ORIGINAL ARTICLE

Enhanced Depth Imaging of Central Lamellar Thickness in Optic Neuropathy: Comparison with Normal Eyes

Suntaree Thitiwichienlert, Hitoshi Ishikawa, Ken Asakawa, Tetsuya Ikeda, and Kimiya Shimizu

Department of Ophthalmology, Kitasato University School of Medicine, Kanagawa, Japan

ABSTRACT

The purpose of this study was to compare central lamellar thickness (LT) among patients with glaucomatous optic neuropathy (GON), patients with non-GON, and normal subjects using enhanced-depth imaging optical coherence tomography (EDI-OCT). Enrolled were 57 patients ($n=64$ eyes), including 30 women and 27 men. Three groups were identified: GON ($n=18$ eyes), non-GON ($n=16$ eyes), and control ($n=30$ eyes). The GON group comprised eyes with primary open-angle glaucoma (POAG) ($n=9$) and normal-tension glaucoma (NTG) ($n=9$). The non-GON group comprised eyes with demyelinating optic neuritis ($n=9$), anterior ischemic optic neuropathy (AION) ($n=2$), compressive ON ($n=2$), Leber hereditary ON ($n=2$), and traumatic ON ($n=1$). GON and non-GON groups were further divided into mild, moderate, and severe subgroups. Inclusion in the GON group was based on mean deviations (MDs) of visual fields; inclusion in the non-GON group was based on critical flicker frequency (CFF) responses. Intraclass correlation coefficients (ICCs) were used to verify reproducibility of measurements. LTs of GON and non-GON group eyes were thinner than those of control group eyes ($p<0.01$); LTs of GON group eyes were thinner than those of non-GON group eyes ($p=0.01$). LTs of severe GON subgroup eyes were thinner than those of moderate and mild GON subgroup eyes ($p<0.001$; $p=0.024$, respectively). LTs of severe non-GON subgroup eyes were thinner than those of mild non-GON subgroup eyes ($p=0.002$). These results show that EDI-OCT is valuable for documenting structural abnormalities in optic neuropathy (ON).

Keywords: Enhanced depth imaging optical coherence tomography, glaucomatous optic neuropathy, lamina cribrosa, non-glaucomatous optic neuropathy

INTRODUCTION

The lamina cribrosa (LC) is a porous-like connective tissue structure located on the inner surface of the optic nerve head.¹ The LC is the exit site of the optic nerve. It also provides a mechanical support for the retinal ganglion cell (RGC) axons that travel through the scleral canal,² acts as a pressure barrier between the intraocular and retrobulbar cerebrospinal fluid (CSF) spaces, and helps stabilize the intraocular pressure (IOP).³

In glaucoma, the IOP mechanically compresses the optic nerve head, causing tissue deformation and alterations in blood flow to the lamellar region, all of which events that result in connective tissue changes, including lamellar scarring and thinning.⁴ Anatomical studies of LC changes in both normal and glaucomatous eyes suggest the LC to be the initial site of RGC axon damage in glaucoma.⁵ Previous *in vitro* studies have revealed that lamellar thickness (LT) increases significantly with age in the normal human globe, and that LCs of glaucomatous

Received 26 June 2014; revised 8 February 2015; accepted 9 February 2015; published online 23 June 2015

Correspondence: Suntaree Thitiwichienlert, MD, Clinical Lecturer, Department of Ophthalmology, Thammasat Eye Center, Thammasat Hospital, Thammasat University, 95 Paholyothin Road, Klong Neung, Klong Laung, Pathumthani, Thailand. E-mail: punoipunoio@hotmail.com

