Ophthalmic Research

Research Article

Ophthalmic Res 2021;64:447–457
DOI: 10.1159/000512925

Received: September 5, 2020
Accepted: November 6, 2020
Published online: November 10, 2020

Intereye Comparison of Focal Lamina Cribrosa Defect in Normal-Tension Glaucoma Patients with Asymmetric Visual Field Loss

Yunxiao Sun[a, b] Yiqin Guo[a, b] Yuan Xie[a] Kai Cao[b] Xiangxiang Liu[a, b] Yiquan Yang[a] Yan Shi[a] Sujie Fan[c] Huaizhou Wang[a] Ningli Wang[a, b]

[a]Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing, China; [b]Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China; [c]Department of Ophthalmology, The Third Hospital of Handan (Handan City Eye Hospital), Handan, China

Keywords
Normal-tension glaucoma · Asymmetric visual field loss · Intereye comparison · Focal lamina cribrosa defect · Tilt of optic disc

Abstract
Introduction: To evaluate the association of focal lamina cribrosa (LC) defect with asymmetric visual field (VF) loss in normal-tension glaucoma (NTG) through intereye comparisons. ***Methods:*** Paired eyes were divided into better and worse eyes according to the mean deviation (MD), and ocular parameters were compared between them. Furthermore, patients in the asymmetric group were classified as subgroup A (one eye with LC defect and the fellow one without), subgroup B (both eyes without LC defect), and subgroup C (both eyes with LC defect). Generalized estimation equation approach was used to evaluate the association between ocular parameters and asymmetric VF. ***Results:*** A total of 140 eyes of 70 NTG patients were included in the asymmetric group. LC defects were more common in better eyes than that in worse eyes (27/70 [38.57%] vs. 10/70 [14.29%], p = 0.001), and all eyes with LC defect had myopia. Multivariate analysis revealed that the presence of LC defect was significantly associated with better eyes in the asymmetric group (odds ratio, 0.27; p = 0.001). For subgroup A, eyes with LC defects exhibited lower peak IOP (p = 0.011) and lower mean IOP (p = 0.018) than the fellow eyes without. In addition, longer AL (p = 0.025) and larger tilt ratio (p = 0.032) were found in eyes with LC defects. For subgroup B without LC defects, larger tilt ratio was shown to be a risk factor for VF loss (odds ratio, 6.13; p = 0.001). There was no significant difference of binocular parameters except for MD (p < 0.001) in subgroup C. ***Conclusions:*** LC defects in myopia were suggested to be associated with better eyes in NTG with asymmetric VF loss. However, in patients without LC defect, larger tilt ratio was a risk factor for VF defect. There might be different pathological mechanisms in asymmetric VF loss for different NTG subtypes.

Introduction

Normal-tension glaucoma (NTG) is a progressive optic neuropathy characterized by glaucomatous optic disc changes and corresponding visual field (VF) defect, with consistent normal range of intraocular pressure (IOP) [1]. Some other non-IOP-related mechanisms including

Yunxiao Sun and Yiqin Guo contributed equally to the work and should be regarded as co-first authors.

karger@karger.com
www.karger.com/ore

Ningli Wang
Beijing Institute of Ophthalmology, Capital Medical University, Beijing Tongren Hospital
Dongcheng District, 1 Dongjiaominxiang Street
Beijing 100730 (China)
wningli@vip.163.com

low BMI, increased transoptic nerve pressure gradient, vascular dysregulation, and other systemic factor abnormalities have been reported to be related to the pathogenesis of NTG [2–6]. Therefore, it is important to understand the difference of binocular parameters in NTG patients with asymmetric VF defect, which will eliminate the systemic confounding factors in intereye comparison. Binocular parameter difference might account for the severity of the VF defect and the following rapid aggravation of the optic nerve damage.

Lamina cribrosa (LC) of the optic nerve head (ONH) is considered as a principal site of initial retinal ganglion cell axonal injury in the pathogenesis of glaucoma [7, 8]. The biomechanical stress in the site might be influenced by the level of IOP [9]. Reducing IOP by 30% has been considered as an effective way to control the progression for some NTG patients by the Normal-Tension Glaucoma Trial Group [10]. In addition to IOP, some other ocular parameters do play a role in glaucomatous optic nerve damage. Myopic optic disc changes could affect the pathogenesis of glaucoma, whereas the exact effect remains unclear [11–13]. A recent evidence-based review provided a more accurate illustration that myopia might be involved in the development of glaucoma, but not for its progression [14]. Meanwhile, a study found that LC defects were more common in glaucoma with myopia [15]. Further, the location of LC defect corresponding spatially to the location of VF loss was confirmed [16, 17]. Nevertheless, in a study of Japanese primary open-angle glaucoma patients with myopia, LC defects were proved to be associated with nonprogressive glaucomatous VF defect [16]. It would account for why myopia was not related to the progression of glaucoma. LC defects might play a role through some unclear mechanism.

Therefore, NTG patients with asymmetric VF loss were enrolled in the current study to investigate the role of LC defects in the pathogenesis of glaucoma through intereye comparisons. Moreover, in order to better clarify the mechanism of binocular asymmetry in the case of presence of LC defects or not, patients were divided into subgroups for further analysis.

Materials and Methods

This cross-sectional study was approved by the Institutional Review and Ethics Committee of the Beijing Tongren Hospital and performed according to the Declaration of Helsinki. All participants signed a written informed consent. The study had been registered at http://www.chictr.org.cn (Study No. ChiCTR1900021465).

Patients diagnosed as NTG by 2 experienced glaucoma experts in Beijing Tongren Hospital, Beijing, China, were reviewed. The diagnostic criteria of NTG were as follows: (1) typical glaucomatous optic nerve change (i.e., neuroretinal rim thinning, retinal nerve fiber layer [RNFL] defect, or disc hemorrhage), corresponding to repeatable (≥2 consecutive) and reliable (fixation loss <20% and false-negative and false-positive rates <15%) glaucomatous VF defects; (2) an open angle on gonioscopy; (3) untreated IOP (peak IOP in 24-h monitoring and all recorded IOP) was no more than 21 mm Hg; and (4) neuroradiologic and general medical examinations did not reveal any pathological findings leading to optic nerve damage or VF defect except for glaucoma. NTG patients were classified into symmetric and asymmetric groups by mean deviation (MD) difference of binocular VF. An MD difference less than 3 dB was defined as the symmetric group, while the difference of at least 3 dB was defined as the asymmetric group. The cutoff value was considered according to the long-term fluctuation of the VF in stable glaucoma [18]. The asymmetry had to be consistent in the following at least 2 subsequent VF examinations. Paired eyes in NTG patients were divided into worse and better eyes according to the MD, and ocular parameters were compared between them. Furthermore, patients in the asymmetric group were divided into subgroup A (one eye with LC defect and the fellow one without), subgroup B (both eyes without LC defect), and subgroup C (both eyes with LC defect).

