Optic Disc Characteristics in Patients With Glaucoma and Combined Superior and Inferior Retinal Nerve Fiber Layer Defects

Jin A Choi, MD, PhD; Hae-Young Lopilly Park, MD, PhD; Hye-Young Shin, MD; Chan Kee Park, MD, PhD

IMPORTANCE Eyes with initial bihemifield defects show faster progression compared with eyes with initial single-hemifield involvement, suggesting greater optic nerve susceptibility to glaucomatous damage. We hypothesized that certain disc phenotypes may exist in patients with glaucoma who have bihemispheric structural damage at the initial stage of the disease.

OBJECTIVE To identify the optic disc characteristics related to bihemispheric retinal nerve fiber layer (RNFL) defects in early-stage glaucoma.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study of 136 patients with early-stage primary open-angle glaucoma from a glaucoma referral practice. Eyes were divided into those with RNFL defects in the superior or the inferior hemisphere (group 1) and those with bihemispheric RNFL defects (group 2). We measured the degree of horizontal tilt angle and RNFL thickness using spectral-domain optical coherence tomography. We performed multivariate logistic regression analysis to determine potential risk factors related to the bihemispheric RNFL defects.

EXPOSURES Bihemispheric RNFL defects.

MAIN OUTCOMES AND MEASURES Disc ovality (defined as the ratio between the longest and shortest diameters of the optic disc), the degree of horizontal tilt angle, and the presence of bihemispheric RNFL defects. Asymmetry in RNFL thickness between hemispheres was defined as the difference between the superior and inferior mean RNFL thickness.

RESULTS Disc ovality (mean [SD], 1.09 [0.12] in group 1 vs 1.18 [0.18] in group 2; difference, −0.09; 95% CI, −0.14 to −0.03), proportion of tilted discs (5.3% vs 17.5%, respectively; difference, −12.2; 95% CI, −13.0 to −11.4), and horizontal tilt angle (mean [SD], 4.17° [4.13°] vs 5.93° [4.84°], respectively; difference, −1.76; 95% CI, −3.47 to −0.03) were significantly different between groups 1 and 2 (P = .001, P = .03, and P = .045, respectively). The asymmetry in RNFL thickness decreased with increased disc ovality (exponentiation of the B coefficient, 1.67; 95% CI, 1.10-2.55; P = .02), although associations were not identified with spherical equivalent, axial length, or the angle between the temporal retinal veins. In multivariate logistic analysis, disc ovality was suggested to be an independent risk factor for bihemispheric RNFL defects, after controlling for mean deviation, age, axial length, and disc area (P = .02).

CONCLUSIONS AND RELEVANCE Optic disc tilt appears to be associated with bihemispheric RNFL defects in patients with early glaucoma, regardless of their refractive status. These data suggest that disc tilt, associated with bihemispheric structural damages, is a risk factor for glaucoma progression.
Glaucomatous functional damage usually respects the horizontal meridian and the anatomic features of the retinal nerve fiber layer (RNFL), particularly at the initial stage. In a cohort study, 70% of eyes had initial visual field (VF) damage limited to an isolated hemifield, and 57% had only isolated hemifield involvement during follow-up. In terms of glaucoma progression, the most common pattern of functional and structural progression occurs as widening and then deepening of the preexisting lesion, followed by relatively rare occasions of new lesion development.

De Moraes et al reported that eyes with initial bitemporal RNFL defects were associated with more rapid disease progression compared with eyes with initial single-hemifield involvement. They suggested that damage to both hemifields at the initial stage of the disease is associated with greater optic nerve susceptibility to glaucomatous damage. Individual susceptibility to glaucoma is determined by the geometry and the mechanical properties of the sclera and lamina cribrosa. Therefore, certain disc phenotypes are hypothesized to exist in patients with glaucoma who have concurrent superior and inferior damage at the initial stage of the disease.

