Factors Associated With Focal Lamina Cribrosa Defects in Glaucoma

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Purpose. To assess factors associated with focal lamina cribrosa (LC) defects in glaucoma.

Methods. Serial enhanced depth imaging (EDI) optical coherence tomography (OCT) B-scans of the optic nerve head were obtained from glaucoma patients. EDI OCT scans were reviewed for focal LC defects (laminar holes or disinsertions). Evaluated clinical factors included age, central corneal thickness, visual field (VF) mean deviation (MD), exfoliation syndrome, normal-tension glaucoma (NTG), disc hemorrhage, and intraocular pressure (IOP) during past follow-up.

Results. One hundred forty-eight glaucomatous eyes (148 patients; mean age, 68 ± 12 years; mean VF MD, −11.63 ± 6.96 dB) were included. Sixty-seven (45%) eyes had focal LC defects and 81 (55%) did not. Eyes with focal LC defects had a higher prevalence of both disc hemorrhage (25% vs. 6%) and NTG (33% vs. 9%) and worse VF MD (−14.12 vs. −9.58 dB) than those without focal LC defects ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively). In the multivariate logistic regression analysis, higher frequency of disc hemorrhage detection (odds ratio [OR], 3.63; $P = 0.032$), a diagnosis of NTG (OR, 4.23; $P = 0.005$), and worse VF MD (OR, 1.11; $P < 0.001$) were significant factors associated with the presence of focal LC defects. Disc hemorrhage developed in the same half of the disc as the largest or the second largest focal LC defect in 15 of 17 eyes (88.2%).

Conclusions. Disc hemorrhage, a diagnosis of NTG, and more advanced glaucoma status are associated with focal LC defects. Future studies are needed to elucidate the cause-and-effect relationships between focal LC defects and these factors.

Keywords: lamina cribrosa, optical coherence tomography, glaucoma

Glaucoma is a progressive optic neuropathy with structural changes in the optic disc, retinal nerve fiber layer, and lamina cribrosa (LC) and associated functional loss. The LC is a sieve-like structure in the neural canal of the optic nerve head, through which bundles of retinal ganglion cell axons pass to form the optic nerve.[1–3] The LC is considered the primary and principal site of retinal ganglion cell axonal injury in glaucoma.[4–6] Glaucomatous deformation of the LC has been extensively studied histologically[6–11] and in vivo, using ocular imaging devices.[12–15] Most previous studies demonstrated generalized deformation of the LC structure. However, the localized nature of retinal nerve fiber layer defects and optic disc neuroretinal rim loss in glaucoma leads us to expect localized structural changes of the LC in addition to generalized LC deformation.

Newer imaging technologies, such as enhanced depth imaging (EDI) optical coherence tomography (OCT)[16–18] and swept-source OCT,[19–21] have permitted in vivo investigation of the deeper optic nerve head structures, including the LC. Using EDI OCT, localized structural abnormalities in the LC have been demonstrated in glaucomatous eyes.[22] This localized LC deformation at the laminar insertion area was also shown in histological sections and three-dimensional reconstructions of the glaucomatous optic nerve head (Girkin CA, et al. *IOVS* 2011;52:ARVO E-Abstract 3957). These focal LC defects, which appeared to involve localized loss of laminar beams, were associated with characteristic glaucomatous optic disc changes such as focal neuroretinal rim loss and acquired pits of the optic nerve.[23] However, the pathogenetic mechanisms and clinical implications of focal LC defects have yet to be evaluated in detail. The purpose of this study was to identify clinical characteristics associated with focal LC defects in glaucomatous eyes, which may shed light on the origin of glaucomatous 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.

