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Position of Central Retinal Vascular Trunk and Preferential Location of Glaucomatous Damage in Myopic Normal-Tension Glaucoma

Kyoung Min Lee, MD,[1,2] *Martha Kim, MD,*[3] *Sohee Oh, PhD,*[4] *Seok Hwan Kim, MD*[1,2]

Purpose: To investigate the spatial correlation between the central retinal vascular trunk and the preferential location of glaucomatous damage in myopic normal-tension glaucoma (NTG) eyes.

Design: Cross-sectional study.

Participants: One hundred thirty-seven subjects with myopic NTG (137 eyes).

Methods: The position of the vascular trunk was measured from the center of the Bruch membrane opening (BMO), which was delineated by optical coherence tomography imaging. The angular deviation was measured, with the horizontal nasal midline as 0° and the superior location as a positive value. The shift index was calculated as the distance of the vascular trunk from the BMO center relative to that of the BMO margin. The angular location of the midpoint of the retinal nerve fiber layer (RNFL) defect was measured from the BMO center. In cases with bi-hemispheric RNFL defects, the angular location was measured for the RNFL defect of larger width. For categorical analysis, hemispheric dominancy was determined if the RNFL defect in one hemisphere was larger than twofold that in the opposite hemisphere. In cases with no dominant hemisphere, the eye was classified as bi-equivalent involvement.

Main Outcome Measures: The vascular trunk position within the BMO and the location of glaucomatous damage.

Results: The moderate- and severe-shift groups (shift index ≥ 0.5) were associated with younger age, longer axial length, smaller angular deviation, and lesser incidence of focal lamina cribrosa (LC) defect. A multiple regression analysis showed a significant correlation between the vascular trunk position and the RNFL defect location ($P < 0.001$). A logistic regression analysis revealed that the dominant RNFL defect occurred in the opposite hemisphere of the vascular trunk ($P < 0.001$), and bi-equivalent involvement in both hemispheres was associated with a larger shift index ($P = 0.001$). A conditional inference tree analysis showed that both the angular deviation ($P < 0.001$) and the extent of vascular trunk shift ($P < 0.001$) determined the RNFL defect location.

Conclusions: In myopic NTG eyes, the vascular trunk is located in the direction opposite of the RNFL defect with reference to the BMO. Because the vascular trunk is embedded in the LC, this implies that LC shift during axial elongation is associated with greater vulnerability of myopic eyes to glaucomatous damage. *Ophthalmology Glaucoma 2018;1:32-43 © 2018 by the American Academy of Ophthalmology*

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Glaucoma is characterized by progressive axonal loss of retinal ganglion cells that is initiated at the optic nerve head (ONH).[1] Although intraocular pressure (IOP) plays a role in glaucoma pathogenesis, normal-tension glaucoma (NTG) has a statistically normal IOP level, a fact which is suggestive of a major role for susceptibility factors other than IOP. Myopia is one of the important risk factors for glaucoma development.[2–4] Because axial elongation in myopic eyes is accompanied by scleral remodeling of the ONH and peripapillary area where glaucomatous changes occur, ONH change during axial elongation might be associated with non-IOP-related susceptibility to glaucoma.[5,6]

ONH-structure changes by axial elongation include oval-shaped optic disc, optic disc torsion,[7,8] and parapapillary atrophy (PPA).[7,9] These anatomic changes have been reported to be associated with the preferential site of damage in glaucoma patients.[10–12] Along with these ONH changes, lamina cribrosa (LC) change could provide a clue to the association of myopia with glaucoma, because the LC is the principal site of axonal injury in glaucoma.[13] Therefore, to understand which factor is associated with vulnerability of the glaucomatous damage of myopic eyes, it is important to evaluate the LC change during axial elongation.

In the recent Boramae Myopia Cohort Study, we found, during axial elongation, a shift of LC in contrast to the

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relative preservation of the Bruch membrane opening (BMO).[14,15] LC shift can be measured by tracing the positional change of the central retinal vascular trunk that is embedded in the LC's connective tissue.[16] Therefore, we postulate that the position of the central retinal vascular trunk relative to the center of the BMO can represent the change and stress exerted on the LC. The purpose of the present study, correspondingly, was to determine the association of the position of central vascular trunk relative to the center of the BMO and the location of glaucomatous optic nerve damage in myopic NTG eyes.

Methods

This investigation was based on NTG patients included in the Boramae Glaucoma Imaging Study, an ongoing prospective study at Seoul National University Boramae Medical Center (Seoul, Korea). Written informed consent to participate was obtained from all of the subjects. The study protocol was approved by the Seoul National University Boramae Medical Center Institutional Review Board and conformed to the tenets of the Declaration of Helsinki.

