

EVALUATION OF RETINAL NERVE FIBER LAYER THICKNESS IN ASYMMETRIC GLAUCOMA AMONG INDIAN POPULATION

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ABSTRACT: CONTEXT: Asymmetric glaucoma provides the opportunity to study effects of varying severity of glaucoma in the same subject. Retinal Nerve Fibre Layer thickness (RNFL) measurement and comparison between better and worse eye may provide useful inputs in diagnosis and monitoring progress of glaucoma. **AIMS:** To measure the Retinal Nerve Fibre Layer thickness in asymmetric glaucoma by stratus OCT and GDxVCC and compare between affected and less affected eye. **SETTINGS AND DESIGN:** This prospective study was conducted at Regional Institute of Ophthalmology, Kolkata from September 2007 to September 2009. **METHOD:** 50 glaucoma patients were enrolled in the study who manifested asymmetric Glaucomatous Optic Neuropathy (GON), characterized by Relative Afferent Pupillary Defect (RAPD), in more affected eye. The reduction of Retinal Nerve Fibre Layer thickness (RNFL) has been measured by OCT and GDxVCC. Parameters measured by OCT were mean RNFL thickness around the entire circumference and average thickness within the 4 quadrants (temporal, superior, nasal, inferior). TSNIT average, TSNIT standard deviation, superior average, inferior average and Nerve Fibre Indication (NFI) and Inter Eye Symmetry were measured by GDxVCC. **STATISTICAL ANALYSIS:** Independent t-test for difference of mean between the RNFL thickness measures for better and worse eye. **RESULTS:** RNFL thickness is significantly lower in more advanced eyes than contralateral eyes. Average RNFL thickness difference between less advanced eyes and more advanced eye as well quadrant RNFL difference was significant ($P < 0.0001$) by OCT. By GDxVCC TSNIT Average, Superior Average and inferior average was significantly lower in the worse eye ($P < 0.0001$). **CONCLUSION:** The average RNFL thickness around the optic disc is reduced in more affected eyes compared to less affected eye both by stratus OCT and GDxVCC in asymmetric glaucomatous optic neuropathy.

KEYWORDS: RAPD, RNFL thickness, GDxVCC, Status OCT.

KEYMESSAGE: RNFL measurement provides an objective, non-invasive tool for monitoring progress of glaucoma. Either or both stratus OCT and GDxVCC can be used for this purpose.

INTRODUCTION: Glaucoma is a group of disorders characterized by progressive optic neuropathy resulting in characteristic appearance of the optic disc and a specific pattern of irreversible visual field defects that are associated frequently but not invariably with raised intraocular pressure.¹ Glaucomatous optic neuropathy (GON) is essentially a bilateral disease but few patients present unilaterally or asymmetrically.² Cases with asymmetry of cup more than 0.30 were classified as asymmetric glaucoma.³ Krupin et al reported that 27.9% patients of primary open angle glaucoma (POAG) were unilaterally involved.² Asymmetric glaucomatous scotomas (30-2-program, Humphrey Field Analyzer, difference in mean deviation ≥ 8 dB) are reported with equal intraocular pressure of both eyes.⁴

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Asymmetric glaucoma is also detected in a patient with relative afferent pupillary defect (RAPD) or asymmetric optic nerve cupping without an RAPD. Presence of RAPD indicates optic nerve damage has exceeded the threshold and it can be quantified by automated perimetry.⁵ Contrast sensitivity also alters in glaucoma and can detect early glaucomatous damage. Glaucoma alters central vision and field defects far from fixation even when visual acuity is normal.⁶ Asymmetry in papillary light response, the RAPD, is an objective parameter which quantifies neural loss in asymmetric optic and retinal disorder.⁷ Patients with Asymmetric glaucoma shows an RAPD in more advanced eye. In asymmetric GON the degree of axonal loss and clinically detectable RAPD is still a matter of interest.^{8,9} Normally RNFL is also reduced by aging process (2-3.8micrometre/year).¹⁰