A substantial proportion of retinal ganglion cell axons are known to be lost before standard automated perimetry reliably detects functional damage. Glaucomatous eyes with isolated hemifield VF loss are reported to accompany RNFL thinning in perimetrically normal hemifields, compared with healthy control eyes. Visible localized RNFL defects, which are often considered an early sign of glaucoma, are associated with large neuronal losses. In this regard, observation of structural rather than functional changes appears to be more relevant to document the early changes of glaucoma. Therefore, in this study, we investigated disc characteristics related to combined superior and inferior RNFL defects in eyes with early-stage glaucoma.

Methods

Study Samples

We retrospectively reviewed the medical records of all consecutive patients with open-angle glaucoma examined by a glaucoma specialist (C.K.P.) from August 1, 2010, through July 30, 2011, at the glaucoma clinic of Seoul St Mary’s Hospital. We reviewed patient medical records for medical history and results of a complete ophthalmic examination, including best-corrected visual acuity, refraction, slitlamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc, color disc and red-free fundus photography (Nonmyd 7; Kowa), and 24-2 Swedish interactive threshold algorithm standard automated perimetry (Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc). This study was performed according to the tenets of the Declaration of Helsinki after approval by the institutional review and ethics boards of Seoul St Mary’s Hospital.

All patients met the following inclusion criteria: best-corrected visual acuity of 20/40 or better, normal anterior chamber angles on slitlamp biomicroscopy and gonioscopy in both eyes, and results of 2 or more consecutive VF tests. Patients with neurological or intraocular diseases that could cause VF defects, eyes with consistently unreliable VF results (defined as >25% false-negative results, >25% false-positive results, or >20% fixation losses), or eyes with extremely high myopia and a spherical equivalent (SE) of no greater than −10 diopters (D) were excluded.

A glaucoma diagnosis was made when a patient had 1 or more localized wedge-shaped RNFL defects on red-free fundus photography associated with typical glaucomatous disc damage (diffuse or localized rim thinning on red-free fundus photographs) and glaucomatous VF defects on 2 consecutive and reliable standard automated perimetric examinations. A glaucomatous VF change was defined as the consistent presence of a cluster of 3 or more points on the pattern deviation plot with a probability of occurrence of less than 5% in the healthy population, 1 point with the probability of occurrence in less than 1% of the healthy population, glaucoma hemifield test results outside the reference limits, or a pattern standard deviation with P < 5%. Patients with glaucoma were enrolled if their mean deviation (MD) was greater than −8 dB. When both eyes met the inclusion criteria, we selected the eye with bihemispheric RNFL defects. In cases with a bilateral single-hemispheric RNFL defect, 1 eye was chosen using a random number table.

Evaluation of the RNFL Defects and Optic Disc Variables From Digital Retinal Photography

Color disc and red-free RNFL photographs were obtained using standardized settings on a nonmydriatic retinal camera (Nonmyd 7; Kowa). Fifty-degree views of the optic disc and RNFL photographs were reviewed using a liquid-crystal display monitor. Color disc photographs and red-free RNFL images were independently evaluated in a random order and blinded fashion by 2 of us (J.A.C. and H.-Y.L.P).

First, we analyzed the overall pattern of RNFL defects in eyes with early glaucoma using red-free RNFL photographs. Localized RNFL defects were diagnosed as previously described. A decision on the red-free photographs was made based on consensus between the 2 independent observers. Eyes with diffuse atrophy or ambiguous lesions were excluded from further analysis. Using this information, patients with glaucoma were divided into the following 2 groups based on the presence of RNFL defects in both hemispheres: group 1 patients had single-hemispheric RNFL defects, and group 2 patients had bihemispheric RNFL defects.

From the color disc photographs, the degree of optic disc tilt was determined using the disc ovality, which is the ratio between the longest and shortest diameters (orthogonal to one another) of the optic disc. When the disc ovality was greater than 1.30, the optic disc was classified as a tilted disc. The beta zone peripapillary atrophy, defined as an inner crescent of chorioretinal atrophy with visible sclera and choroidal vessels, was plotted using a mouse-driven cursor to trace the disc and peripapillary atrophy margin directly on the image. The pixel areas of the beta zone peripapillary atrophy were calculated using public domain ImageJ software (http://rsb.info.nih.gov/ij/index.html).

