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Retinal Structure and Microvasculature in Symmetrical Advanced Glaucoma in Paired Eyes with Vision Asymmetry

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BACKGROUND

Glaucoma, a chronic progressive optic neuropathy, is the leading cause of irreversible blindness worldwide. Although relatively well-preserved until the late stages of the disease, central visual acuity is a major concern for all glaucoma patients and one which directly affects their quality of life. Despite this, it is an understudied functional parameter as suggested by a dearth of literature on structural correlation of vision in glaucoma patients.

During our routine clinical setting, we often come across primary glaucoma patients with bilaterally-symmetrical advanced structural glaucomatous damage on clinical evaluation having significant inter-eye vision asymmetry. The reason for the same remains elusive, and this motivated us to analyze the structural-functional relationship between logMAR Best Corrected Visual Acuity (BCVA) and Optical Coherence Tomography (OCT) based structural/microvascular parameters with a special focus on imaging of the macular area which contains ganglion cells sub serving foveal visual acuity.

Paired eyes of each study subject (better vision eye vs. worse vision eye), were compared with regard to Optic Nerve Head (ONH) parameters, Retinal Nerve Fibre Layer (RNFL) & macular Ganglion Cell Complex (mGCC) thickness, and peripapillary and macular vessel densities, in order to find the correlation of these structural parameters with functional outcome in our study, the central visual acuity. We further assessed these parameters in an attempt to find predictors of vision loss in advance glaucoma which could help the clinicians closely monitor at-risk patients and ensure timely and more aggressive vision saving interventions.

AIMS AND OBJECTIVES

- ✓ Correlate inter-eye visual acuity asymmetry with the parameters of macular GCC and OCT-A, in patients with bilaterally symmetrical advanced glaucoma.
- ✓ Determine predictors of visual loss in advanced glaucoma.

Primary outcome

- ✓ Correlation of structural markers (macular GCC and cpRNFL) with visual acuity in advanced glaucoma
- ✓ Correlation of TSNIT vessel density with visual acuity in advanced glaucoma.

Secondary outcome

- ✓ Identification of visual loss markers in advanced glaucoma

Study design

This is a hospital based, observational cross-sectional study, conducted at the in a tertiary care medical college and hospital of North India over a period of 12 months.

Inclusion criteria

- ✓ Bilaterally advanced (cup: disc ratio of > 0.7) primary glaucoma having glaucomatous optic disc with similar CDR (asymmetry in cupping of ≤ 0.1)
- ✓ Glaucoma patients with inter-eye vision asymmetry (≥ 2 lines Snellen acuity)
- ✓ Visual fields with advanced glaucomatous damage as per Hodapp-Parrish-Anderson criteria

Exclusion criteria

- ✓ Media opacity precluding good quality OCT scans (corneal opacities, significant cataracts, chronic uveitis)
- ✓ Refractive error outside – 6.0 D, + 3.0 D spherical equivalent and cylindrical correction outside ± 3.0 D
- ✓ Any other non-glaucomatous macular or optic nerve pathology that may affect vision
- ✓ History of vitreoretinal surgery or previous retinal laser procedures

Methodology

48 advanced primary glaucoma patients meeting the inclusion criteria and providing an informed consent, were enrolled in the study and evaluated on the basis of parameters mentioned below.

All participants underwent a comprehensive ocular examination, including a detailed medical history, current glaucoma treatment history, along with the demographic data, best corrected visual acuity (BVCA) measurement by Snellen chart (converted to logMAR scale). This was followed by slit-lamp biomicroscopy, Goldmann applanation tonometry (GAT) for IOP, central corneal thickness (CCT - by AS-OCT, OPTOPOL Tech.), axial length (AL - by A-scan, Sonomed EscalonTM), 4-mirror Gonioscopy (Sussman), dilated fundus examination (by 90D lens), visual field (VF) assessment with a Humphrey Field Analyser (HFA) using 24-2 SITA-Fast strategy.

The OCT measurements of the peripapillary RNFL and the macular parameters were obtained using 'SOCT Copernicus REVO' (Version: 9.7.0, OPTOPOL Technology) and OCT-A imaging was done using AngioScan (Nidek Inc., Aichi, Japan). Peripapillary RNFL thickness (in µm) was determined in ONH mode (3D 6×6 mm), in which data along a 3.20-mm-diameter circle around the optic disc, along with ONH parameters and average & sectoral RNFL thickness, were computed. The macular GCC & GCL+IPL thickness (in µm) measurement utilized an automated segmentation algorithm of the SD-OCT machine, was acquired in superior, inferior, superonasal, superotemporal, inferonasal, & inferotemporal sectors.

Sample size for analysis of OCTA based vessel densities (mm-1) had to be curtailed to 12 patients (25% study subjects) owing to very low vision and fixation issues encountered in advanced glaucoma patients. The ONH vessel density (VD) was measured in 3 slabs – Nerve Head (NH) layer, – Radial Peripapillary Capillary (RPC) layer, and – Lamina Cribrosa. The macular VD was assessed in two capillary plexus levels: Superficial Layer (SL) and Deep Layer (DL).

