

Evaluation of Optic Disc and Retinal Nerve Fibre Layer Changes and its Association with Visual Field Defects in Patients with Normal Tension Glaucoma: A Hospital Based Interventional Study

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ABSTRACT

Introduction: Normal Tension Glaucoma (NTG) is a spectrum of primary open angle glaucoma, characterised by optic nerve head change in the form of glaucomatous cupping, visual field defects despite Intraocular Pressure (IOP) <21 mmHg. Patients remain asymptomatic until significant visual field loss occurs. An early sign of NTG is Retinal Nerve Fiber layer (RNFL) thinning. Although IOP is within normal range, further reduction can slow the disease progression. Early diagnosis of NTG is challenging due to absence of raised intraocular pressure, thus structural evaluation by optic disc, RNFL and functional evaluation by visual field indices helps in earlier diagnosis and disease progression.

Aim: The aim of this study was to assess the relationship of optic nerve head and RNFL changes with visual field findings in NTG patients.

Materials and Methods: The present prospective, interventional, hospital based study included 40 eyes with NTG conducted at SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai, Tamil Nadu, India and duration of study was one year and six months. Thorough history, ophthalmic examination was done which includes visual acuity, anterior and posterior segment, IOP, Central Corneal Thickness (CCT), visual fields and Optical coherence Tomography (OCT).

Patients started on 0.2% brimonidine eye drops twice a day and progression was tracked by repeat visual fields six months later. Data was analysed using independent samples t test and correlation was assessed using Pearson's rank correlation. Statistical Package for Social Sciences (SPSS) software version 26 was used for the statistical analysis.

Results: Forty eyes were studied. Mean age was 49.75 years with majority males 15 (56%). Average IOP was 14.825 mmHg, Average CCT was 528.58 micrometres. Correlation between IOP and Average RNFL was statistically insignificant ($p=0.857$). CCT had weak positive correlation with average RNFL, which was not significant statistically ($p=0.659$). Average CDR was 0.61. Average RNFL thickness was 81.4 μm . CDR weakly correlated to RNFL thickness ($r=-0.179$; $p=0.269$) but strongly correlated to visual field indices (Average Mean Deviation (MD) $r=+0.955$; $p<0.00001$). RNFL correlated with Mean Sensitivity (MS). Follow-up after six months showed that only two eyes (7%) had visual field progression and was changed to latanoprost 0.005% eye drops once daily.

Conclusion: CCT and Diurnal IOP variation tests play an important role in diagnosis of NTG. Hypoperfusion might be an etiological factor in NTG. OCT aids in identifying RNFL thinning even before field defects. The progression of field defects in NTG was reduced by lowering IOP.

Keywords: Central corneal thickness, Cup disc ratio, Intraocular pressure, Optical coherence tomography

INTRODUCTION

Glaucoma is universally defined as progressive, irreversible and chronic optic neuropathy, which is associated with visual field defects, where intraocular pressure may or may not be elevated" [1]. In 2020, approximately 3.61 million people were blind due to glaucoma, representing about 8.4% of global blindness [2]. The prevalence of glaucoma in Tamil Nadu was 2.6%, with Primary Open-Angle Glaucoma (POAG) of 1.7%, 0.6% of Primary Angle-Closure Glaucoma (PACG) and 0.3% were secondary glaucoma [3].

Aqueous humour is the fluid that is present in the anterior segment of the eye which acts a replacement for blood to the lens and cornea. It provides nutrition, transports neurotransmitters, removes metabolic byproducts, provides structural stability for the eye and helps in maintaining the physiologic equilibrium of these ocular tissues. It is produced by ciliary epithelium of the ciliary processes. Three mechanisms via which formation occurs: ultrafiltration, diffusion and active secretion. The rate of aqueous humour turnover accounts to $2.4\pm0.6 \mu\text{L}/\text{min}$. The major components are carbohydrates, amino

acids, glutathione, organic and inorganic ions, and proteins, urea, CO_2 , oxygen and water.

