18(85.71%) had no RAPD. However, in the advance stage, 8(57.14%) out of 14 showed RAPD. In advanced cases, 5(71.43%) out of 7 patients showed RAPD. The association between staging and RAPD was found statistically significant with p-value of 0.0039.

Table 3: Association of glaucoma staging and RAPD in patients

Glaucoma staging	Number (%)		Total
	RAPD	None	
Early	1(12.5%)	7(8%)	8(16%)
Moderate	3(14.29%)	18(85.71%)	21(42%)
Advanced	8(57.14%)	6(42.86%)	14(28%)
Severe	5(71.43)	2(28.57%)	7(14%)
Total	17(34%)	33(66%)	50

Table 4: Association between glaucoma staging and colour vision in patients

Glaucoma staging	Colour vision defect (No %)		Total
	RGD	WNL	
Early	0	8(100%)	8
Moderate	4(19%)	17(81%)	21
Advanced	5(35.7%)	9(64.3%)	14
Severe	5(71.4%)	2(28.6%)	7
Total	14(28%)	36(72%)	50

The association between glaucoma staging and colour vision was determined with the results obtained as shown in the table above. In the early stage, all the 8 cases had no colour vision defect.

In the moderate category, 17 (81%) out of 21 cases had no defect. Even in the advanced stage cases, majority ie 9 (64.3) cases had no colour vision defect. However, in the severe category, out of 7 patients, 5 (71.4%) had defect, as a result the association between stage and colour vision defect was found statistically significant with p-value of 0.0132 (p<0.05). A graphical representation of the data is given in the figure below.

Figure 3: Bar chart showing the distribution of patients according to glaucoma staging and colour vision.

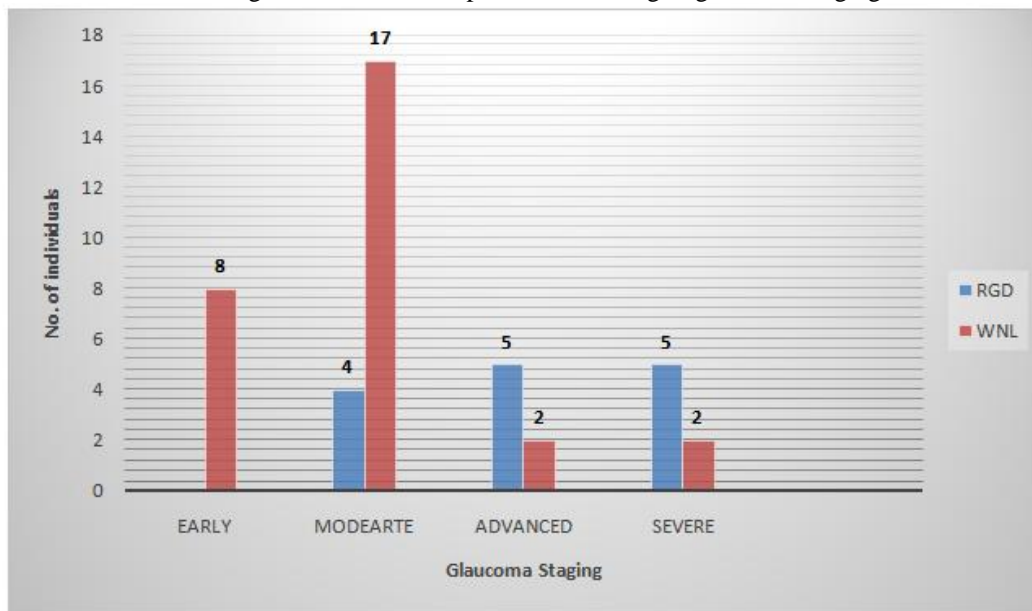


Table 5: Association of glaucoma staging and visually evoked potential latency in patients

Glaucoma staging	Visually evoked potential latency (No %)		Total
	<102(P100)	>102(P100)	
Early	6(75%)	2(25%)	8
Moderate	9(42.8%)	12(57.2%)	21
Advanced	0	14(100%)	14
Severe	1(14.3%)	6(85.7%)	7
Total	16(32%)	34(68%)	50

Table 5 provides association between glaucoma staging and visually evoked potential (VEP) latency. In the early stage, majority ie 6 (75%) cases had VEP latency < 102 (P100), while in patients with subsequent stages, the proportion of cases with VEP latency was more in >102(P100) category, as evident from the table. As a result, the association between glaucoma staging and VEP Latency was found statistically significant with p-value of 0.0005.

