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Multiple Temporal Lamina Cribrosa Defects in Myopic Eyes with Glaucoma and Their Association with Visual Field Defects

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Purpose: To investigate characteristics of lamina cribrosa (LC) defects in myopic eyes with open-angle glaucoma (OAG) using spectral-domain (SD) optical coherence tomography (OCT).

Design: Cross-sectional study.

Participants: One hundred thirty-three eyes with OAG and 83 eyes without OAG, with axial length of 24 mm or more.

Methods: Serial enhanced depth imaging SD OCT B-scans of the optic disc were acquired and reviewed for LC defects (diameter, $\geq$100 μm) and large pores (diameter, 60−100 μm). The numbers and locations of LC defects and large pores in each eye were assessed. In eyes with OAG, factors related to the number of LC defects were evaluated, as well as the association between the locations of LC defects and visual field (VF) defects (e.g., paracentral scotoma [PCS] and superior or inferior hemifield defects).

Main Outcome Measures: Numbers and locations of LC defects and large pores.

Results: In myopic eyes with and without OAG, the average numbers of LC defects were 3.8 and 0.8 and numbers of large pores were 1.9 and 1.6, respectively. In both groups, LC defects and large pores were located predominantly at the temporal periphery. Among eyes with OAG, the number of LC defects was relatively high in the eyes with greater optic disc tilt angle and worse mean deviation of the VF (both $P < 0.001$). The number of temporal LC defects and tilt angle were associated with presence of PCS, whereas the number of inferior and superior LC defects and torsion direction were associated with presence of superior and inferior VF defects.

Conclusions: Myopic eyes with OAG exhibited LC defects and large pores at similar locations as those without OAG, but in greater numbers, suggesting that these focal alternations of the LC in myopic eyes may evolve into larger defects when glaucoma develops in the eye. The number of LC defects, which was related to the optic disc tilt angle, was associated significantly with glaucomatous VF defects in both severity and location. This suggests that myopia may influence glaucomatous VF defects through optic disc tilt by way of an increased number of LC defects at the temporal periphery. *Ophthalmology 2017;■:1−12 © 2017 by the American Academy of Ophthalmology*

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The lamina cribrosa (LC) is considered to be the principle site of axonal injury in glaucoma.[1,2] Deformation of the LC promotes glaucomatous optic neuropathy by blocking axoplasmic flow within the optic nerve head.[3] The configuration of LC in glaucomatous eyes has been studied using histologic methods[1−7] and more recently with optical coherence tomography (OCT),[8,9] and deformations such as posterior displacement,[4,8,9] posterior migration of the insertion,[5,6] initial thickening and subsequent thinning,[2,6,7] and localized defect[10−14] have been described. These deformations are considered to be induced by intraocular pressure (IOP)−related stress and strain or biometric remodeling of the laminar tissue.[15]

Myopia is accepted as one of the risk factors for the development of glaucoma.[15−17] The association between myopia and glaucoma has been studied intensively, and it gradually becomes clear that myopia influences glaucomatous damage not through refractive error itself, but through deformation of the parapapillary region.[18,19] Myopic eyes present characteristic deformations of the parapapillary region, including optic disc tilt and torsion and parapapillary atrophy. Because LC is a deep component of the optic nerve head, it is reasonable to think that the LC, too, is deformed in myopic eyes and that it affects axonal injury in glaucoma. Myopic glaucoma exhibits characteristic clinical features such as prevalence at a relatively young age and development of paracentral scotoma (PCS) from an early stage. Together with these clinical characteristics, we hypothesized that there may be a unique mechanism to myopic glaucoma that induces axonal injury apart from previously described glaucomatous mechanisms.

Deformation of the LC in glaucoma includes focal loss of laminar beams. The association of focal LC defects with neuroretinal rim thinning and visual field (VF) loss was demonstrated previously.[10,11] In addition, recent studies have described the association of focal LC defects with

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factors related to myopic deformation of the parapapillary region.[20,21] These findings suggest that LC defects related to the myopic deformation of the parapapillary region may contribute to glaucomatous defects. However, there is not enough data regarding how LC defects in myopic eyes contribute to the glaucomatous defects spatially and quantitatively. Therefore, the present study aimed to investigate the characteristics of LC defects in myopic eyes with glaucoma and to determine their association with location and extent of glaucomatous VF defects.

Methods

This cross-sectional observational study was approved by the institutional review board of Akita University Graduate School of Medicine, Akita, Japan, and followed the tenets of the Declaration of Helsinki. All participants provided written informed consent.

We prospectively recruited myopic patients with open-angle glaucoma (OAG) from the outpatient clinic of Akita University Graduate School of Medicine from June 2015 through December 2016. Myopic participants without glaucoma were recruited among hospital staff and their friends and family as control participants. All participants underwent comprehensive ophthalmic assessment, including refraction test, measurement of best-corrected visual acuity, measurement of central corneal thickness and axial length by ultrasound pachymetry (Tomey Corporation, Nagoya, Japan), Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, dilated fundus stereoscopic examination, color fundus stereo photography (Canon, Tokyo, Japan), spectral-domain (SD) OCT (Spectralis version 5.4.6; Heidelberg Engineering GmbH, Heidelberg, Germany), and standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Dublin, CA). Untreated IOP was determined as the average of at least 2 measurements before the use of IOP-lowering medication, and last IOP was determined as the average of the last 3 IOP measurements.