Two pathways exist via which passive outflow of aqueous humour occurs at the angle of the anterior chamber. The Conventional pathway is via "the trabecular meshwork-> Schlemm's canal-> collector channels-> episcleral veins" [4], which accounts for 75% of the drainage. The Uveoscleral route is via "the uveal part of trabeculum-> anterior aspect of the ciliary muscle-> the suprachoroidal space" [4]. There is usually a balance between the formation and outflow of aqueous humour. Any disturbance mainly to the conventional aqueous drainage path, causes rising of IOP. This is a major attributable factor for glaucoma.

NTG is a clinical entity in one end of the spectrum of POAG, characterised by glaucomatous cupping and visual field defects despite IOP less than 21 mmHg. CCT based correction should be done because the risk of glaucoma progression is greater in thinner corneas, thus needing more aggressive treatment in such patients [5].

The pathogenesis of optic atrophy in glaucoma has been a controversial matter. Muller proposed the mechanical theory in which raised IOP leads to the direct compression and irreversible death of the neurons by hindering axoplasmic flow [6]. Von-Jaeger proposed the vasogenic theory wherein the functional and structural defects are due to reduced blood supply to the optic disc [6]. Hayreh proposed that the pressure in the choroidal vessels also had an impact, leading to failure of perfusion in the retrolaminar ocular vessels, which are incapable of autoregulation. Optic cupping and nerve death are caused by chronic reduction of blood supply to the ONH [7].

Humphrey field analyser is the most commonly used automated perimetry. The other type is the OCTOPUS machine. The central 24-2 or 30-2 testing pattern is used. The patient's test reliability is assessed by: false-positives, false negatives, fixation losses, number of stimuli and Global indices- Mean deviation which reflects diffuse changes by taking the mean of all deviation points. MD upto +/- 2 db is acceptable. Pattern Standard Deviation (PSD) denotes localised defects. PSD upto 6 dB is acceptable. Glaucoma Hemifield Test (GHT) assesses the perimetric outcome by comparing threshold in upper and lower retinal hemifields in analogous. GHT provides the outcome as: within normal limits, general reduction of sensitivity, outside normal limits, borderline, and abnormally high sensitivity. This is a useful simplified method of assessing glaucomatous field damage [1].

OCT, a low-coherence 843 nm infrared light is used to quantify RNFL thickness. A diode light source is used as an alternative to sound waves. It measures the delay of light scattered back from the RNFL. The difference is used to produce retinal and disc images like in B scan [1].

The aim of this study was to assess the relationship of ONH appearance and RNFL changes with visual field findings in NTG patients. The objectives were to analyse intraocular pressure and centre corneal thickness in these patients. To evaluate the response to treatment with topical 0.2% brimonidine by comparison of visual field findings before and after 6 months of treatment in NTG patients.

MATERIALS AND METHODS

This is a prospective, interventional, hospital-based study conducted over one year and six months at SRM Medical college, Hospital and Research Centre, Kattankulathur, Chennai, Tamil Nadu, India which included 40 eyes with NTG. (IEC No. 137/IEC/2018).

Inclusion criteria:

- Patients with NTG {typical glaucomatous disc changes, Mean IOP ≤ 21 mmHg (after CCT correction)}
- Visual acuity equal to or better than 6/18.

Exclusion criteria:

- Narrow angle/Angle closure glaucoma cases.
- IOP > 21 mmHg even once during various instance of measurement.
- Already existing primary open angle glaucoma cases on treatment.
- Patients who have undergone glaucoma surgeries.
- Glaucoma secondary to other established causes like uveitis, trauma, cataract induced, steroid intake etc.,
- Patients with dense lens changes or hazy media.
- Ocular findings suggestive of neurological disorders.
- Patients less than 18 years age.
- Pregnant women and Patients not willing to participate.

Sample size calculation: Purposive sampling method. The sample size was derived using standard sample size calculation for correlation analysis.

