Effect of Focal Lamina Cribrosa Defect on Glaucomatous Visual Field Progression

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Objective: To evaluate the association between focal, structural defects of the lamina cribrosa (LC) and glaucomatous visual field (VF) progression.

Design: Retrospective, observational study.

Participants: A total of 169 patients with glaucoma (169 eyes) with a range of glaucomatous damage.

Methods: Serial horizontal and vertical enhanced-depth imaging optical coherence tomography (EDI OCT) B-scans of the optic nerve head were obtained from patients with glaucoma with 5 or more prior Humphrey 24-2 VFs (Carl Zeiss Meditec, Inc, Dublin, CA). The EDI OCT scans were reviewed for the presence of focal LC defects (laminar holes or disinsertions with a diameter >100 μm). The VF progression was defined as having ≥2 significantly progressing test points (with a slope calculated using pointwise linear regression [PLR], worse than −1.0 dB/year at $P<0.01$). Age, intraocular pressure (IOP), baseline VF mean deviation (MD), disc hemorrhage, and central corneal thickness (CCT) were recorded.

Main Outcome Measures: The relationship between focal LC defects and the rate and risk of VF progression.

Results: Mean age and VF MD at the time of EDI OCT were 69±12 years and −11.49±6.87 dB, respectively. Sixty eyes (36%) progressed according to PLR criteria. Progression was more common in eyes with, rather than without, focal LC defects (38/81 eyes [47%] vs. 22/88 eyes [25%], $P = 0.003$). Among the evaluated parameters, the presence of focal LC defects, disc hemorrhage, higher mean follow-up IOP, greater number of VFs, and longer follow-up period were significantly associated with VF progression in the multivariable analyses (odds ratios, 2.90, 4.66, 1.22, 1.25, and 1.27, respectively; $P = 0.010$, $P = 0.002$, $P = 0.002$, $P<0.001$, and $P<0.001$, respectively). The mean global progression rate was significantly faster in the group with focal LC defect than in the group with no focal LC defect (−0.54±0.99 dB/year vs. −0.28±0.52 dB/year; $P = 0.031$). Among the 60 progressing eyes, despite no significant difference in the mean number of progressing VF points per eye (6.7±7.0 vs. 6.5±4.4; $P = 0.899$), the mean localized progression rate was significantly faster in the eyes with focal LC defects than in the eyes with no focal LC defects (−2.85±1.85 dB/year vs. −1.75±0.56 dB/year; $P = 0.009$).

Conclusions: Focal LC defects are strongly associated with glaucomatous VF progression, and eyes with focal LC defects tend to progress faster than those without. *Ophthalmology 2014;■:1−7 © 2014 by the American Academy of Ophthalmology.*

Risk factors for the development and progression of glaucoma include elevated intraocular pressure (IOP),[1−6] older age,[1,2,4] lower central corneal thickness (CCT),[1,2,4,5] decreased ocular perfusion pressure,[4,7] disc hemorrhage,[6,8,9] and beta-zone parapapillary atrophy,[10,11] among others. Structural features of the lamina cribrosa (LC) have not been investigated as a potential risk factor for glaucoma progression.

The LC, an array of collagen beams with intervening pores, serves as a conduit for retinal ganglion cell (RGC) axons and retinal blood vessels through the scleral canal.[12,13] Histologic studies in animals and enucleated human specimens have revealed displacement and deformation of the LC in glaucoma and are consistent with hypotheses suggesting the LC as the likely principal site of glaucoma injury.[14−19] Other studies have revealed regional differences in LC structure, suggesting a mechanism of localized damage in glaucoma pathogenesis.[20−22] Therefore, certain structural features of the LC may be associated with, and serve as biomarkers for, increased risk of glaucoma progression.

Most previous investigations of the LC, using histologic specimens or a variety of imaging devices, described the gross morphology of the LC, including its posterior displacement or thinning in glaucoma or ocular hypertension,[14−19,23,24] but not localized changes in the LC structure. We have reported the occurrence of focal LC defects in patients with glaucoma and their absence in normal controls using enhanced-depth imaging optical coherence tomography (EDI OCT).[25] Normal LC had a smooth, curvilinear anterior surface with a flat or slightly upward sloping as it approaches the laminar insertion, whereas some glaucomatous eyes had localized irregularities of various shapes and sizes in the anterior LC surface.[25] Focal LC defects at the laminar insertion area also have been identified in a histologic study of glaucomatous optic nerve head (Invest Ophthalmol Vis Sci 2011;52:E-Abstract 3957). These focal LC defects likely represent localized loss of laminar tissue and correlate spatially with ophthalmoscopic structural glaucomatous changes, such as neuroretinal rim loss and acquired pits of the optic nerve

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(APON).[25,26] However, the relationship between focal LC defects and glaucoma progression is unclear. In this study, we assessed the association between focal LC defects and glaucomatous visual field (VF) progression and compared VF progression rates between glaucomatous eyes with and without focal LC defects.

Methods

This study was approved by the New York Eye and Ear Infirmary Institutional Review Board. Written informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

We prospectively enrolled patients with glaucoma who had undergone at least 5 VF tests of either eye using standard automated perimetry (Humphrey VF Analyzer, 24-2 Swedish Interactive Threshold Algorithm Standard strategy; Carl Zeiss Meditec, Inc, Dublin, CA). Glaucoma was defined by the presence of characteristic glaucomatous disc and retina changes (localized or diffuse neuroretinal rim thinning or retinal nerve fiber layer defect) associated with typical, reproducible VF defects on standard automated perimetry. An abnormal VF was defined as a glaucoma hemifield test result outside normal limits on at least 2 consecutive VF tests and the presence of at least 3 contiguous test points within the same hemifield on the pattern deviation plot at $P<0.01$, with at least 1 point at $P<0.005$. The VF tests required all reliability indices better than 25%.

