Focal Lamina Cribrosa Defects Associated With Glaucomatous Rim Thinning and Acquired Pits

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Importance: Considering the potential clinical importance of focal lamina cribrosa (LC) defects as a characteristic structural feature in glaucoma and a risk factor for glaucomatous visual field progression, it may be helpful to know the structure of focal LC defects and the spatial relationship between them and glaucomatous optic disc changes such as neuroretinal rim thinning/notching and acquired pits of the optic nerve (APON).

Objective: To investigate structural and spatial relationships between focal LC defects and glaucomatous neuroretinal rim thinning/notching and APON.

Design: In a cross-sectional analysis of data from an ongoing, prospective, longitudinal study, serial enhanced-depth imaging (EDI) optical coherence tomographic (OCT) images of the optic nerve head were obtained from patients with glaucoma and reviewed for focal LC defects (laminar holes or disinsertions). Anterior laminar insertion points and edges of laminar holes or disinsertions were marked in EDI-OCT images, reconstructed 3-dimensionally, and superimposed on optic disc photographs.

Setting: A glaucoma referral practice.

Participants: Two hundred thirty-nine eyes (120 patients) were examined. Fifty-four eyes were excluded because of an incomplete horizontal or vertical set of serial EDI-OCT images or poor-quality EDI-OCT images owing to media opacity, irregular tear film, or poor patient cooperation. Among the remaining 185 eyes, 40 (from 31 patients) had laminar holes or disinsertions and were included for analysis.

Main Outcome Measures: Presence, extent, and location of laminar holes or disinsertions.

Results: Among 185 eyes, 11 laminar holes and 36 laminar disinsertions were found in 40 eyes. Superimposed images of the 3-dimensionally reconstructed focal LC defects and disc photographs showed that the outline of the LC defect corresponded almost precisely to that of clinical APON for 6 laminar holes and that the LC defect was much larger than and enclosed APON for 10 laminar disinsertions. The remaining 5 laminar holes and 26 laminar disinsertions corresponded to focal neuroretinal rim loss, with no evidence of APON in disc photographs.

Conclusions and Relevance: Focal LC defects (laminar holes or disinsertions) are associated with neuroretinal rim loss and APON. The extent of LC defects can be visualized more effectively on EDI-OCT images than by clinical examination.

The purposes of this study are to illustrate the extent and location of focal LC defects graphically using cross-sectional EDI-OCT scans and their 3-dimensional reconstructions and to assess the structural and spatial relationships between focal LC defects and glaucomatous neuroretinal rim thinning/notching and APON.

This cross-sectional analysis of data obtained from an ongoing, prospective, longitudinal 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 included patients with a range of glaucomatous optic neuropathy and visual field loss representing various stages of glaucomatous damage. Glaucoma was defined by the presence of glaucomatous optic disc damage (localized or diffuse neuroretinal rim thinning or retinal nerve fiber layer defect) associated with typical, reproducible visual field defects defined as a glaucoma hemifield test result outside normal limits on at least 2 consecutive visual field tests and the presence of at least 3 contiguous test points within the same hemifield on the pattern deviation plot at P < .01, with at least 1 point at P < .005. The visual field tests required reliability indices better than 25%.

All participants provided a detailed medical history and underwent slitlamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and stereoscopic optic disc and fundus examination. For both eyes of each participant, serial horizontal and vertical cross-sectional images (interval between examination. For both eyes of each participant, serial horizontal or vertical set of serial EDI-OCT images or with poor quality. We also excluded eyes with an incomplete horizontal or vertical set of serial EDI-OCT images or with poor quality EDI-OCT images because of media opacity, irregular tear film, or poor patient cooperation.

The OCT images were carefully reviewed for laminar holes or laminar disinsertions violating the smooth curvilinear U- or W-shaped contour that is observed in healthy eyes.18 This review was done by a glaucoma specialist (S.C.P.) masked to clinical information of participants including the infrared optic disc photograph, rephotography (stereo camera model 3-DX; Nidek Inc) and stereoscopic optic disc photographs (stereo camera model 3-DX; Nidek Inc) and standard automated perimetry (Humphrey visual field analyzer, 24-2 Swedish Interactive Threshold Algorithm standard strategy; Carl Zeiss Meditec) performed within 4 months of EDI-OCT scans was confirmed in appropriate serial vertical OCT scans and vice versa. We previously reported 5 categories of focal LC defects based on shape: smooth indentation, moth-eaten-appearance defect, steplike depression, holelike defect, and altered laminar insertion.15 Among these, holelike defects (laminar holes) and prominently altered laminar insertions (laminar disinsertions) were included in the present study because, by using stricter criteria, we wanted to avoid misclassification of normal anatomical variations and artifacts as real glaucomatous focal LC defects.