Study Procedure

After obtaining informed consent, a thorough history was taken. Detailed ophthalmic examinations of visual acuity, Anterior segment by slit lamp bio-microscope including anterior chamber depth. IOP using Goldmann Applanation Tonometer, Gonioscopy using Goldman's 4 mirror. CCT by Ultrasound Pachymetry and corrected IOP. Fundus examination using +90 D slit lamp biomicroscopy and glaucomatous optic disc changes noted. Field charting by Humphrey's Field Analyser. OCT to assess RNFL thickness and optic nerve head changes. Patients were started on 0.2% Brimonidine eye drops twice a day.

The relationship between the optic disc appearance Cup Disc Ratio (CDR), RNFL and visual field changes was statistically analysed.

The response to treatment was analysed by comparing IOP, CDR and visual field pre and post treatment after six months and Latanoprost 0.005% once daily was started to patients with disease progression.

STATISTICAL ANALYSIS

Correlation was analysed by independent sample t-test and Pearsons rank correlation. A rank of 0 taken as no correlation, upto ±0.3 as weak correlation, ±0.8-1 as strong correlation and ±0.4-0.7 as moderate correlation; Association by Chi-square test; Progression by paired t-test. SPSS software version 26 was used for the statistical analysis.

RESULTS

The mean age was 49.75 years, with majority in the 41-50-year-old age group [Table/Fig-1]. Males 15 (56%) were more than females 12 (44%). All patients' eyes had an uncorrected visual acuity of 6/18 or better [Table/Fig-2]. The best corrected visual acuity is presented in [Table/Fig-3].

Age group	No. of eyes	Percentage
11-20	2	5%
31-40	5	12.5%
41-50	16	40%
51-60	5	12.5%
61-70	7	17.5%
71-80	5	12.5%

[Table/Fig-1]: Age distribution.

UVCA	6/6	6/6P	6/9	6/12	6/18
No.	11	2	10	13	4
Percentage	32.5%	10%	27.5%	5%	25%

[Table/Fig-2]: Uncorrected visual visual acuity.

BCVA	6/6	6/6P	6/9	6/9P
No.	22	10	7	1
Percentage	55%	25%	17.5%	2.5%

[Table/Fig-3]: Best corrected visual acuity.

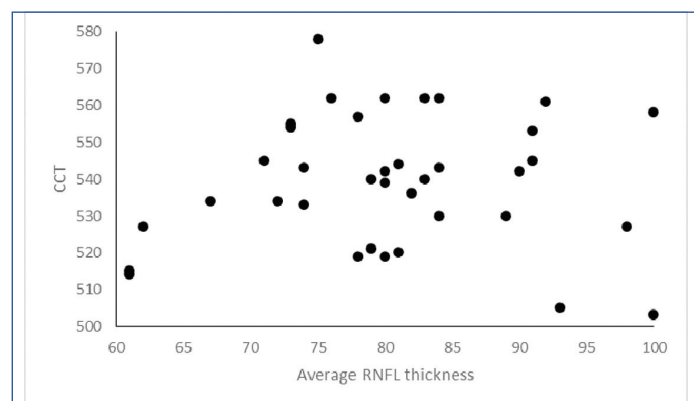
Intraocular pressure: The average IOP was 14.825 mmHg. Majority of the eyes had in mid-teens i.e., 14-17 mmHg (42.5%) [Table/Fig-4]. The average thickness of RNFL was 81.4 µm. Correlation between IOP and Average RNFL- p-value 0.857, r~0.025 and statistically insignificant.

IOP	10-13 mmHg	14-17 mmHg	18-21 mmHg
No.	13	17	10
Percentage	32.5%	42.5%	25%

[Table/Fig-4]: Intraocular pressure distribution.

Central Corneal Thickness (CCT): The average CCT was 528.58 micrometres. In the patients with NTG, the CCT was lesser than

