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Original Scientific Paper

CORRELATION BETWEEN VISUAL FIELD SENSITIVITY AND RETINAL NERVE FIBER LAYER THICKNESS IN UNILATERAL EXFOLIATION SYNDROME

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SUMMARY – This study aimed to evaluate retinal nerve fiber layer thickness in exfoliation syndrome (XFS), present unilaterally, using optical coherence tomography (OCT). This prospective study included 90 examinees with unilateral syndrome. However, examinees with higher intraocular pressure or findings implicative of glaucoma were excluded from the study, as well as examinees with optic nerve changes. In individuals with unilateral XFS, OCT findings were compared between the two groups: the affected eye group and the fellow eye group.

The study results show that the average thinning of the retinal nerve fiber layer, especially in the inferior and superior quadrants, has not resulted in visual field defects in examinees with unilateral XFS. In the group of eyes without XFS, 85.55% exhibited reference inferior quadrant thickness values, and 91.11% exhibited reference superior quadrant thickness values. In the group of eyes with manifest XFS, 82.22% exhibited reference inferior quadrant thickness values, and 88.88% exhibited reference superior quadrant thickness values. Most examinees in both groups had normal average retinal nerve fiber layer (RNFL) thickness (72.22%). In examinees with clinically unilateral XFS, RNFL thinning occurs in both eyes before XFS becomes bilateral and before hypertensive intraocular pressure can be measured.

Keywords*: Retinal nerve fiber layer*; *Exfoliation*

Introduction

Exfoliation syndrome (XFS) often appears unilaterally on clinical examinations and may remain so for an extended period. Recent research has shown that the clinical unilateral form is not unilateral. In clinical unilateral syndrome, exfoliative material is proven in blood vessels of the iris, pupil dilatator, and conjunctiva without visible exfoliative material in a slit lamp. XFS is a bilateral condition with a unilateral manifestation that is proven by microfibrillar deposits into the dilator muscle or on the periphery of the iris vessels in the fellow eye. Optic disc damage in unilateral XFS is recorded in both eyes, with or without a clinically visible accumulation of the exfoliation material. The exfoliative process is a risk factor for optic disc excavation. Other risk factors for glaucoma are onset-like dispersion and the accumulation of melanin granules, vascular risks, and lamina cribrosa connective tissue changes[2-5].

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Exfoliative glaucoma is a form of secondary open-angle glaucoma that occurs with very high intraocular pressure (IOP) values. However, even without raised intraocular pressure, XFS represents an independent risk factor for the development of glaucoma[6-8].

Glaucoma is a chronic, progressive optic neuropathy that damages retinal ganglion cell axons. The thinning of the retinal nerve fiber layer (RNFL) happens due to the progressive loss of retinal ganglion cell axons.

Structural and functional changes characterize glaucoma. Structural changes develop due to damage to retinal ganglion cells, resulting in RNFL thinning. A minimum loss of 35% of retinal ganglion cells leads to visual field damage detectable with standard automated perimetry (SAP). Optical coherence tomography (OCT) detects RNFL thinning in the earliest stage of glaucoma, as well as peripapillary thickness. The OCT imaging data are compared with the normative database group. Diagnostics of these early structural changes can detect the damage before functional tests.

This study aimed to connect the structural and functional changes in examinees with unilateral XFS and to address the significance of these parameters in early glaucoma detection in groups of examinees.

Subjects and Methods

From January 2012 to January 2016, ninety examinees were recruited at the Sestre milosrdnice University Hospital Center, University Department of Ophthalmology, Zagreb, Croatia. All examinees gave consent to participate in the study. The Ethics Committees of the Sestre milosrdnice University Hospital Center approved the study. Ethical guidelines of the Declaration of Helsinki were followed during the study.

All examinees underwent applanation tonometry, gonioscopy, and slit lamp examination with a plus 78-D lens. Standard visual field (VF) testing was performed (Octopus® Visual Field analyzer with standard white/white perimetry using the dG2 program; Haag-Streit AG, Switzerland). All eyes underwent spectral-domain Cirrus OCT (Carl Zeiss Meditec). Also, the disc area was measured using the head mode of OCT. Clinical examination and all diagnostic tests were completed on the same day for every examinee.

