Retinal Nerve Fiber Layer Defects in Highly Myopic Eyes with Early Glaucoma

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PURPOSE. To compare the retinal nerve fiber layer (RNFL) defects in early glaucomatous eyes between highly and non–highly myopic eyes.

METHODS. Sixty-one highly myopic eyes (<−6.0 diopters [D]) of 61 patients and 55 non–highly myopic eyes of 55 patients with early visual field (VF) defects were studied. The angular locations and widths of the RNFL defects were measured from red-free fundus photographs. The RNFL defect closest to the fovea was designated the “nearest RNFL defect” of each hemisphere.

RESULTS. In total, 131 RNFL defects were found in highly myopic eyes and 82 in non–highly myopic eyes. Twenty-seven (44.3%) of the 61 highly myopic eyes, but only 8 (14.5%) of the 55 non–highly myopic eyes had their nearest RNFL defects between 0° and 10° (P < 0.001). Although the frequencies of paracentral scotomas were comparable between the two groups, the rate of inferotemporal paracentral scotomas was significantly higher in the high myopia group (P = 0.02). The numbers of nearest RNFL defects in the superior hemisphere or extending over both hemispheres were significantly higher in the high-myopia group. Multiple logistic regression analyses showed that high myopia and the nearest RNFL defect involving the papillomacular bundle were significantly associated with paracentral scotomas (odds ratio [OR]: 4.78, P < 0.05, and OR: 5.31, P < 0.001, respectively). High myopia was significantly associated with the nearest RNFL defect involving the papillomacular bundle (OR: 2.95, P < 0.05).

CONCLUSIONS. These findings suggest that highly myopic eyes are more susceptible to papillomacular bundle damage in early glaucoma. (Invest Ophthalmol Vis Sci. 2012;53:6472–6478) DOI:10.1167/iovs.12-10319

Visual field (VF) defects in early glaucoma are usually detected peripherally (e.g., nasal step or arcuate scotomas). Although the paracentral area is usually spared until the end stages of glaucoma, some patients develop paracentral scotomas threatening fixation during early stage glaucoma, and are at greater risk for impaired quality of vision.1–3 Risk factors for developing paracentral scotomas are normal-tension glaucoma (NTG),1,5 low maximum untreated IOPs,6 frequent disc hemorrhage,8 systemic factors,6 and high myopia.7–9 Myopia is highly prevalent in East Asia10–12 and is a risk factor for glaucoma.13 In advanced glaucoma, higher myopia has been associated with significantly higher frequencies of cecocentral scotomas located just temporal and inferior to the fixation point.14,15 However, VF defects characteristic of high myopia have not been properly studied in early glaucoma,16 and whether highly myopic eyes are at greater risk for impaired paracentral vision during early glaucoma is unknown.

Atypical retinal nerve fiber layer (RNFL) defects, including papillomacular bundle defects, are found in highly myopic eyes with primarily moderate-to-severe VF defects. Longer axial length, larger optic disc, and NTG are risk factors for papillomacular bundle defects.7 Whether or not the frequency of such RNFL defects is greater in patients with highly myopic eyes in early-stage glaucoma remains unknown. Because the RNFL defects often precede the VF defects, RNFL defects are useful indicators of the locations of early glaucomatous damage.20 Measurement of the angular location and size of RNFL defects should allow quantitative comparison of RNFL defects between eyes with and without high myopia.21–23 We have investigated the rate of papillomacular bundle defects in highly myopic eyes compared with non–highly myopic eyes during early-stage glaucoma by determining the angular locations and widths of RNFL defects in highly and non–highly myopic eyes with early-stage glaucoma.