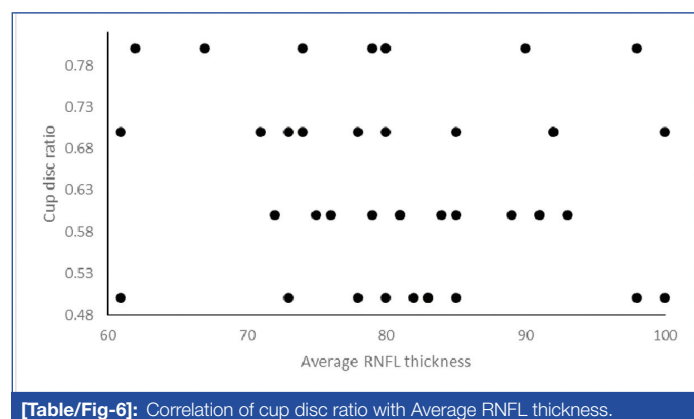
the normal range. The CCT had weak positive correlation with the average RNFL thickness, which was not significant statistically ($r=0.0721$; $p=0.659$) [Table/Fig-5].



Risk factors: 12 (41%) patients were diabetics, and 5 (18.51%) patients were hypertensives, showing that diabetes has association to NTG. 2 (7.40%) patients gave a family history of glaucoma, 3 (11.11%) patients had migraine, 1 (3.70%) patient gave past history of hypotension, one patient (3.70%) of obstructive sleep apnoea, and 1 (3.70%) patient had known history of hypotensive episodes.

Optic disc appearance: The average CDR was 0.612 in this study. 8 (20%) eyes had inferior notching and 4 (10%) eyes had superior notching. None of the eyes had any disc haemorrhages. 6 (15%) eyes had inferior neuroretinal rim thinning and 3 (7.5%) eyes has superior rim thinning. 2 (5%) eyes has both superior and inferior rim thinning.

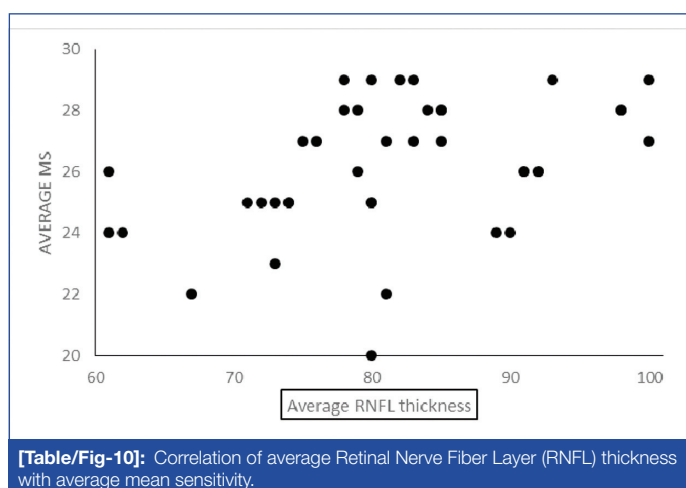
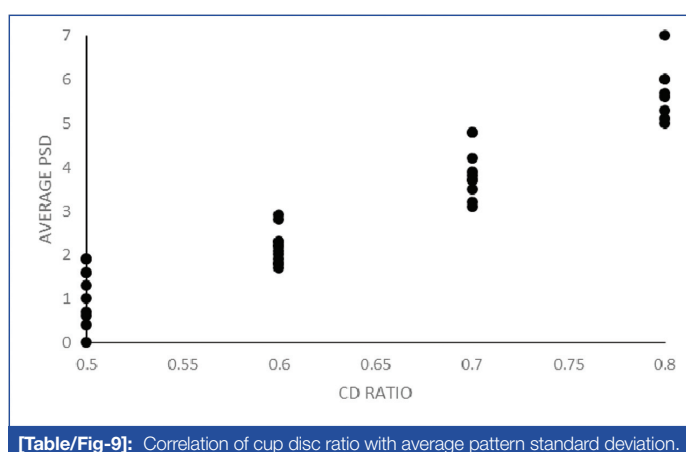
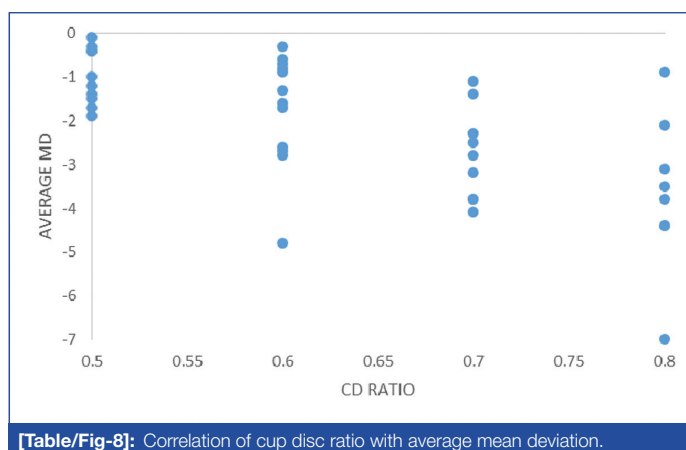
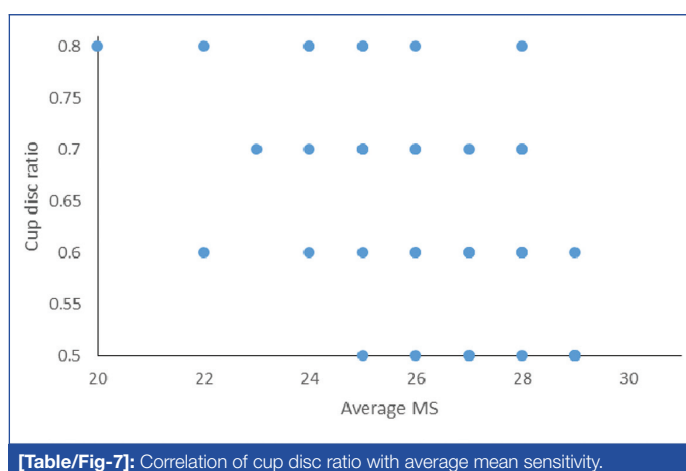
Correlation of cup disc ratio with RNFL thickness: The average thickness of RNFL was 81.4 μ m. Data points are scattered and showing lower RNFL thickness was associated with higher CDR ratio. This scatter plot analysis demonstrates weak negative correlation. (Pearsons correlation coefficient $r=-0.179$; $p=0.269$), which was not statically significant [Table/Fig-6].