Exclusion criteria were as follows: (1) possibility of secondary glaucoma; (2) a history or findings of any other ocular or systemic diseases that could affect the VF, such as ocular trauma, congenital optic disc abnormalities, ischemic optic neuropathy, and compressive optic neuropathy; (3) antiglaucoma medications used for more than a month, or the duration and type of medications were different in both eyes before diagnosis; (4) asymmetric grade of cataract between the eyes; (5) eyes with previous laser treatment, antiglaucoma, or other ocular surgery (except strabismus surgery and cataract surgery in both eyes); (6) best-corrected visual acuity (BCVA) worse than 20/40; (7) high myopia (axial length [AL] ≥28 mm), or eyes with sign of myopic macular changes, including lacquer cracks, patchy chorioretinal atrophy, or choroidal neovascularization; and (8) poor-quality OCT images which cannot distinguish optic nerve structure because of irregular tear film, media opacity, or poor patient cooperation.

Demographics and Systemic Measurements

Basic parameters collected included age, sex, BMI, waist, hip, and waist-hip ratio. BMI was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure was measured using a standardized mercury sphygmomanometer at least 5 min after the subject sat down. Mean arterial blood pressure was calculated as 1/3 × systolic blood pressure + 2/3 × diastolic blood pressure.

Basic Ophthalmologic Examination

All subjects underwent comprehensive ophthalmic assessments including measurement of the spherical equivalent (SE) refractive error, BCVA (logMAR units), central corneal thickness, and AL measurement (Lenstar LS900; Haag-Streit Koeniz, Switzerland), slit-lamp examination, gonioscopy, fundus examination, and fundus color stereo photography (Nonmyd WX 3D; Kowa Co. Ltd., Japan). A Humphrey Field Analyzer II 750 (Carl Zeiss Meditec, Dublin, CA, USA) was used for VF examinations, with the

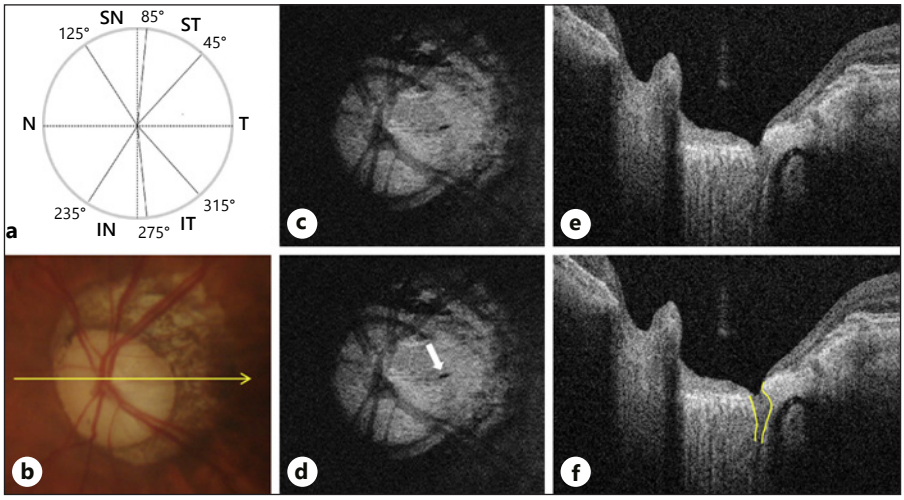

Fig. 1. Representative LC defect in SS-OCT. **a** Schematic diagram of 6 ONH sectors (ST, superotemporal; SN, superonasal; N, nasal; IN, inferonasal; IT, inferotemporal; and T, temporal). **b** Yellow arrow in the fundus image shows the scan line of SS-OCT. **c** En face images of the optic disc at level of LC as reconstructed from the 3D SS-OCT data set. **d** White arrow in en face images points to the focal LC defect. **e** B-scan image corresponding to LC defect from the SS-OCT. **f** Outline of LC defect is indicated by the yellow line. LC, lamina cribrosa; SS-OCT, swept-source optical coherence tomography; ONH, optic nerve head.

Swedish interactive threshold algorithm fast strategy. At least 2 continuous qualified VF tests were performed to confirm the asymmetric glaucomatous VF loss.

24-h IOP Measurements

All of the untreated subjects newly diagnosed were hospitalized to perform 24-h IOP measurements. For glaucoma suspects without 24-h IOP measurements but treated with IOP-lowering medications in both eyes simultaneous in other hospitals for the safety reasons, 24-h IOP would be measured after discontinuing the drugs for 4 weeks referring to a previous study [10], which would be conducive to the further diagnosis by glaucoma experts in our hospital. The procedure began at 10:00 a.m. after adapting to the hospital environment. The following IOP measurements taken in the sitting position were performed every 2 h for the next 24 h by the same trained nurse using a Goldmann applanation tonometer. Then, the peak IOP, mean IOP, and IOP fluctuation were calculated for further analysis.

SS-OCT Imaging

SS-OCT device (DRI-OCT; Topcon, Tokyo, Japan) was used to image the ONH in 3D scan mode. Poor-quality images (quality score <50) caused by media opacity or fixation loss and poor visibility of the LC (<80% visibility of the anterior laminar surface within the ONH area) were excluded for further analysis. A focal LC defect was defined as a laminar hole or laminar disinsertion violating the normal U- or W-shaped contour of the anterior laminar surface based on previous reports [17, 19–21], which need to be present in at least 2 neighboring scans to avoid false positives and at least 100 μm in diameter, >30 μm in depth. The circumferential location of LC defects was classified into 6 ONH sectors: superotemporal (45°–85°), superonasal (85°–125°), nasal (125°–235°), inferonasal (235°–275°), inferotemporal (275°–315°), and temporal (315°–45°). Spacial consistency was assessed between LC defect and neuroretinal rim abnormalities according to the circumpapillary RNFL thickness graph.

A schematic diagram of 6 ONH sectors and a representative LC defect in SS-OCT is shown in Figure 1. The evaluation of the LC defect was performed by 2 observers separately (Y.X.S. and Y.Q.G.), who were masked to all patient clinical data. Disagreements between them were resolved by consensus.

Measurement of ONH Parameters

Color fundus photographs were evaluated for tilt ratio with Image J software (version 1.52; National Institutes of Health, Bethesda, MD, USA). The tilt ratio was defined as the ratio between the longest and shortest diameters of the optic disc in a previous study [22, 23]. The measurements of the tilt ratio were calculated by 2 observers separately (Y.X.S and Y.Q.G), who were masked to all patient clinical data.