Enhanced-Depth Imaging Optical Coherence Tomography

At the time of enrollment, serial horizontal and vertical cross-sectional scans (interval between scans, ~30 μm) of the optic nerve head were obtained for both eyes of each participant using EDI OCT (Spectralis; Heidelberg Engineering, GmbH, Dossenheim, Germany). The OCT device was set to image a 15×10-degree rectangle for horizontal scans (and a 10×15-degree rectangle for vertical scans) centered on the optic disc. This rectangle was scanned with 97 sections, and each section had 20 OCT frames averaged. The EDI OCT images were obtained by selecting the EDI mode of the OCT device or by pushing the OCT device closer to the eye to move the zero reference plane more posteriorly to create an inverted image (the inner portion of the retina shown facing downward). We excluded eyes with previous posterior segment intraocular surgery, nonglaucomatous ocular or systemic diseases known to affect optic nerve head structure or VF, or poor-quality OCT images because of media opacity, irregular tear film, or inadequate patient cooperation.

For the eyes with 5 or more VFs, the EDI OCT images were carefully reviewed for the presence of laminar holes and laminar disinsertions violating the smooth curvilinear U- or W-shaped cross-sectional contour that is observed in healthy eyes.[26] This review was done by an experienced glaucoma specialist masked to the clinical information of participants, including the infrared optic disc photographs provided by the OCT device. A laminar hole was defined as a localized discontinuity of the LC tissue (a punched-out or hole-like LC defect) (Fig 1A). A laminar disinsertion was defined as a posteriorly displaced laminar insertion with downward sloping at the far periphery of the LC toward the neural canal wall (Fig 1B and C). The LC lesions with combined features of a laminar hole and a laminar disinsertion were classified as focal LC defects (Fig 1D). Focal LC defects were required to be at least 100 μm in diameter on the basis of our experience during previous studies on LC morphology using EDI OCT.[22,25,26] To avoid false-positives, a focal LC defect detected in serial horizontal OCT scans was confirmed in appropriate serial vertical OCT scans and vice versa. When both eyes had 5 or more VFs, (1) the eye with a laminar hole or disinsertion was selected for analysis or (2) 1 eye was randomly selected if both eyes had a laminar hole or disinsertion or none of the 2 eyes had a laminar hole or disinsertion. To assess the intraobserver reproducibility of focal LC defect evaluation, EDI OCT images of 100 randomly selected glaucomatous eyes were evaluated. Analysis was based on 3 independent series of re-evaluations. The absolute agreement of the single observer's evaluation was calculated with the intraclass correlation coefficient from a 2-way mixed effect model.

Clinical Parameters

At the initial visit, all participants provided a detailed medical history and underwent slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, CCT measurement using ultrasonic pachymetry (DGH-550, DGH Technology Inc, Exton, PA), simultaneous color optic disc stereophotography (Stereo Camera Model 3-DX; Nidek Inc, Palo Alto, CA), and standard automated perimetry. Typical examination intervals before EDI OCT ranged from 3 to 6 months: Slit-lamp biomicroscopy, Goldmann applanation tonometry, and optic disc examination for disc hemorrhage detection were repeated for each visit. Optic disc stereophotography and standard automated perimetry were repeated usually at 6- to 12-month intervals.

We recorded age at the time of EDI OCT, baseline VF mean deviation (MD) at the initial visit, and CCT. The IOPs were recorded for each visit. Glaucomatous optic disc hemorrhage was defined as a splinter-like or flame-shaped hemorrhage on or within the retinal nerve fiber layer or neuroretinal rim. Stereoscopic disc photographs and medical records were reviewed for the presence of disc hemorrhage. Peak IOP was the highest measured IOP during the entire follow-up time. The mean IOP during the entire follow-up period was calculated by averaging all pressure measurements. To avoid the undesired effect that numerous sequential IOP measurements during a short period of time would have on the final average, we used the average IOP for each 6-month period to calculate the mean follow-up IOP.[27] The IOP fluctuation was defined as the standard deviation of this value. We excluded all IOP measurements occurring 4 weeks after any type of incisional surgery or laser procedure to avoid the effect of transitory IOP changes that often occur during this period.

Visual Field Progression Analysis

Automated pointwise linear regression (PLR) analysis was performed using Progressor software (Version 3.3, Medisoft, Ltd, Leeds, UK), providing progression rates or slopes of progression (decibels/year) both globally and locally for each test point based on threshold sensitivity maps, as well as its level of significance (P values). Details of the software have been described.[28] Significantly progressing VF test points were defined as those having a progression rate (slope of VF sensitivity) over time worse than −1.0 dB/year with $P<0.01$, which is a commonly used criterion for trend-based PLR analysis of VF progression.[27–30] Because using a single progressing point meeting the aforementioned criteria could result in high false-positive rates,[31] we used more stringent criteria and increased the specificity of our analysis by requiring at least 2 progressing points within the same hemifield to denote the eye as progressing.[32] The global VF progression rate of each eye was calculated by averaging the progression rates of all test points for the entire follow-up period. The localized VF progression rate of each eye was calculated by averaging the progression rates of significantly progressing test points based on the PLR criteria described.