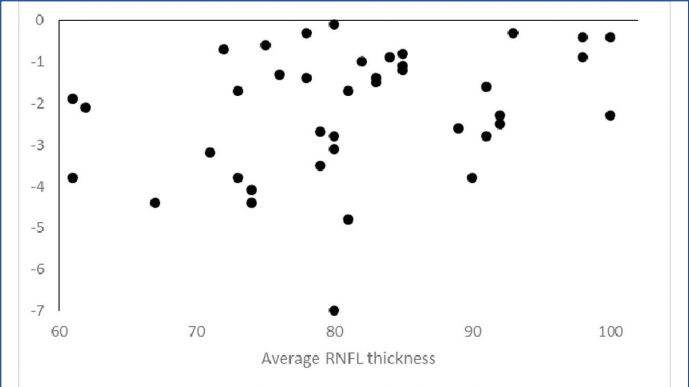
Correlation of CDR with visual field indices: There was a moderate negative correlation between the CDR and Mean sensitivity which was significant ($r=-0.5936$; $p=0.000053$) [Table/Fig-7]. There was a moderate negative correlation between CDR and Mean deviation which was strongly significant statistically. ($F=0.661$; $p<0.00001$) [Table/Fig-8]. The CDR and Pattern standard deviation had a strong positive correlation which proved to be very statistically significant. (Pearsons correlation coefficient $r=+0.955$, $p<0.00001$) [Table/Fig-9].

Correlation of RNFL with visual field indices. There was a moderate positive correlation of Average RNFL with Average Mean sensitivity which was significant statistically ($F=+0.406$; $p=0.009$) [Table/Fig-10].