METHODS

Participants

Medical records of patients who were examined at the Glaucoma Clinic of the Department of Ophthalmology, Kyoto University, Kyoto, Japan from October 2007 to April 2011 were reviewed. All participants underwent complete ophthalmic examinations, including best-corrected visual acuity (BCVA) with a 5-meter Landolt chart, refraction, slit-lamp biomicroscopy, IOP measurements with a Goldmann applanation tonometer, gonioscopy, axial length measurements by partial laser interferometry (IOL master; Carl Zeiss Meditec, Dublin, CA), dilated biometric examination, stereoscopic color optic disc photography (with a 3-Dx simultaneous stereo disc camera; Nidek, Gamagori, Japan), red-free fundus photography with a Heidelberg Retina Angiogram 2 (HRA2; Heidelberg Engineering, Heidelberg, Germany), Heidelberg Retina Tomography 2 (HRT 2; Heidelberg Engineering), and standard automated perimeter (SAP) using the Swedish interactive threshold algorithm standard 24-2 with a Humphrey Visual Field Analyzer (Carl Zeiss Meditec). The refractive error was converted to
RNFL Defects in Glaucoma and High Myopia

Definition of Visual Field Defects

A glaucomatous VF was defined by a glaucoma hemifield test value that was outside normal limits, the presence of at least three vertical, horizontal, or diagonal contiguous test points within the same hemifield on the pattern deviation probability plot at $P$ less than 5% with at least one point at $P$ less than 1% and excluding points directly above or below the blind spot, or a pattern standard deviation (PSD) of less than 5% of the normal reference values confirmed by at least two VF tests. Eyes were included only when fixation losses, false-positive errors, and false-negative errors were less than 20%.

Definition of the Angular Locations of Retinal Nerve Fiber Layer Defects

When more than two RNFL defects were detected in the superior or inferior hemisphere, the RNFL defect closest to the reference line was designated the “nearest RNFL defect” of that hemisphere. The total width of the RNFL defects in each eye was calculated by summing the angular widths of all of the RNFL defects of that eye. When an RNFL defect crossed the reference line, its angular width was measured on each side of the reference line, and its angular location was recorded as $0^\circ$ in each hemisphere. A RNFL defect was considered to involve the papillomacular bundle when the proximal border of the nearest defect was located within $20^\circ$ of the reference line.

Visual Field Testing

A glaucomatous VF was defined by a glaucoma hemifield test value that was outside normal limits, the presence of at least three vertical, horizontal, or diagonal contiguous test points within the same hemifield on the pattern deviation probability plot at $P$ less than 5% with at least one point at $P$ less than 1% and excluding points directly above or below the blind spot, or a pattern standard deviation (PSD) of less than 5% of the normal reference values confirmed by at least two VF tests. Eyes were included only when fixation losses, false-positive errors, and false-negative errors were less than 20%.

Definition of Visual Field Defects

To investigate the relationship between the locations of RNFL defects and patterns of VF defects in eyes with early glaucoma, glaucomatous VF defects were classified as paracentral or nonparacentral scotomas as previously reported, with modifications.6 Paracentral scotoma was defined as a glaucomatous VF defect in one hemifield within $10^\circ$ of fixation with at least one point at $P$ less than 1% lying at the two innermost paracentral points, regardless of the presence of VF defects outside of the central $10^\circ$. A nonparacentral scotoma was defined as a glaucomatous defect in one hemifield outside of the central $10^\circ$ of fixation. The number of eyes with paracentral scotoma with abnormal test points at $P$ less than 1% within the central $5^\circ$ in each quadrant (superior temporal, superior nasal, inferior temporal, and inferior nasal) or hemisphere (superior and inferior) were also counted.

Optic Disc Measurements with HRT 2

Heidelberg Retina Tomography 2 (HRT 2) images were obtained from undilated pupils. The area of the optic disc was measured in all eyes by using the built-in HRT 2 software (Heidelberg Engineering, Heidelberg, Germany) according to published techniques.24 The measurement was included in analysis only if the SD of the mean topographic image was
less than 40 μm. An experienced examiner, masked to the other findings, outlined the optic disc margin manually while viewing fundus color photographs. Magnification errors were corrected by the HRT2 software using the patient’s refractive error and corneal curvature.

