Original Article

Pattern of RNFL Damage in Early- and Late-Stage Primary Open-Angle Glaucoma Using the Disc Damage Likelihood Scale and Optical Coherence Tomography

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Abstract

Objectives: To determine patterns of peripapillary retinal nerve fiber layer (RNFL) damage in early- and late-stage glaucoma based on the Disc Damage Likelihood Scale (DDLS).

Materials and Methods: This cross-sectional, multi-center study involved 267 eyes of 135 patients aged 18 years or older with suspected or diagnosed glaucoma. Exclusion criteria were high refractive errors, media opacities, trauma history, and systemic conditions affecting the optic disc. After a comprehensive ocular examination, the DDLS was used for glaucoma staging. Disease severity was classified into three zones: green, orange, and red. RNFL thickness was measured in four quadrants using optical coherence tomography. Patterns of RNFL damage were analyzed, especially in terms of the ISNT (inferior>superior>nasal>temporal) rule, and compared between the three groups.

Results: The male-to-female ratio was 1.59:1 and the mean age was 45.12±15.76 years. There were statistically significant differences among the groups for average, inferior, superior, and temporal RNFL thickness ($p<0.00001$). However, the difference in nasal RNFL was insignificant. The ISNT rule was the commonest pattern in the study participants (64.4%) and progressive loss of pattern was observed with increased disease severity.

Conclusion: This study revealed an association between disease severity and RNFL thinning in the inferior, superior, and temporal quadrants, while nasal RNFL showed no significant association with disease severity. The ISNT rule was more frequently observed in the early stages and diminished with advanced glaucoma. These results highlight RNFL thinning based on the DDLS as an important marker for glaucoma monitoring.

Keywords: Primary open-angle glaucoma, retinal nerve fiber layer, Disc Damage Likelihood Scale

Introduction

In 2020, approximately 3.6 million people worldwide suffered vision loss due to glaucoma, contributing to about 11% of blindness in adults over the age of 50 years.[1] This staggering number may even be an underestimate since the current definition of glaucoma requires visual field loss for diagnosis. Many individuals may have glaucoma without documented visual field loss, highlighting the critical need for early detection and intervention to prevent or delay progression.

In glaucoma, structural damage to the optic nerve often occurs before visual field loss detectable by standard perimetry. Therefore, quantitative analysis of the retinal nerve fiber layer (RNFL), optic nerve head (ONH), and macular cube with ganglion cell layer thickness are considered more reliable for assessing glaucoma.

Among the optic disc parameters, the ISNT rule (inferior>superior>nasal>temporal) has widely been discussed as a key diagnostic tool in glaucoma. It is frequently violated in glaucoma patients because the neuroretinal rim (NRR) is often preferentially affected in the inferior and superior quadrants of the optic disc.[2] However, studies have primarily relied on optic disc photographs or subjective assessments by ophthalmologists. Only a few studies have utilized scanning techniques to measure RNFL thickness for assessing the ISNT rule in glaucoma detection and progression. Moreover, there are conflicting results

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regarding the clinical usefulness of the ISNT rule in glaucoma screening.[3,4,5] The ISNT rule also varies depending on optic disc size.[6] To address the impact of disc size on the NRR, we employed the Disc Damage Likelihood Scale (DDLS), which considers disc size when ranking the severity of optic nerve damage, thus providing a more accurate assessment of glaucoma progression. We used optical coherence tomography (OCT) scans to quantitatively measure peripapillary RNFL (pRNFL) thickness in different quadrants to evaluate the ISNT pattern across various stages of glaucoma, classified according to the DDLS. To date, no other study has analyzed RNFL patterns in primary open-angle glaucoma (POAG) based on DDLS grading.

The aim of this study was to determine patterns of pRNFL damage in early- and late-stage glaucoma based on the DDLS.

Materials and Methods

A cross-sectional, observational, multi-center study was conducted at Mughal Trust Eye Hospital and Lahore General Hospital from April 2023 to April 2024. The study was conducted according to the Declaration of Helsinki and approval was obtained from the Mughal Eye Hospital Trust Review Board (0264/IRB/MEHT, dated March 2023). Patients were recruited after obtaining informed consent. Patients over 18 years old with suspected or diagnosed glaucoma were included. Glaucoma suspects were defined as patients who had either higher than normal intraocular pressure (defined as between 10 and 21 mmHg) or optic disc cupping but with normal visual fields and normal RNFL.