Figure 4: Bar chart showing distribution of patients according to glaucoma staging and visually evoked potential latency.

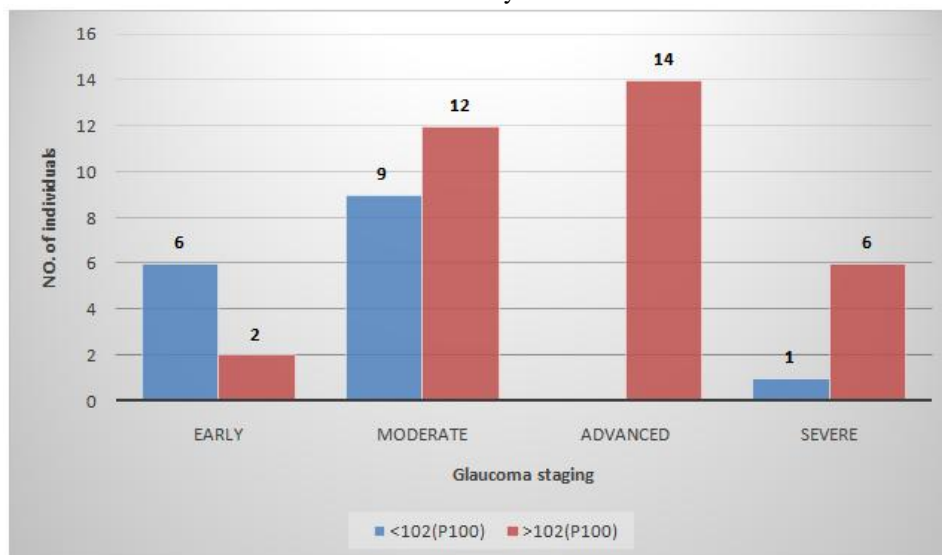
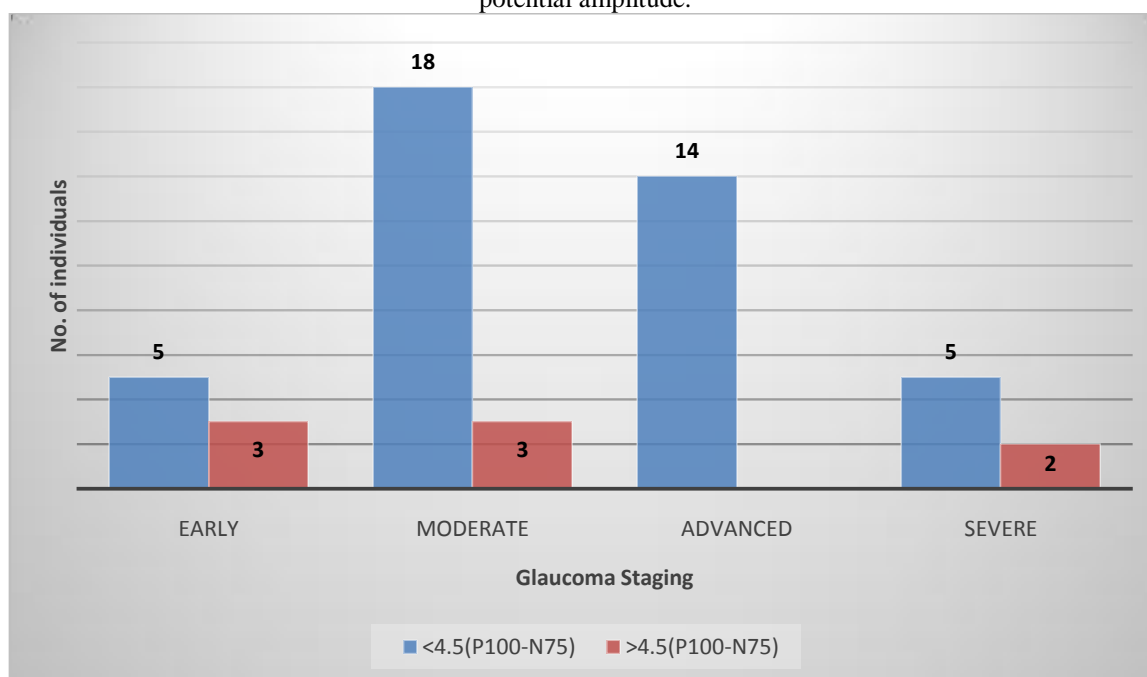