Statistical Analysis

All statistical analyses were performed with SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA). The Shapiro-Wilk W test was used to check for normal distribution of data, and the Levene test was used to examine homogeneity of the variance. Data were presented as mean values ±standard deviation. Independent samples *t* test or Mann-Whitney U test was performed to compare the parameters between symmetric and asymmetric groups depending on the normality of data distribution. One-way analysis of variance was performed to compare the difference among subgroups A, B, and C. χ^2 test was used to compare categorical data between the groups. Comparison of binocular parameters was assessed by the paired *t* test or Wilcoxon signed-ranks test, depending on the normality of data distribution. Related-samples McNemar's test was used to compare categorical data. Factors associated with asymmetric VF defect were assessed by the generalized estimation equation approach with the model of binary logistic regression for the reason to account for using 2 eyes from the same subject. A p value <0.05 was considered statistically significant. Two independent observers (Y.X.S. and Y.Q.G.) assessed interobserver reproducibility of the tilt ratio measurement and calculated corresponding intraclass correlation coefficients (ICCs) and confidence intervals (CIs). Interobserver agreement of the presence or absence of LC defects was assessed using kappa statistics.

Table 1. Demographics and systemic measurements in symmetric and asymmetric groups

	Symmetric group	Asymmetric group	*p* value	Subgroup A	Subgroup B	Subgroup C	*p* value
n	23	70	–	25	39	6	–
Age	50.96±14.05	52.86±14.25	0.579†	50.40±11.85	54.23±15.88	53.00±13.48	0.584¶
Sex (male/female)	11/12	36/34	0.764‡	18/7	14/25	4/2	**0.012**‡
BMI, kg/m^2	22.59±2.95	23.49±3.76	0.299§	24.12±5.19	23.12±2.80	23.31±2.07	0.596¶
Waist, cm	84.61±9.86	85.48±8.46	0.714†	86.71±8.15	84.48±8.82	86.50±8.21	0.621¶
Hip, cm	98.21±6.57	99.68±5.66	0.354†	100.21±5.21	99.16±5.76	100.58±7.34	0.745¶
Waist-hip ratio	0.86±0.06	0.86±0.06	0.877†	0.86±0.05	0.85±0.07	0.86±0.03	0.684¶
Arterial blood pressure, mm Hg							
Systolic	116.75±15.57	117.92±12.20	0.811§	117.12±10.37	117.93±13.02	121.17±15.54	0.772¶
Diastolic	74.83±9.14	75.04±10.04	0.976§	77.28±9.16	72.55±9.65	81.08±12.71	0.056¶
Mean arterial pressure	88.80±10.67	89.34±9.82	0.933§	90.56±8.93	87.68±9.65	94.44±13.48	0.219¶

Bold values indicate a statistically significant difference ($p < 0.05$). † *p* value between groups was calculated by the independent samples *t* test. ‡ *p* value between groups was calculated by the χ^2 test. § *p* value between groups was calculated by the Mann-Whitney U test. ¶ *p* value among groups was calculated by one-way ANOVA.

Results

Patient Characteristics

From 240 eyes of 120 subjects, 27 eyes of 27 subjects were excluded for the following reasons: AL ≥28 mm ($n = 4$), fundus diseases that might affect VF ($n = 3$), antiglaucoma surgery ($n = 5$), myopic refractive surgery ($n = 5$), unreliable VF test results ($n = 4$), and poor-quality OCT images ($n = 6$). Finally, a total of 186 eyes from 93 NTG patients (23 in the symmetric group and 70 in the asymmetric group) were enrolled in the analysis. Eighty-nine untreated cases (89/93, 95.70%) were newly diagnosed, and 4 cases (4/93, 4.30%) were rediagnosed according to 24-h IOP measurements after a 4-week wash out of medication. All of the included subjects were native Han Chinese. The demographics and systemic measurements in different groups are summarized in Table 1. There was no statistically significant difference in age, sex, BMI, waist-hip ratio, and blood pressure between the symmetric and asymmetric groups. For subgroup analysis, there were 25 patients in subgroup A, 39 patients in subgroup B, and 6 patients in subgroup C.

The ICC value (95% CI) for interobserver reproducibility of the tilt ratio was 0.858 (0.79–0.91). The interobserver agreement values for the presence or absence of LC defect were excellent (k = 0.904).

Ophthalmologic Data

Comparison of ocular parameters between better and worse eyes is summarized in Table 2. There was no significant difference of binocular parameters except for MD ($p < 0.001$) in the symmetric group. In intereye comparison for the asymmetric group, MD ($p < 0.001$), BCVA ($p = 0.025$), and mean untreated 24-h IOP ($p = 0.048$) were significantly different. LC defects were more common in better eyes than that in worse eyes (27/70 [38.57%] vs. 10/70 [14.29%], $p = 0.001$). The incidence of myopia in the asymmetric group was 86.43% (121/140), and all eyes with LC defect had myopia. A total of 41 LC defects were found in the asymmetric group, 68.29% (28/41) of the LC defects were in the temporal sector, and the location of that corresponded spatially to RNFL defect well (32/41, 78.05%). The results in multivariate analysis showed that the presence of LC defect was significantly associated with better eyes in the asymmetric group (odds ratio [OR], 0.27; 95% CI: 0.13–0.58; $p = 0.001$, Table 3).

Inconsistent results were presented according to the subgroups (Table 4). For subgroup A, MD ($p < 0.001$) and mean untreated 24-h IOP ($p = 0.034$) were significantly different factors. LC defects were also common in better eyes (21/25 [84.00%] vs. 4/24 [16.00%], $p = 0.001$). For subgroup B without LC defect, MD ($p < 0.001$), SE ($p = 0.046$), AL ($p = 0.010$), and tilt ratio ($p = 0.001$) were significantly different between the paired eyes. There was no significant difference of binocular parameters except for MD ($p < 0.001$) in subgroup C.