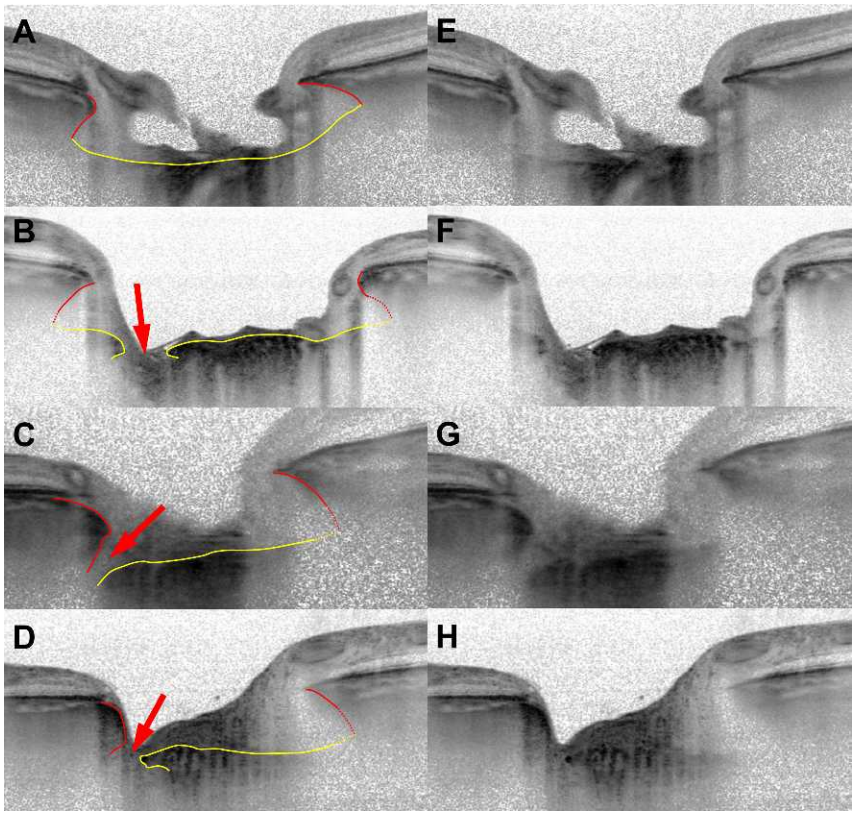

FIGURE 1. Enhanced depth imaging optical coherence tomographic scans of glaucomatous optic discs (**A–D**) and the same images without the labels (**E–H**). (**A**) No focal LC defects. A laminar hole (**B**) and a laminar disinsertion (**C**) (*red arrows*). (**D**) A focal LC defect with combined features of a laminar hole and a laminar disinsertion (*red arrow*). *Red lines* indicate the border tissue of Elschnig and scleral canal wall. *Yellow lines* indicate the anterior surface of the LC. *Dotted lines* indicate extrapolation.

We prospectively recruited patients with a range of optic neuropathy and visual field (VF) loss representing various stages of glaucomatous damage. Glaucoma was defined by the presence of characteristic optic 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 (Humphrey VF Analyzer, 24-2 SITA-Standard strategy; Carl Zeiss Meditec, Inc., Dublin, CA). An abnormal VF was defined as a glaucoma hemifield test result outside normal limits on at least two consecutive VF tests and the presence of at least three contiguous test points within the same hemifield on the pattern deviation plot at $P < 0.01$, with at least one point at $P < 0.005$. We used stricter criteria for an abnormal VF than suggested initially by Hodapp et al.[24] in order to increase the specificity of glaucoma diagnosis. The VF tests required reliability indices better than 25%.

All participants provided a detailed medical history and underwent slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and dilated optic disc and fundus examination. For both eyes of each participant, serial horizontal and vertical cross-sectional images (interval between images, approximately 30 μm) of the optic nerve head were obtained using EDI OCT (Spectralis; Heidelberg Engineering, GmbH, Dossenheim, Germany). All participants had simultaneous color optic disc stereophotography (Stereo Camera 3-DX; Nidek, Inc., Palo Alto, CA) and standard automated perimetry within 4 months of EDI OCT. We excluded eyes with previous posterior segment intraocular surgery; nonglaucomatous ocular or systemic diseases known to affect the optic nerve head structure or VFs; or poor-quality OCT images of the LC because of media opacity, irregular tear film, or poor patient cooperation.

Enhanced Depth Imaging Optical Coherence Tomography

For EDI OCT of the optic nerve head, the OCT device was set to image a $15° \times 10°$ rectangle for horizontal scans (and a $10° \times 15°$ 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 either 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 and create an inverted image (the inner portion of the retina shown facing downward).

The EDI OCT images were carefully reviewed for laminar holes and laminar disinsertions violating the smooth curvilinear U- or W-shaped cross-sectional contour that is observed in healthy eyes.[23] This review was done by an experienced glaucoma specialist masked to 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. 1B). 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. 1C). Lamina cribrosa lesions with combined features of a laminar hole and a laminar disinsertion were also classified as focal LC defects (Fig. 1D). Focal LC defects were required to be at least 100 μm in diameter based on our experience during

Table 1. Comparison of the Clinical Factors Between the Eyes With Focal Lamina Cribrosa Defects and the Eyes Without Defects

Factors	Eyes With Focal Lamina Cribrosa Defect, 67 Eyes, 67 Patients	Eyes Without Focal Lamina Cribrosa Defect, 81 Eyes, 81 Patients	*P* Value
Age, y*	69 ± 11, 38–89	67 ± 13, 25–89	0.399†
CCT, μm*	532 ± 33, 412–615	541 ± 36, 469–680	0.319†
24-2 VF MD, dB*	−14.12 ± 6.89, −28.70 to −1.22	−9.58 ± 6.35, −26.87 to −0.46	**<0.001†**
24-2 VF PSD, dB*	10.64 ± 3.20, 1.98–16.96	8.23 ± 4.00, 1.46–16.31	**<0.001†**
Mean follow-up IOP, mm Hg*	14.3 ± 3.6, 7.3–26.1	14.4 ± 2.9, 9.0–24.3	0.658†
Peak IOP, mm Hg*	23.1 ± 6.5, 14–50	24.1 ± 5.5, 11–40	0.078†
SD IOP, mm Hg*	2.6 ± 1.8, 0.7–10.4	2.8 ± 1.4, 0.6–7.3	0.089†
Disc hemorrhage detection	17, 25%	5, 6%	**0.002‡**
Normal-tension glaucoma, %	22, 33	7, 9	**<0.001‡**
Exfoliation syndrome, %	8, 12	9, 11	0.919‡