Optic Disc and RNFL Imaging

To measure the disc area, we performed topographic analysis of the optic discs using confocal scanning laser ophthalmos-
Next, all patients underwent imaging using high-definition spectral-domain optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec, Inc). Imaging was performed using an optic cube scan consisting of 200 × 200 axial scans (pixels) of the optic nerve region. Image quality was assessed by an experienced examiner blinded to the patient’s identity and other test results. Only well-focused, well-centered images without eye movement and signal strengths of 7/10 or greater were used.

For measurement of the disc horizontal tilt angle, the extracted horizontal tomogram images, obtained from the OCT, were saved and analyzed using the ImageJ software as described previously, with some modifications (Figure 1). In the extracted horizontal tomogram, the retinal pigment epithelium (RPE)/Bruch membrane complex and the end point of RPE/Bruch membrane into the disc boundaries are shown. A line was drawn from each RPE border/Bruch membrane opening (Figure 1A). An additional line (Figure 1B) connected 2 points that are located at an arbitrarily chosen distance of 80 pixels from the RPE/Bruch membrane opening on each side. The first line was then shifted toward an additional line to measure the angle of tilt (Figure 1C).

Based on the method of Fererras et al, clock-hour segments of the peripapillary RNFL (except the 4 and 9 o’clock segments) were divided into superior (10, 11, 12, 1, and 2, and 3 o’clock segments) and inferior (5, 6, 7, and 8 o’clock segments) RNFL. We calculated mean RNFL thicknesses in each hemisphere. The asymmetry in RNFL thickness between each hemisphere was defined as the difference in mean RNFL thickness (in micrometers) between the superior and inferior hemispheres (ie, the superior mean RNFL thickness minus the inferior mean RNFL thickness).

Finally, to assess the effect of refractive status on the posterior pole, we measured the angles between the superior and inferior temporal retinal veins in each patient. On RNFL deviation maps, lines were drawn from the center of the optic disc to each point where the superior and inferior temporal veins intersected with the circle shown in the map (a diameter of 3.46 mm). The angles between the lines were measured using the ImageJ software. The superior and inferior temporal veins were identified using disc fundus photographs.