In multivariate analysis for factors associating with binocular asymmetry in subgroups (Table 5), the presence of LC defect (OR, 0.04; 95% CI: 0.00–0.30; $p = 0.002$) was also significantly associated with better eyes in subgroup A. However, in subgroup B without LC defects,

Table 2. Comparison of ocular parameters between better and worse eyes in symmetric and asymmetric groups

	Symmetric group (N = 23)			Asymmetric group (N = 70)		
	better eye	worse eye	p value	better eye	worse eye	p value
MD, dB	−7.10±9.09	−8.79±9.36	**<0.001**[†]	−6.79±6.91	−12.93±7.90	**<0.001**[†]
BCVA, logMAR units	0.04±0.09	0.06±0.10	0.599[†]	0.04±0.09	0.07±0.11	**0.025**[†]
SE, D	−4.72±3.19	−4.68±3.07	0.894[‡]	−4.42±3.78	−4.55±3.69	0.408[‡]
Eyes with myopia, N (%)	20 (86.95)	19 (82.61)	1.000[§]	59 (84.29)	62 (88.57)	0.375[§]
AL, mm	25.82±1.77	25.67±1.62	0.245[‡]	25.71±1.90	25.87±1.79	0.198[‡]
Tilt ratio	1.22±0.12	1.24±0.12	0.433[‡]	1.22±0.15	1.24±0.16	0.188[‡]
CCT, μm	535.17±23.44	533.83±22.01	0.242[‡]	525.80±25.87	525.61±26.14	0.813[‡]
IOP, mm Hg						
Peak IOP	16.58±2.52	17.00±2.77	0.336[‡]	17.14±2.21	17.51±2.37	0.111[‡]
Mean IOP	13.79±1.82	14.23±2.00	0.148[‡]	14.67±1.87	14.95±1.87	**0.048**[‡]
IOP fluctuation	4.85±1.90	5.05±2.40	0.607[‡]	4.88±1.72	5.00±1.92	0.547[‡]
Eyes with disc hemorrhage, N (%)	1 (4.35)	0 (0.00)	1.000[§]	6 (8.57)	2 (2.86)	0.289[§]
Eyes with LC defects, N (%)	5 (21.74)	4 (17.39)	1.000[§]	27 (38.57)	10 (14.29)	**0.001**[§]
Myopia in eyes with LC defects, N (%)	5 (100)	3 (75.00)	–	27 (100)	10 (100)	–
LC defects, N	6	6	–	31	10	–
Temporal sector, N (%)	5 (83.33)	4 (66.67)	–	23 (74.19)	5 (50.00)	–
Inferotemporal + superotemporal sector, N (%)	1 (16.67)	2 (33.33)	–	8 (25.81)	5 (50.00)	–
LC defect corresponding to RNFLD, N (%)	4 (66.67)	5 (83.33)	–	22 (70.97)	10 (100)	–

Bold values indicate a statistically significant difference ($p < 0.05$). MD, mean deviation; SE, spherical equivalent; BCVA, best-corrected visual acuity; AL, axial length; CCT, central corneal thickness; IOP, intraocular pressure; LC, lamina cribrosa. [†] p value between groups was calculated by the Wilcoxon signed-ranks test. [‡] p value between groups was calculated by the paired t test. [§] p value between groups was calculated by the related-samples McNemar's test.

Table 3. Factors associating with better eyes in the binocular asymmetry group

Factors	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	p value	odds ratio	95% CI	p value
SE, D	0.99	0.97–1.01	0.404			
AL, mm	1.05	0.98–1.12	0.205			
Tilt ratio	1.36	0.72–2.58	0.346			
CCT, μm	1.00	0.99–1.00	0.810			
IOP, mm Hg						
Peak IOP	1.07	0.99–1.17	0.091	1.02	0.80–1.32	0.852
Mean IOP	1.08	0.99–1.17	0.084	1.02	0.76–1.37	0.889
IOP fluctuation	1.04	0.92–1.17	0.542			
Presence of disc hemorrhage	0.31	0.06–1.67	0.175			
Presence of LC defect	0.27	0.13–0.56	**0.001**	0.27	0.13–0.58	**0.001**

Bold values indicate a statistically significant difference ($p < 0.05$). SE, spherical equivalent; AL, axial length; CCT, central corneal thickness; IOP, intraocular pressure; LC, lamina cribrosa.

larger tilt ratio (OR, 6.13; 95% CI: 2.01–18.68; $p = 0.001$) was a risk factor for VF loss.

To evaluate the role of LC defect in the binocular asymmetry group, eyes in subgroup A were divided into eyes with or without LC defect (Table 6). The eyes with LC defect exhibited significantly better MD ($p = 0.006$), lower peak IOP ($p = 0.011$), and lower mean IOP ($p = 0.018$), but longer AL ($p = 0.025$) and larger tilt ratio ($p =$

Ophthalmic Res 2021;64:447–457
DOI: 10.1159/000512925

Table 4. Comparison of ocular parameters in subgroups with binocular asymmetry eyes

	Subgroup A ($N = 25$)			Subgroup B ($N = 39$)			Subgroup C ($N = 6$)		
	better eye	worse eye	*p* value	better eye	worse eye	*p* value	better eye	worse eye	*p* value
MD, dB	−6.21±6.02	−12.69±7.50	**<0.001**[†]	−7.02±7.29	−12.82±7.86	**<0.001**[†]	−7.64±8.84	−14.67±10.81	**0.022**[‡]
BCVA, logMAR units	0.04±0.09	0.07±0.11	0.260[†]	0.05±0.09	0.07±0.11	0.108[†]	0.00±0.06	0.04±0.11	0.363[‡]
SE, D	−5.55±3.57	−5.20±3.28	0.188[‡]	−3.69±3.91	−4.11±4.02	**0.046**[‡]	−4.75±3.44	−5.03±3.50	0.315[‡]
AL, mm	26.15±1.90	26.12±1.60	0.919[‡]	25.46±1.92	25.72±1.91	**0.010**[‡]	25.53±1.78	25.74±1.86	0.255[‡]
Eyes with myopia, *N* (%)	24 (96.00)	25 (100)	1.000[§]	29 (74.36)	31 (79.49)	0.625[§]	6 (100)	6 (100)	1.000[§]
Tilt ratio	1.26±0.16	1.22±0.17	0.131[‡]	1.18±0.13	1.24±0.16	**<0.001**[†]	1.26±0.07	1.36±0.13	0.059[‡]
CCT, μm	524.56±23.66	524.44±24.55	0.906[‡]	525.26±25.86	525.46±25.89	0.858[‡]	534.50±37.01	531.50±37.36	0.439[‡]
IOP, mm Hg									
Peak IOP	17.03±2.05	17.65±2.39	0.104[‡]	17.25±2.26	17.53±2.41	0.392[‡]	16.85±2.90	16.77±2.30	0.914[‡]
Mean IOP	14.69±1.52	15.21±1.69	**0.034**[‡]	14.76±2.06	14.92±1.93	0.424[‡]	14.01±2.07	14.10±2.25	0.807[‡]
IOP fluctuation	4.76±1.85	4.75±2.01	0.973[‡]	4.88±1.73	5.07±1.93	0.486[‡]	5.40±1.06	5.67±1.51	0.742[‡]
Eyes with disc hemorrhage, *N* (%)	2 (8.00)	1 (4.00)	1.000[§]	3 (7.69)	1 (2.56)	0.625[§]	1 (16.67)	0 (0.00)	1.000[§]
Eyes with LC defects, *N* (%)	21 (84.00)	4 (16.00)	**0.001**[§]	–	–	–	6 (100)	6 (100)	1.000[§]
Myopia in eyes with LC defects, *N* (%)	21 (100)	4 (100)	–				6 (100)	6 (100)	–
LC defects, *N*	22	4	–	–	–	–	9	6	–
Temporal sector, *N* (%)	18 (81.82)	2 (50.00)	–	–	–	–	5 (55.56)	3 (50.00)	–
Inferotemporal + superotemporal sector, *N* (%)	4 (18.18)	2 (50.00)	–	–	–	–	4 (44.44)	3 (50.00)	–
LC defect corresponding to RNFLD, *N* (%)	16 (72.73)	4 (100)	–	–	–	–	6 (66.67)	6 (100)	–