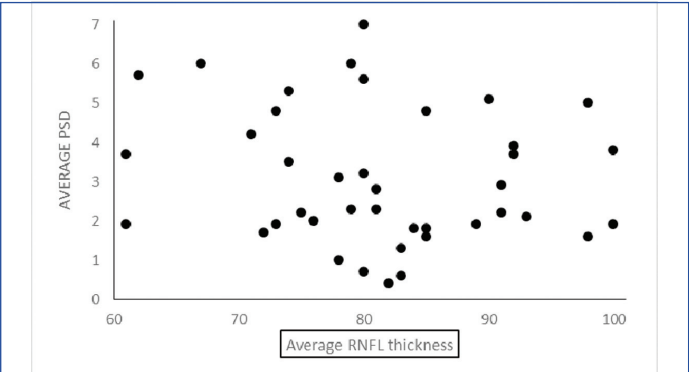
The correlation of average RNFL with average mean deviation was weakly positive which was not significant ($p=0.058$) [Table/Fig-11].



There was a weak negative correlation of average RNFL with average pattern standard deviation which was not significant ($r=-0.165$; $p=0.309$) [Table/Fig-12]. When the inferior quadrants of RNFL by OCT were compared to superior quadrants of Visual field indices,



[Table/Fig-11]: Correlation of average Retinal Nerve Fiber Layer (RNFL) thickness with average mean deviation.



[Table/Fig-12]: Correlation of average Retinal Nerve Fiber Layer (RNFL) thickness with average pattern standard deviation.

there was a strong correlation with the mean sensitivity [Table/Fig-13]. When the superior quadrants of RNFL were compared to inferior quadrants of visual field indices, there was a strong correlation with the mean sensitivity [Table/Fig-14].

Parameters	Pearsons correlation coefficient	p-value	Correlation significance
Inferior RNFL and superior mean sensitivity	+0.414	0.008	Significant moderate positive correlation
Inferior RNFL and superior mean deviation	+0.273	0.008	Not significant weak positive correlation
Inferior RNFL and superior pattern standard deviation	-0.310	0.051	Not significant weak negative correlation

[Table/Fig-13]: Correlation of visual field indices of superior quadrants with RNFL of inferior quadrants.

Parameters	Pearsons correlation coefficient	p-value	Correlation significance
Superior RNFL and inferior mean sensitivity	+0.375	0.017	Significant Moderate positive correlation
Superior RNFL and inferior mean deviation	+0.305	0.056	Not Significant Weak positive correlation
Superior RNFL and inferior pattern standard deviation	-0.107	0.512	Not Significant Weak negative correlation

[Table/Fig-14]: Correlation of visual field indices of inferior quadrants with RNFL of superior quadrants.

Association of RNFL with glaucoma hemifield test: There was no association between the Average RNFL and the Glaucoma Hemifield test by Pearson Chi square test ($p=0.591$). Combining all the above data, 26% of eyes showed RNFL thinning but no significant Visual field defects. Thus OCT shows early glaucomatous changes and is important in diagnosing glaucoma at an early stage.

Visual fields follow-up after 6 months: The patients were started on eye drops Brimonidine 0.2 % BD and followed up after six months. On follow-up, there was significant change in the global indices: average MD ($p=0.009$) and average MS ($p=0.047$) but not the average PSD ($p=0.604$). The changes in the indices were found to be highly variable. Two eyes had a significant progression, and switched over to Latanoprost 0.005 % eye drops once daily.

DISCUSSION

Labeling patients with NTG is a challenge and a thorough history and systematic evaluation is essential before coming to the diagnosis. In patients having glaucomatous changes such as greater CDR, Neuroretinal Rim Thinning, visual field changes but consistently normal IOP (<21 mmHg), it is pertinent to classify them as NTG. The mean age in my study was 49.75 years, with majority in 41-50 years age group. A probable reason for the older age prevalence is the late detection and late presentation of the patients for ophthalmological evaluation.

The patients in the present study all had an uncorrected vision better than or equal to 6/18. Since the acuity of vision is generally not affected in early glaucoma, this adds further to the late presentation of the patients. Levene reported a higher female prevalence of NTG [8]. The Beaver Dam study had equal prevalence amongst both sexes [9]. However, in my study males (56%) were more than females.