P values of <0.05 are noted in boldface.
* Values are mean ± standard deviation (range).
† By Mann-Whitney *U* test.
‡ By χ^2 test.

previous studies on LC morphology using EDI OCT.[22,23,25] 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. One eye was randomly selected from each patient if both eyes had a laminar hole or disinsertion or if neither of the two eyes had a laminar hole or disinsertion. When a laminar hole or disinsertion was present in only one eye of a patient, the eye with a laminar hole or disinsertion was selected for analysis.

Clinical Parameters

We recorded age at the time of EDI OCT, VF mean deviation (MD), and VF pattern standard deviation (PSD) on the most recent VF test (within 4 months of EDI OCT), presence or absence of exfoliation syndrome, presence or absence of normal-tension glaucoma (NTG), and central corneal thickness (CCT) measured using ultrasonic pachymetry (DGH-550; DGH Technology, Inc., Exton, PA). Exfoliation syndrome was defined as the presence of characteristic exfoliation material on the pupil border or on the lens capsule following pupil dilation. Normal-tension glaucoma was defined as primary open-angle glaucoma (POAG) with a maximum known untreated intraocular pressure (IOP) reading ≤ 21 mm Hg. We also recorded disc hemorrhage detection and IOP during past follow-up. 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.[26] The location of disc hemorrhage (superior or inferior half of the optic disc) was recorded and correlated with the location of focal LC defects. 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] Intraocular pressure 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.

Statistical Analysis

Clinical parameters (age, CCT, VF MD, VF PSD, and IOP variables [mean follow-up IOP, peak IOP, and IOP fluctuation]) were compared between the eyes with and without focal LC defects (laminar holes or disinsertions) using independent *t*-test or Mann-Whitney *U* test depending on the normality test results. Categorical variables (exfoliation syndrome, NTG, and disc hemorrhage detection) were compared between the two groups using χ^2 test. To identify clinical parameters associated with the focal LC defect, each variable was first tested in a univariate model using logistic regression analysis. Those with a *P* value of <0.10 were then entered in a multivariate model. The multivariable model was performed using a stepwise approach; that is, significant variables ($P < 0.05$) were entered sequentially. Analyses were conducted using MedCalc (MedCalc, Inc., Mariakerke, Belgium), and statistical significance was defined at $P < 0.05$.

Results

A total of 148 eyes (148 patients, 82 women) were included for analysis. Mean VF MD, mean VF PSD, and mean age were −11.63 ± 6.96 dB (range, −28.70 to −0.46), 9.32 ± 3.84 dB (range, 1.46–16.96), and 68 ± 12 years (range, 25–89), respectively. All eyes had been treated with a variety of antiglaucoma medications, laser procedures, and/or surgery. There were 81 eyes with POAG, 29 with NTG, 17 with exfoliative glaucoma, 10 with pigmentary glaucoma, and 11 with chronic angle-closure glaucoma. Subjects self-identified as white (111), black (10), Hispanic (11), or Asian (16). Based on the EDI OCT, 67 (45%) eyes had focal LC defects (laminar holes or disinsertions) and 81 (55%) did not. The mean follow-up period for IOP and disc hemorrhage data collection was similar between eyes with and without focal LC defects (8.5 ± 4.1 vs. 7.8 ± 3.9 years; $P = 0.25$). All patients were examined usually at 3- to 6-month intervals, and IOP and disc hemorrhage were assessed at every visit.

Clinical factors in the eyes with and without focal LC defects are described in Table 1. Eyes with focal LC defects had significantly higher prevalence of disc hemorrhage (25% vs. 6%), higher prevalence of NTG (33% vs. 9%), worse VF MD (−14.12 vs. −9.58 dB), and worse VF PSD (10.64 vs. 8.23 dB) than those without focal LC defects ($P = 0.002$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Age, CCT, prevalence of exfoliation syndrome, and IOP variables (mean follow-up IOP, peak IOP, and IOP fluctuation) were not significantly different between the two groups (all $P > 0.07$), although peak IOP and IOP fluctuation showed borderline significance ($P = 0.078$ and $P = 0.089$, respectively).