We then assessed the extent and location of identified laminar holes and disinsertions using 3-dimensional reconstruction. Either a horizontal or vertical set of serial EDI-OCT images, which had been automatically aligned by the built-in software of the OCT device, was exported and then uploaded to the 3-dimensional reconstruction software (Amira version 5.3.3; Visage Imaging, Inc). The anterior laminar insertion points, the edges of the laminar hole or disinsertion, and retinal vessels (1 branch for each quadrant of the optic disc) were manually marked and reconstructed 3-dimensionally (Figure 2A-D). When any of these structures was unclear in an EDI-OCT image, we did not mark it in that image. The diameter of each focal LC defect was measured using the built-in measurement tool in the 3-dimensional reconstruction software. The reconstructed 3-dimensional images (orthographic view, not perspective view) were superimposed on the color optic disc photographs using Adobe Photoshop version 7.0 (Adobe Systems Inc) (Figure 2E-G). This alignment involved zoom and/or rotation of the reconstructed 3-dimensional images. Reconstructed blood vessels were used for alignment and then removed later for better visibility of the structures of interest (Figure 2H). For eyes with a laminar hole or disinsertion, the optic disc photograph was reviewed for glaucomatous optic disc changes (neuroretinal rim thinning/notching with or without APON) by a glaucoma specialist (C.C.T.) masked to other clini-
or retinal detachment.

adjacent to the pit; and (3) no evidence of optic nerve coloboma.

cal depression of the LC with deep excavation and loss of

removed allows for better visibility (H).

reconstructed 3-dimensional image and color optic disc photograph are

reconstructed using serial optical coherence tomographic images. The

defects (laminar holes or disinsertions) and glaucomatous optic disc changes

structural and spatial relationships between focal LC defects (laminar

were sometimes con-

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prelaminar neural tissue was covered by unspecified ho-

Figure 5E, K, Q, and T). This depressed area in the

scleral and neuroretinal rims of the optic disc. The re-

rims of the optic disc. The re-

losses were identified and matched with clinical parameters, includ-

that of APON (Figure 3). For the 10 laminar disinsertions, the LC defect was much larger than

the APON and its outline enclosed the APON (Figure 4). That is, part of the LC defect was clinically visible as

the other part, which was larger than the clinically visible part, was obscured from clinical view by the

scleral and neuroretinal rims of the optic disc. The remaining 31 focal LC defects (5 of 11 laminar holes and

26 of 36 laminar disinsertions) corresponded to clinical neuroretinal rim thinning/notching, with no evidence of

laminar deformation or APON in optic disc photographs. We also identified

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laminar deformation or APON in optic disc photographs (Figure 5).

We found dimpling or pitting of the prelaminar neural tissue over the area of all 11 laminar holes and 33 of

36 disinsertions (Figure 3E and K, Figure 4E and K, and Figure 5E, K, Q, and T). This depressed area in the

prelaminar neural tissue was covered by unspecified homogeneous tissue of variable thickness and shape for 11

focal LC defects (Figure 4N). This unspecified tissue was not apparent in optic disc photographs. We also identified

hyperreflective remnant LC tissue of variable sizes and shapes in the area of laminar holes or disinsertions for 24 focal LC defects (6 laminar holes and 18 laminar disinsertions) (Figure 3M and N, Figure 4M, and Figure 5S). These remaining shreds of LC tissue in the area of laminar holes or disinsertions were sometimes connected with the LC (Figure 4M).

Our superimposed images of the 3-dimensionally reconstructed focal LC defects (laminar holes or disinsertions) and optic disc photographs demonstrated that one-third (16 of 47) of the focal LC defects identified on
EDI-OCT imaging were clinically visible either partially or in their entirety, and the boundary of the clinically visible portion of the focal LC defects corresponded to an APON. For 6 laminar holes, the entire boundary matched clinical APON. For 10 laminar disinsertions, part of the boundary matched clinical APON and the remaining part was clinically unidentifiable. The remaining 31 of 47 LC defects (66%) corresponded to neuroretinal rim thinning/notching but were clinically unidentifiable. Therefore, EDI-OCT–guided evaluation of the LC is required to detect laminar holes and disinsertions and to assess their structures more accurately.

Laminar holes were better visualized clinically than laminar disinsertions. First, 6 of 11 laminar holes (55%) and 10 of 36 laminar disinsertions (28%) manifested clinically as APON, although this difference (55% vs 28%)
Clinical APONs. Because APONs are frequently associated with the same sense, some laminar disinsertions may be precluded at their advanced stage. That is, some APONs may occur at the LC insertion area, can be detected clinically when the gap between the LC and the neural canal wall becomes sufficiently large. Also, the neuroretinal rim needs to be sufficiently thin to detect the laminar disinsertion portion extending from beneath the scleral rim into the optic disc area. Future investigation is needed on whether these 2 types of focal LC defect (laminar hole and disinsertion) have different underlying pathogenic mechanisms.

In 10 of 36 laminar disinsertions, the clinically obscured portion was larger than the clinically identifiable portion (corresponding to APON). In the remaining 26 of 36 laminar disinsertions, the entire LC defect was clinically obscured by the scleral and neuroretinal rims. Keeping these in mind and considering the usual anatomy of the laminar insertion area (scleral, choroidal, and neuroretinal tissue overlying the laminar insertion area), it can be postulated that laminar disinsertion originates at the very edge of the LC, grows, and manifests clinically as APON at its advanced stage. That is, some APONs may be clinical presentations of advanced laminar disinsertions that are larger than the clinically seen APONs. In the same sense, some laminar disinsertions may be preclinical APONs. Because APONs are frequently associated with visual field defects involving the paracentral area and threatening fixation and increased risk for progressive optic disc damage and visual field loss, this subject needs to be further investigated in longitudinal studies.