Scans of sufficient image quality for optimal evaluation, having a good signal strength index (SSI) of > 7, without any significant motion artifacts or segmentation errors were acquired. Each patient underwent all the above-mentioned scans at the same visit.

Statistical Evaluation

The collected data was transformed into variables, coded and entered in Microsoft Excel spreadsheet, followed by analysis and statistical evaluation using Statistical Package for Social Sciences (SPSS), IBM, USA, version 25.0.

Normality of each variable was assessed by using the Kolmogorov – Smirnov test and Shapiro – Wilk test.

Quantitative data was expressed by mean ± standard deviation (SD) or median with interquartile range depending on normal distribution. The difference between the two means was tested by Student t-test or Mann–Whitney U test.

Qualitative data was expressed in frequency and percentage (%) and difference between the proportions was tested by Chi Square test or Fisher's Exact test.

Correlation of logMAR BCVA with various ocular parameters, as mentioned above, was evaluated using Spearman's rank correlation.

Finally, area-under-receiver-operator-characteristic (AUROC) curve analysis was performed to obtain cutoff values for different ocular (baseline and OCT-based) parameters to determine predictors of decreased visual acuity (defined as Snellen ≤6/60) in advanced glaucoma and their sensitivity & specificity was also calculated. 'p' value less than 0.05 was considered statistically significant.

RESULTS AND CONCLUSIONS

There has been a significant transition in the way structural damage was assessed in glaucoma – optic nerve head examination paved way for peripapillary RNFL which was followed by ganglion cell analysis, and now OCTA based microvascular analysis is on the way to become an important adjuvant monitoring tool in the glaucoma specialists' armamentarium.

✓ RNFL and mGCC were significantly thinner in eyes with poor vision, despite both eyes having similar advanced cupping and field defects. In addition to this, vessel density in nerve head layer of ONH area and both superficial & deep layer of macular area was significantly less in these eyes (all $p<0.05$).

✓ Among RNFL parameters, superior RNFL thickness (r = - 0.348, p=0.001) showed the highest negative correlation with logMAR BCVA, followed by average (r= - 0.285, p=0.005), temporal (r= - 0.284, p=0.005) and inferior RNFL (r= - 0.246, p=0.016). The correlation of nasal RNFL thickness to vision was not statistically significant.

✓ All 6 sectors of mGCC thickness were significantly correlated to vision. Inferior mGCC thickness (r = -0.553, p=0.000) showed the highest negative correlation, followed by inferonasal and inferotemporal sectors. GCL+IPL sectoral thickness analysis also followed similar trend of correlation with logMAR BCVA.

✓ Macular GCC was clearly superior (with higher correlation coefficient) to peripapillary RNFL thickness in terms of correlation to vision loss in advanced glaucoma (higher correlation coefficient). Thus, GCC mapping may provide good alternative to optic disc imaging and RNFL analysis in advance glaucoma with poor fixation.

✓ Despite limited sample size, vessel density in macular area outshone above parameters and showed a strong negative correlation with logMAR BCVA ($p<0.005$), making it a promising investigation relatively unaffected by the 'floor effect' that limits the diagnostic utility of conventional structural parameters in advanced glaucoma.

✓ Sectoral analysis of all OCT parameters, indicated that sectors involving papillo-macular bundle (PMB) area provided a better correlation with logMAR BCVA and should be the focus of imaging to better monitor vision decline in advanced glaucoma.

✓ Predictors of vision asymmetry and vision loss in advanced glaucoma (Snellen BCVA <6/60; logMAR BCVA ≥1.0) were determined using AUROC curves, to obtain a cut-off for various OCT and OCTA parameters. Macular GCC and macular vessel density emerged as significant predictors for decreased vision, with macular VD especially showing high sensitivity and specificity for each of the sectoral VD cutoffs.

This study highlights the need for further research with a much larger dataset, to better delineate change or progression by analyzing scans of the same paired eyes over time. Focus on macular nerve fibres and microvasculature with detailed modeling could help in predicting future functional progression from existing structural damage.

LIMITATIONS

Finally, we would like to acknowledge the limitations in this study. The present study had a small sample size, limited duration, was single-centered, cross-sectional and lacked ethnic variety. Our findings cannot be generalized, as the results address only the *SOCT Copernicus REVO (Version: 9.7.0, OPTOPOL Technology)* SD-OCT and *AngioScan (Nidek Inc., Aichi, Japan)* OCT-A machine, which may have different technical features, database and segmentation algorithms.

Furthermore, just like the Kim JH et al. study63, we used the transformed logMAR BCVA derived from Snellen chart instead of the gold standard logMAR Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, which may not have reflected subtle changes of visual acuity especially in very low vision patients. Since advanced glaucoma patients generally present with very low vision, there occurred significant fixation issues resulting in motion artifacts and segmentation errors during OCT imaging, and hence imaging techniques need to evolve for optimal monitoring of patients in the severe end of disease spectrum.

Despite these limitations, our results were significant, yielding important information, and made the current exploratory study the first of its kind in Indian population, evaluating structure-function relationship, treating BCVA as a main functional outcome and combining it with inter-eye comparison of multiple structural parameters measured by SD-OCT.