**Measurements of Optic Disc Ovality**

To define tilted disc, the degree of tilting is customarily estimated by the disc ovality index, which is the ratio of the minimum to the maximum optic disc diameter. An examiner examined color fundus photographs of the optic disc taken at a 45° viewing angle and plotted 14 points along the disc margin. Software developed by our group automatically drew an ellipse along the contour of the optic disc to determine centers of gravity and maximum and minimum diameters of each optic disc. Disc ovality indexes were calculated as the ratios of the minimum to the maximum diameters.

**Statistical Analyses**

Differences in continuous values between groups were determined by unpaired *t*-tests or Mann-Whitney *U* tests. The effect of age was offset by analysis of a covariance model that included age as the covariance factor. Differences in categorical variables were evaluated by χ² tests. The Kolmogorov-Smirnov test was used to determine whether the angular locations of RNFL defects were normally distributed. Cohen’s *κ* coefficient was calculated to estimate interobserver agreement for number of RNFL defects. Interclass correlation (ICC) was calculated to estimate interobserver reliability of measurements of the angular locations and widths of RNFL defects. Univariate and multivariate logistic regression analyses were performed to determine the association of various factors with paracentral scotoma or papillomacular bundle defects. The independent variables were large disc area (>2.82 mm²), small disc area (<1.69 mm²), tilted disc (ovality index ≤0.8), high myopia, and presence of papillomacular bundle defects for paracentral scotoma as a dependent variable. For papillomacular bundle defects as a dependent variable, the independent variables were large disc area (>2.82 mm²), small disc area (<1.69 mm²), tilted disc (ovality index ≤0.8), and high myopia. All statistical analyses were performed using SPSS software version 11.01 J (SPSS, Inc., Chicago, IL).

**Results**

A total of 104 eyes of 73 patients with high myopia and 93 eyes of 68 patients with non–high myopia met the inclusion criteria. Of these, 25 eyes with high myopia and 28 with non–high myopia were excluded because of previous cataract surgery (10 with high myopia, 12 with non–high myopia) or vitreoretinal diseases including epiretinal membranes or macular degeneration (eight with high myopia, five with non–high myopia), diabetic retinopathy (three with high myopia, eight with non–high myopia), or superior segmental optic hypoplasia (four with high myopia, three with non–high myopia). Eight eyes with high myopia and six with non–high myopia were also excluded after random selection of their fellow eye in patients with two eligible eyes. Ten eyes with high myopia and four without high myopia were excluded because group discussion did not reach agreement as to the presence of RNFL defects. Finally, data from 61 eyes of 61 patients with high myopia and 55 eyes of 55 patients with non–high myopia were analyzed.

Patient demographics and optic disc characteristics are shown in Table 1. Age, spherical equivalent refractive error, and axial length differed significantly between eyes with and without high myopia. Sex distribution, mean IOP during follow-up, mean deviation (MD) and PSD did not differ significantly between the groups. The high-myopia group had significantly lower ovality indices. Disc area did not differ significantly between the groups.

**Retinal Nerve Fiber Layer Defect Measurements**

Interevaluator agreement, as represented by the Cohen κ value, for the number of RNFL defects was 0.80 for all eyes, 0.78 for highly myopic eyes, and 0.81 for non–highly myopic eyes. The ICC for the angular location was 0.93 for all eyes, 0.94 for highly myopic eyes, and 0.93 for non–highly myopic eyes. The ICC for the angular width was 0.85 for all eyes, 0.89 for highly myopic eyes, and 0.85 for non–highly myopic eyes. These findings indicate good reliability in the detection and measurement of RNFL defects.

A total of 131 RNFL defects were found in eyes with high myopia and 82 in eyes without high myopia. After adjustment for age and MD, the mean number of RNFL defects per eye was significantly higher, the mean angular location of all RNFL defects significantly lower, and the total width of the RNFL defects significantly larger in the high-myopia group than in the non–high-myopia group (Table 2).