During the investigation of the structural and spatial relationships between focal LC defects and conventional glaucomatous optic disc changes, we detected hyperreflective remnant LC tissue in the area of laminar holes and disinsertions in approximately half of the focal LC defects. Considering that some of these remaining fragments of LC tissue were connected with the LC, we postulate that this remnant tissue was in the process of gradual loss. We also found dimpling or pitting of the prelaminar neural tissue over the area of laminar holes and disinsertions in more than 90% of our cases. This finding may be attributed to the retinal ganglion cell (RGC) axonal loss and/or prelaminar tissue ectasia associated with focal LC defects and may be considered a sign of glaucomatous structural change. This depressed area in the prelaminar tissue was sometimes covered by unspecified tissue, which may be a thick posterior hyaloid face or prominent meniscus tissue of Kuhnt partially attached to the optic disc surface.

The laminar holes and disinsertions we observed corresponded to neuroretinal rim thinning or APON seen in optic disc photographs. This suggests that the mechanism of LC deformation in glaucoma includes focal loss of laminar beams, as demonstrated in our previous study. However, the implication of LC tissue loss in glaucoma is unclear. The LC is a meshlike structure composed of overlapping and branching collagenous beams. These laminar beams are covered with astrocytes, which provide structural and cellular support to the RGC axons. In addition, the capillaries running inside laminar beams...
likely act as a source of blood perfusion to the laminar portion of the optic nerve. When laminar tissue is damaged and/or lost, the RGC axons lose their structural, cellular, and metabolic support, which may lead to glaucomatous optic disc changes and retinal nerve fiber layer defects. However, it is unclear whether glaucomatous RGC damage follows, coincides with, or precedes LC tissue loss. Further investigation is needed to elucidate the relationship between focal LC tissue loss and RGC loss in glaucoma.

This study is limited by the intrinsic properties of OCT, particularly by decreasing sensitivity and signal strength with depth, wavelength- and depth-dependent light scattering, and signal loss in the image path. Although EDI-OCT allows deeper penetration of light to delineate more posterior structures of the optic nerve head and ocular wall, the technique is still constrained by its limited penetration depth. It is possible that laminar holes or disinsertions located in areas with poor OCT beam penetration, such as areas with more abundant neuroretinal rim tissue, thicker scleral rim, and/or vascular structures, may have been missed. The anterior laminar insertion points in the area of laminar disinsertions were marked based on the expected anterior laminar surfaces that were extrapolated from their visible portions. That is, these anterior laminar insertion points were subjectively marked and therefore may not represent original insertion points accurately. Because the EDI-OCT images were exported from the OCT device and then uploaded to the 3-dimensional reconstruction software, our results depend on the ability of Spectralis OCT’s image alignment/registration software. Our results depend solely on the EDI-OCT findings, which may be different from those of histologic examination or other imaging modalities. Beside the 16 APONs described in the present study, we found several more APONs during our review of 185 eyes. Those APONs corresponded to localized defects in the LC on EDI-OCT, but the LC defects did not meet our definition for laminar hole or disinsertion. Focal LC defects were required to be at least 100 μm in diameter in this study. In the LC photographs in previous histologic studies, the maximum LC pore diameter was approximately 100 μm. Although a few pores were slightly larger than 100 μm in those photographs, we have not seen an LC pore that was larger than 100 μm during our previous studies on normal LC morphology using EDI-OCT. This discrepancy may be attributable to histologic specimen preparation and trypsin or detergent digestion used in the previous studies, and we believe that our size criterion for focal LC defects (≥100 μm) is reasonable for a study using EDI-OCT.

We graphically illustrated the structural and spatial relationships between focal LC defects (laminar holes and disinsertions) and clinical optic disc findings in glaucoma and enhanced clinicians’ and researchers’ understanding of focal LC defects, which may be a characteristic feature in glaucoma and a risk factor for glaucomatous visual field progression. Based on our results, we could postulate that some APONs may represent advanced laminar disinsertions and that clinically obscured laminar disinsertions may be a precursor to APON. The clinical importance of imaging modalities that can be used to examine the LC structure and its deformation in glaucoma as well as the cellular and molecular mechanisms of focal LC defects require further investigation.

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REFERENCES

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**Correction**

Incorrect Journal Club Designation. In the table of contents and in Clinical Trials, the article titled “Sensitivity and Specificity of the AdenoPlus Test for Diagnosing Adenoviral Conjunctivitis” by Sambursky et al, published in the January issue of *JAMA Ophthalmology* (2013; 131[1]:17-22), was incorrectly designated as a Journal Club article. Consequently, the entry titled “Online-Only Material” should not have appeared at the end of the “Acknowledgements.”