Statistical Analysis
Interobserver reliability of the optic disc tilt measurements was assessed with additional grading of 30 randomly selected eyes by 2 observers (J.A.C. and H.-Y.L.P) and was calculated using the intraclass correlation coefficient. The mean values of the disc ovality from the 2 observers were used as the final values. For independent samples, we used unpaired, 2-tailed t tests and χ2 tests to compare between-group means (SD) and percentages. The relationships among the asymmetry in RNFL thickness hemispheres with SE, axial length (AL), and the angle between the retinal veins were evaluated using linear regression analyses. To determine the factors related to bihemispheric RNFL defects, univariate and multivariate logistic regression analysis was performed. The presence of bihemispheric RNFL defects was the dependent variable, and the independent variables were age, MD, AL, disc area, and disc ovality. The OCT-measured horizontal tilt angle was excluded from final analyses owing to its high correlation with disc ovality.
Table 1. Comparison of Variables Between Eyes With Single-Hemispheric and Bihemispheric RNFL Defects in Early-Stage Glaucoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Single-Hemispheric)</th>
<th>Group 2 (Bihemispheric)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54.0 (13.9)</td>
<td>54.2 (14.1)</td>
<td>−0.1 (−5.5 to 5.2)</td>
<td>.96</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>43.5</td>
<td>57.9</td>
<td>−14.4 (−12.7 to −16.1)</td>
<td>.56</td>
</tr>
<tr>
<td>SE, D</td>
<td>−1.41 (2.34)</td>
<td>−2.24 (2.59)</td>
<td>0.83 (−2.54 to 1.83)</td>
<td>.12</td>
</tr>
<tr>
<td>AL, mm</td>
<td>24.50 (1.55)</td>
<td>25.05 (1.69)</td>
<td>−0.54 (−1.31 to 0.23)</td>
<td>.16</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>15.9 (3.4)</td>
<td>14.9 (2.7)</td>
<td>1.00 (−0.96 to 2.92)</td>
<td>.32</td>
</tr>
<tr>
<td><strong>Visual field</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD, dB</td>
<td>−2.89 (1.84)</td>
<td>−3.41 (1.84)</td>
<td>0.52 (−0.13 to 1.23)</td>
<td>.15</td>
</tr>
<tr>
<td>PSD, dB</td>
<td>4.40 (2.69)</td>
<td>5.04 (2.59)</td>
<td>−0.64 (−1.67 to 0.30)</td>
<td>.22</td>
</tr>
<tr>
<td><strong>Posterior pole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tilted disc, %</td>
<td>5.3</td>
<td>17.5</td>
<td>−12.2 (−11.0 to −11.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Disc ovality</td>
<td>1.09 (0.12)</td>
<td>1.18 (0.18)</td>
<td>−0.09 (−0.14 to −0.03)</td>
<td>.001</td>
</tr>
<tr>
<td>PPA area, pixels</td>
<td>8268 (6366)</td>
<td>9840 (6958)</td>
<td>−1572 (−4142 to 1026)</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Confocal scanning laser</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmoscopy</td>
<td>Disc area, mm^2</td>
<td>2.25 (0.46)</td>
<td>0.02 (−0.17 to 0.21)</td>
<td>.83</td>
</tr>
<tr>
<td>OCT</td>
<td>RNFL thickness, μm</td>
<td>76.41 (8.63)</td>
<td>4.06 (0.88 to 7.88)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>RNFL asymmetry between</td>
<td>15.24 (11.36)</td>
<td>4.22 (0.40 to 7.84)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>hemispheres, μm^2</td>
<td>11.02 (8.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Horizontal tilt angle, degrees</td>
<td>4.17 (4.13)</td>
<td>−1.76 (−4.47 to −0.03)</td>
<td>.045</td>
</tr>
<tr>
<td></td>
<td>Angle between the temporal</td>
<td>148.36 (27.10)</td>
<td>−2.75 (−12.33 to 5.47)</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td>retinal veins, degrees</td>
<td>151.11 (26.44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All statistical analysis was performed using commercially available software (SPSS for Windows, version 14.0; SPSS Inc). P < .05 indicated statistical significance.

Results

According to our classification criteria, 136 eyes with glaucoma (from 136 patients) were enrolled in the study. Among the patients with early glaucoma, 41 (30.1%) had bihemispheric RNFL defects (group 2), whereas 95 (69.9%) had single-hemispheric RNFL defects (group 1). Optic disc tilt measurement reliability was found to be excellent, with an intraclass correlation coefficient of 0.92 (95% CI, 0.84–0.96).

Comparison of the clinical variables between groups is shown in Table 1. Compared with group 1, myopia in group 2 was 0.83 D greater (95% CI, −2.54 to 1.83; P = .12). The differences in MD and pattern standard deviation between groups 1 and 2 were 0.52 DB (95% CI, −0.13 to 1.23; P = .15) and −0.64 DB (95% CI, −1.67 to 0.30; P = .22). In group 2, the tilted disc percentage was 12.2% greater (95% CI, −13.0 to −11.4; P = .03) and disc ovality was 0.09 greater (95% CI, −0.14 to −0.03; P = .001). The differences in peripapillary atrophy area and optic disc area measured by confocal scanning laser ophthalmoscopy between groups were 1572 pixels less (95% CI, −4142 to 1026; P = .23) and 0.02 mm^2 greater (95% CI, −0.17 to 0.21 mm^2; P = .83) in group 2. Among OCT variables, the mean RNFL thickness in group 2 was 4.06 μm thinner (95% CI, 0.88–7.88; P = .02).