**Frequency Distribution and Angular Location and Width of Nearest RNFL Defects**

The frequency distributions according to the angular locations (in 10° steps) of the nearest retinal nerve fiber layer defects were plotted separately for high-myopia and non–high-myopia groups (Fig. 2). The angular locations of the non–high-myopia group were normally distributed (P = 0.20), with a peak angular location between 21° and 30° (17 of 55 eyes, 30.9%). The angular locations of the high-myopia group were not...
normally distributed ($P < 0.001$) and peaked between 0° and 10°. Twenty-seven of 61 (44.3%) highly-myopic eyes and 8 of 55 (14.5%) non–highly-myopic eyes had nearest RNFL defects between 0° and 10° ($P < 0.001$). The number of eyes with nearest RNFL defects involving the papillomacular bundle (i.e., those within 20° of the reference line) was significantly higher ($P = 0.002$) in highly myopic (34 eyes, 55.7%) than in non-highly-myopic (15 eyes, 27.2%) eyes.

Figure 3 shows examples of cases with high myopia, in which the nearest RNFL defect involved the papillomacular bundle. After adjustment for age and MD, the mean angular locations of the nearest RNFL defects were significantly lower in the eyes with high myopia (Table 3). In contrast, the mean widths of the nearest RNFL defects did not differ significantly between the two groups (Table 3). The proportion of nearest RNFL defects involving the papillomacular bundle was significantly larger in high myopia (Table 3).

### Abnormal Paracentral Points and Nearest RNFL Defects in Eyes with Paracentral Scotomas

Paracentral scotomas were found in 29 (47.5%) eyes with high myopia and 28 (50.9%) eyes without high myopia ($P = 0.72$). In eyes with paracentral scotoma, the mean number of VF test points at $P$ less than 1% per eye did not differ significantly ($P = 0.46$) between high (mean number = 1.77) and non-high myopia (mean number = 1.50) groups. However, comparison of the locations of the abnormal test points at $P$ less than 1% showed that the number of eyes with abnormal test points in the inferior temporal quadrant was significantly higher ($P = 0.02$) in the high-myopia group (Table 4).

The number of nearest RNFL defects in the superior hemisphere, but not that in the inferior hemisphere, was significantly higher in the high-myopia group (Table 5). Nearest RNFL defects extending over both hemispheres were rare in eyes without high myopia (7.1%) but were significantly more frequent in eyes with high myopia (41.3%).

### Univariate and Multivariate Analyses

Nearest RNFL defects located within the papillomacular bundle were significantly associated with the presence of paracentral scotoma in both univariate ($P < 0.01$) and multivariate (odds ratio [OR]: 5.56, 95% confidence interval [CI]: 2.17–14.2, $P < 0.001$) logistic regression analyses. High myopia was also significantly associated with the presence of a paracentral

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**Table 2.** Comparison of All RNFL Defects between High Myopia and Non–High Myopia

<table>
<thead>
<tr>
<th>High Myopia</th>
<th>Non–High Myopia</th>
<th>$P$ Value*</th>
<th>$P$ Value Adjusted for Age and MD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of RNFL defects per eye</td>
<td>2.1 (1.1)</td>
<td>1.5 (0.8)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Angular location of each RNFL defect (degrees)</td>
<td>24.4 (20.0)</td>
<td>35.4 (17.9)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Angular width per RNFL defect (degrees)</td>
<td>21.2 (11.9)</td>
<td>21.1 (11.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total angular width per eye (degrees)</td>
<td>45.4 (24.4)</td>
<td>31.4 (17.4)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Decimal values are expressed as the mean with SD in parentheses.

* Mann-Whitney $U$ test.

† Analysis of covariance.