All examinees had corrected visual acuities of ≥0.7 according to Snellen, ≤21 mmHg IOP. On the slit lamp, the appearance of exfoliation material on the anterior segment of the eye was visible in comparison to the fellow eye without visible exfoliation. All examinees had normal fundus appearance and normal VFs (<20% fixation losses; <10% false-positive and negative responses; mean deviation [MD] or corrected loss variance [sLV] within the 95% confidence interval). There was no evidence of increased excavation (cup-to-disc ratio >0.7) or asymmetric excavation (difference in cup-to-disc ratio >0.2 between the eyes), neuroretinal rim notching, focal thinning, optic disc hemorrhages or vertical elongation of the optic disc excavation. Individuals with a history of ocular surgery, ocular diseases, or diabetes were excluded from the study.

The RNFL thickness was measured using the optic disc cube protocol. In this study, we compared quadrant maps of RNFL thickness and average RNFL thickness with the MD index in automated VF.

Statistical analysis

The results are shown with descriptive statistic parameters: qualitative variables (ie. those are shown in comparison to referent values) are shown with absolute and relative frequencies. Quantitative variables such as RNFL are shown with arithmetic means, corresponding standard deviations (SD), and minimal and maximal measured values. Since the distribution does not follow the Gaussian curve, MD and sLV are presented with the median, minimal, and maximal measured values.

Functional and structural parameter relations were tested with Spearman's rank correlation. Differences in relationships were considered statistically significant if the P-value was less than 0.005.

Results

At clinically manifested XFS, as well as the fellow eye with MD value increase, there is a statistically significant increase of sLV (P=0.01), as well as a statistically significantly higher thickness of the inferior quadrant at clinically manifested XFS (P=0.32) and fellow eye (P=0.046).

Table 1. Correlation of MD with structural changes

	Clinically manifested XFS (N=90) r (P)		**Fellow eye in bilateral XFS (N=90) r (P)**	
Inferior quadrant	0.42	(0.032)	0.39	(0.046)
Superior quadrant	0.35	(0.070)	0.16	(0.425)
Nasal quadrant	-0.12	(0.495)	0.03	(0.935)
Temporal quadrant	-0.08	(0.599)	-0.33	(0.060)
Average RNFL thickness	0.50	(0.008)	0.15	(0.440)
sLV	0.58	(0.001)	0.44	(0.001)

XFS = exfoliation syndrome; RFNL = retinal nerve fiber layer; sLV = loss variance

Table 2. Values of examined variables in groups of examinees

	XFS syndrome (N=90)				**Fellow eye (N=90)**			
	min	**max**	**x**	**sd**	**min**	**max**	**x**	**sd**
Inferior	80	126	96.5	11.4	88	128	96.8	10.1
Superior	80	134	96.5	11.2	88	131	96.8	10.1
Nasal	54	81	72.1	8.7	62	86	74.8	7.2
Temporal	48	79	60.2	7.4	51	83	61.8	8.6
Average RNFL	70	94	82.0	6.6	73	98	84.7	6.2
MD*	2(0-10)				0.5(0-4)			

XFS = exfoliation syndrome; RNFL = retinal nerve fiber layer; MD* = median; x = arithmetic mean; sd = standard deviation

Table 3. Contribution of examinees within referent values in the RNFL quadrants

	Inferior			**Superior**		**Nasal**		**Temporal**	
	(89.4 – 138.3μ)*			**(88.9-136.7μ)***		**(50.0-86.2μ)***		**(45.1-82.2μ)***	
Groups	N	n	%	n	%	n	%	n	%
XFS sy	90	74	82.22	80	88.88	90	100.00	90	100.00
Fellow eye	90	77	85.55	82	91.11	90	100.00	90	100.00

*referent values; XFS = exfoliation syndrome; RNFL = retinal nerve fiber layer

Table 4. Contribution of participants within referent values in average RNFL thickness

Average RNFL thickness (>80μ)*			
groups	**N**	**n**	**%**
XFS sy	90	65	72.22
fellow eyes	90	65	72.22

*referent value; RNFL = retinal nerve fiber layer; XFS = exfoliation syndrome

Average RNFL thickness is statistically significantly related to the MD group of eyes with clinically manifested XFS (P=0.008), whereas that relation is not statistically significant with fellow eyes.

In the group of examinees with unilateral XFS, all the inferior and superior quadrant thickness values are not within the referent values. All the values of the nasal and temporal quadrants are within the referent values.

Average RNFL thickness is equal in clinically manifested XFS and fellow eyes.

Discussion

XFS syndrome represents the most common cause of open-angle glaucoma, and 20% of all open-angle glaucomas consist of exfoliation glaucoma (XFG)[10]. The exfoliative process and intraocular pressure are independent risk factors for developing glaucomatous defects. Considering that XFG is characterized by a more aggressive representation, a fast progression of the disease, as well as a poor outcome, the aim is to recognize this disease as soon as possible. Before any manifest signs of disease, structural changes of the macula and RNFL can occur in eyes with XFS.