The asymmetry of RNFL thickness between hemispheres in group 2 was 4.22 μm less (95% CI, 0.40–7.84; P = .02). In addition, the OCT-measured horizontal tilt angle in group 2 was 1.76° larger (95% CI, −3.47 to −0.03; P = .045). The OCT-measured horizontal tilt angle correlated with disc ovality (r = 0.146; P = .001) and AL (r = 0.27; P = .01), whereas it negatively correlated with disc area (r = −0.33; P < .001) and the angle between the temporal retinal veins (r = 0.20; P = .02). The horizontal tilt angle had a marginal negative correlation with SE (r = −0.19; P = .052).

The asymmetry in RNFL thickness between hemispheres negatively correlated with disc ovality (tilt ratio) (r = −0.21; P = .02) and marginally correlated with the OCT-measured horizontal tilt angle (r = −0.16; P = .07) (Figure 2). However, associations were not identified with SE, AL, or the angle between the temporal retinal veins (r = 0.01 [P = .92] for SE, r = −0.146 [P = .19] for AL, and r = −0.08 [P = .41], respectively) (Figure 2). Multivariable logistic regression analysis controlling for age, AL, disc area, and MD revealed that disc ovality was an independent risk factor for bihemispheric RNFL defects in early glaucoma (P = .02) (Table 2).

Discussion

The present study was designed to evaluate factors related to the combined superior and inferior RNFL defects in early-stage glaucoma. Approximately 30% of eyes with glaucoma...
The asymmetry in RNFL thickness between each hemisphere was defined as the difference in mean RNFL thickness between the superior and inferior hemispheres. Correlation coefficients are calculated using the Pearson product moment correlation test. A, Disc ovality. B, Horizontal tilt angle measured by high-definition spectral-domain optical coherence tomography (OCT). C, Spherical equivalent. D, Axial length. E, Angle between the temporal retinal veins. D indicates diopter. The black lines indicate the regression line.
have bihemispheric RNFL defects. When we examined the morphological features of the disc associated with bihemispheric RNFL defects, disc tilt appears to be an independent risk factor for bihemispheric RNFL defects, even after controlling for MD, age, disc area, and AL. Representative cases are shown in Figure 3.

Previous studies have shown that localized RNFL defects can be detected ophthalmoscopically if more than 50% of the thickness of the RNFL is lost. Therefore, to compare eyes with relatively symmetrical damage and those with asymmetrical damage in the early stage of the disease, we included eyes with bihemispheric RNFL defects rather than eyes with bitemporal VF defects. In addition, the morphological features of the disc may be affected by glaucoma stage, as reported by Hosseini et al. For this reason, eyes in the early stage of glaucoma were included. In the present study, the MD and pat-
tern standard deviations were not statistically different between eyes with single-hemisphere vs bihemispheric RNFL defects (Table 1).

As with disc ovality, we measured the horizontal tilt angle using extracted horizontal B-scan images provided by high-definition OCT. The current generation of spectral-domain OCT provides high-resolution images within and surrounding the optic nerve head. We considered the disc margin the end point of the RPE/Bruch membrane, as demonstrated by Reis et al,21 because the end point of the Bruch membrane is a more consistent anatomic structure than the clinically perceived disc margin. As expected, the OCT-measured horizontal tilt angle highly correlated with disc ovality ($r = 0.51$). In addition, horizontal tilt angle was moderately associated with disc area, SE, AL, and the angle between the temporal retinal veins ($r = -0.34$, $r = -0.19$, $r = 0.27$, and $r = -0.20$, respectively).

As the degree of disc ovality and tilt angle increased, the asymmetry of RNFL thickness between hemispheres decreased ($P = .02$ and $P = .07$, respectively) (Figure 2A and B). In an intriguing finding, associations were not identified with refractive status (SE and AL) or the angle between temporal retinal veins (Figure 2C-E). Moreover, the degree of disc tilt was independently associated with bihemispheric RNFL defects after adjusting for AL, suggesting that disc tilt may be related directly to increased susceptibility to symmetric RNFL loss in the superior and inferior hemispheres.