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**Figure 2.** Frequency distributions of the angular locations (degrees) of the nearest RNFL defects in eyes with high and non–high myopia. *$P < 0.01$ ($x^2$ test). The number of eyes in which the nearest RNFL defect was detected within the corresponding range was plotted for each angular location.
Scotoma in multivariate logistic regression analysis (OR: 3.08, 95% confidence interval [CI]: 1.14–8.33, \( P = 0.03 \)). High myopia and tilted disc were significantly associated with nearest RNFL defects located within papillomacular bundle on both univariate (high myopia, \( P = 0.001 \); tilted disc, \( P = 0.01 \)) and multivariate (high myopia, OR: 3.72, 95% CI: 1.64–8.45, \( P = 0.002 \); tilted disc, OR: 2.73, 95% CI: 1.13–6.61, \( P = 0.03 \)) logistic regression analyses.

**Discussion**

The frequency distribution profile of the angular locations of the nearest RNFL defects differed significantly between eyes with and without high myopia; 44.3% and 55.7% of highly myopic eyes had their nearest RNFL defects in the central region (\( \leq 10^\circ \)) and over the papillomacular bundle region (\( \leq 20^\circ \)), respectively, versus 14.5% and 27.2% of non-highly myopic eyes. Therefore, measurement of the angular locations of RNFL defects was useful to demonstrate the unusual distribution profile of early glaucomatous RNFL damage in eyes with high myopia.

The frequency distribution of the angular locations of RNFL defects in eyes without high myopia has been previously reported. Lee et al.\(^{28}\) showed that RNFL defects detected on red-free photographs were most commonly found in the 7 to 11 o’clock sectors. Leung et al.\(^{29}\) reported that the RNFL measured by Cirrus HD-OCT (Carl Zeiss-Meditec) was thinnest in the inferotemporal meridians between 72\(^\circ\) and 90\(^\circ\). The results from our non-high myopia group are nearly consistent with those of these earlier studies. The high frequency of papillomacular bundle defects, therefore, appears to be characteristic of highly-myopic eyes.

Although the angular locations of the RNFL defects differed significantly between eyes with and without high myopia, the rate of paracentral scotomas in early glaucomatous eyes did not, nor did the mean number of abnormal points at \( P \) less than 1% affecting the 4 paracentral points in eyes with paracentral scotomas. However, paracentral scotomas were found in the inferior temporal quadrant significantly more often in the eyes with high myopia. Araie et al.\(^{14}\) and Mayama et al.\(^{15}\) reported that higher myopia was significantly associated with VF damage just temporal and inferior to the fixation point in advanced glaucomatous eyes. Our results agree with theirs, and we further suggest that these lower cecocentral VF defects develop more frequently in highly myopic eyes than in non-highly myopic eyes, even in early stage glaucoma.

Nearest RNFL defects located in the superior hemisphere and/or extending over both hemispheres were found more

![Table 3. Comparison of Angular Location and Width of Nearest RNFL Defects](https://tvst.arvojournals.org/content/53/10/6476.full.pdf)
frequently in the high-myopia group in the current study. Multiple logistic regression analysis indicated that papillomacular bundle defects were significantly associated with paracentral scotomas. Therefore, a higher rate of papillomacular bundle defects involving the superior hemisphere appears to be related to a higher frequency of inferotemporal paracentral scotomas in highly myopic eyes.

An inferior paracentral scotoma can significantly affect a patient’s quality of life, and it is important to detect these abnormalities. RNFL defects are often detected earlier than VF defects, and detection of superior papillomacular bundle defects could be useful to predict development of inferotemporal paracentral scotomas.

Seven of the highly myopic eyes without papillomacular bundle defects in the present study had paracentral scotomas, while 12 highly myopic eyes with papillomacular bundle defects lacked paracentral scotomas. Thus, the paracentral scotomas detected by SAP and papillomacular bundle defects did not completely match. A possible reason for this discordance is that RNFL defects that do not involve the papillomacular bundle can also cause paracentral scotomas, particularly in the nasal paracentral points. Another possibility is that because RNFL defects precede VF defects, there may have been areas of RNFL damage involving the papillomacular bundle that were not yet detectable on SAP.