eyes are significantly thinner than those of normal eyes.^{6,7}

As the LC is on the posterior surface of the optic nerve head, it has been difficult to study due to technical limitations. With the recently developed combination of enhanced-depth imaging (EDI) optical coherence tomography (OCT) (EDI-OCT), visualisation of deep optic nerve head structures has improved. Consequently, EDI-OCT has been used to identify laminar changes in glaucomatous optic neuropathy (GON).^{8–11} A pilot study by Park *et al.* compared EDI-OCT-measured LTs between normal, primary open-angle glaucoma (POAG), and normal-tension glaucoma (NTG) eyes, and found that laminar thicknesses (LTs) of both POAG and NTG eyes were significantly thinner than those of normal eyes.¹² However, if GON affects LT, the sources responsible for interrupted axoplasmic flow in non-GON may also cause alterations in the LC. As no previous study of the LC in non-GON eyes exists, the purpose of the present study was to (i) compare LTs of normal, GON, and non-GON eyes; and (ii) determine age-related laminar changes in normal eyes.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the Medical Ethics Committee of Kitasato University School of Medicine, Sagamihara, Japan, and was conducted in accordance with the tenets of the Declaration of Helsinki. This cross-sectional case-control study inspected three groups of eyes: normal control, GON, and non-GON. Control group patients had normal IOPs (range, 10–21 mm Hg) and no ocular or systemic diseases that might have affected the optic nerve or visual function. GON, defined according to specifications of the Japanese Glaucoma Society, is characterised by chronic progressive glaucomatous optic neuropathy (ON), thinning of the neuroretinal rim, and retinal nerve fibre layer (RNFL) defects. An IOP of 20 mm Hg, accompanied by a visual field defect, was considered the boundary between POAG and NTG.^{13,14} GON with an IOP ≤ 21 mm Hg during the repeated measurements taken on different days was defined as NTG.¹² A glaucomatous visual field defect was defined according to the guidelines of the Japanese Glaucoma Society as any of the following: (i) pattern deviation probability plot showing clusters of at least three non-edge points with sensitivities occurring in $<5\%$ of the normal population ($p < 5\%$) and one of the points with sensitivities occurring $<1\%$ of the population ($p < 1\%$); (ii) pattern standard deviation (or corrected pattern standard deviation) with a value occurring in $<5\%$ of normal reliable

fields ($p < 5\%$); and (iii) glaucoma hemifield test indicating an abnormal field. Visual field defects had to be repeatable on at least two subsequent tests.¹³ Inclusion criteria for non-GON included inflammatory optic neuritis (ON; based on visual symptoms, relative afferent pupillary defects, and normal or swollen optic disc in the affected eye)¹⁵; ischaemic ON; compressive ON; traumatic ON; toxic ON; and hereditary ON. Patients with high (greater than -6 dioptres) degrees of myopic refractive error were excluded.¹⁶

We examined a total of 57 persons ($n = 64$ eyes, 27 men and 30 women). Participants were grouped as follows: control ($n = 30$ eyes), GON ($n = 18$ eyes, including 9 with POAG and 9 with NTG), and non-GON ($n = 16$ eyes), including 9 eyes with demyelinating optic neuritis, 2 with anterior ischaemic optic neuropathy (AION), 2 with compressive ON, 2 with Leber hereditary ON, and 1 with traumatic ON).

All participants provided histories and were given ophthalmologic examinations, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, Goldmann applanation tonometry, and fundus examination. Patients with GON were administered colour optic disc stereophotography (Stereo Camera model 3-DX; Nidek Inc., Tokyo, Japan) and automated perimetry (24-2 SITA standard program, Humphrey Visual Field Analyzer; Carl Zeiss Meditec Inc., Dublin, CA, USA). We categorised GON according to the modified Hodapp-Anderson-Parrish grading scale—based on mean deviations (MDs) of visual fields—into mild, moderate, and severe subgroups, as follows: mild (MD larger or equal to -6 dB), moderate (MD -6 to -12 dB), and severe (MD less than -12 dB).^{17,18} We categorised non-GON according to critical flicker frequency (CFF) responses into mild and severe subgroups,^{19,20} as follows: mild (CFF > 10 Hz), severe (CFF ≤ 10 Hz). CFF is a measure of chromatic temporal contrast sensitivity, with the chromatic modulation function limit at ~ 10 – 15 Hz—although parvocellular retinal ganglion cells (RGCs) will respond up to 30–40 Hz.²¹ Hence, we used a cutoff value of 10 Hz.