There were 267 eyes of 135 patients that qualified for the study. Patients with refractive error of more than ±5.0 diopters (D) sphere and ±3.0 D cylinder, media opacities, history of trauma, neurological and systemic abnormalities affecting the optic disc, pigment dispersion, pseudoexfoliation, ocular inflammation, and OCT with poor signal strength were excluded. Patients with best corrected visual acuity (BCVA) of 6/60 or better and clear media were included in this study.

After taking a detailed medical and ocular history, patients underwent a thorough ocular examination which included BCVA, intraocular pressure measurement, slit-lamp examination, and fundoscopy using a 78D lens. The measured optic disc size was adjusted by multiplying by 1.1 to correct for the magnification error from the 78D lens. Both the average and vertical cup-to-disc ratios, as well as the rim-to-disc ratio, were documented.

The observations agreed between the two observers and in cases of disagreement, opinion of a third observer was sought. DDLS stage was first determined based on optic disc size and neural rim width. Glaucoma stage was then classified based on DDLS stages using the Glaucoma Color Graph (Figure 1).[7] Amount of disc damage was categorized as green (DDLS 1-4, not definite disc damage; n=153), orange (DDLS 5-7, asymptomatic glaucoma damage; n=62), or red (DDLS 8-10, glaucomatous disease or disability; n=52).

Visual fields were assessed using the Humphrey 24-2 SITA-Fast strategy. RNFL thickness was measured using SD-OCT (Cirrus), and only images with good signal strength were included in the analysis. The parameters recorded included average RNFL thickness, along with superior, temporal, inferior, and nasal quadrant pRNFL thickness. The average RNFL thickness and the mean RNFL thickness in each of the four quadrants were calculated and compared with severity of glaucoma based on DDLS.

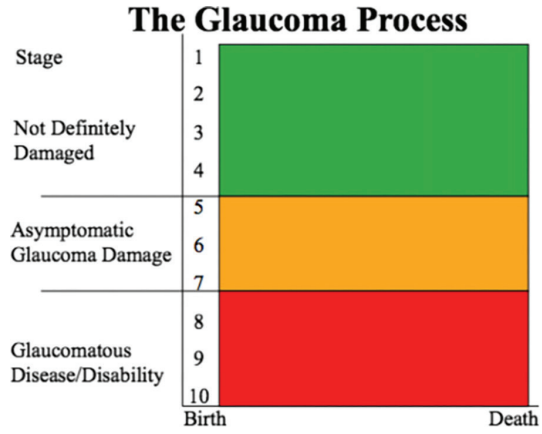

Figure 1. Grading of disease based on the Disc Damage Likelihood Scale. Adapted from Spaeth and Paulus,[7] 2010. Image available through Creative Commons Attribution-NonCommercial-NoDerivs 3.0

Statistical Analysis

The Shapiro-Wilk test was used to test normality of continuous variables. Quantitative variables were presented as mean±standard deviation, and qualitative variables as percentages. The Mann-Whitney U test was used to compare the RNFL thickness with normative data derived from a previous study.[8] The Kruskal-Wallis test with post-hoc Dunn's test was done to compare RNFL thickness among the groups. The chi-square test was used to compare the frequency of the ISNT pattern among the groups. A p value of <0.05 was considered significant.

Results

A total of 267 eyes of 135 patients were included in the study. There were 134 right and 133 left eyes. The mean intraocular pressure was 18.2±6.4 mmHg. The mean age was 45.12±15.76 years.

There was no statistically significant difference in pRNFL thickness by gender ($p>0.05$). Comparison with normative data showed statistically significant differences between the control values from the previous study and the different groups in this study (Table 1).

Comparisons between the groups revealed statistically significant differences among the groups for average, inferior, superior, and temporal RNFL thickness ($p<0.00001$). However, the difference for nasal RNFL thickness was statistically insignificant (Table 1). Post-hoc analysis (adjusted using Bonferroni correction) showed that the green group consistently had greater RNFL thickness compared to the red group for the inferior, superior, and temporal quadrants. However, differences between the orange and red group were less pronounced or not

significant. No significant differences in nasal RNFL thickness were found between any of the groups.

The different patterns of RNFL thickness damage observed in the groups are shown in Table 2. The ISNT rule was the commonest pattern among the study participants (64.4%). It was present in 79.7% of eyes in the green group, 46.8% of those in the orange group, and 40.4% in the red group, indicating significant progressive loss of ISNT pattern with disease severity (p<0.00001).