In the multiple logistic regression analysis, high myopia (< –6 D) was significantly associated with the paracentral scotoma and papillomacular bundle defects. Greve et al. examined the VF and reported cecocentral RNFL defects in 16.7% of highly myopic eyes (< –6 D) with glaucoma but only 0.69% of eyes without high myopia (≥ 5.75 D). Our results agree with these findings in that unusual RNFL defects, including papillomacular bundle defects, were more frequently found in eyes with high myopia. Therefore, although the papillomacular bundle is generally believed to be one of the last nerve fibers lost in patients with glaucoma, this may not be the case in highly myopic eyes. On the other hand, the frequency of papillomacular bundle defects was much higher in our study (42.0%) than in the earlier report, and Chihara et al. found papillomacular bundle defects in only 22 (11.1%) of 199 glaucomatous eyes. One reason for this may be that we studied only eyes with early VF defects, whereas the earlier report included many eyes with severe VF defects.

Our results suggest that highly myopic eyes may, at least in part, have a different mechanism of retinal ganglion cell (RGC) damages. One possible mechanism for damages to papillomacular bundle would be the mechanical stress from scleral stretching associated with myopic eyeball elongation. Kim et al. recently reported that progressive tilting of the optic disc with nasal shift of temporal optic disc margin and concurrent development/enlargement of PPA occurred in children with myopic shift. Their findings indicated that the lamina cribrosa, thought to be a principal site of glaucomatous damages, also shifts to the nasal direction in eyes with a tilted disc. This myopic tilting of the optic disc may generate tensile stretch of the temporal side of the lamina cribrosa and the RGC axons in the papillomacular bundle. The significant association between tilted discs and papillomacular bundle defects in our study may support this speculation. The following two recent studies showed focal lamina cribrosa defects associated with VF defects in eyes with glaucoma and in eyes with pathologic myopia: Kiumehr et al. reported that focal lamina cribrosa defects detected in eyes with glaucoma spared the temporal and nasal 45° sectors, but Ohno-Matsui et al. reported that 31.6% of lamina cribrosa defects (acquired optic nerve pits) found in high myopia were located along the temporal edge of the lamina cribrosa, indicating that this area may be susceptible to mechanical stress in high myopia. Further studies regarding these mechanisms would be worthwhile.

In conclusion, papillomacular bundle defects and inferotemporal paracentral scotomas were more frequent in highly myopic than in non–high myopic early glaucomatous eyes. The papillomacular bundle defects were associated with paracentral scotomas. Multiple logistic regression analyses confirmed high myopia as a risk factor for papillomacular bundle defects and paracentral scotomas. Longitudinal studies are needed to

### Table 4. Number of Eyes with Abnormal Visual Field Points at P Less than 1% Affecting at Least One Paracentral Point in Each Quadrant and Hemisphere in Eyes with and without High Myopia

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>High Myopia (n = 29)</th>
<th>Non–High Myopia (n = 28)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior nasal</td>
<td>26 (89.7%)</td>
<td>23 (82.1%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>9 (31.0%)</td>
<td>14 (50.0%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Inferior nasal</td>
<td>7 (24.1%)</td>
<td>3 (10.7%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>9 (31.0%)</td>
<td>2 (7.1%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>High Myopia (n = 29)</th>
<th>Non–High Myopia (n = 28)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>26 (89.7%)</td>
<td>26 (92.9%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Inferior</td>
<td>11 (37.9%)</td>
<td>5 (17.9%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* χ² test.

### Table 5. Number of Eyes with Nearest RNFL Defects in the Superior, Inferior, and Across Both Hemispheres in Eyes with Paracentral Scotoma

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>High Myopia (n = 29)</th>
<th>Non–High Myopia (n = 28)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior hemisphere</td>
<td>16 (55.2%)</td>
<td>4 (14.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior hemisphere</td>
<td>25 (86.2%)</td>
<td>26 (92.9%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Across both hemispheres</td>
<td>12 (41.3%)</td>
<td>2 (7.1%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values indicate the number (%) of eyes with nearest RNFL defects in each location.

* χ² test.
determine the progression of these central vision-threatening RNFL defects in highly myopic eyes.

References


