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Influence of Lamina Cribrosa Thickness and Depth on the Rate of Progressive Retinal Nerve Fiber Layer Thinning

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Objective: To determine whether lamina cribrosa (LC) depth (LCD) and LC thickness (LCT) are associated with a faster rate of progressive retinal nerve fiber layer (RNFL) thinning in primary open-angle glaucoma (POAG).

Design: Prospective, observational study.

Participants: One hundred ten eyes diagnosed with POAG (n = 110 patients) in which RNFL thickness had been measured by serial spectral-domain (SD) optical coherence tomography (OCT) for at least 2.5 years.

Methods: The participants underwent enhanced depth imaging volume scanning of the optic nerve, and circumpapillary RNFL thickness measurements were obtained using SD OCT. The participants were followed up regularly with serial RNFL thickness measurements at 6-month or longer intervals. Lamina cribrosa depth was measured at 7 equidistant planes and LCT was measured at 3 locations (superior midperipheral, midhorizontal, and inferior midperipheral). The rate of RNFL thinning was determined by linear regression of serial OCT RNFL thickness measurements over time.

Main Outcome Measures: Factors associated with the rate of OCT RNFL thinning.

Results: A faster rate of RNFL thinning was associated with disc hemorrhage during follow-up ($P < 0.001$), wider β-zone parapapillary atrophy with Bruch's membrane ($P = 0.037$), larger global RNFL thickness ($P = 0.026$), larger LCD ($P < 0.001$), and smaller LCT ($P = 0.002$). The association between LCD and the rate of RNFL thinning was explained better using a fractional polynomial model ($R^2 = 0.223$) than a linear model ($R^2 = 0.134$; $P = 0.010$). Davies' test revealed a statistically significant breakpoint for LCD (489.7 μm), above which a faster rate of global RNFL thinning was associated with a larger LCD.

Conclusions: A thinner LC and a larger LC displacement had a significant influence on the rate of progressive RNFL thinning. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

Glaucoma is a progressive optic neuropathy characterized by degeneration of the retinal ganglion cells and their axons and a corresponding visual field defect. The lamina cribrosa (LC) has long been considered the primary site of axonal injury in glaucoma. This concept is based on the results of histologic studies that demonstrated compression and backward bowing of the LC underlying glaucomatous cupping.[1,2] Such deformation may cause kinking and pinching of the axons passing through the laminar pores, thereby promoting or initiating blockade of the axonal flow.[3–5] In addition, LC deformation may cause ischemic insult to the axons by exerting a compressive effect on the laminar capillaries.[1,6] Experimental studies have shown that displacement of the LC precedes early surface-detected structural damage and retinal nerve fiber layer (RNFL) loss.[7–10] This finding further suggests that LC deformation is the primary event that induces axonal damage.

It is well known that the rate of disease progression varies markedly among glaucoma patients. The factors reported to be involved in the progression of primary open-angle glaucoma (POAG) include older age, higher intraocular pressure (IOP), disc hemorrhage (DH), and β-zone parapapillary atrophy (PPA) without Bruch's membrane (BM).[11–15] Given the principal involvement of LC deformation and its precedence of axonal damage in glaucomatous optic neuropathy, it may be hypothesized that LC characteristics significantly influence the future rate of disease progression.

The advent of spectral-domain (SD) optical coherence tomography (OCT) has rendered possible the evaluation of the LC in vivo. Studies found that the LC was displaced more posteriorly[16] and was thinner[17,18] in glaucomatous eyes compared with control eyes, consistent with earlier histologic findings.[1,6] The purpose of this study was to determine whether LC depth (LCD; as a parameter reflecting backward bowing) and LC thickness (LCT; as a parameter reflecting compression), as assessed by enhanced depth imaging (EDI) SD OCT, are associated with the future rate of progressive RNFL thinning.

Methods

This investigation was based on the Investigating Glaucoma Progression Study (IGPS), which is an ongoing prospective study of glaucoma patients at the Seoul National University Bundang Hospital Glaucoma Clinic, Seoul, South Korea. The study included

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consecutive subjects who met the eligibility criteria, all of whom provided written informed consent to participate. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board and followed the tenets of the Declaration of Helsinki.

Study Subjects

Subjects who were enrolled in the IGPS underwent a comprehensive ophthalmic examination, including visual acuity assessment, Goldmann applanation tonometry, refraction tests, slit-lamp biomicroscopy, gonioscopy, dilated stereoscopic examination of the optic disc, disc photography (EOS D60 digital camera; Canon, Utsunomiyashi, Tochigiken, Japan), SD OCT infrared fundus imaging, circumpapillary RNFL scanning, optic disc scanning (Spectralis; Heidelberg Engineering, Heidelberg, Germany), standard automated perimetry (Humphrey Field Analyzer II 750; 24-2 Swedish interactive threshold algorithm; Carl Zeiss Meditec, Dublin, CA), and measurements of corneal curvature (KR-1800; Topcon, Tokyo, Japan), central corneal thickness (Orbscan II; Bausch & Lomb Surgical, Rochester, NY), and axial length (IOL Master version 5; Carl Zeiss Meditec).

The IGPS excluded subjects with a history of intraocular surgery other than cataract extraction and glaucoma surgery, an intraocular disease (e.g., diabetic retinopathy or retinal vein occlusion) or a neurologic disease (e.g., pituitary tumor) that could cause visual field loss, and visual acuities worse than 20/40.