Optical coherence tomography (OCT) is a near infrared, low coherent illumination- assisted, non-invasive technique. It provides cross- sectional imaging of the layered structure of the retina with axial resolution of 10 micron.^{11,12} OCT is useful for assessment of macular thickness in retinal disease and RNFL thickness reduction in glaucoma and other optic nerve disorders.¹³⁻¹⁴ Another objective method to assess the RNFL is through scanning laser polarimetry. The GDxVCC is a scanning laser polarimeter that measures RNFL thickness using polarized light. GDxVCC provides objective RNFL information that is compared to an extensive normative database and provides information regarding the RNFL status with respect to healthy eyes of same age. Clinician can interpret deviation from normal.^{15,16} GDxVCC detects small changes over time due to progression of the disease. Reus and Lemij recently reported that GDxVCC had a sensitivity of 89% and a specificity of 98%.¹⁶ Medeiros et al. found that the GDxVCC was more accurate in detecting glaucoma than expert grading of red-free RNFL photograph.¹⁷

The purpose of this study is to assess the use of OCT and GDxVCC estimated RNFL thickness in more advanced eyes compared to contralateral less advanced eyes of the patient with asymmetric GON. Rationale of selecting cases of asymmetric glaucoma is effects of relatively advanced and less advanced disease can be demonstrated in the same patient thus controlling for other confounding factors.

SUBJECTS AND METHODS: All glaucoma patients of any age and both sexes with clinically detectable RAPD who visited glaucoma clinic in Regional Institute of Ophthalmology, Kolkata were eligible to participate in the study. Diagnosis of glaucoma was based on glaucomatous visual field loss with accompanying optic nerve abnormality. For each patient, best corrected visual acuity was measured with Snellen's visual acuity chart. RAPD was quantified by swinging light reflex (flash light test) in a dark room. Characteristic observation was release or dilatation of both pupils when light is moved from better eye to the affected eye.⁸ Interpretations were: - +++++ (Amaurotic pupil and non-reacting pupil in blind eye). +++ (Pupil dilated readily when more affected eye is stimulated), ++ (When pupil fails to constrict or dilate slightly on light), + (Minimally detectable asymmetry). Patients with +++++ RAPD was excluded because OCT and GDxVCC could not be performed due to low vision. Visual field examination with Humphrey field analyzer using SITA standard 30-2 or 24-2 and macular program was performed within 3 months of quantification of RAPD. Subjects were excluded if fixation loss greater than 20% and false positive and false negative errors were greater than 33%.³ Other exclusion criteria were history of blunt ocular injury, severe uveitis, exfoliation glaucoma, diabetes mellitus, intraocular surgery, refractive error higher than +3.00 D or lower than -6.00 D, visual acuity <3/60, media opacity including cataract and laser treatment.

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Ultimately fifty glaucoma patients were selected. All patients were phakic. Out of 50 patients 1 patient had unilateral glaucoma; remaining 49 patients had bilateral asymmetric glaucoma. Unilateral glaucoma was defined as normal visual field in contralateral eye with standard automated perimetry. The study was conducted from September 2007 to September 2009. All enrolled subjects underwent full clinical and ophthalmologic evaluation, IOP measurement by Goldmann applanation tonometry, Slit lamp biomicroscopy, Goldmann 2 mirror Gonioscopy, Automated Perimetry (Humphrey 24-2 or 30-2 and macular program), OCT and GDxVCC.

Optical Coherence Tomography Technique: RNFL thickness around optic disc was determined by OCT 3000 (V4.2.4 Zeiss-Humphrey, Dublin, California, USA). Three circular scans each 3.4 mm diameter centered on optic disc was obtained after full pupillary dilatation, which was averaged by fast RNFL thickness 3.4 program. Measurements involved having the subject seated with his chin on a chin rest and the machine properly aligned. The OCT lens was adjusted for the patient's refractive error. The subject was then instructed to fixate with the eye being measured on the internal fixation target to bring the optic nerve head with in view of the examiner in real time. The Z offset was adjusted to bring the OCT image into view. Polarization was optimized to maximize the reflective signal. The position of the aiming circle was adjusted by the operator to match the optic nerve head so that the nerve head scan would acquire an OCT image of an even radius of 1.73mm around the optic nerve head. Scan quality was monitored by constantly assessing the colour coding of the scans, paying particular attention to maximizing the red reflectivity of the retinal pigment epithelial cell layer.