Table 9: Association of glaucoma staging and visually evoked potential amplitude in patients

Glaucoma staging	Visually evoked potential amplitude [No (%)]		Total
	<4.5(P100- N75)	>4.5(P100- N75)	
Early	5(62.5%)	3(37.5%)	8
Moderate	18(85.7%)	3(14.3%)	21
Advanced	14(100%)	0(0%)	14
Severe	5(71.4%)	2(28.6%)	7
Total	42(84%)	8(16%)	50

The association between glaucoma staging and VEP amplitude was determined based on the frequency distribution shown in table 3. In the early stage, 5 (62.5%) out of 8 cases had VEP amplitude <4.5(P100- N75), while in patients with moderate staging, 18 patients had amplitude <4.5(P100- N75). In the subsequent stages, majority of the patients had amplitude <4.5(P100- N75). The resulting association between stages and VEP amplitude was found statistically insignificant with p-value of 0.0606 (p>0.05).

Figure 5: Bar chart showing distribution of patients according to glaucoma staging and visually evoked potential amplitude.



IV. Discussion

In this study, we have established relationship of various parameters of glaucoma using GSS. An increased number of stages helps in giving glaucomatous disease severity of any type a precise stage, and there is a good standardization of all parameters. Hence, stating the significance of GSS in POAG evaluation.

Correlation of GSS with CDR:

Using GSS, it was found that as disease progresses, severity of optic nerve head changes also increased. Our study shows correlation of CDR with stages, i.e. maximum number of patients with >0.7 CDR were in severe stage of glaucoma. In advance cases, maximum patients were with 0.6-0.7CDR. In the early stages, cases had CDR <0.5. Our comparison was found to be statistically significant(p< 0.0099) using fisher’s exact test.

Similar results were reported in other studies.

Sreedevi K.V.N. et al correlated the optic disc changes with visual field defects in POAG(5).

Correlation of GSS with RAPD:

We also compared symmetry of pupillary light reflex with stages of glaucoma in Table 6. A total of 5 out of 7 (71.43%) patients of severe stage were found to have RAPD, as well as 57.14% patients showed RAPD in the advance cases. This was highly suggestive of the fact that as glaucoma advances and neuropathy ensuing glaucoma, RAPD also advances in PAOG patients.

In the study conducted by **Chang DS et al**, it was found that the between-eye asymmetry in PLR amplitude measured using pupillography correlated strongly with both the difference in RNFL thickness and difference in VF MD between the two eyes, it was similar to our study where correlation of visual field defect with RAPD was established(6).

Correlation of GSS with colour vision defect:

In our study maximum cases of severe stage of glaucoma had colour vision defect mainly red green colour defect, as also the advance and moderate stage had the same finding, thus inferring that colour vision defect in POAG is common in advance stages of glaucoma especially, the red green colour defect.

In a study conducted by **Papaconstantinou D. et al** it was found that the study of colour vision deficiency shows a significant deterioration in those patients who later developed severe glaucomatous defects in HVF tests. Thus there is a statistically significant correlation between the results of colour perception testing and HVF indices which is similar to correlation established in our study(7).

Correlation of GSS with VEP:

Visual evoked potential was compared with stages of glaucoma using latency(P-100) and amplitude (P-100-N75) as in table 8. 6 out of 7 patients of severe stage showed delayed latency. And 100% of the patients in advance stage showed similar result. In amplitude correlation, maximum number of cases of advance and severe stages of glaucoma showed significant result.

Ruchi Kothari et al evaluated whether glaucomatous visual field defect particularly the pattern standard deviation (PSD) of Humphrey visual field could be associated with visual evoked potential parameters of patients having primary open angle glaucoma. The results of the study were found to be similar to what was observed in our study(8).

V. Conclusion

Symmetry of pupillary light (RAPD) was found to be significantly correlated in glaucoma patients thus can be used as a diagnostic tool in glaucoma. VEP can serve as an important diagnostic tool for evaluation in POAG patients. Color vision and visual field defect can be important diagnostic tool to early diagnosis staging & treatment in glaucoma.

Thus, we conclude that since glaucoma is considered to be second most common cause of blindness in India but having a major advantage of being preventable by early diagnosis and regular prompt treatment, early diagnostic tools like RAPD, color vision and VEP have proved an assistive tool to perimetry and optic nerve head changes in POAG patients.

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