Central LT Measurement

We used the Heidelberg Spectralis OCT (software version 5.1.1.0, Heidelberg Engineering, Heidelberg, Germany), at a wavelength of 870 nm, to provide up to 40,000 A scans/s, and tissue resolutions of 7 μ m in depth and 14 μ m in transverse scans. The EDI mode scans around the optic nerve head with six radial scans of 20°/scan. Since previous studies reported no inter-regional differences between various areas of the optic nerve head, we measured only the central region.^{7,12} To enhance visualisation, we changed the

FIGURE 1 EDI-OCT images in six radial scans, with enhancement of the lamina cribrosa by replacement of the black-on-white image with a white-on-black image.

FIGURE 2 The central region of the optic nerve head, defined on the temporal side of the trunk where the central retinal vessels emerge. Vertical line drawn passing through the central region of the lamina cribrosa.

image from the “black on white” to the “white on black” setting (Figure 1). We demarcated the central region of the optic nerve head on the temporal side of the trunk of central retinal vessels,¹² drew a vertical line passing through this region of the LC (Figure 2), and magnified the cross-sectional image on the computer so that 1.1 pixel = 1 μm . Since the anterior and posterior laminar borders were at the point where the white reflective region began and ended, we drew two horizontal lines at the levels of the anterior and posterior laminar borders. The central LT was considered as being the depth of the white reflective column, i.e. where the two horizontal lines met the vertical line in the central region of the optic nerve head (Figures 3 and 4).

In a double-blind procedure, two examiners measured the same image by masking ages and study group information. Intra-/inter-observer reproducibility was evaluated using an intra-class correlation coefficient (Table 1). Correlation coefficients of 0.61–0.75 indicated substantial agreement.

FIGURE 3 Central LT, measured as the depth of the white reflective column between the points at which the two horizontal lines meet the vertical line.

Statistical Analysis

Statistical analyses were performed using version 14.0 SPSS software (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) post hoc test was used

FIGURE 4 Enlargement of two areas of Figure 3.

TABLE 1 Reproducibility of the central lamina cribrosa thickness measurements.

	ICC	<i>p</i> Value
Intra-observer		
(observer 1)	0.937 (0.899–0.961)	0.001
(observer 2)	0.935 (0.896–0.960)	0.001
Inter-observer	0.926 (0.882–0.954)	0.001

ICC = intra-class correlation coefficient.

to compare groups/subgroups. Spearman's rank correlation coefficient was used to determine relationships between central LT and age, MD, and CFF. A *p* value of <0.05 indicated statistical significance.

RESULTS

Age, IOP, and spherical equivalents were similar for all groups. BCVAs of non-GON group eyes were significantly lower than those of control group eyes ($p=0.001$), but did not differ significantly from those of GON group eyes ($p=0.082$). There were differences among groups with regard to vertical cup-to-disc ratios and average RNFL thicknesses (Table 2). Central LTs were 343.4 ± 15.3 , 210.1 ± 40.4 , and $247.1 \pm 36.0 \mu\text{m}$ for control, GON, and non-GON group eyes, respectively. Central LTs of GON and non-GON group eyes were significantly thinner ($p<0.01$, for both) than those of control group eyes ($p<0.01$). Central LTs of GON group eyes were significantly thinner than those of non-GON group eyes ($p=0.01$) (Table 2).

MDs of visual field damage in GON group eyes were -1.1 ± 2.3 , -7.9 ± 0.8 , and -19.4 ± 5.1 dB for the mild, moderate, and severe subgroups, respectively. BCVAs were similar for all subgroups. Average RNFL thicknesses in severe subgroup eyes were significantly thinner than those in mild subgroup eyes ($p<0.001$), but did not differ significantly from those of the moderate subgroup eyes ($p=0.647$). Central LTs of

GON group eyes were 244.3 ± 19.0 , 182.3 ± 4.5 , and $158.4 \pm 11.5 \mu\text{m}$ in the mild, moderate, and severe subgroups, respectively. Central LTs of severe subgroup eyes were significantly thinner ($p<0.001$) than those of moderate or mild subgroup eyes ($p=0.024$, for both); central LTs of GON group eyes were significantly correlated (linear regression analysis) with MDs ($r^2=0.67$; $p=0.003$) (Table 3, Figure 5).

