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 images, approximately 30 \( \mu \)m) of the optic nerve head were obtained using EDI-OCT (Spectralis; Heidelberg Engineering GmbH). All participants had simultaneous color optic disc stereophotography (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-lyzer, 24-2 Swedish Interactive Threshold Algorithm 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. For EDI-OCT of the optic nerve head, we used the method described in a previous article.21 In brief, the OCT device was set to image a \( 15^\circ \times 10^\circ \) rectangle for horizontal scans (and a \( 10^\circ \times 15^\circ \) 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 device was pushed close enough to the eye to create an inverted image with the inner portions of the retina shown facing downward. The OCT images were inverted after being exported from the OCT device.

Age, intraocular pressure, visual field mean deviation, and glaucoma diagnosis were recorded. We excluded eyes with previous posterior segment intraocular surgery, nonglaucomatosous ocular or systemic diseases known to affect the optic nerve head structure or visual fields, and optic disc photographs of 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 laminae holes or laminae 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 provided by the OCT device. A laminae hole was defined as a localized discontinuity of the LC tissue (a punched-out or holelike LC defect) (Figure 1A). A laminae disinsertion was defined as a posteriorly displaced laminae insertion with downward sloping at the far periphery of the LC toward the neural canal wall,19 requiring the visible end of the anterior laminae surface positioned at or below the expected posterior laminae surface that was extrapolated from its visible portions (Figure 1B). Both types of LC defects were required to be at least 100 \( \mu \)m in diameter based on our experience during previous studies on LC morphology using EDI-OCT.13,18 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. We previously reported 5 categories of focal LC defects based on shape: smooth indentation, moth-eaten-appearance defect, steplike depression, holelike defect, and altered laminae insertion.18 Among these, holelike defects (laminae holes) and prominently altered laminae insertions (laminae 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 laminae 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 laminae insertion points, the edges of the laminae 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 laminae 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-

![Figure 1. Schematic diagrams of the optic nerve heads with laminar hole (arrow) (A) and laminar disinsertion (arrow) (B). Thick dotted lines indicate unclear laminar surfaces in the optical coherence tomographic images. Thin dotted lines indicate the expected laminar surfaces that were extrapolated from their visible portions (B). Note that the visible anterior laminar surface ends below the extrapolated posterior laminar surface.](image_url)
Among the remaining 185 eyes, a total of 40 eyes (31 patients; 18 women and 13 men) had laminar hole(s) or disinsertion(s) and were included for analysis. The mean (SD) age of these 31 patients was 67 (13) years (range, 35-85 years), and the mean (SD) visual field mean deviation for these 40 eyes was $-13.5 (6.2)$ dB (range, $-26.62$ to $-3.79$ dB). All patients had been treated with ocular hypotensive medications and/or surgery. The mean (SD) intraocular pressure at the time of EDI-OCT was 14.2 (2.8) mm Hg. There were 28 eyes with primary open-angle glaucoma, 5 with exfoliative glaucoma, 5 with pigmentary glaucoma, and 2 with chronic angle-closure glaucoma.

We identified 11 laminar holes and 36 laminar disinsertions in 40 eyes. All laminar holes occurred exclusively in the far periphery of the LC near its insertion. Ten laminar holes and 29 laminar disinsertions were detected in the inferior area of the LC; the remaining 1 laminar hole and 7 laminar disinsertions were found in the superior area, sparing the temporal and nasal 45° sectors. Seven eyes had 2 laminar disinsertions: 6 of these had a laminar disinsertion in both the superior and inferior areas, and the remaining eye had both laminar disinsertions in the inferior area.

The clinical presentation of laminar holes and disinsertions is described in the Table. A total of 16 focal LC defects (6 of 11 laminar holes and 10 of 36 laminar disinsertions) manifested clinically as APON. For the 6 laminar holes, the outline of the LC defect corresponded almost precisely to 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 APON, and 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 (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).

### RESULTS

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, a total of 40 eyes (31 patients; 18 women and 13 men) had laminar hole(s) or disinsertion(s) and were included for analysis. The mean (SD) age of these 31 patients was 67 (13) years (range, 35-85 years), and the mean (SD) visual field mean deviation for these 40 eyes was $-13.5 (6.2)$ dB (range, $-26.62$ to $-3.79$ dB). All patients had been treated with ocular hypotensive medications and/or surgery. The mean (SD) intraocular pressure at the time of EDI-OCT was 14.2 (2.8) mm Hg. There were 28 eyes with primary open-angle glaucoma, 5 with exfoliative glaucoma, 5 with pigmentary glaucoma, and 2 with chronic angle-closure glaucoma.

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### COMMENT

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 associ-
ted with visual field defects involving the paracentral
area and threatening fixation22-23 and increased risk for
progressive optic disc damage and visual field loss,24 this
subject needs to be further investigated in longitudinal
studies.

During the investigation of the structural and spatial
relationships between focal LC defects and conven-
tional 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 pos-
tulate that this remnant tissue was in the process of gradual
loss. We also found dimpling or pitting of the prelami-
nar neural tissue over the area of laminar holes and dis-
insertions in more than 90% of our cases. This finding
may be attributed to the retinal ganglion cell (RGC) axo-
nal loss and/or prelaminar tissue ectasia26 associated with
focal LC defects and may be considered a sign of glau-
comatous 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 Kuhnt27 partially at-
tached to the optic disc surface.

The laminar holes and disinsertions we observed cor-
responded to neuroretinal rim thinning or APON seen
in optic disc photographs. This suggests that the mecha-
nism of LC deformation in glaucoma includes focal loss
of laminar beams, as demonstrated in our previous study.18
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 coated with astrocytes, which pro-
vide structural and cellular support to the RGC axons.2 stubbornly
In addition, the capillaries running inside laminar beams1,29

was not statistically significant (\(P = .10, \chi^2\) test). Sec-
ond, all 6 laminar holes were clinically visible in their
entirety, whereas all 10 laminar insertions were only
partially visible clinically. These findings can be attrib-
uted to the difference in locations between the laminar
holes and disinsertions. Laminar holes occur in the far
periphery but not at the very edge of the LC (laminar
insertion area). Therefore, they are less likely to be ob-
served by the scleral and neuroretinal rims and are
more easily detected clinically compared with laminar
disinsertions. However, laminar disinsertions, which
occur at the LC insertion area, can be detected clinically
only 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 underly-
ing pathogenic mechanisms.

In 10 of 36 laminar disinsertions, the clinically ob-
served 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. Keep-
ing these in mind and considering the usual anatomy of
the laminar insertion area (scleral, choroidal, and neu-
roretinal 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 disinsert-
ions that are larger than the clinically seen APONs. In
the same sense, some laminar disinsertions may be pre-
clinical APONs. Because APONs are frequently associ-
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 preceeds 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 dissections 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’ 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


13. Park SC, Kiumehr S, Teng CC, Tello C, Liebmann JM, Ritch R. Horizontal central...


**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.”