The software version used had signal strength of 7-10 to get high accuracy image.¹⁸ Three sets of standard scan RNFL measurements were made in quick succession. Each of this scans consisted of 512 A- scan measurements taken in a single circular path around the optic disc with a standard diameter of 3.4mm in 1.28 sec. The fast scan was obtained, which consists of three successive circular sub-scans around the disc with A-scan measurements at 256 locations per revolution, over a total of 1.92 sec. These three scans were averaged to report the thicknesses as a combined set of 768 A-scans in a circle of 3.4mm diameter around the disc. The testing was supplemented with at least three separate fast scans (each consisting of three circular sub scans) to assess within- session variability of fast scan measurements.¹⁸ The RNFL analysis used an automated computer algorithm to identify the anterior and posterior margins of the band of reflectance representing the RNFL, making the margins with two white lines in the visual display. The distance between the margins makes up the RNFL thickness. In this study mean RNFL thickness around the entire circumference and average thickness within the 4 quadrants (temporal, superior, nasal, inferior) were recorded.¹³

GDxVCC Technique: RNFL thickness of optic disc was also determined by GDxVCC (software version 5.5.1 Carl Zeiss Meditec, Dublin, CA, scanning laser polarimetry) without pupillary dilatation. GDxVCC measures the summed retardation of a laser light beam that double passes the RNFL. Images were included in this study only if they were well focused and evenly illuminated and had good centering. Scan images with a quality score <7, atypical birefringence pattern (Peripapillary high retardation arranged circumferentially or in a spoke like pattern, or blotchy areas of high retardation nasally and temporally), peripapillary atrophy or vitreous degeneration affecting the measurement eclipse were excluded.¹⁹ Three circular scans each of 2.4, 2.8 and 3.2 mm were taken 4 mm around optic disc in normal pupil size without dilatation. Images of signal strength of 7-10 were of high accuracy. TSNIT

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average, TSNIT standard deviation, superior average, inferior average and Nerve Fibre Indication (NFI) and Inter Eye Symmetry has been analyzed. GDxVCC provides the probability measures of abnormality for the first four measures by comparing RNFL mean with normative database. The NFI is calculated using a support vector machine algorithm based on several RNFL measurements. It has cut-off values to optimally differentiate glaucoma from normal. In this study, $p < 5\%$, for each TSNIT parameter and $NFI \geq 31$ was chosen as the cut off for abnormal test.¹⁷ Inter eye symmetry values ranged from -1 to +1, where values near 1 represent good symmetry. Normal eyes have good symmetry with values around 0.9.¹⁸ OCT and GDxVCC output for RNFL thickness of bilateral eyes were compared. RNFL is a continuous variable so difference of means was tested for statistical significance. Difference was considered significant at $p < 0.05$. The study protocol was been approved by Institutional Ethics Committee of West Bengal University of Health Science. All patients provided written informed consent to participate in the study.

RESULTS: Among 50 patients who were enrolled in our study, 39(78%) were male patients and 11(22%) were female. Male patients presented at an older age than female patients with mean age of 54.17 yrs compared to 46.72 yrs of female patients. Mean age of all subjects was 52.10 years, ranging from 3 to 69 years. Mean refraction \pm SD was -1.65 ± 2.55 Dioptre in less advanced eyes and -1.71 ± 2.65 Dioptre in more advanced eyes, which were not significantly different ($P = .9399$). Based on etiological diagnosis, there were 38 cases of Primary open angle glaucoma, 10 cases of primary angle closure glaucoma, 1 case of developmental glaucoma and 1 case and steroid induced glaucoma.

RNFL thickness measured by stratus OCT and GDxVCC are presented in Table 1 and 2 respectively. All measures by both GDxVCC and status OCT measures were significantly lower in more advanced eyes than contra lateral eyes. While OCT measures optic disc in quadrants, GDxVCC measures in halves, but both gives a global average. Measures by OCT were higher than GDxVCC values. By OCT, RNFL thickness average was highest for superior quadrant and lowest for temporal quadrant in both better and worse eye. However difference of RNFL thickness between better and worse eye was maximum for inferior quadrant (Table 1) Average RNFL thickness around optic disc was reduced by 26.37% in more affected eyes compared to less affected eyes.