Results of logistic regression analyses for testing the association between the presence of focal LC defect and

Table 2. Logistic Regression Testing the Association Between the Presence of Focal Lamina Cribrosa Defect and Clinical Factors

Factors	Univariate Model		Multivariate Model 1*		Multivariate Model 2*	
	Odds Ratio, 95% CI	*P* Value	Odds Ratio, 95% CI	*P* Value	Odds Ratio, 95% CI	*P* Value
Age, per decade older	1.01, 0.99–1.04	0.342				
CCT, per 40 μm thinner	0.99, 0.98–1.00	0.133				
24-2 VF MD, per decibel worse	1.11, 1.05–1.17	**<0.001**	1.11, 1.05–1.18	**<0.001**		
24-2 VF PSD, per decibel worse	1.20, 1.09–1.32	**<0.001**			1.17, 1.06–1.30	**0.002**
Mean follow-up IOP, per mm Hg higher	0.99, 0.90–1.10	0.881				
Peak IOP, per mm Hg higher	0.97, 0.92–1.03	0.277				
SD IOP, per mm Hg higher	0.91, 0.74–1.13	0.403				
Disc hemorrhage detection	5.17, 1.79–14.90	**0.002**	3.63, 1.12–11.76	**0.032**	3.45, 1.17–10.97	**0.036**
Normal-tension glaucoma	5.17, 2.04–13.07	**<0.001**	4.23, 1.55–11.54	**0.005**	3.31, 1.20–9.12	**0.021**
Exfoliation syndrome	1.08, 0.40–2.99	0.875				

P values of <0.05 are noted in boldface. CI, confidence interval.
* Adjusted for all variables with *P* of <0.10 in the univariate model.

clinical factors are described in Table 2. In the univariate logistic regression analysis, disc hemorrhage detection (odds ratio [OR], 5.17; $P = 0.002$), NTG (OR, 5.17; $P < 0.001$), VF MD (OR, 1.11; $P < 0.001$), and VF PSD (OR, 1.20; $P < 0.001$) were significantly associated with the presence of focal LC defects. Age, CCT, exfoliation syndrome, and IOP variables (mean follow-up IOP, peak IOP, and IOP fluctuation) were not significantly associated with the presence of focal LC defects (all $P > 0.13$). Because VF MD and VF PSD were significantly correlated ($P < 0.001$, $R = 0.546$), these two variables were separately included in the multivariate model to avoid multicollinearity. In the multivariate analysis with VF MD included, disc hemorrhage detection (OR, 3.63; $P = 0.032$), NTG (OR, 4.23; $P = 0.005$), and VF MD (OR, 1.11; $P < 0.001$) remained significant factors associated with the presence of focal LC defects. In the multivariate analysis with VF PSD included, disc hemorrhage detection (OR, 3.45; $P = 0.036$), NTG (OR, 3.31; $P = 0.021$), and VF PSD (OR, 1.17; $P = 0.002$) also remained significant factors associated with the presence of focal LC defects.

Among the 17 eyes with both focal LC defects and disc hemorrhage, focal LC defects and disc hemorrhage were spatially correlated in 15 eyes (88.2%). The disc hemorrhage developed in the same half of the optic disc as the largest focal LC defect in 12 eyes (70.6%) and as the second largest focal LC defect in 3 eyes (17.6%). A representative case is shown in Figure 2.

Discussion

In this prospective study, we evaluated the clinical characteristics associated with glaucomatous focal LC defects (laminar holes or disinsertions) detected using EDI OCT. Our study demonstrated that patients with disc hemorrhage, NTG, and worse VF global indices are at an increased risk of having focal LC defects. Mechanisms of LC deformation in glaucoma other than focal LC defects have been reported in previous articles: posterior bowing of the LC,[6–11,28,29] posterior migration of the laminar insertion,[30,31] and thinning of the LC.[15,32,33] However, these mechanisms describe generalized morphologic changes in the LC rather than localized pathology. Since glaucomatous structural and functional damage occurs in a rather localized fashion, focal LC defects may be a better surrogate for optic nerve head damage than generalized LC deformation. Considering that focal LC defects occur in tandem with neuroretinal rim loss and acquired pits of the optic nerve[22,23] and that focal LC defects may be associated with glaucomatous VF progression (Faridi OS, et al. *IOVS* 2012;53:ARVO E-Abstract 3694), knowledge of the clinical characteristics related to focal LC defects gives important clues to better understand the pathophysiology of glaucoma and may advance patient management.

We found a significant association between disc hemorrhage and focal LC defects. Also, disc hemorrhage corresponded spatially to the focal LC defects. Although the etiology of disc hemorrhage is unclear, with both mechanical[5,34] and vascular mechanisms[35,36] having been hypothesized, microstructural anatomy of the LC and clinical characteristics of disc hemorrhage and focal LC defects suggest that these two entities may be etiologically related. First, structural disruption of laminar beams during the development of focal LC defects may lead to clinically visible disc hemorrhage if capillaries located inside these beams[2,37] are concomitantly ruptured. Second, focal LC defects occur mostly in the far periphery of the LC at or near laminar insertion,[22,23] and similarly, disc hemorrhage occurs preferentially at the disc margin.[38–40] Disc hemorrhage occurred in the same half of the optic disc as the focal LC defects in 15 of 17 eyes in the our study, but more detailed spatial relationship needs to be investigated by colocalizing these two entities. Localized failure of LC insertion area may create stress and strain in other parts of the LC, which may lead to vascular compromise and disc hemorrhage. Finite element modeling will be helpful in demonstrating this. Patients with NTG have an increased propensity for disc hemorrhages compared to patients with POAG.[41,42] In our study also, disc hemorrhage occurred more frequently in the eyes with NTG (11/29 eyes [38%]) than in the eyes with POAG (6/81 eyes [7%]; $P < 0.001$) or in the eyes with high-tension glaucoma (POAG, exfoliative glaucoma, pigmentary glaucoma, and chronic angle-closure glaucoma; 11/119 eyes [9%]; $P < 0.001$). Therefore, the fact that NTG was more prevalent in the eyes with focal LC defects (33%) than in the eyes without (9%) may have affected the higher prevalence of disc hemorrhage in the eyes with focal LC defects (25%) than in those without (6%). However, disc hemorrhage was independently associated with the presence of focal LC defects in the multivariate logistic regression analysis, which controlled for other factors including the presence of NTG.