Minimum CFF responses were 31.1 ± 9.0 Hz in non-GON group eyes and 9.3 ± 1.1 Hz in both mild and severe subgroup eyes. MDs of visual field damage in non-GON group eyes were -6.3 ± 6.7 and -11.5 ± 4.4 dB in mild and severe subgroup eyes, respectively. MDs of visual field damage in severe subgroup eyes did not differ significantly from those of mild subgroup eyes ($p=0.36$). BCVAs were significantly less, and average RNFL thicknesses significantly thinner in severe subgroup eyes compared with mild subgroup eyes ($p<0.001$, $p=0.10$, respectively). Central LTs of non-GON group eyes were 259.0 ± 26.2 and $195.6 \pm 27.3 \mu\text{m}$ in mild and severe subgroup eyes, respectively. Central LTs of severe subgroup eyes were significantly thinner than those of mild subgroup eyes ($p=0.002$), but central LTs showed no significant correlations with CFF in linear regression analysis ($r^2=0.042$; $p=0.248$) (Table 4, Figure 6).

The control group comprised 14 women and 16 men. Mean ages were 61.8 ± 15.3 and 67.5 ± 11.0 years in women and men, respectively, and mean LTs were 341.0 ± 16.7 and $345.5 \pm 14.7 \mu\text{m}$ in women and men, respectively, neither parameter being statistically significant ($p=0.24$, $p=0.690$, respectively) (Table 5). Central LTs had no significant correlation with age in linear regression analysis ($r^2=0.06$; $p=0.19$) (Figure 7).

DISCUSSION

Results of the present study demonstrated that (i) central LTs of both GON and non-GON group eyes were significantly thinner than those of normal control group eyes; (ii) central LTs of GON group eyes were significantly thinner than those of non-GON group eyes; (iii) central LTs of severe GON subgroup eyes were significantly thinner than those of moderate and mild subgroup eyes; (iv) central LTs of severe non-GON subgroup eyes were significantly thinner than those of mild subgroup eyes; (v) central LTs of GON group eyes were significantly correlated with MD, but central LTs of non-GON group eyes were not significantly correlated with CFF; and (vi) central LTs of normal control group eyes did not increase significantly with age.

LTs of GON group eyes in our study were significantly thinner than those of normal control group eyes. These findings are similar to those of another recent study, despite differences in sample size and

TABLE 2 Demographic data of participants and comparison of central LTs.

Characteristic	Control eyes (<i>n</i> = 30)	GON eyes (<i>n</i> = 18)	Non-GON eyes (<i>n</i> = 16)	<i>p</i> Value*	<i>p</i> Value†	<i>p</i> Value‡
Age (years)	65.9 ± 11.5	61.5 ± 12.9	51.8 ± 15.9	0.57	0.087	0.114
BCVA (logMAR score)	−0.04 ± 0.06	0.09 ± 0.42	0.47 ± 0.69	0.124	0.001	0.082
IOP (mm Hg)	13.6 ± 2.9	15.0 ± 3.1	14.3 ± 2.9	0.386	0.472	0.523
Spherical equivalent	−1.2 ± 2.0	−0.8 ± 2.3	−1.9 ± 1.9	0.859	0.264	0.127
Vertical C:D ratio	0.3 ± 0.01	0.7 ± 0.1	0.3 ± 0.1	<0.01	0.08	<0.01
RNFL average thickness (μm)	98.6 ± 12.8	67.9 ± 19.5	64.5 ± 19.6	<0.01	<0.01	0.918
LT (μm)	343.4 ± 15.3	210.1 ± 40.4	247.1 ± 36.0	<0.01	<0.01	0.01

GON = glaucomatous optic neuropathy; non-GON = non-glaucomatous optic neuropathy. *p** between control and GON group; *p*† between control and non-GON group eyes; *p*‡ between GON and non-GON group eyes.

