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ARTICLE

Comparison of the retinal nerve fiber layer and ganglion cell complex thickness in Korean patients with unilateral exfoliation syndrome and healthy subjects

Su-Ho Lim[1] · Won Mo Gu[2] · Soon Cheol Cha[3]

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Abstract

Purpose To compare retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness in patients with unilateral exfoliation syndrome (XFS) and age-matched controls using spectral domain-optical coherence tomography (SD-OCT).

Materials and methods This prospective case–control study included 54 eyes (the XFS-affected and the fellow eyes) of 27 unilateral XFS patients and 27 eyes of 27 age-matched control subjects. The RNFL and GCC thicknesses were measured using SD-OCT (RT-Vue 100, Optovue, Fremont, CA) after pupillary dilation. RNFL and GCC thicknesses were compared between case and control groups.

Results The mean age of XFS patients was 73.3 years and that of age-matched controls was 74.3 years. Both groups demonstrated a male preponderance. Superior RNFL thickness of XFS-affected eyes were significantly thinner than those of the healthy age-matched controls ($P = 0.002$ by ANOVA). There were no statistically significant differences in the RNFL thickness between both eyes of unilateral XFS patients. Moreover, superior GCC thickness of both eyes in unilateral XFS patients were thinner than those in controls ($P = 0.002$ by ANOVA).

Conclusions Thinner RNFL and GCC thicknesses were observed in unilateral XFS patients without visual field defects. These findings imply that XFS itself might be a risk factor for development of glaucomatous optic disc and RNFL damage.

Introduction

Exfoliative glaucoma (XFG) is a common sight-threatening form of glaucoma which develops as a result of exfoliation syndrome (XFS) [1–5]. Blockage of the trabecular meshwork by exogenous or endogenous exfoliative materials (XFM), dysfunction of the trabecular meshwork, and concomitant primary open-angle glaucoma (POAG) could cause glaucomatous damage [1, 2]. XFG is associated with a greater mean intraocular pressure (IOP) and more advanced visual field defects at diagnosis than POAG. Consequently, XFS itself is thought to be associated with glaucoma.

XFS is also associated with numerous systemic diseases, including cardiovascular disease, cerebrovascular disease, sensorineural hearing loss, and Alzheimer's dementia [3–5]. In particular, XFS seems to widely affect various ocular vasculatures, including the ophthalmic artery, ciliary circulation, iris vessels, and central retinal vessels [6, 7]. Previous studies using color Doppler imaging have reported reduced blood-flow velocities and increased resistivity in the ophthalmic artery, central retinal artery, and short posterior ciliary artery in XFS [8, 9]. Besides ocular vasculature, some studies have reported reduced retrobulbar blood flow and ipsilateral carotid blood flow in the XFS-affected eye [10, 11]. These hemodynamic changes may result in retinal nerve fiber thinning and ganglion cell layer changes, even in eyes without glaucomatous damage [12].

Assessment of the macula allows investigation of the clinical impact of the diagnosis of early glaucomatous change [13]. About 50% of retinal ganglion cells are located

These authors contributed equally: Su-Ho Lim, Won Mo Gu

✉ Soon Cheol Cha
sccha@ynu.ac.kr

[1] Department of Ophthalmology, Daegu Veterans Health Service Medical Center, Daegu, Republic of Korea

[2] Department of Ophthalmology, Daegu Premier Eye Center, Daegu, Republic of Korea

[3] Department of Ophthalmology, Yeungnam University College of Medicine, Daegu, Republic of Korea

in the macula [14]. In this context, evaluation of both the ganglion cell complex (GCC, a combination of the nerve fiber layer, ganglion cell layer, and inner plexiform layer) and circumpapillary retinal nerve fiber layer (cpRNFL) is important because glaucomatous retinal atrophy mostly affects the RNFL and GCC.

However, few studies have compared the RNFL and GCC thicknesses in XFS patients without glaucomatous damage and healthy controls [12, 15], and no studies in an Asian population have been reported to date. Thus, the purpose of this study was to evaluate automated measurements of cpRNFL and GCC thickness, using the RT-Vue 100 (Optovue, Fremont, CA) SD-OCT system, in patients with unilateral XFS without glaucomatous damage.

Materials and methods

Patients

This prospective cross-sectional study was approved by the institutional review board of Daegu Veterans Health Service Medical Center. All participants gave informed consent to participate. This study was performed in accordance with the tenets of the Declaration of Helsinki. The subjects were enrolled and investigated between January 2015 and December 2015 at Daegu Veterans Health Service Medical Center in South Korea. A total of 54 eyes of 27 unilateral XFS patients (the affected and the fellow eyes) and 27 eyes of 27 age-matched control subjects (the right eye) were included in the study.