Diagnosis of NTG was also a significant factor that was associated with focal LC defects in our study. Focal LC defects occurred preferentially in the eyes with NTG compared to those with high-tension glaucoma. Javitt et al.[43] reported that acquired pit of the optic nerve (APON) is more prevalent in NTG than in high-tension glaucoma. Our result is consistent with that study[43] because an APON is a clinical manifestation

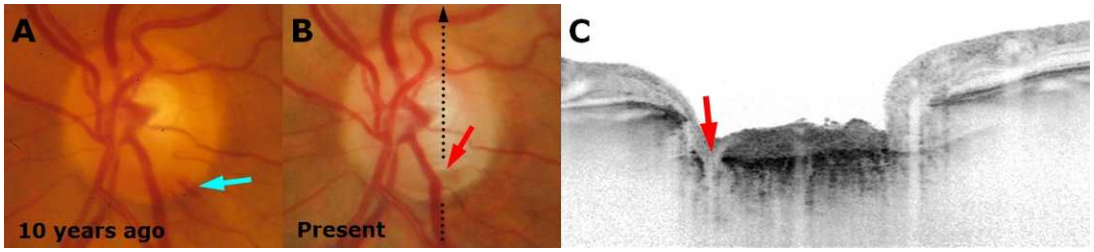

FIGURE 2. A representative case showing spatial correlation between a focal LC defect and a previous disc hemorrhage. (**A**) Optic disc photograph 10 years ago with a disc hemorrhage (*aqua arrow*). (**B**) Optic disc photograph and (**C**) EDI OCT image at present with a focal LC defect at the same location as the previous disc hemorrhage (*red arrows*). The *black dotted arrow* in (**B**) denotes the location and direction of the EDI OCT scan (**C**).

of laminar hole and laminar disinsertion, as evidenced in our previous article.[24] Our result may have an important implication on the previous finding that patients with NTG tend to have more localized retinal nerve fiber layer and VF defects compared to patients with POAG.[44,45] Focal LC defects likely result from localized loss of laminar beams and occur in tandem with glaucomatous neuroretinal rim loss.[22,23] Therefore, it can be postulated that the laminar beams are more likely to be damaged or lost in a localized fashion in NTG than in other types of glaucoma, resulting in more localized glaucomatous defects in NTG[44,45] and higher prevalence of NTG in the eyes with focal LC defects. Although NTG and POAG are classified using an arbitrary cutoff IOP value, it seems likely that in most eyes with NTG, the IOP-independent factors play a relatively larger role than in eyes with POAG.[46] Therefore, both IOP-dependent mechanisms and mechanisms in addition to IOP such as impaired blood perfusion, increased endothelin-1, disrupted blood–brain barrier at the optic nerve head, increased astrocyte or enzymatic activities, and increased immunologic reaction may be applicable to the pathogenesis of focal LC defects, as we proposed in our previous article.[22]

More advanced disease status (worse VF MD and PSD) was also associated with focal LC defects. This is consistent with previous reports that demonstrated worse LC deformation[5,29] and a greater number of focal LC defects[22] in eyes with greater glaucomatous damage. When laminar beams in a focal LC area are damaged and lost in association with glaucomatous processes, the remaining laminar beams in the adjacent area may have greater mechanical stress and strain than before and so become more susceptible to subsequent damage and loss, forming a vicious cycle. When a large number of laminar beams are lost, the area can be detected as a focal LC defect (laminar hole or disinsertion) on EDI OCT. Another possibility is that the LC may be visualized better in eyes with more advanced glaucoma and thinner prelaminar tissue, leading to easier detection of focal LC defects.