TABLE 3 Central LTs of GON subgroup eyes.

GON subgroup	Mild (<i>n</i> = 10)	Moderate (<i>n</i> = 3)	Severe (<i>n</i> = 5)	<i>p</i> *	<i>p</i> †	<i>p</i> ‡
MD visual field (dB)	−1.1 ± 2.3	−7.9 ± 0.8	−19.4 ± 5.1	0.03	0.015	0.004
BCVA (log MAR score)	−0.05 ± 0.01	−0.1 ± 0.1	0.5 ± 0.8	0.541	0.469	0.500
RNFL average thickness (μm)	81.4 ± 14.3	57.3 ± 14.2	47.2 ± 8.2	0.17	0.647	<0.001
LT (μm)	244.3 ± 19.0	182.3 ± 4.5	158.4 ± 11.5	<0.001	<0.001	0.024

*p** Between mild and moderate subgroups; *p*† between moderate and severe subgroups; *p*‡ between mild and severe subgroups.

FIGURE 5 Relationship between central LT and MD of visual field damage in GON group eyes.

study population between the two studies.¹² Presently, there are no previous studies of LTs in non-GON eyes. Our study revealed LTs of non-GON group were significantly thinner than those of control eyes. In relation to the papillary area of the optic nerve head, it is known that the LC receives nutrients and oxygen from the laminar capillaries passing through the laminar collagenase matrix. Mechanical IOP stress, inflammation, and ischaemia act to interrupt axoplasmic flow, thus damaging RGC axons.^{4,22} The subsequent loss of RGC axons leaves the pores of the

LC open, with the resulting connective tissue damage apt to induce scarring. Scar formation, in turn, leads to tissue shrinkage and laminar thinning. Both GON and non-GON eyes experience a loss of RGC axons; thus, the laminar thinning of non-GON eyes may result from similar mechanisms.

A previous experimental study of glaucomatous optic nerve damage in monkeys revealed that LTs were significantly thinner in eyes with non-glaucomatous optic nerve damage.²³ The characteristic optic nerve damage that occurs in GON differs from

that of non-GON, but it was unclear from the histological findings of that study whether the LC differed between GON and non-GON eyes. Because optic nerve fibres exit the eye through the LC, and because the LC acts as a pressure barrier between the intraocular space and the cerebrospinal space, such trans-laminar pressure differences influence the aetio-pathogenesis of optic nerve diseases. In GON, the influence of both IOP-dependent and -independent factors are important.²⁴ In POAG eyes, higher IOPs cause higher trans-laminar pressure differences, which lead to greater susceptibility for optic nerve damage. Recent reports have shown that NTG eyes have lower trans-laminar pressure differences than do POAG eyes, and that vascular factors (e.g. ischaemia) affect ocular blood flow, with the consequent fluctuation of perfusion pressures leading to optic nerve damage. In addition, NTG eyes may have abnormally low cerebrospinal fluid (CSF) pressures, which lead to higher trans-laminar pressure differences, despite the fact that IOPs remain within the normal range.²⁵ In non-GON eyes, although optic nerve damage

may be caused by any of a number of factors (ischaemia, inflammation, compression, infiltration, toxicity, and/or heredity), IOPs are typically within the normal range. Taken together, these facts may explain why, in the present study, LTs of GON group eyes were thinner than those of non-GON group eyes.