Bold values indicate a statistically significant difference ($p < 0.05$). LC, lamina cribrosa; MD, mean deviation; BCVA, best-corrected visual acuity; SE, spherical equivalent; AL, axial length; CCT, central corneal thickness; IOP, intraocular pressure. [†] *p* value between groups was calculated by the Wilcoxon signed-ranks test. [‡] *p* value between groups was calculated by the paired *t* test. [§] *p* value between groups was calculated by the related-samples McNemar's test.

Table 5. Factors associating with binocular asymmetry in subgroups

Factors	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Subgroup A						
SE, D	1.03	0.98–1.08	0.207			
AL, mm	0.99	0.82–1.19	0.916			
Tilt ratio	0.56	0.15–2.12	0.390			
CCT, μm	1.00	0.99–1.00	0.903			
IOP, mm Hg						
Peak IOP	1.14	0.99–1.31	0.073	0.77	0.55–1.07	0.118
Mean IOP	1.20	0.99–1.46	0.059	1.49	0.99–2.24	0.057
IOP fluctuation	1.00	0.83–1.20	0.972			
Presence of disc hemorrhage	0.48	0.04–6.06	0.570			
Presence of LC defect	0.04	0.00–0.31	**0.002**	0.04	0.00–0.30	**0.002**
Subgroup B						
SE, D	0.97	0.95–1.00	**0.048**	1.01	0.97–1.06	0.513
AL,mm	1.08	1.01–1.15	**0.033**	0.92	0.81–1.05	0.237
Tilt ratio	4.67	1.88–11.56	**0.001**	6.13	2.01–18.68	**0.001**
CCT, μm	1.00	0.99–1.00	0.855			
IOP, mm Hg						
Peak IOP	1.05	0.94–1.18	0.365			
Mean IOP	1.04	0.94–1.15	0.426			
IOP fluctuation	1.06	0.91–1.23	0.482			
Eyes with disc hemorrhage, *N* (%)	0.32	0.30–3.33	0.338			

Bold values indicate a statistically significant difference ($p < 0.05$). SE, spherical equivalent; LC, lamina cribrosa; AL, axial length; CCT, central corneal thickness; IOP, intraocular pressure.

Table 6. Comparison of ocular parameters in subgroup A with or without LC defect

	Eyes with LC defect (*N* = 25)	Fellow eyes without LC defect (*N* = 25)	*p* value
MD, dB	−7.31±5.94	−11.59±8.34	**0.004**[†]
BCVA, logMAR units	0.05±0.09	0.07±0.11	0.594[†]
SE, D	−5.62±3.44	−5.13±3.41	0.060[‡]
Eyes with myopia, *N* (%)	21 (84)	19 (36)	0.500[§]
AL, mm	26.44±1.64	25.83±1.81	**0.025**[‡]
Tilt ratio	1.27±0.16	1.21±0.17	**0.032**[‡]
CCT, μm	525.32±23.71	523.68±24.46	0.097[‡]
IOP, mm Hg			
Peak IOP	16.88±2.01	17.81±2.37	**0.011**[‡]
Mean IOP	14.67±1.46	15.24±1.74	**0.018**[‡]
IOP fluctuation	4.45±2.00	5.05±1.80	0.070[‡]
Eyes with disc hemorrhage, *N* (%)	2 (8.00)	1 (4.00)	1.000[§]
Better eyes, *N* (%)	21 (84.00)	4 (16.00)	**0.001**[§]

Bold values indicate a statistically significant difference ($p < 0.05$). MD, mean deviation; BCVA, best-corrected visual acuity; AL, axial length; SE, spherical equivalent; CCT, central corneal thickness; IOP, intraocular pressure; LC, lamina cribrosa. [†] *p* value between groups was calculated by the Wilcoxon signed-ranks test. [‡] *p* value between groups was calculated by the paired *t* test. [§] *p* value between groups was calculated by the related-samples McNemar's test.

0.032) compared to the contralateral eye. Better eyes were observed commonly in eyes with LC defects (21/25 [84.00%] vs. 4/25 [16.00%], $p = 0.001$).

Discussion

This study was conducted to estimate the influence of LC defect on NTG with asymmetric VF defect by intereye comparisons, which could minimize the effects of other systemic factors among individuals. Our data demonstrated that the presence of LC defect in myopia was significantly associated with better VF loss. However, in patients without LC defect, eyes with larger tilt ratio from myopia deformation were associated with more severe VF loss. Therefore, there might be different pathological mechanisms in asymmetric VF loss according to whether there are LC defects.

The association of focal LC defects with corresponding neuroretinal rim thinning and VF loss was proved in a previous study [17, 20, 21, 24]. While its influence on the progression of glaucoma remains controversial [16, 19, 25, 26], some studies reported that LC defects were strongly associated with glaucomatous VF progression [19, 27]. They proposed that once a localized area of the LC is damaged and deformed, that area with the focal LC defect and its adjacent areas may become more vulnerable to glaucomatous damage inviting a vicious cycle, leading to progressive RGC and VF loss [19]. Besides, a recent longitudinal cohort study found that the glaucoma progression just corresponded topographically to the LC defect [25]. However, a study which enrolled POAG patients in Japanese population reported that specific LC defects were suggested to be associated with nonprogressive glaucomatous VF defect [16]. This result was consistent with the findings of our study. LC defects in myopia were observed more common in better eyes.

To the best of our knowledge, this is the first study to report the influence of LC defects on the asymmetric VF loss in paired-eye comparisons. However, since the current study is not a longitudinal prospective study, the causal relationship between LC defects and better VF loss is conjectured. Especially, we cannot compare the ocular parameters before and after the presence of LC defect.