Discussion

In this study, highly statistically significant differences were found in average, inferior, superior, and temporal RNFL thickness across the groups, while the difference in nasal RNFL thickness was not significant. The ISNT rule was followed by 79.7% of patients in the green group, 46.8% in the orange group, and 40.4% in the red group. A notable difference in the pattern of RNFL thickness damage was found between the green and orange groups, but no significant difference was observed between the orange and red groups in terms of adherence to the ISNT rule.

Although gender is not typically considered a risk factor for POAG, the male-to-female ratio in our study was 1.59:1. This is contrary to previous data in which 60.8% of patients with glaucoma were female.[9] The average age of the patients in our study was 45.12±15.76 years, while another study reported a mean age of 54.5±13.6 years, with 66.9% males and 33.1% females.[10]

We found an average RNFL thickness of 90.85±12.95 µm in glaucoma suspects (green group), 78.00±14.16 µm in early glaucoma cases (orange group), and 68.00±14.96 µm in advanced glaucoma cases (red group). Comparatively, another study reported RNFL thickness of 101.58±5.24 µm in normal eyes, 92.35±5.56 µm in glaucoma suspects, and 79.00±7.97 µm in glaucoma patients (p<0.001 for all pairwise comparisons).[11]

Patients with preperimetric glaucoma exhibit a significantly thinner RNFL compared to healthy individuals. Among all RNFL thickness values, average and inferior RNFL thickness are reported to provide useful information about the severity of RNFL damage. However, as RNFL thickness shows a floor effect in the late stages, these measurements provide complementary information to perimetry reports and clinical observation.[12]

The lack of a difference in nasal RNFL thickness despite progressive reductions in the inferior, superior, and temporal quadrants across the groups in our study reinforces that nasal thickness is generally not a reliable indicator for predicting the progression of glaucoma. There is a common perception that RNFL thickness is preserved in the temporal quadrant even in the late stage of the disease, which is responsible for the preserved central vision. However, this is not always true, as temporal RNFL thickness was also significantly reduced in our patients.

Xu et al.[13] reported an average global thickness of 66.38±11.13 µm in patients with moderate POAG. In our

Table 1. Comparison of normative data[8] for RNFL thickness and the mean values for different stages of primary open-angle glaucoma

RNFL thickness (µm)	Normal*	Green (n=153)	Orange (n=62)	Red (n=52)	p value**
Average	101.43±8.63	90.85±12.95	78.00±14.16	68.00±14.96	<0.00001
Inferior	135.34±20.40	110.63±22.94	95.07±25.38	79.08±26.78	<0.00001
Superior	129.15±16.87	104.47±22.46	94.98±19.98	82.06±19.96	<0.00001
Nasal	79.73±12.05	65.55±11.81	62.83±12.28	62.82±16.44	0.058
Temporal	71.95±7.73	62.42±14.26	59.90±15.73	55.92±15.42	0.002

*All groups differed significantly from normative values (Mann-Whitney U test, p<0.00001 for all), **All parameters except nasal RNFL thickness differed significantly among the glaucoma severity groups (Kruskal-Wallis test, p<0.05). RNFL: Retinal nerve fiber layer

Table 2. Frequency of patterns of RNFL damage by glaucoma severity group

Pattern	Green, n (%)	Orange, n (%)	Red, n (%)	Total, n (%)
ISNT*	122 (79.7)	29 (46.8)	21 (40.4)	172 (64.4)
Non-ISNT	31 (20.3)	33 (53.2)	31 (59.6)	95 (35.6)
SITN	10 (6.5)	9 (14.5)	9 (17.3)	28 (10.5)
STIN	1 (0.7)	1 (1.6)	2 (3.9)	4 (1.5)
SINT	20 (13.1)	16 (25.8)	11 (21.2)	47 (17.6)
STNI	0	2 (3.2)	2 (3.9)	4 (1.5)
SNIT	0	4 (6.5)	6 (11.5)	10 (3.8)
SNTI	0	1 (1.6)	1 (1.9)	2 (0.8)
All	153	62	52	267

*The frequency of the ISNT pattern differed significantly among the groups (chi-square test, p<0.00001). RNFL: Retinal nerve fiber layer, I: Inferior, S: Superior, N: Nasal, T: Temporal

study, however, the thickness ranged from 90.85±12.95 µm in early disease to 68.00±14.96 µm in patients with more advanced damage. Among the four quadrants, inferior RNFL thickness offered the best diagnostic capability for glaucoma. This is further supported by Hood et al.,[14] who reported that RNFL thinning is more pronounced in the inferior retina, which corresponds to the superior visual field.