LTs of severe GON subgroup eyes were significantly thinner than those of moderate and mild subgroup eyes, and LTs of GON subgroup eyes were correlated with MD, findings similar to those of a recent study.¹² In the early stages of GON, IOP-related mechanical compression may be responsible for the onset RGC axonal damage and laminar tissue alterations. In a manner similar to that of the slow chronic progression of GON, LTs would be expected to be thinner and, in the severe stage of GON with its greater number of RGC axons, such damage could result in increased laminar thinning. There is evidence supporting the relationship between RNFL thinning and visual field damage to optic nerve head structures in GON.²⁶ Such findings are similar to ours, i.e. RNFL thicknesses of severe subgroup eyes are significantly thinner than those of moderate subgroup eyes. The fact that we had very few eyes in the moderate subgroup may explain why we found no significant differences between moderate and severe subgroup eyes.

There are data correlating RNFL thinning and visual field damage to optic nerve head structures in non-GON.²⁷ These data correspond to our findings that MDs of visual field damage in severe subgroup eyes are greater than those of mild subgroup eyes, although this finding was not of statistical significance. Moreover, non-GON can cause different

TABLE 4 Central LT in non-GON subgroups.

Subgroup of non-GON	Mild (n = 13)	Severe (n = 3)	<i>p</i> ‡
CFF response (Hz)	31.1 ± 9.0	9.3 ± 1.1	0.001
MD visual field (dB)	-6.3 ± 6.7	-11.55 ± 4.4	0.36
BCVA (log MAR score)	0.2 ± 0.3	1.5 ± 0.7	<0.001
RNFL average thickness (µm)	68.3 ± 19.7	48 ± 8.71	0.01
LT (µm)	259.0 ± 26.2	195.6 ± 27.3	0.002

p‡ Between mild and severe subgroups.

FIGURE 6 Relationship between central LT and CFF damage in non-GON group eyes.

patterns of optic nerve dysfunction, e.g. different degrees of central VA and visual field loss, thus potentially limiting the usefulness of visual field measurements for non-GON patients. Previous reports have shown CFF to be useful in assessing the integrity of the visual system, and that CFF abnormalities are present in optic nerve diseases, especially demyelinating ones.²⁸ Because most of our non-GON group eyes had demyelinating ON, and because there exists no definite classification of severity in non-GON, we used not only CFF measurements to assess optic nerve function, but also automated field defects, BCVA, and OCT-determined average RNFL thickness. We found that LTs of severe subgroup eyes were significantly thinner than those of mild subgroup eyes, as were RNFL thicknesses. This relationship of RNFLs to optic nerve structures in non-GON warrants further investigation. Moreover, in some cases of non-GON, optic neuritis leads to inflammatory damage of axons and to subsequent loss of RGCs. CFF not only reflects neural processing with respect to the speed and transmission of neural responses, but also is indicative of whether integrity of myelination has been maintained.²⁹ However, as

this does not directly indicate the degree of RGC axonal damage, it may explain why we found no correlation between LTs and CFF responses.

Although several previous studies reported that healthy males have thicker LCs than do females, this finding was not of statistical significance.^{6,30} The present study also showed that male eyes have greater LTs than do female eyes, a finding not of statistical significance. Gender-specific differences may be due to differences in anatomical characteristics of the optic nerve head between genders, with males having slightly larger optic discs.

Previous histological studies suggest that biochemical alterations in the ageing collagenase matrix in, i.e. increases in total collagen, but decreases in type III collagen, result in increased thickness and rigidity of the aging LC.^{6,31} In contrast, we did not find that LTs of control group eyes increased significantly with age, perhaps because of differences in ethnicity, age, and methods of locating the LC. One *in vitro* study defined LT as the measurement from the first collagenous plate to the point where myelinated axons become visible.⁶ In that study, the LC beam was clearly delineated in sections at 40× magnification. In contrast, we could not directly pinpoint the location of LC beam, as in the *in vitro* study, because the LC is located on the inner surface of the optic nerve head. Thus, we applied the EDI-OCT technique to provide visualisation of the deep optic nerve head structures. EDI-OCT has a tissue resolution of 7 µm in depth, so we presumed the reflective white column to be the LC beam. There are, therefore, clear differences between *in vitro* and *in vivo* methods. However, since our results are similar to those of another previous

TABLE 5 Gender-specific central LTs in control group eyes.