In the current study, LC defects were more common in better eyes than those in worse eyes. In addition, significantly lower peak IOP and lower mean 24-h IOP were observed in eyes with LC defect than that of the fellow eyes without LC defects, which was consistent with some other previous studies that eyes with a focal LC defect had lower baseline untreated IOP [28–30]. The LC defect in better eyes seemed more likely to be related with myopia itself rather than glaucoma, since all eyes with LC defect had myopia and exhibited some typical myopia deformation including longer AL and larger tilt ratio. Meanwhile, disc tilt has been found to be related to the presence of LC defects in myopic eyes [15, 28, 31]. These findings let us hypothesize the possible process that caused better VF in eyes with LC defect. LC defects were formed with stretching of the optic disc by axial elongation and optic disc tilt of the aggravating myopic eyeball, which might influence the pressure difference between vitreous cavity and subarachnoid space by the means of fluids' slow diffusion but not the direct communication, then releasing the pressure in the eyeball. That process might rebalance the higher trans-LC pressure gradient, which was supposed to be one of the recognized risk factors for NTG [32]. The possibility of fluids' diffusion between cerebrospinal fluid and vitreous has been discussed previously. Studies of the optic disc pit associated with serous retinal detachment have proposed that the formation of subretinal fluid appears to be caused by slow diffusion of vitreous and/or cerebrospinal fluid [33]. In addition, intracranial migration of silicone oil was found in some clinical cases after intraocular silicone oil endotamponade because of the congenital ONH anatomical abnormalities [34–36]. Intermediary tissue of Kuhnt lying in the prelaminar region was considered as a barrier preventing fluid communication between vitreous cavity and subarachnoid space [37]. Therefore, we speculated that focal LC defect accompanied with Kuhnt tissue injury might be responsible for the fluid diffusion. However, further electron microscopic studies are still needed to confirm this.

Previous studies found that LC defects were located in the inferotemporal or superotemporal sector in glaucoma with low myopia (SE >−2.0 D or AL <25 mm) [21, 25, 38]. But in the current study, the location of LC defects in better eyes was common in the temperal sector rather than in the inferotemporal or superotemporal sector (74.19:25.81%), which might further confirm that the formation of LC defect was associated with increased optic disc tilt due to myopia, but not just caused by glaucoma. In addition, the mean IOP was lower in better eyes than that in worse eyes. Therefore, the better eyes in the asymmetric group might be a mixture of glaucoma and myopia, which might contribute to the lower IOP than the fellow eyes.

Myopia is mentioned as one of the risk factors for the development of glaucoma [23, 39]. It influences axonal injury through the deformation of the optic disc [40]. In subgroup B eyes without LC defects, tilt ratio presented

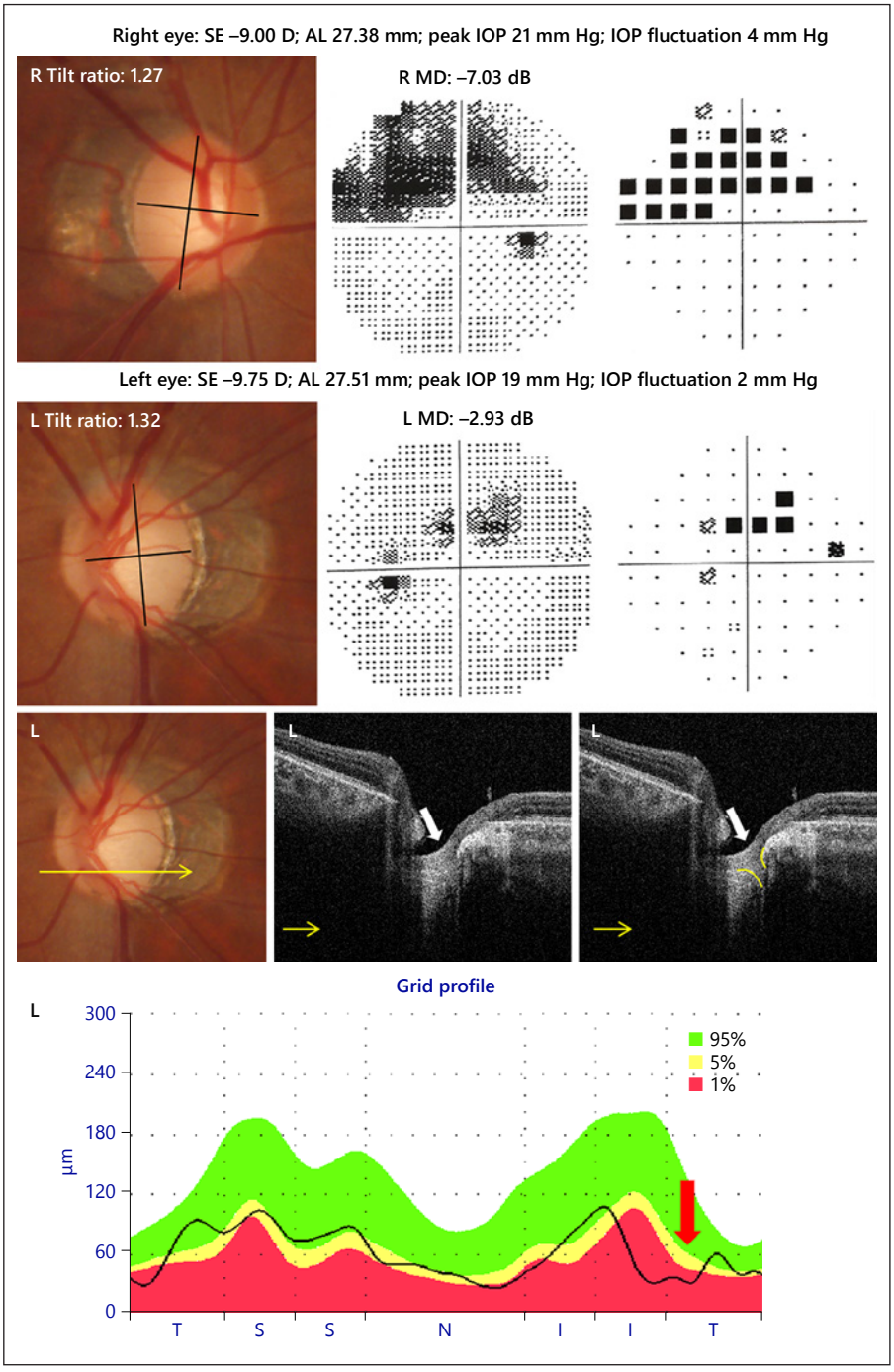

Fig. 2. A representative case of an NTG patient with asymmetric VF loss: a 44-year-old male; the left eye with LC defect exhibiting better glaucomatous VF loss even with tilted optic disc. Yellow arrow in the fundus image (third row) shows the scan line of SS-OCT. White arrow in the B-scan SS-OCT image (third row) points to the focal LC defect (yellow lines trace the LC defect surface) at the temporal-inferior region of the optic disc. RNFL thickness (bottom row) shows the corresponding thinning (red arrow). NTG, normal-tension glaucoma; VF, visual field; LC, lamina cribrosa; SS-OCT, swept-source optical coherence tomography; RNFL, retinal nerve fiber layer; MD, mean deviation; SE, spherical equivalent; AL, axial length; IOP, intraocular pressure.