We hypothesized in our previous article[22] that IOP may play an important role in the development of focal LC defects. The relationship between LC deformation in glaucoma and IOP has been investigated extensively. Intraocular pressure generates mechanical stress (force/cross-sectional area) and strain (physical deformation of the tissue) within the LC, leading to LC deformation.[31,47] The LC connective tissue structure is inhomogeneous and anisotropic, with thinner connective tissue and larger pores in the superior and inferior LC regions.[48–50] It is not a simple disc or plate, but has a more complex shape with a horizontal central ridge.[25] Therefore, mechanical stress and strain within the LC, which are correlated with local laminar density,[51] may be greater in focal LC regions and eventually lead to focal LC defects. However, the mean follow-up IOP was not significantly associated with focal LC defects and was similar between the eyes with focal LC defects and the eyes without in our study. This may be due to higher proportion of NTG eyes in the focal LC defect group (33%) compared to the no focal LC defect group (9%). Clinicians usually set the target IOP lower for patients with NTG than for those with higher untreated IOP readings. In our study also, the mean follow-up IOP for the eyes with NTG was significantly lower than in the eyes with high-tension glaucoma (13.1 ± 1.3 vs. 14.6 ± 3.6 mm Hg; $P = 0.015$). In the subgroup analysis, although statistically insignificant, mean follow-up IOP was greater in the eyes with focal LC defects than in the eyes without in both NTG (13.2 ± 1.4 vs. 12.7 ± 1.1 mm Hg; $P = 0.435$) and high-tension glaucoma (14.9 ± 4.1 vs. 14.4 ± 3.2 mm Hg; $P = 0.616$) groups. Therefore, we believe that IOP should also be considered a potential risk factor for focal LC defects. Studies with a larger sample size are warranted to confirm this hypothesis.

In our previous article,[22] we defined a focal LC defect as an anterior laminar surface irregularity (diameter >100 μm; depth >30 μm) violating the smooth curvilinear U- or W-shaped contour that is observed in normal eyes. In our recent study[23] and the present study, however, we used stricter definitions for focal LC defects to avoid bias and controversy that may be caused by using our previous definition. We previously classified focal LC defects based on their shapes: smooth indentations, moth-eaten-appearance defect, step-like depressions, hole-like defects, and altered laminar insertions.[22] Among these, we included in our recent study[23] and the present study the most prominent LC defects that are likely full-thickness defects: laminar holes ("hole-like defects") and laminar disinsertions (extreme cases of "altered laminar insertions") (Fig. 1). We believe our stricter criteria allowed us to exclude normal anatomic variations and artifacts from real glaucomatous LC defects and make our subjects with focal LC defects more homogeneous. Conversely, our stricter criteria for focal LC defects may also have led to classification of eyes with smaller LC defects as eyes without focal LC defects. Then, the identified factors (disc hemorrhage, NTG, and more advanced VF defect) would represent clinical factors that are associated with "larger, more prominent" focal LC defects, which may still be important information in the pathogenesis of focal LC defects and in the management of glaucoma patients. Separately from the issue of focal LC defect definition, LC defects at the laminar insertion area below thick scleral rim, choroid, or retinal layers may not have been detected using EDI OCT. The high prevalence of focal LC defects in our study may be in part attributed to the severe glaucoma present in our subjects (mean VF MD = −11.63 dB). When a laminar hole or disinsertion was present in only one eye of a patient, the eye with a laminar hole or disinsertion was selected for analysis instead of random selection. This likely increased the prevalence of focal LC defects in the studied eyes. When subjects were recruited, disc photographs and VFs were evaluated to confirm the diagnosis of glaucoma. During this process, eyes with a higher possibility of having focal LC

defects (e.g., eyes with an APON) may have been enrolled more selectively. For these reasons, the prevalence of focal LC defects in the present study is likely higher than that in the general glaucoma population. Our diagnosis of NTG was based on untreated IOP readings during office hours, not using diurnal IOP monitoring. Additionally, we did not see any difference in the quality between the EDI OCT images obtained using the Spectralis OCT software and those obtained by moving the zero reference plane posteriorly.

In conclusion, we demonstrated that a higher frequency of disc hemorrhage detection, a diagnosis of NTG, and more advanced disease status are significantly associated with focal LC defects. Because disc hemorrhage[52–54] and more advanced disease status[27,55] are well-known risk factors for the development and/or progression of glaucoma, our findings suggest that focal LC defects may be considered an important structural parameter in glaucoma. Based on the three-way association among disc hemorrhage, NTG, and focal LC defects in the present study and the association between glaucomatous neuroretinal rim loss and focal LC defects in our previous studies,[22,23] it can be postulated that the primary pathology that leads to localized glaucomatous defects may be focal laminopathy, especially in NTG. Future studies are needed to elucidate the cause-and-effect relationships between focal LC defects and these associated factors. In addition to our previous articles,[22,23] the present study underscores the importance of LC evaluation in glaucoma, focusing on localized deformation and defects within it.