All patients included in the IGPS were followed up every 3 to 6 months with regular follow-up fundus photography, and SD OCT RNFL thickness measured at intervals ranging from 6 months to 1 year. Patients included in the present study were required to be newly diagnosed with POAG, to have been followed up for at least 2.5 years with treatment, and to have undergone at least 5 serial OCT measurements. Primary open-angle glaucoma was defined as the presence of glaucomatous optic nerve damage (e.g., the presence of focal thinning, notching, and an RNFL defect), an associated glaucomatous visual field defect, and an open angle, as revealed by gonioscopy. A glaucomatous visual field defect was defined as (1) values outside the normal limits on the glaucoma hemifield test; (2) 3 abnormal points, with a probability of being normal of $P < 0.05$, and 1 point with a pattern deviation of $P < 0.01$; or (3) a pattern standard deviation of $P < 0.05$. Those visual field defects were confirmed on 2 consecutive reliable tests (fixation loss rate, $\leq$20%; false-positive and false-negative error rates, $\leq$25%).

Eyes with optic disc torsion of more than 15°[19] or a tilt ratio (minimum-to-maximum optic disc diameter) less than 0.75[20] and those with any abnormalities (including a large PPA) in the circumpapillary region that affected the scan ring where the OCT RNFL thickness measurements were obtained were excluded from this study. A history of cataract surgery before the baseline examination was not an exclusion criterion in this study, but patients who underwent cataract surgery during the study were excluded because cataract extraction affects the signal quality of OCT scans and thus may influence the RNFL thickness data. Patients who underwent IOP-lowering surgery before or during the study also were excluded because the LC configuration may change substantially when the IOP re-elevates[21] (see "Discussion").

Eyes also were excluded when a good-quality image (i.e., quality score >15) could not be obtained at more than 5 sections of EDI SD OCT disc scans (when the quality score does not reach 15, the image acquisition process automatically stops and the image of the respective sections is not obtained). In addition, eyes were excluded when the images did not allow clear delineation of both the anterior and posterior borders of the central portion of the LC.

Untreated IOP was defined as the mean of at least 2 measurements before IOP-lowering treatment. The amount of IOP reduction was determined by calculating the percentage reduction of IOP at the final follow-up compared with the pretreatment level. The mean follow-up IOP measurement was obtained by averaging the IOP measured at 6-month intervals, and IOP fluctuation was determined using the standard deviation of these values.

A DH was defined as an isolated hemorrhage seen on the disc tissue or in the peripapillary retina connected to the disc rim.[11] A DH was detected by slit-lamp examination using a 78-diopter lens or a fundus photograph. Either of these was performed at every follow-up visit.

Enhanced Depth Imaging Optical Coherence Tomography of the Optic Disc

The optic nerve head (ONH) was imaged using the Spectralis OCT with the EDI technique. The details and advantages of this technology for evaluating the LC have been described previously.[22,23] Imaging was performed using a 10°×15° rectangle covering the optic disc. This rectangle was scanned with approximately 70 sections, which were 30 to 34 μm apart (the slicing distance is determined automatically by the machine). Forty-two frames were averaged for each section, which provided the best trade-off between the image quality and patient cooperation.[22]

Measurement of Lamina Cribrosa Depth and Lamina Cribrosa Thickness

This study measured LCD and LC thickness (LCT) on EDI OCT scans that were obtained 6 months after initiating IOP-lowering treatment. This was performed to evaluate the relatively stabilized status of LC deformation. We demonstrated previously that LCD and LCT may be reversed after IOP-lowering treatment.[21,24] It is possible that a long-term disease prognosis would be affected more strongly by the LC deformation remaining after the reversal than by the initial deformation because the stress on the axons passing through the LC may be relieved partly by reversal of the LC deformation.[25] In our experience, the reversal is mostly complete by the third postoperative month after commencing IOP-lowering therapy.[25] We therefore considered that the time point of 6 months after initiating treatment was a good point at which to evaluate the LC in this study.

Lamina cribrosa depth was determined by measuring the distance from the BM opening plane to the level of the anterior LC surface in 7 equidistant planes that vertically divided the optic disc diameter into 8 equal parts in each eye.[24–26] A reference line connecting the 2 termination points of BM was drawn on each B-scan image. The distance from the reference line to the level of the anterior border of the LC was measured at 3 points: the maximally depressed point and 2 additional points (100 and 200 μm apart from the maximally depressed point in a temporal direction). Only the temporally adjacent points were selected because the maximally depressed point often was close to the central vessel trunk, the shadow of which obscured the LC. The measurements from the 7 planes were used to calculate the mean LCD of the eye.

Lamina cribrosa thickness was measured at 3 locations in each eye (the midhorizontal and the superior and interior midperipheral regions of the ONH) using thin-slab maximum intensity projection (MIP) images. The thin-slab MIP image was used because it allows detection of a straighter posterior LC border.[27] The technique of generating thin-slab MIP images is described in detail elsewhere.[27] In brief, 3-dimensional volumetric reconstruction of the ONH was performed from the B-scan images by MIP rendering using image-processing software (Amira 5.2.2; Visage Imaging, Berlin, Germany). The thin-slab image then was obtained by selecting 2 planes (approximately 64 μm apart) inside the 3-dimensional volumetric