Unilateral XFS was defined as having one eye with XFS, diagnosed using slit-lamp biomicroscopy, tonometry, and dilated fundus examination, and a fellow eye without glaucomatous damage or retinal diseases. XFS was defined as follows [2]: (1) presence of characteristic fibrillar exfoliation materials at the pupillary border or on the anterior capsule after pupillary dilation, (2) IOP < 21 mmHg, without antiglaucoma treatment, (3) no glaucomatous optic nerve head (ONH) changes confirmed by dilated fundus exam and SD-OCT, (4) open-angle status on gonioscopic examination, without visual field defects confirmed by automated perimetry in all XFS patients. The control group was defined as those without a glaucomatous ONH or RNFL defect, visual field defect, or other retinal diseases in either eye.

The exclusion criteria were as follows: (1) patients older than 80 years or younger than 40 years; (2) eyes with a refractive error of less than −6 diopters or more than +4 diopters; (3) glaucomatous changes including glaucomatous ONH changes and glaucomatous visual field defects; (4) a history of antiglaucoma treatment, including medication and laser treatment; (5) media opacity that reduced the image quality (as described in the following section); (6) previous ocular surgery or ocular trauma; (7) the presence of neurological diseases that might affect the RNFL thickness, such as Alzheimer's disease, vascular dementia, or Parkinsonism.

Ophthalmic examinations

All subjects underwent complete ophthalmic examinations, including a best-corrected visual acuity measurement, Goldmann applanation tonometry, slit-lamp biomicroscopy, and gonioscopy using Goldmann three-mirror lens, a dilated fundus examination, and RNFL and GCC thickness measurements using SD-OCT.

The margins of the optic cup were defined as the point of maximal inflection of vessels crossing the neuroretinal rim. The vertical cup diameter was measured as the vertical distance between the points of maximum centrifugal extension of the cup between 11 and 1 o'clock and 5 and 7 o'clock. Disc hemorrhage, notching of the neuroretinal rim, and thinning of the RNFL were also documented. A dilated fundus examination was performed by a single glaucoma specialist (S.H.L).

When glaucomatous changes were suspected on fundus examination in control group, automated perimetry was performed using a Humphrey Visual Field Analyzer 740i (Carl Zeiss Meditec Inc, Dublin, CA) and the 24–2 Swedish Interactive Threshold Algorithm. Visual field defects were defined as follows [16]: (1) glaucomatous visual field defects corresponding to ONH or RNFL changes; (2) glaucoma hemifield test results outside of the normal limits; and (3) a cluster of three or more nonedge, contiguous points, not crossing the horizontal meridian, with P values < 0.05 as compared with the age-matched normal on the pattern deviation plot, one of which must have a P value < 0.01.

The RNFL and GCC thicknesses were measured using a SD-OCT device (RT-Vue 100, RT Vue, Fremont, CA) after pupillary dilation. An internal nasal fixation light was used to center the ONH in the rectangle image mode, and cpRNFL thickness was measured. To improve the scan quality, scans with signal strength intensity < 40 were excluded from the analyses. Average RNFL thickness and RNFL thickness in eight peripapillary sectors (superior nasal, superior temporal, temporal upper, temporal lower, inferior temporal, inferior nasal, nasal upper, and nasal lower sector) were calculated automatically. Thereafter, we grouped eight peripapillary sectors into four sectors. Superior RNFL thickness indicates the average of the superior nasal and superior temporal sectors. Temporal RNFL thickness indicates the average of the temporal upper and temporal lower sectors. Inferior RNFL thickness indicates the average of the inferior temporal and inferior nasal

sectors. Nasal RNFL thickness indicates the average of the nasal upper and nasal lower sectors.

GCC thickness was also measured in two areas (superior and inferior sector). All OCT images were evaluated by the same observer (S.H.L).

Statistical analysis

Statistical analyses were performed using SPSS for Windows software version 18.0 (SPSS Inc, Chicago, IL). Independent *t*-tests and chi-square tests were used to compare baseline characteristics of unilateral XFS patients and controls. One-way analysis of variance (ANOVA) was used to compare RNFL and GCC thickness among three groups (XFS-affected eye, fellow eye, and control group). In post-hoc analysis, Tukey's test was used to compare two groups. After Bonferroni's correction of multigroup comparisons, a *P* value of 0.0167 was considered statistically significant, at a significance level of 0.05.