Characteristic	Control group (n = 30)		p Value*
	Women (n = 14)	Men (n = 16)	
Age (years)	61.8 ± 15.3	67.5 ± 11.0	0.24
LT (µm)	341.0 ± 16.7	345.5 ± 14.7	0.69

*p Between women and men.

FIGURE 7 Relationship between central LT and age in control group eyes.

study,¹² our study provides reliable estimates for the thickness of the LC *in vivo*.

Potential limitations to the present study include the following: (i) inter-observer differences in LC measurements, including variations in identifying locations of the anterior and posterior laminar borders, even with magnified images. However, because the two examiners did not differ significantly in their LT measurements, we do not believe that inter-observer differences markedly affected our conclusions; (ii) lack of CFF measurements in control or GON group eyes and lack of comparisons to non-GON group eyes to find a correlation between LT and CFF responses. The number of demyelinating optic neuritis cases was, perhaps, small enough to affect the results; and (iii) narrow age range and small sample size of control group eyes. Both of which might have affected the correlation of central LT and age. Future studies should increase sample sizes and use a wider age range of subjects in determining results.

In conclusion, we found EDI-OCT to be a useful method for documenting structural abnormalities in ON. Further studies are needed to determine the role of OCT in detecting progression of ONs of various types.

ACKNOWLEDGEMENTS

We are grateful to Dr. Kathryn Pokorny for her careful revision of the description of this study. The study was supported by a grant from the Japan National Society for the Prevention of Blindness.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figures 1–7 are available in colour online at <http://informahealthcare.com/oph>.