All of the participants underwent a full ophthalmologic examination that included best-corrected visual acuity assessment, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated funduscopic examination, keratometry (RKT-7700; Nidek, Hiroshi, Japan), axial length measurement (IOLMaster version 5; Carl Zeiss Meditec, Dublin, CA), disc photography and red-free fundus photography (TRC-NW8; Topcon, Tokyo, Japan), spectral-domain optical coherence tomography (SD OCT; Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany), and standard automated perimetry (Humphrey Field Analyzer II 750, 24-2 Swedish Interactive Threshold Algorithm; Carl-Zeiss Meditec, Dublin, CA). During the acquisition of SD OCT images, the subjects were asked to fixate on the target, and images were acquired with the forehead and chin stabilized by the headrest. Extra care was taken during each examination to confirm that the forehead and chin were correctly positioned and did not move. Before the treatment, IOP was measured repeatedly (typically 5 times) on the same or different days. The average value, which was defined as the baseline IOP, was used for the subsequent analysis.

Glaucomatous optic nerve damage was defined by rim thinning, notching, and the presence of retinal nerve fiber layer (RNFL) defects and was evaluated by a glaucoma specialist (S.H.K.). NTG was defined as glaucomatous optic nerve damage and associated visual field defects, an open iridocorneal angle, and IOP $\leq$ 21 mmHg at any point before or after treatment. Glaucomatous visual field defect was defined as (1) outside normal limits on glaucoma hemifield test; or (2) 3 abnormal points, with a *P* value less than 5% probability of being normal and 1 with a *P* value less than 1% by pattern deviation; or (3) pattern standard deviation of less than 5%. Visual field defects were confirmed on 2 consecutive reliable tests (fixation loss rate of $\leq$20%, and false-positive and false-negative error rates of $\leq$25%).

The inclusion criteria were NTG and myopia (axial length $\geq$24.0 mm). The exclusion criteria were best-corrected visual acuity of $<$20/40, posterior staphyloma (which can deform the contour of the eyeball) that appeared sharply defined in the funduscopic examination, a history of ocular surgery other than cataract extraction or corneal refractive surgery, retinal or neurologic disease other than glaucoma that could cause visual field defect, and a poor-quality image (i.e., quality score $<$15) of any section on enhanced depth imaging (EDI) SD OCT radial scans, when neither RNFL defect margin could be delineated on red-free fundus photography and when the position of the central retinal vascular trunk was located within the BMO but could not be determined clearly. If both eyes were eligible, 1 eye was randomly selected as the study eye.

Localization of Central Retinal Vascular Trunk

The peripapillary area was imaged by SD OCT. The corneal curvature of each eye was entered into the SD OCT system (Spectralis, Heidelberg Engineering) before SD OCT scanning was performed so as to compensate for potential magnification error. The Glaucoma Module Premium Edition of the Spectralis machine enables the detection of the BMO. With 24 high-resolution radial scan images of the ONH, 15° apart from each other, each averaged from 24 individual B-scans, SD OCT automatically detects the margin of the BMO. Every detected BMO margin was reviewed by 1 of the authors (K.M.L.), and errors were corrected manually. Based on the edited BMO margin, the Spectralis machine calculated the area and center of the BMO and determined the foveal-BMO axis.

The location of the central vascular trunk was demarcated on funduscopic infrared images and color-disc photography (Fig 1). Its location was confirmed by cross-sectional SD OCT imaging in all cases. In cases with an invisible vascular trunk on the infrared fundus photographs and B-scan EDI SD OCT images, fluorescein angiography was used to determine the presence of the vascular trunk within the BMO. The position of the central retinal vascular trunk was defined in 2 aspects: (1) its angular deviation (Fig 1B, α), and (2) the extent of shift (Fig 1B, *a*). The angle was measured based on the right-eye orientation, with the nasal horizontal midline as 0° (a positive value indicating a vascular trunk located superiorly, and a negative value indicating a vascular trunk located inferiorly). To evaluate the extent of the shift, the distance of the vascular trunk from the center of the BMO (*a*) was divided by the distance of the BMO margin from the center of the BMO in that direction (*b*) and was defined as the "shift index" (Fig 1B, *a*/*b*). In cases of invisible vascular trunk owing to its being located outside the BMO, the shift index was defined as 1.0, and the angular deviations were not determined. Using the ImageJ program (version 1.51; National Institutes of Health, Bethesda, MD), 1 of authors (K.M.L.), who was blinded to the participants' clinical information, measured the distances and angles. The reproducibility of the locating of the central retinal vascular trunk was evaluated as described below.

Assessment of Retinal Nerve Fiber Layer Defects

The angular location of the RNFL defect was defined in the same image used for the vascular trunk localization based on the right-eye orientation. First, an infrared fundus image was overlapped with a red-free fundus photograph using commercial software (Photoshop; Adobe, San Jose, CA) (Fig 1A). The points where the boundaries of the RNFL defect meet the BMO margin were determined. The angular location of the midpoint of the RNFL defect on the BMO margin was measured from the center of the BMO, with the temporal horizontal midline as 0° (a positive value indicating an RNFL defect located superiorly, and a negative value indicating an RNFL defect located inferiorly) (Fig 1B, β).

In cases of RNFL defects in both hemispheres, the angular location was measured to the larger RNFL defect based on angular width. For robust determination of the more damaged hemisphere, we defined hemispheric dominancy as follows: a hemisphere with an RNFL defect twofold larger than that in the opposite hemisphere. If there was no dominant hemisphere, the eye was classified