Results

Table 1 compares the baseline characteristics of the XFS and control groups. The mean age was 73.3 ± 6.3 for XFS patients and 74.3 ± 7.2 for healthy controls ($P = 0.536$). There was no difference in the numbers of males and females comprising either group ($P = 0.551$).

The mean IOP of XFS-affected eyes (17.2 ± 2.8 mmHg) was higher than that of fellow eyes (16.8 ± 2.2 mmHg) and healthy controls (14.5 ± 2.3 mmHg) ($P = 0.004$). A total of 28 pseudophakic eyes (8 XFS-affected eyes, 11 fellow eyes and 9 controls) were included, but, there was no significant difference between groups in terms of lens status ($P = 0.772$) or cup to disc ratio ($P = 0.759$), and there were no patients with abnormal myopic optic disc features such as severe disc tilt and peripapillary atrophy in any groups.

RNFL parameters are summarized in Table 2. Although there was borderline statistical significance ($P = 0.057$ by one-way ANOVA), post-hoc analysis revealed average RNFL thickness of XFS-affected eyes was slightly thinner than that of controls ($P = 0.014$). In particular, the superior quadrant RNFL thickness of XFS-affected eyes (108.5 ± 13.5 μm) was thinner than that of controls (114.3 ± 12.2 μm) ($P = 0.002$ by ANOVA; $P = 0.001$ by Tukey's post-hoc test).

GCC parameters are summarized in Table 3. There was a significant difference in the average and superior GCC parameters between groups by one-way ANOVA ($P = 0.032$, $P = 0.002$, respectively). In particular, the superior GCC thickness decreased in both XFS-affected eyes and fellow eyes (86.1 ± 6.5 μm, 87.8 ± 6.3 μm, respectively) as compared with healthy controls (94.6 ± 5.7 μm) ($P = 0.001$, $P = 0.004$, respectively, by Tukey's test). However, the inferior quadrant GCC thickness did not show a statistically significant difference between three groups ($P = 0.125$).

Table 1 Baseline characteristics of subjects

	XFS-affected eyes ($n = 27$)	Fellow eyes ($n = 27$)	Controls ($n = 27$)	*P* value
Mean age	73.3 ± 6.3		74.3 ± 7.2	0.536
Sex (M/F)	18/9		20/7	0.551
IOP (mmHg) [Range]	17.2 ± 2.8 [13–20]	16.8 ± 2.2 [12–20]	14.5 ± 2.3 [12–19]	0.004[a]
Lens status				
Phakic	19	16	18	0.772
Pseudophakic	8	11	9	
C/D ratio	0.54 ± 0.16	0.53 ± 0.22	0.49 ± 0.19	0.759

Data are presented as mean ± SD; *P* values for mean age, sex, and lens status were calculated by independent *t*-tests and chi-square tests; other *P* values were calculated by one-way ANOVA

ANOVA analysis of variance, *C/D* cup/disc ratio, *IOP* intraocular pressure, *XFS* exfoliation syndrome

[a]Post-hoc analysis was performed using Tukey's test; the *P* values for comparison of XFS affected eyes and fellow eyes was 0.763; the *P* value for comparison of XFS affected eyes and control eyes was 0.002; and the *P* value for comparison of fellow eyes and control eyes was 0.016

Discussion

RNFL and GCC thickness measurements provide clinically important information about early glaucomatous changes [17]. However, few studies have compared the RNFL and GCC thicknesses between patients with XFS without glaucomatous damage and healthy controls [12, 15]. In the present study, patients with unilateral XFS without glaucomatous optic nerve changes or visual field defects showed thinner RNFL and GCC thicknesses than those of control individuals. Our results were similar to those of previous individual studies and meta-analysis [12, 15, 18]. Our study demonstrated reduced RNFL and GCC thicknesses in superior quadrants. Similarly, Aydin et al. [12] found that RNFL thickness in the superior quadrant was thinner in XFS patients than in healthy subjects using Cirrus HD OCT-4000. They reported the GCC thickness was thinner in XFS patients than in healthy subjects, except in the inferior and inferonasal quadrants. In addition, Eltutar et al. [15] reported that in eyes of XFS, the superior and total macular NFL (nerve fiber layer) thickness; superior and total GCL + IPL (ganglion cell layer + inner plexiform layer) thickness were significantly thinner than those of control subject.