myopic deformation was proved to be associated with the worse VF loss eyes. The tilting of the optic disc might occur in the development of myopia, and these changes could make eyes susceptible to the glaucomatous stress leading to the characteristic loss of axons. Therefore, we hypothesized that myopic deformation of the optic disc was one of risk factors for VF loss in NTG patients.

Therefore, we propose that optic disc tilt might play a different role in subgroup A and subgroup B, which was related to whether the tilt could cause LC defects. LC defects caused by larger tilt ratio might be involved in the development of glaucoma, but not for its progression, according to the condition of myopia. The LC defect in myopia leads to the corresponding VF loss, but the scope of VF loss would

be fixed because of the cessation of LC defect enlargement after the cessation of myopia progression. When the tilt of the optic disc was not larger enough to make a LC defect, it would only increase the susceptibility of the optic disc to glaucomatous stress then leading to progressive glaucomatous VF loss. However, the above hypothesis needs to be confirmed by further prospective studies.

A representative case of NTG with asymmetric VF loss is shown in Figure 2. The left eye with LC defect exhibiting better glaucomatous VF loss had greater SE, longer AL, and larger tilt ratio but lower peak IOP and lower IOP fluctuation than the fellow eye without. This was a typical case to explain that LC defect in myopia was a potential protective factor for VF loss, even in combination with a risk factor of larger tilt ratio.

Several limitations of this study should be mentioned. Firstly, asymmetric NTG was defined as an MD difference of at least 3 dB in the present study. The definition of asymmetric VF loss was inconsistent in previous articles with an MD difference from 0.01 to 6 dB [40, 41]. The greater the difference of MD, the more the reliable risk factors can be found. So, due to the limited MD difference in our study, we may not find out some other possible influencing factors. Secondly, 86.43% (121/140) of the eyes in the asymmetry group were myopia. Therefore, the current study results may be more applicable to NTG patients with myopia. For those without myopia, the pathogenesis of asymmetric VF loss needs further study. Thirdly, the current study included 6 patients with LC defects in both eyes. But, no significant difference of binocular parameters was found, which may be due to the lower number of cases or the particularity of the binocular LC defects. Similar patients still need to be collected in order to do the further analysis. Fourthly, this is not a longitudinal study; thus, we are unable to verify whether the related factors play a similar role in disease progression. Further VF progression evaluation may provide us with deeper insight into the cause-effect relationship between ocular parameters and VF damage asymmetry. Finally, only native Han Chinese patients were included in this study; therefore, the current results may not be able to infer the population of other races.

In conclusion, the present study showed that LC defect in myopia was significantly associated with better eyes in NTG with asymmetric VF loss. However, in patients without LC defect, larger tilt ratio caused by myopia deformation was a significant risk factor for VF loss. LC defect may be a protective factor for VF loss in NTG patients with myopia, even in combination with a risk factor of larger tilt ratio. Different types of myopia deformation of the optic disc may play different roles in the pathological mechanisms of asymmetric VF loss. These findings suggest that risk factors to asymmetric VF loss should be assessed in different subgroups. Longitudinal studies are needed to determine the association between influence factors and progression of VF defect.

Acknowledgements

The authors thank the participants of the present study for their contribution: the Beijing iCOP study group. Professor Ningli Wang is the Principal Investigator of the iCOP study group.

Statement of Ethics

Subjects have given their written informed consent, and that the study protocol was approved by the Ethics Committee of the Beijing Tongren Hospital (Reference No. TRECKY2019-023). And, the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest.

Funding Sources

The study was funded by the National Natural Science Foundation of China (GZR-2012-009).

Author Contributions

Conception and design: Ningli Wang and the Beijing iCOP study group; data analysis: Yunxiao Sun, Yiqin Guo, and Kai cao; drafting the article: Yunxiao Sun and Yiqin Guo; revising the article: Ningli Wang; acquisition of data: Yunxiao Sun, Yiqin Guo, Yuan Xie, Xiangxiang Liu, Yiquan Yang, Yan Shi, Sujie Fan, and Huaizhou Wang.

References

1 Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014 May;311(18):1901–11.
2 Pasquale LR, Willett WC, Rosner BA, Kang JH. Anthropometric measures and their relation to incident primary open-angle glaucoma. Ophthalmology. 2010 Aug;117(8):1521–9.
3 Ren R, Jonas JB, Tian G, Zhen Y, Ma K, Li S, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology. 2010 Feb;117(2):259–66.