The GDxVCC output shows similar higher value for superior fibres with a wide difference between superior and inferior average in the better eye. However for the worse eye the means were overlapping with only a wider standard deviation for the superior average indicating more heterogeneous values. All patients had probability $< 5\%$ that test results are because of chance as all subjects were diagnosed cases of asymmetric glaucoma. TSNIT average around optic disc was reduced by 17.10% in more affected eye compared to less affected eye. 56 eyes out of 100 eyes had $NFI \geq 31$. NFI mean was much above cut off value for the worse eyes. Inter eye symmetry was also quite low at 0.5 for our study subjects. (Table 2)

DISCUSSION: In our study we have documented characteristic visual field loss associated with optic nerve head (ONH) damage in glaucoma. For more scientific, accurate and reproducible measurement of RNFL thickness loss along with ONH damage we have used OCT and GDxVCC. Only arcuate nerve fibres are damaged in early glaucoma and all quadrants are damaged in advanced glaucoma with sparing of only papillomacular fibres and persistence of central vision till the end. RAPD was inversely associated with the loss of RNFL thickness around the optic disc.⁸ In our study, more affected eyes having lower RNFL thickness clinically presented with RAPD. Cathering jui-ling Liu et al, evaluated the diagnostic sensitivity of Scanning Laser Polarimetry in primary angle closure glaucoma

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as compared with that in primary open angle glaucoma and to compare the Retinal Nerve Fibre Layer distribution between PACG and POAG. They used GDxVCC for TSNIT parameters, including TSNIT average, TSNIT standard deviation, superior average, inferior average and Nerve Fibre Indication (NFI). They used logistic marginal regression model that defined an abnormal test as $P < 5\%$ for each of the TSNIT parameters or $NFI \Rightarrow 31$. All cases in the present study had abnormal test and the mean NFI for worse eye was much above cut-off level. So, these diagnostic cut-off levels were also applicable for our dataset.

Regarding the RNFL distribution, the parameter inferior average was greater than the superior average. In the study by Cathering jui-ling Liu et al, Significant superior-inferior asymmetry in mild angle closure glaucoma ($P=0.022$) was documented but not in mild POAG ($P=0.279$). The diagnostic sensitivity of GDxVCC is quite comparable in these two forms glaucoma.²⁰ In our study there was superior - inferior asymmetry in the better eye but not so in the worse eye. Absence of superior -inferior asymmetry coupled with low TSNIT average can be a predictor for severe disease. Peripapillary RNFL thickness by OCT can discriminate between Glaucoma and normal eyes.²¹ Similarly our study results have showed marked differences in RNFL thickness parameters for early (better eye) and late (worse eye) GON. Both OCT and GDxVCC can be used for diagnosis of glaucoma and progress of disease based on RNFL thickness pattern.

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Table 1: RNFL thickness measurements by stratus OCT			
RNFL thickness in μm	Less advanced eye	More advanced eye	P-Value
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
Average RNFL thickness	77.08 +_16.04	56.75 +_17.99	<0.0001
Superior quadrant average	97.98 +_28.53	72.26 +_25.62	<0.0001
Inferior quadrant Average	88.76 +_26.41	58.65 +_24.18	<0.0001
Temporal quadrant Average	59.04 +_16.29	47.79 +_17.10	<0.0001
Nasal quadrant Average	62.58 +_14.59	55.36 +_19.30	<0.0001

Table 2: RNFL thickness measurement by GDVCC

RNFL thickness	less advanced eyes	more advanced eyes	P-Value
	Mean (SD)	Mean (SD)	
TSNIT average (temporal- superior- Nasal-inferior-temporal)	54.19 +_15.33	44.92 +_16.23	<0.0001
TSNIT average (SD) range	25.8(±12.2) – 114.3(±27.9)	18.1 (±6.3) – 106(±17.9)	-----
Superior average	62.53 +_16.29	47.90 +_17.47	<0.0001
Inferior average	56.91 +_11.43	47.34 +_14.13	<0.0001
NFI	28.52 +_25.27	60.51 +_27.75	<0.0001
Inter eye symmetry	0.5		

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