However, controversies regarding location of thinning still abound. Previous meta-analysis showed that RNFL

Table 2 Comparison of retinal nerve fiber layer thickness among groups

RNFL thickness (μm)	XFS-affected eyes ($n = 27$)	Fellow eyes ($n = 27$)	Controls ($n = 27$)	P value
Average	93.4 ± 10.4 (85–116)	94.2 ± 9.3 (88–117)	96.3 ± 8.1 (89–124)	0.057[a]
Nasal	64.3 ± 12.1 (55–93)	67.3 ± 10.1 (57–96)	65.3 ± 9.3 (52–92)	0.257
Superior	108.5 ± 13.5 (91–141)	110.2 ± 15.2 (90–145)	114.3 ± 12.2 (95–153)	0.002[b]
Temporal	72.3 ± 9.5 (59–101)	74.3 ± 10.2 (61–104)	74.2 ± 9.2 (65–105)	0.681
Inferior	121.2 ± 14.2 (103–148)	123.3 ± 15.2 (107–152)	125.3 ± 10.4 (108–157)	0.489

Data are presented as mean ± SD (range); P value was calculated by one-way ANOVA

ANOVA analysis of variance, *RNFL* retinal nerve fiber layer, *XFS* exfoliation syndrome

[a]Although the p value by ANOVA demonstrated statistical borderline significance, post-hoc analysis was performed using Tukey's test. The P value for comparison of XFS-affected eyes and fellow eyes (P1) was 0.739; the P value for comparison of XFS-affected eyes and control (P2) eyes was 0.014; and the P value for comparison of fellow eyes and control eyes (P3) was 0.151

[b]Post-hoc analysis was performed using Tukey's method: P1 = 0.607; P2 = 0.001, and P3 = 0.033

Table 3 Comparison of ganglion cell complex thickness among groups

GCC thickness (μm)	XFS-affected eyes ($n = 27$)	Fellow eyes ($n = 27$)	Control ($n = 27$)	P value
Average	86.2 ± 6.4	87.5 ± 6.9	93.5 ± 6.0	0.032[a]
Superior	86.1 ± 6.5	87.8 ± 6.3	94.6 ± 5.7	0.002[b]
Inferior	86.3 ± 6.3	87.2 ± 7.4	92.3 ± 6.4	0.125

Data are presented as mean ± SD; P value was calculated by one-way ANOVA

ANOVA analysis of variance, *GCC* ganglion cell complex, *XFS* exfoliation syndrome

[a]Post-hoc analysis was performed using Tukey's methods. The P value for comparison of XFS-affected eyes and fellow eyes (P1) was 0.629; the P value for comparison of XFS-affected eyes and control eyes (P2) was 0.026; and the P value for comparison of fellow eyes and control eyes (P3) was 0.049

[b]Post-hoc analysis was performed with Tukey's method: P1 = 0.993; P2 = 0.001, and P3 = 0.004

thickness was significantly lower in all quadrants in XFS patients compared with control group [18]. In their study, the weighted mean difference was −10.68 in superior, −8.20 in inferior, −6.39 in temporal, and −3.05 in nasal quadrants [18]. Subgroup analysis demonstrated no significant differences in the nasal quadrant regardless of OCT type in their study [18]. Moreover, publication bias was found in average RNFL thickness and inferior RNFL thickness [18]. Thus, their results seem similar to our own. These variations in measurements may be attributable to the small sample size, different ethnicities, and possible systemic diseases of the study participants, and this was the first study comparing the RNFL thickness using Optovue SD-OCT

The reasons for superior thinning of RNFL thickness may be attributable to vascular factors besides IOP. Recent OCTA studies have shown that superficial capillary density is significantly lower in the superior quadrant, but not in the inferior quadrant [19]. These vascular differences were supported by some studies that report reduced RNFL thickness in XFS patients with normal IOP [20, 21]. It has, therefore, been suggested that RNFL changes in XFS patients are not only caused by high IOP but also by other factors, such as insufficient blood flow to the ONH and peripapillary retina [22, 23].

In particular, XFS is greatly affected by genetic and environmental factors. Many epidemiological studies have found significant variability in the prevalence of XFS among different ethnic groups (0.4–18.1%) [24–27]. Similarly, the risk allele of *LOXL1* rs1048661 is reversed in the Asian (Japanese, Chinese, and Korean) population, and rs1048661 is not associated with XFG risk in Greek, Indian, Mexican, and Polish populations [28]. Given the conflicting genetic association results and the variable prevalence, genetic, environmental, and racial differences should be kept in mind. To the best of our knowledge, the RNFL and GCC thicknesses have not yet been compared between XFS patients and controls in an Asian population.

Our results raise the question about the reason for thin RNFL and GCC thickness in XFS patients and the clinical relevance of these changes. First of all, the mean IOP in XFS-affected and fellow eyes appears to be higher than reported by the Korean National Health and Nutrition Survey (KNHANES) [29]; it was 13.7 ± 2.8 mmHg in those more than 70 years of age. Therefore, mean IOP of XFS-affected and fellow eyes were higher than what was seen in that population; this could be a reason for the RNFL loss.