Disc tilt is a well-known characteristic of myopic eyes, particularly in the Asian population.16,22 However, in a recent study by Hosseini et al,23 the degree of optic disc tilt was found to be associated with the stage of glaucoma (MD) and the AL. The posterior sclera, the supporting tissue of the posterior pole, is the main stress-bearing tissue of the eyeball. In the human posterior sclera, regional variations in the mechanical strains exist, and the peripapillary sclera in particular is subjected to higher tensile strain compared with the adjacent midperipheral sclera.23 Eyes with glaucoma had a different strain response in the peripapillary sclera compared with normal eyes, but not in the mid-posterior sclera.24 In this regard, the degree of optic disc tilt seems to be an indicator of altered biomechanics of the posterior peripapillary sclera (particularly on its temporal side) in eyes with glaucoma. Our study suggests that optic disc tilt is associated with bihemispheric RNFL defects in patients with glaucoma, regardless of their refractive status. Therefore, in consideration of the different biomechanics of the peripapillary sclera, eyes with glaucoma and increased optic disc tilt may be associated with the relatively symmetrical shearing forces across the superior and inferior sides of the lamina cribrosa compared with eyes with other disc phenotypes. To confirm this hypothesis, further studies are required, because we did not address this issue directly in this study. In addition, in our study, participants had mild myopia (mean [SD], -1.41 [2.34] D in group 1 and -2.24 [2.59] D in group 2 [Table 1]). However, patients with extremely high myopia (with an SE of -10 D or less) were excluded. Thus, our findings are limited to eyes with glaucoma and no pathologic myopia.

Controversy may arise regarding the role of disc tilt in glaucoma progression. Myopic refractive error, which is closely related to optic disc tilt, was not associated with glaucoma progression in patients with normal-tension glaucoma in a recent meta-analysis.25 In addition, in a case series examining nonprogressive glaucomatous cupping and VF abnormalities during a 7-year period,26 most patients had myopia and tilted disc. De Moraes et al6 reported that bihemifield defects at the initial stage of glaucoma was a risk factor associated with faster progression. These data may suggest that disc tilt, associated with bihemispheric structural damages in this study, is a risk factor for glaucoma progression. However, in their study, De Moraes et al6 included patients with open-angle glaucoma regardless of baseline intraocular pressure. Therefore, further investigation of disc tilt as a risk factor for glaucoma progression is warranted, particularly in patients with glaucoma and high intraocular pressure.

Our study has several limitations. To detect RNFL defects, we used red-free fundus photography, which is superior to color fundus photography. Patients with diffuse atrophy or ambiguous results were excluded from our analysis, which may have affected the study results. Because this study was cross-sectional, a causal relationship cannot be reported, and our results should be interpreted with caution. Finally, we excluded patients with extremely high myopia to increase the diagnostic precision on red-free fundus photography. Exclusion of these patients may have inadvertently introduced a selection bias.

Conclusions

The present study suggests that the degree of optic disc tilt was an independent risk factor for bihemispheric RNFL defects in early-stage glaucoma. Careful examination and special caution with both hemispheres may be necessary, particularly when patients with glaucoma exhibit tilted optic disc. Further studies seem necessary to determine optic nerve susceptibility to glaucomatous damage according to disc phenotype.

ARTICLE INFORMATION

Submitted for Publication: November 5, 2013; final revision received and accepted February 25, 2014.

Published Online: June 12, 2014. doi:10.1001/jamaophthalmol.2014.1056.

Author Contributions: Dr C. K. Park had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Choi, H.-Y. L. Park. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Choi. Critical revision of the manuscript for important intellectual content: H. Y. L. Park, Shin, C. K. Park. Statistical analysis: Choi, H.-Y. L. Park, Shin. Administrative, technical, or material support: H.-Y. L. Park, C. K. Park. Study supervision: C. K. Park. Conflict of Interest Disclosures: None reported.

REFERENCES