The inclusion criteria were as follows. Eyes were included that had OAG, an open iridocorneal angle, glaucomatous optic disc changes such as localized or diffuse rim thinning and retinal nerve fiber defects, and glaucomatous VF defects corresponding to the glaucomatous structural changes. Glaucomatous VF defects were defined by glaucoma hemifield test results outside the normal range or presence of at least 3 contiguous test points within the same hemifield on the pattern deviation plot at less than 5%, with at least 1 of these points at less than 1%, confirmed by 2 consecutive reliable tests (fixation loss rate, $\leq$20%; false-positive and false-negative error rates, $\leq$15%). A spherical equivalent (SE) of -2 diopters (D) or less and axial length of 24.0 mm or more also were required. Pseudophakic eyes were evaluated for eligibility on the basis of preoperative SE. The exclusion criteria were as follows: ocular injury or intraocular diseases other than glaucoma; congenital optic disc abnormalities; extremely high myopia (axial length $>$28.5 mm or SE <-10 D) because of the increased risk of myopic degeneration of the fundus that may affect the VF; and eyes with poor-quality OCT images that did not present a clear image of anterior LC surface because of media opacity, irregular tear film, or poor patient cooperation. Poor-quality OCT images were defined by less than 80% visibility of the anterior LC surface within Bruch's membrane opening in more than 2 of 48 of radial scans.[14] Myopic eyes without glaucoma were included as controls when they exhibited SE of -2 D or less and axial length of 24.0 mm or more, an open iridocorneal angle, IOP between 10 and 21 mmHg, a nonglaucomatous optic disc, and no VF defects.

Enhanced Depth Imaging Optical Coherence Tomography

For optic disc evaluation, images were acquired using the enhanced depth imaging (EDI) SD OCT. Imaging was performed within 3 months of VF evaluation. The EDI OCT images were acquired using 65 serial horizontal and vertical lines (interval between images, 30 μm) and 48 radial lines centered on the optic disc in the infrared fundus image, each at an angle of 3.75°. During the study, we found that LC pores in myopic eyes often were stretched and elongated toward the temporal direction, particularly at the temporal periphery of the LC. These elongated pores exhibited parallel arrangement, as observed in infrared images in the Spectralis viewer (Fig 1). In eyes where such parallel arrangements of elongated pores were identified on infrared images, lines parallel to the pore arrangement also were scanned, because they often captured clear images of the LC defects (Fig 1). They were used to measure the accurate size of the defects. Among these OCT images, the ones that captured the best view of LC defects were used for analysis. Each section had 42 OCT frames averaged. Magnification error was corrected using a formula provided by the manufacturer, on the basis of results of autorefraction keratometry and focus setting during image acquisition. The scaling of OCT images was corrected to 1:1 before evaluation.

The EDI OCT images were reviewed carefully for the focal LC defects violating the smooth contour that is observed in healthy eyes, and the number of LC defects in each eye was counted. A focal LC defect was required to exhibit a diameter of 100 μm or more and a depth of 30 μm or more in cross-sectional OCT images.[10–14] An LC defect detected in an OCT image was required to have at least 1 additional adjacent OCT image with a similar finding to avoid a false-positive characterization. This image review was performed by 2 experienced glaucoma specialists (Y.S. and M.I.) masked to the clinical information of the participants. Disagreements were dealt with by discussion between the 2 reviewers to achieve consensus, and failing that, disagreements were resolved by a third adjudicator (T.Y.). In a preliminary analysis of healthy nonmyopic eyes, the diameter of LC pores usually ranged from 10 to 30 μm, and rarely exceeded 60 μm. Therefore, we defined an LC pore with a diameter between 60 and 100 μm as a large pore and counted them, also.

The circumferential location of LC defects was evaluated using the fovea–Bruch's membrane opening center axis as a reference line.[22] It was categorized as supratemporal ($>$0°–45°), superior ($>$45°–135°), nasal ($>$135°–225°), inferior ($>$225°–315°), or inferotemporal ($>$315°–360°). A defect located on the border between 2 areas was fitted into the area containing a greater proportion of the defect area. The LC defects also were categorized as peripheral or middle defects. A peripheral LC defect was defined as a defect adjusted to the insertion, with the anterior LC visible only on the central side of the defect and the peripheral LC not visible. A middle LC defect was defined as a defect with the LC visible on either side.[14]

Measurement of Optic Disc Tilt and Torsion

Optic disc tilt and torsion were measured in accordance with the previously described methods with some modification.[21,23,24] Optic disc tilt angle was measured using EDI OCT B-scan[21,23] (Fig S2, available at www.aaojournal.org). It was defined as the angle between the reference plane, which connects the inner edge of the nasal and temporal Bruch's membrane, and the optic disc canal plane, which connects the inner edge of the nasal Bruch's membrane and temporal margin of the optic disc canal that was defined as the end of externally oblique border tissue. Optic disc