REFERENCES

- [1] Jonas JB, Mardin CY, Schlötzer-Schrehardt U, Naumann GO. Morphometry of the human lamina cribrosa surface. *Invest Ophthalmol Vis Sci* 1991;32:401–405.
- [2] Downs JC, Roberts MD, Burgoyne CF. Mechanical environment of the optic nerve head in glaucoma. *Optom Vis Sci* 2008;85:425–435.
- [3] Jonas JB, Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. *Invest Ophthalmol Vis Sci* 2003;44:5189–5195.
- [4] 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.
- [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] Kotecha A, Izadi S, Jeffery G. Age-related changes in the thickness of the human lamina cribrosa. *Br J Ophthalmol* 2006;90:1531–1534.
- [7] Ren R, Wang N, Li B, Li L, Gao F, Xu X, Jonas JB. Lamina cribrosa and peripapillary sclera morphometry in normal and advanced glaucomatous Chinese eyes with various axial lengths. *Invest Ophthalmol Vis Sci* 2009;50:2175–2184.
- [8] Tezel G, Trinkaus K, Wax MB. Alterations in the morphology of lamina cribrosa pores in glaucomatous eyes. *Br J Ophthalmol* 2004;88:251–256.
- [9] Miki A, Ikuno Y, Jo Y, Nishida K. Comparison of enhanced depth imaging and high-penetration optical coherence tomography for imaging deep optic nerve head and parapapillary structures. *Clin Ophthalmol* 2013;7:1995–2001.
- [10] Park SC, Ritch R. High resolution *in vivo* imaging of the lamina cribrosa. *Saudi J Ophthalmol* 2011;25:363–372.
- [11] Park HY, Park CK. Diagnostic capability of lamina cribrosa thickness by enhanced depth imaging and factors affecting thickness in patients with glaucoma. *Ophthalmology* 2013;120:745–752.
- [12] 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.
- [13] Japanese Glaucoma Society. *Guidelines for Glaucoma. 2nd Edition*. Tokyo: Japanese Glaucoma Society; September 2006:13–15.
- [14] Anderson DR, Patella VM. *Automated Static Perimetry*. 2nd ed. St. Louis: Mosby; 1999:121–190.
- [15] Wakakura M, Minei-Higa R, Oono S, Matsui Y, Tabuchi A, Kani K, Shikishima K, Kawai K, Nakao Y, Tazawa Y, Kiyosawa M, Abe H, Ohba N, Yago K, Maeda S, Sugita M, Ishikawa S. Baseline features of idiopathic optic neuritis as determined by a multicenter treatment trial in Japan. Optic Neuritis Treatment Trial Multicenter cooperative Research Group (ONMRG). *Jpn J Ophthalmol* 1999;43:127–132.
- [16] Miyake M, Yamashiro K, Nakanishi H, Nakata I, Akagi-Kurashige Y, Tsujikawa A, Moriyama M, Ohno-Matsui K, Mochizuki M, Yamada R, Matsuda F, Yoshimura N. Association of *paired box 6* with high myopia in Japanese. *Mol Vis* 2012;18:2726–2735.
- [17] Kozaki H, Inou Y. Disease stage classification of chronic glaucoma according to visual field. *Acta Soc Ophthalmol Jpn* 1972;76:1258–1267 [in Japanese].
- [18] Kozaki H, Nakatani H, Tsukamoto N, Shimizu Y, Kinoshita S. Visual field progression patterns in glaucoma. *Jpn J Clin Ophthalmol* 1978;32:39–49 [in Japanese].
- [19] Woung LC, Wakakura M, Ishikawa S. Critical flicker frequency in acute and recovered optic neuritis. *Jpn J Ophthalmol* 1993;37:122–129.
- [20] Mason RJ, Snelgar RS, Foster DH, Heron JR, Jones RE. Abnormalities of chromatic and luminance critical flicker frequency in multiple sclerosis. *Invest Ophthalmol Vis Sci* 1982;23:246–252.
- [21] Swanson WH, Pan F, Lee BB. Chromatic temporal integration and retinal eccentricity: psychophysics, neurometric analysis and cortical pooling. *Vision Res* 2008;48:2657–2662.
- [22] Yan DB, Coloma FM, Metheetratit A, Trope GE, Heathcote JG, Ethier CR. Deformation of the lamina cribrosa by elevated intraocular pressure. *Br J Ophthalmol* 1994;78:643–648.
- [23] Jonas JB, Hayreh SS, Yong T. Thickness of the lamina cribrosa and peripapillary sclera in Rhesus monkeys with nonglaucomatous or glaucomatous optic neuropathy. *Acta Ophthalmol* 2011;89:423–427.
- [24] Jonas JB. Trans-lamina cribrosa pressure difference. *Arch Ophthalmol* 2007;125:431. doi:10.1001/archophth.125.3.431-a.

- [25] Burgoynes CF, Downs JC, Belezza 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.
- [26] El Beltagi TA, Bowd C, Boden C, Amini P, Sample PA, Zangwill LM, Weinreb RN. Retinal nerve fiber layer thickness measured with optical coherence tomography in related to visual function in glaucomatous eyes. *Ophthalmology* 2003;110:2185–2190.
- [27] Danesh-Meyer HV, Carroll SC, Foroozan R, Savino PJ, Fan J, Jiang Y, Vander Hoorn S. Relationship between retinal nerve fiber layer and visual field sensitivity as measured by optical coherence tomography in chiasmal compression. *Invest Ophthalmol Visc Sci* 2006;47:4827–4835.
- [28] Wells EF, Bernstein GM, Scott BW, Bennett PJ, Mendelson JR. Critical flicker frequency responses in visual cortex. *Exp Brain Res* 2001;139:106–110.
- [29] Costello F. The afferent visual pathway: designing a structural-functional paradigm of multiple sclerosis. *ISRN Neurol* 2013;2013:134858.
- [30] Paik DW, Lee JH, Kim JS. Age-related changes in the thickness of the lamina cribrosa measured by spectral domain OCT. *J Korean Ophthalmol Soc* 2013;54:1261–1268.
- [31] Albon J, Karwatowski WS, Avery N, Easty DL, Duance VC. Changes in the collagen matrix of the aging human lamina cribrosa. *Br J Ophthalmol* 1995;79:368–375.