Besides the impact of IOP, we postulate that the reasons for the thin RNFL and GCC thickness in the present study are related to (1) systemic, or (2) local vascular factors, and

(3) mechanical factors related to lamina cribrosa. First, systemic vascular factors might affect the retrobulbar blood flow and ONH changes. Retinal and choroidal tissues have a high oxygen demand. Holló et al. [4] reported the association of cardiovascular disease and XFS, while Wang et al. [5] demonstrated a higher prevalence of carotid disease in XFS. Moreover, systemic vascular stiffness and thickened vascular walls may result in decreased retrobulbar ocular blood flow; this has been supported by several studies [9, 11]. These retinal ischemia can lead to ganglion cell death and ONH atrophy [30], and it has been suggested that diminished ocular blood flow contributes to the development of RNFL damage in XFS patients. Second, local vascular factors should also be considered. XFM accumulation in short posterior ciliary arteries, central retinal vessels, the optic nerve sheath, and vortex veins could cause vascular alterations, ischemic changes and subsequent RNFL and GCC thinning [21]. Ocakoglu et al. [31] reported that microvascular blood flow in the optic nerve and peripapillary retina was decreased, based on Heidelberg retinal flowmeter measurements. Their study supported our hypothesis.

Besides compromised vasculature, the effect of mechanical changes of the ONH should be considered. A thin lamina cribrosa of XFS was reported by some studies [32, 33]. The decreased stiffness of the lamina cribrosa and peripapillary scleral tissues caused by XFS may reflect an inherent tissue weakness, especially in older patients [34]. This may in turn render these eyes more vulnerable to IOP fluctuations and optic nerve damage. In addition, Jonas [35] reported that the obstruction of the venous outflow system could be caused by mechanical distortion of the lamina cribrosa. Structural alterations of the lamina cribrosa may also influence hemodynamic changes, such as increased venous outflow resistance or turbulence.

In this study, thin RNFL and GCC thicknesses were also observed in the fellow eyes of patients with unilateral XFS, as compared with that of healthy control subjects. These findings suggest that both eyes of patients with unilateral XFS could have structural changes or vulnerability to the development of glaucoma, considering that the RNFL and GCC thicknesses were found to be thinner in glaucoma patients than in healthy control subjects in previous studies [12, 15]. In particular, XFS is considered an asymmetric bilateral disease. XFS often occurs unilaterally, but within 5 years, 14–41% of cases may convert to the bilateral form [36, 37]. Iris vasculopathies are also detected in both eyes of patients with unilateral XFS [38]. In this context, our study shows thin RNFL and GCC thicknesses in both eyes of patients with unilateral XFS.

Our study had some limitations. First, the sample sizes were relatively small; this was especially apparent in our subgroup analysis. Second, blood pressure and diurnal IOP fluctuations were not considered in this study. However, all patients were enrolled at a similar time of the morning, minimizing the effect of diurnal variation. Third, a total of 28 pseudophakic eyes were included because elderly patients were enrolled in our study. IOP could be influenced by pseudophakia, but there was no significant difference between groups in terms of lens status. Fourth, we could not exclude the effect of IOP on RNFL and GCC thickness. The mean IOP of XFS patients was slightly higher than that of controls. However, the mean IOP and IOP fluctuation of the XFS patients were higher than controls levels in other studies [39, 40]. These results are compatible with those of other studies [12]. In addition, the difference in IOP was only about 2.7 mmHg in our study; thus, IOP might not affect the thickness of GCC and RNFL markedly.

In conclusion, RNFL and GCC thicknesses were significantly thinner in Asian patients with XFS without glaucomatous damage compared with healthy controls. Systemic or local vascular changes and mechanical alterations could play a role. Thus, physicians should consider that diagnosis of XFS itself might predict a thin retinal change and may be a risk factor for development of a glaucomatous optic disc and RNFL damage.

What was known before

- Measurement of RNFL and GCC thickness facilitates investigation of the clinical impact of the diagnosis on early glaucomatous change
- There have been few studies comparing RNFL and GCC thickness in XFS patients without glaucomatous damage and healthy controls

What this study adds

- RNFL and GCC thicknesses were significantly thinner in Asian patients with XFS without glaucomatous damage than in healthy controls
- Diagnosis of XFS itself might predict thinning of the retina and could be a risk factor for development of a glaucomatous optic disc and retinal nerve fiber layer damage

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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