The ISNT rule is widely regarded as a valuable tool for glaucoma screening. However, Silim et al.[15] found that among the 65.6% of eyes that violated the ISNT rule, only 34.7% showed abnormal OCT results, raising questions about the rule's reliability. In this study, the most common pRNFL thickness pattern across all stages of glaucoma was ISNT, followed by SINT, where the superior quadrant was thicker than the inferior quadrant, likely due to more severe damage in the inferior RNFL thickness. This pattern was also observed in another study.[16] However, in advanced disease, RNFL defects extended through nearly all sectors. Contrary to the early inferior thinning, superior thinning in early glaucoma was reported by El-Naby et al.[17] and Soliman et al.[18], supporting the SINT rule. However, the concentric nature of RNFL thickness damage may explain why some glaucoma patients retain the ISNT pattern despite disease progression.

The specificity of the ISNT rule is influenced by several factors, including disc size, disc tilt, and vascular patterns within the disc. Normal eyes that violate this rule often have longer axial lengths and larger disc areas. These eyes are also associated with ISNT rule violations.[19] However, since we used the DDLS for glaucoma staging, which accounts for disc size, this effect was mitigated to some extent. Despite this, the ISNT rule should not be relied upon as the sole criterion for diagnosing or monitoring glaucoma progression.

Beyond the ISNT rule, the IT (inferior rim wider than the temporal rim) and ST rules (superior rim wider than the temporal rim) have also been described in the literature.[20] However, when evaluating the impact of optic disc size and disease severity on the diagnostic performance of these three NRR rules, all were found to have better sensitivity in eyes with smaller discs. A Japanese study further suggested that the IST pattern, rather than the ISNT pattern, was more effective for glaucoma screening.[21] Contrary to this, Law et al.[4] demonstrated that only evaluating the inferior and superior rim (IS rule) yielded better specificity than the ISNT rule in differentiating glaucomatous eyes from normal eyes.

The early RNFL loss typically observed in the inferior and superior quadrants can be attributed to the backward bowing of the lamina cribrosa at the upper and lower poles compared to the mid-nerve head. The more pronounced deformation and remodeling in these regions may lead to RNFL loss being most commonly found in the inferior and superior quadrants in glaucoma.

In another study, the NRR in healthy participants did not follow the ISNT rule, except that the smallest rim area was consistently located in the temporal disc region when Heidelberg retinal tomography (HRT) was used.[22] However, the rim thickness in the superior and inferior sectors was found to be similar based on HRT measurements. It was also found that a greater number of normal eyes adhered to the IST rule compared to the ISNT rule when RNFL thickness was measured using HRT and OCT.[23]

Kostianeva-Zhelinska et al.[24] reported that the inferior and superior RNFL quadrants were specific sites for early glaucomatous damage in POAG. This finding was also confirmed by Singh et al.[25]

Very conflicting results were reported by Abera and W Gessesse[26] They found that temporal and superior thickness performed poorly while average, nasal, and inferior thickness had better diagnostic value.

It must be kept in mind that the floor effect occurs earlier in the pRNFL than the macular region. In these situations, it is advisable to use macular OCT and visual field 10-2 testing. Not only this, but RNFL thickness in patients with high myopia, ONH swelling, and small or tilted ONHs can be misleading. In these instances, macular area parameters are better reference points.[27]

Study Limitations

Although the present study is unique in grading the disease in terms of DDLS, it is limited by the cross-sectional design. Without following the same patients over time, the study cannot fully assess the progression of RNFL thinning or confirm whether DDLS reliably predicts long-term outcomes. The study was focused on structural changes (RNFL thinning). Further work can be done to find the functional relationship using the same scale which would be important to fully understand the impact of the observed RNFL damage.

Conclusion

This study revealed an association between disease severity and RNFL thinning in the inferior, superior, and temporal quadrants, while nasal RNFL showed no significant association with disease severity. The ISNT rule was more frequently observed in the early stages and diminished with advanced glaucoma. These results highlight RNFL thinning based on the DDLS as an important marker for glaucoma monitoring.

Ethics

Ethics Committee Approval: Mughal Eye Hospital Trust Review Board (0264/IRB/MEHT, dated March 2023).

Informed Consent: Informed consent was obtained from the patients.

Declarations

Authorship Contributions

Surgical and Medical Practices: N.U., T.G.M., Concept: N.U., T.G.M., R.M.S, Design: N.U., T.G.M., R.M.S, Data Collection or Processing: N.U., T.G.M., Analysis or Interpretation: N.U., T.G.M., R.M.S, Literature Search: N.U., T.G.M., Writing: N.U., T.G.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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