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References

1. Wilczek M. The lamina cribrosa and its nature. *Br J Ophthalmol*. 1947;31:551–565.
2. Anderson DR. Ultrastructure of human and monkey lamina cribrosa and optic nerve head. *Arch Ophthalmol*. 1969;82:800–814.
3. Emery JM, Landis D, Paton D, Boniuk M, Craig JM. The lamina cribrosa in normal and glaucomatous human eyes. *Trans Am Acad Ophthalmol Otolaryngol*. 1974;78:OP290–OP297.
4. Minckler DS, Bunt AH, Johanson GW. Orthograde and retrograde axoplasmic transport during acute ocular hypertension in the monkey. *Invest Ophthalmol Vis Sci*. 1977;16:426–441.
5. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma, II: the site of injury and susceptibility to damage. *Arch Ophthalmol*. 1981;99:635–649.
6. Quigley HA, Hohman RM, Addicks EM, Massof RW, Green WR. Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. *Am J Ophthalmol*. 1983;95:673–691.
7. Bellezza AJ, Rintalan CJ, Thompson HW, Downs JC, Hart RT, Burgoyne CF. Deformation of the lamina cribrosa and anterior scleral canal wall in early experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2003;44:623–637.
8. Levy NS, Crapps EE. Displacement of optic nerve head in response to short-term intraocular pressure elevation in human eyes. *Arch Ophthalmol*. 1984;102:782–786.
9. Morgan WH, Chauhan BC, Yu DY, Cringle SJ, Alder VA, House PH. Optic disc movement with variations in intraocular and cerebrospinal fluid pressure. *Invest Ophthalmol Vis Sci*. 2002;43:3236–3242.
10. Yan DB, Coloma FM, Metheetrairut A, Trope GE, Heathcote JG, Ethier CR. Deformation of the lamina cribrosa by elevated intraocular pressure. *Br J Ophthalmol*. 1994;78:643–648.
11. Yang H, Downs JC, Girkin C, et al. 3-D histomorphometry of the normal and early glaucomatous monkey optic nerve head: lamina cribrosa and peripapillary scleral position and thickness. *Invest Ophthalmol Vis Sci*. 2007;48:4597–4607.
12. Inoue R, Hangai M, Kotera Y, et al. Three-dimensional high-speed optical coherence tomography imaging of lamina cribrosa in glaucoma. *Ophthalmology*. 2009;116:214–222.
13. Agoumi Y, Sharpe GP, Hutchison DM, Nicolela MT, Artes PH, Chauhan BC. Laminar and prelaminar tissue displacement during intraocular pressure elevation in glaucoma patients and healthy controls. *Ophthalmology*. 2011;118:52–59.
14. Strouthidis NG, Fortune B, Yang H, Sigal IA, Burgoyne CF. Effect of acute intraocular pressure elevation on the monkey optic nerve head as detected by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011;52:9431–9437.
15. Park HY, Jeon SH, Park CK. Enhanced depth imaging detects lamina cribrosa thickness differences in normal tension glaucoma and primary open-angle glaucoma. *Ophthalmology*. 2012;119:10–20.
16. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2008;146:496–500.
17. Lee EJ, Kim TW, Weinreb RN, Park KH, Kim SH, Kim DM. Visualization of the lamina cribrosa using enhanced depth imaging spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2011;152:87–95, e1.
18. Park SC, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Enhanced depth imaging optical coherence tomography of deep optic nerve complex structures in glaucoma. *Ophthalmology*. 2012;119:3–9.
19. Yasuno Y, Hong Y, Makita S, et al. In vivo high-contrast imaging of deep posterior eye by 1-microm swept source optical coherence tomography and scattering optical coherence angiography. *Opt Express*. 2007;15:6121–6139.
20. Srinivasan VJ, Adler DC, Chen Y, et al. Ultrahigh-speed optical coherence tomography for three-dimensional and en face imaging of the retina and optic nerve head. *Invest Ophthalmol Vis Sci*. 2008;49:5103–5110.
21. Ohno-Matsui K, Akiba M, Moriyama M, et al. Acquired optic nerve and peripapillary pits in pathologic myopia. *Ophthalmology*. 2012;119:1685–1692.
22. Kiumehr S, Park SC, Syril D, et al. In vivo evaluation of focal lamina cribrosa defects in glaucoma. *Arch Ophthalmol*. 2012;130:552–559.
23. You JY, Park SC, Su D, Teng CC, Liebmann JM, Ritch R. Focal lamina cribrosa defects associated with glaucomatous rim thinning and acquired pits. *JAMA Ophthalmol*. 2013;131:314–320.
24. Hodapp E, Parrish RK II, Anderson DR. *Clinical Decisions in Glaucoma*. St. Louis, MO: CV Mosby; 1993:52–61.
25. Park SC, Kiumehr S, Teng CC, Tello C, Liebmann JM, Ritch R. Horizontal central ridge of the lamina cribrosa and regional

differences in laminar insertion in healthy subjects. *Invest Ophthalmol Vis Sci*. 2012;53:1610–1616.