4 Kaiser HJ, Flammer J. Systemic hypotension: a risk factor for glaucomatous damage? Ophthalmologica. 1991;203(3):105–8.
5 Flammer J, Konieczka K. The discovery of the Flammer syndrome: a historical and personal perspective. EPMA J. 2017 Jun;8(2):75–97.
6 Vajaranant TS, Ray RM, Pasquale LR, Mares JA, Ritch R, Gower EW, et al. Racial differences in the effects of hormone therapy on incident open-angle glaucoma in a randomized trial. Am J Ophthalmol. 2018 Nov;195:110–20.
7 Levy NS, Crapps EE. Displacement of optic nerve head in response to short-term intraocular pressure elevation in human eyes. Arch Ophthalmol. 1984 May;102(5):782–6.
8 Yan DB, Coloma FM, Metheetrairut A, Trope GE, Heathcote JG, Ethier CR, et al. Deformation of the lamina cribrosa by elevated intraocular pressure. Br J Ophthalmol. 1994 Aug;78(8):643–8.
9 Sigal IA, Grimm JL, Jan NJ, Reid K, Minckler DS, Brown DJ, et al. Eye-specific IOP-induced displacements and deformations of human lamina cribrosa. Invest Ophthalmol Vis Sci. 2014 Jan 2;55(1):1–15.
10 Alward W, Feldman F, Cashwell L, Wilensky JT. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998 Oct;126(4):498–505.
11 Araie M, Shirato S, Yamazaki Y, Matsumoto C, Kitazawa Y, Ohashi Y, et al. Risk factors for progression of normal-tension glaucoma under β-blocker monotherapy. Acta Ophthalmol. 2012 Aug;90(5):e337–43.
12 Suzuki Y, Iwase A, Araie M, Yamamoto T, Abe H, Shirato S, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. Ophthalmology. 2006;113(9):1613–7.
13 Naito T, Yoshikawa K, Mizoue S, Nanno M, Kimura T, Suzumura H, et al. Relationship between visual field progression and baseline refraction in primary open-angle glaucoma. Clin Ophthalmol. 2016;10:1397–403.
14 Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. Ophthalmology. 2013 Mar;120(3):512–9.
15 Kimura Y, Akagi T, Hangai M, Takayama K, Hasegawa T, Suda K, et al. Lamina cribrosa defects and optic disc morphology in primary open angle glaucoma with high myopia. PLoS One. 2014;9(12):e115313.
16 Sawada Y, Araie M, Kasuga H, Ishikawa M, Iwata T, Murata K, et al. Focal lamina cribrosa defect in myopic eyes with nonprogressive glaucomatous visual field defect. Am J Ophthalmol. 2018 Jun;190:34–49.
17 Kiumehr S, Park SC, Syril D, Teng CC, Tello C, Liebmann JM, et al. In vivo evaluation of focal lamina cribrosa defects in glaucoma. Arch Ophthalmol. 2012 May;130(5):552–9.
18 Hutchings N, Wild JM, Hussey MK, Flanagan JG, Trope GE. The long-term fluctuation of the visual field in stable glaucoma. Invest Ophthalmol Vis Sci. 2000 Oct;41(11):3429–36.
19 Faridi OS, Park SC, Kabadi R, Su D, De Moraes CG, Liebmann JM, et al. Effect of focal lamina cribrosa defect on glaucomatous visual field progression. Ophthalmology. 2014 Aug;121(8):1524–30.
20 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 Mar;131(3):314–20.
21 Tatham AJ, Miki A, Weinreb RN, Zangwill LM, Medeiros FA. Defects of the lamina cribrosa in eyes with localized retinal nerve fiber layer loss. Ophthalmology. 2014 Jan;121(1):110–8.
22 Giuffrè G. Chorioretinal degenerative changes in the tilted disc syndrome. Int Ophthalmol. 1991 Jan;15(1):1–7.
23 Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology. 2011 Oct;118(10):1989–e2.
24 Sawada Y, Araie M, Ishikawa M, Yoshitomi T. Multiple temporal lamina cribrosa defects in myopic eyes with glaucoma and their association with visual field defects. Ophthalmology. 2017 Nov;124(11):1600–11.
25 Moghimi S, Zangwill LM, Manalastas PIC, Suh MH, Penteado RC, Hou H, et al. Association between lamina cribrosa defects and progressive retinal nerve fiber layer loss in glaucoma. JAMA Ophthalmol. 2019 Apr;137(4):425–33.
26 Kwun Y, Han G, Choy YJ, Han JC, Kee C. Optic disc characteristics and visual field progression in normal tension glaucoma patients with tilted optic discs. J Glaucoma. 2016 Nov;25(11):901–7.
27 Lee SH, Lee EJ, Kim TW. Structural characteristics of the acquired optic disc pit and the rate of progressive retinal nerve fiber layer thinning in primary open-angle glaucoma. JAMA Ophthalmol. 2015 Oct;133(10):1151–8.
28 Park HY, Hwang YS, Park CK. Ocular characteristics associated with the location of focal lamina cribrosa defects in open-angle glaucoma patients. Eye. 2017 Apr;31(4):578–87.
29 Takayama K, Hangai M, Kimura Y, Morooka S, Nukada M, Akagi T, et al. Three-dimensional imaging of lamina cribrosa defects in glaucoma using swept-source optical coherence tomography. Invest Ophthalmol Vis Sci. 2013 Jul 18;54(7):4798–807.
30 Kim YK, Jeoung JW, Park KH. Effect of focal lamina cribrosa defect on disc hemorrhage area in glaucoma. Invest Ophthalmol Vis Sci. 2016 Mar;57(3):899–907.
31 Shoji T, Kuroda H, Suzuki M, Baba M, Hangai M, Araie M, et al. Correlation between lamina cribrosa tilt angles, myopia and glaucoma using OCT with a wide bandwidth femtosecond mode-locked laser. PLoS One. 2014;9(12):e116305.
32 Jonas JB, Wang N, Yang D, Ritch R, Panda-Jonas S. Facts and myths of cerebrospinal fluid pressure for the physiology of the eye. Prog Retin Eye Res. 2015 May;46:67–83.
33 Hayreh SS. Fluids in the anterior part of the optic nerve in health and disease. Surv Ophthalmol. 1978 Jul;23(1):1–25.
34 Potts MB, Wu AC, Rusinak DJ, Kesavabhotla K, Jahromi BS. Seeing floaters: a case report and literature review of intraventricular migration of silicone oil tamponade material for retinal detachment. World Neurosurg. 2018 Jul;115:201–5.
35 Chiao D, Ksendzovsky A, Buell T, Sheehan J, Newman S, Wintermark M. Intraventricular migration of silicone oil: a mimic of traumatic and neoplastic pathology. J Clin Neurosci. 2015 Jul;22(7):1205–7.
36 Fangtian D, Rongping D, Lin Z, Weihong Y. Migration of intraocular silicone into the cerebral ventricles. Am J Ophthalmol. 2005 Jul;140(1):156–8.
37 Hayreh S S. Fluids in the anterior part of the optic nerve in health and disease. Surv Ophthalmol. 1978 Jul;23(1):1–25.
38 Ghahari E, Bowd C, Zangwill LM, Suh MH, Shoji T, Hasenstab KA, et al. Macular vessel density in glaucomatous eyes with focal lamina cribrosa defects. J. Glaucoma. 2018 04;27(4):342–9.
39 Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology. 1996 Oct;103(10):1661–9.
40 Sawada Y, Hangai M, Ishikawa M, Yoshitomi T. Association of myopic optic disc deformation with visual field defects in paired eyes with open-angle glaucoma: a cross-sectional study. PLoS One. 2016;11(8):e0161961.
41 Yamada Y, Higashide T, Udagawa S, Takeshima S, Sakaguchi K, Nitta K, et al. The relationship between interocular asymmetry of visual field defects and optic nerve head blood flow in patients with glaucoma. J Glaucoma. 2019 03;28(3):231–7.