Mean IOP was 14.825 mmHg, and majority in the mid teens. Additionally, Gramer E and Leydhecker W and Araie M et al., stated that fluctuation in IOP may play a role in disturbing optic nerve head perfusion [10,11]. Diurnal variation was noted- Average increase in IOP of 3 mmHg in nine eyes, average decrease of 2 mmHg in seven eyes and no change in IOP in three eyes. This shows that there is possibility that the mechanism of damage in NTG is probably due to fluctuation of IOP causing perfusion disturbance in the optic nerve leading to disc damage.

Average CCT in this study was 528.58 micrometres. In the patients with NTG, the CCT was seen to be lower than the normal range [12]. It is said that IOP can be lower than expected in thin corneas and more in thick corneas, so a correction factor is essential. The average cup/disc ratio seen in the study is 0.612 with neuro-retinal rim thinning. Alasil T et al., that the mean average RNFL in NTG suspects was 91.15 micrometers [13]. It is seen in my study that mean average RNFL thickness was 81.4 micrometers.

With increase in the CD ratio, there was worsening of field indices i.e., average mean sensitivity, average mean deviation and average pattern standard deviation. Average MD and PSD especially had a strong correlation with the CD ratio. This shows that when there is worsening of the structural parameters, there is worsening of the functional parameters, but it is not necessarily linear. Monitoring both is necessary for follow up of progression of the disease [14].

There was only a weak correlation, which was not significant, between the CDR and the average RNFL thickness. Only when greater than 50% loss of RNFL thickness occurs, the defects can be clinically detected (CDR) [15]. Thus RNFL thinning determined by OCT is an important diagnostic indicator of early Disc damage.

There was a moderate positive correlation of average RNFL with average MS which was significant but there was only a weak correlation to average MD and average PSD which were not statistically significant. MD and PSD denote the generalised field defects and focal field defects respectively, with PSD being a more sensitive indicator of glaucomatous changes [16]. Based on the findings it can be concluded that RNFL thinning can precede visual field changes in glaucoma and it a sensitive tool for analysis in the early stages of NTG. In a study by Sommer and others it was seen that RNFL loss can occur as much as six years before ONH and detectable visual field damage [17]. So, OCT has greater chances of picking up subtle damage.

A 26% of eyes showed RNFL thinning but no significant visual field defects. Thus, OCT shows early glaucomatous changes and is important in diagnosing glaucoma at an early stage. The main aim of glaucoma treatment is IOP reduction even in low tension glaucoma as indicated by the CNTGS Group [18]. When compared with 0.5% timolol, it was seen that Brimonidine which is an Alpha-2 adrenergic receptor agonist caused a reduction in progression probably due to the additional neuroprotective effect [19]. The patients were started on eye drops Brimonidine 0.2% BD and followed-up after six months. Two eyes had significant progression and they were switched to Latanoprost 0.005% eye drops once daily. The progression of NTG is generally slow and develops over a period of time with 40% of patients progressing over a 10 and half year period [20].

Though the global visual field indices may be useful, disadvantage of analyzing only them is small early changes may be missed. Eventhough sequential visual field analysis currently is the ideal standard way of monitoring progression, optic disc change can occur many years prior to visual field changes [21].

Hence, optic disc analysis, by stereoscopic fundus imaging, OCT RNFL analysis and visual field examination are all adjunctive tools which should be used collectively in the diagnosis and for monitoring progression in patients with NTG.

Limitation(s)

Since NTG has slow progression, long-term progression analysis of the parameters is essential, which could not be done beyond six months due to limited time. This study included only NTG patients, including and comparing normal subjects will give larger range of data.

CONCLUSION(S)

The CCT and Diurnal IOP variation test play an important factor in diagnosis of NTG. OCT aids in identifying structural damage in the form of RNFL thinning even before it is evident as field defects. There is definite correlation between the CDR and Visual field indices. The progression of field defects in NTG was reduced by lowering of intraocular pressure, which was achieved by management with topical brimonidine. In conclusion, though perimetry is subjective, at present it cannot be completely replaced by the newer imaging methods. The newer methods are valuable tools that provide objective quantitative and reproducible measurements of RNFL thickness. A combined diagnostic approach will aid in early diagnosis, significantly reducing the morbidity in these patients.

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