26. Airaksinen PJ, Mustonen E, Alanko HI. Optic disc hemorrhages: analysis of stereophotographs and clinical data of 112 patients. *Arch Ophthalmol*. 1981;99:1795–1801.
27. De Moraes CGV, Juthani, VJ, Liebmann JM, et al. Risk factors for visual field progression in treated glaucoma. *Arch Ophthalmol*. 2011;129:562–568.
28. Hayreh SS, Pe'er J, Zimmerman MB. Morphologic changes in chronic high-pressure experimental glaucoma in rhesus monkeys. *J Glaucoma*. 1999;8:56–71.
29. Yang H, Thompson H, Roberts MD, Sigal IA, Downs JC, Burgoyne CF. Deformation of the early glaucomatous monkey optic nerve head connective tissue after acute IOP elevation in 3-D histomorphometric reconstructions. *Invest Ophthalmol Vis Sci*. 2011;52:345–363.
30. Yang H, Williams G, Downs JC, et al. Posterior (outward) migration of the lamina cribrosa and early cupping in monkey experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52:7109–7121.
31. Crawford Downs J, Roberts MD, Sigal IA. Glaucomatous cupping of the lamina cribrosa: a review of the evidence for active progressive remodeling as a mechanism. *Exp Eye Res*. 2011;93:133–140.
32. Jonas JB, Berenshtein E, Holbach L. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. *Invest Ophthalmol Vis Sci*. 2004;45:2660–2665.
33. Ren R, Wang N, Li B, et al. Lamina cribrosa and peripapillary sclera histomorphometry in normal and advanced glaucomatous Chinese eyes with various axial length. *Invest Ophthalmol Vis Sci*. 2009;50:2175–2184.
34. De Moraes CG, Prata TS, Liebmann CA, Tello C, Ritch R, Liebmann JM. Spatially consistent, localized visual field loss before and after disc hemorrhage. *Invest Ophthalmol Vis Sci*. 2009;50:4727–4733.
35. Grieshaber MC, Terhorst T, Flammer J. The pathogenesis of optic disc splinter haemorrhages: a new hypothesis. *Acta Ophthalmol Scand*. 2006;84:62–68.
36. Grieshaber MC, Flammer J. Does the blood-brain barrier play a role in glaucoma? *Surv Ophthalmol*. 2007;52(suppl 2):S115–S121.
37. Mackenzie PJ, Cioffi GA. Vascular anatomy of the optic nerve head. *Can J Ophthalmol*. 2008;43:308–312.
38. Drance SM, Fairclough M, Butler DM, Kottler MS. The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma. *Arch Ophthalmol*. 1977;95:226–228.
39. Drance SM. Disc hemorrhages in the glaucomas. *Surv Ophthalmol*. 1989;33:331–337.
40. Liou SY, Sugiyama K, Uchida H, et al. Morphometric characteristics of optic disk with disk hemorrhage in normal tension glaucoma. *Am J Ophthalmol*. 2001;132:618–625.
41. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. *Ophthalmology*. 1986;93:853–857.
42. Tezel G, Kass MA, Kolker AE, Wax MB. Comparative optic disc analysis in normal pressure glaucoma, primary open-angle glaucoma, and ocular hypertension. *Ophthalmology*. 1996;103:2105–2113.
43. Javitt JC, Spaeth GL, Katz LJ, et al. Acquired pits of the optic nerve. Increased prevalence in patients with low-tension glaucoma. *Ophthalmology*. 1990;97:1038–1043.
44. Yamazaki Y, Koide C, Miyazawa T, Kuwagaki N, Yamada H. Comparison of retinal nerve-fiber layer in high- and normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 1991;229:517–520.
45. Kubota T, Khalil AK, Honda M, Ito S, Nishioka Y, Inomata H. Comparative study of retinal nerve fiber layer damage in Japanese patients with normal- and high-tension glaucoma. *J Glaucoma*. 1999;8:363–366.
46. Sommer A, Tielsch JM. Primary open-angle glaucoma: a clinical-epidemiologic perspective. In: Shields MB, Van Buskirk M, eds. *100 Years of Progress in Glaucoma*. Philadelphia: Lippincott-Raven; 1997:100–107.
47. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog Retin Eye Res*. 2005;24:39–73.
48. Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. *Arch Ophthalmol*. 1981;99:137–143.
49. Radius RL. Regional specificity in anatomy at the lamina cribrosa. *Arch Ophthalmol*. 1981;99:478–480.
50. Winkler M, Jester B, Nien-Shy C, et al. High resolution three-dimensional reconstruction of the collagenous matrix of the human optic nerve head. *Brain Res Bull*. 2010;81:339–348.
51. Roberts MD, Liang Y, Sigal IA, et al. Correlation between local stress and strain and lamina cribrosa connective tissue volume fraction in normal monkey eyes. *Invest Ophthalmol Vis Sci*. 2010;51:295–307.
52. Diehl DL, Quigley HA, Miller NR, Sommer A, Burney EN. Prevalence and significance of optic disc hemorrhage in a longitudinal study of glaucoma. *Arch Ophthalmol*. 1990;108:505–550.
53. Law SK, Choe R, Caprioli J. Optic disk characteristics before the occurrence of disk hemorrhage in glaucoma patients. *Am J Ophthalmol*. 2001;132:411–413.
54. Jonas JB, Martus P, Budde WM, Hayler J. Morphologic predictive factors for development of optic disc hemorrhages in glaucoma. *Invest Ophthalmol Vis Sci*. 2002;43:2956–2961.
55. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004;111:1627–1635.

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