XFS syndrome is a risk factor for glaucomatous optic disc damage. In individuals with unilateral XFS, optic disc damage may be present in the fellow eye even in the absence of clinically visible exfoliation material [11].

Fellow eyes of examinees with unilateral hypertensive XFG have glaucomatous damage in 40% of cases[12].

In this study, in the group of examinees with unilateral XFS syndrome with increased MD, the sLV value is also statistically significantly higher, even though they are within the referent values. In eyes with clinically visible XFS, as well as fellow eyes, a minimal value of average RNFL thickness in the inferior and superior quadrants was perceived. These changes, however, were not manifested with VF damages and support pre-perimetric glaucomatous changes. In the group of eyes without XFS, 85.55% exhibited reference inferior quadrant thickness values, and 91.11% exhibited reference superior quadrant thickness values. In the group of eyes with manifest XFS, 82.22% exhibited reference inferior quadrant thickness values, and 88.88% exhibited reference superior quadrant thickness values. Most examinees in both groups had normal average RNFL thickness (72.22%).

Based on the results of Rao *et al.*, patients with bilateral XFS had thinner RNFL than their unilateral counterparts despite comparable baseline IOP[13]. These patients had normal IOP and did not have clinically visible glaucoma damages; therefore, they coincided with patients in this study.

Concerning the current findings, XFS represents a continuum from unilateral to bilateral disease, with or without raised IOP, optic nerve damage, and VF defects[14-16]. The spectrum between unilateral and bilateral disease and between XFS and XFG remains largely unexplored. Puska *et al.* observed 32% conversion from unilateral to bilateral XFS and direct conversion of the unaffected fellow eye to XFG in 38% of eyes[14]. In their immunohistochemical study, Vesti *et al.* stated that the condition is never strictly unilateral and that the non-exfoliative fellow eye demonstrates exfoliative material[17].

Electron microscopy and ultrastructural studies have confirmed the presence of exfoliation material in the clinically normal fellow eye of unilateral cases and other organs[18].

To summarize, in everyday clinical practice, there should be more focus on the fellow eyes of examinees with unilateral XFS, with or without glaucoma. Minor changes in the optic disc, as well as RNFL thinning on OCT, can be found in both eyes. Therefore, RNFL thinning develops in both eyes in examinees with unilateral XFS before XFS becomes bilateral and before elevated IOP can be measured in either eye.

References

1. Hammer T, Schlőtzer-Schrehardt U, Naumann GOH. Unilateral or Asymmetric Pseudoexfoliation Syndrome? An Ultrastructural Study. Arch Ophthalmol. 2001;119(7):1023-31. doi: 10.1001/archopht.119.7.1023.
2. Prince AM, Streeten BW, Ritch R, Dark AJ, Sperling M. Preclinical Diagnosis of Pseudoexfoliation Syndrome. Arch Ophthalmol. 1987;105(8):1076-82. doi: 10.1001/archopht.1987.01060080078032.
3. Helbig H, Schlőtzer-Schrehardt U, Noske W, Kellner U, Forster MH, Naumann GO. Anterior chamber hypoxia and iris vasculopathy in pseudoexfoliation syndrome. Ger J Ophthalmol. 1994;3(3):148-53. PubMed PMID: 8038683.
4. Küchle M, Ngueyen NX, Hannappel E, Naumann GOH. The Blood-Aqueous Barrier in Eyes with Pseudoexfoliation Syndrome. Ophthalmic Res. 1995;27(Suppl. 1):136-42. doi: 10.1159/000267859.
5. Kivelä T, Hietanen J, Uusitalo M. Autopsy analysis of clinically unilateral exfoliation syndrome. Invest Ophthalmol Vis Sci. 1997;38(10):2008-15. PubMed PMID: 9331264.
6. Exstrőm C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open angle glaucoma. A population-based five-year follow-up study. Acta Ophthalmol. 1993;71:189-95. doi: 10.1111/j.1755-3768.1993.tb04989.x.

7. Mitchell P, Wang JJ, Hourihan F. The Relationship Between Glaucoma and Pseudoexfoliation. The Blue Mountains Eye Study. Arch Ophthalmol. 1999;117(10):1319-24. doi: 10.1001/archopht.117.10.1319.
8. Grødum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology. 2005;112(3):386-90. doi: 10.1016/j.ophtha.2004.09.024.
9. European Glaucoma Society. Terminology and Guidelines for Glaucoma IV Edition. Savona: DOGMA. 2014.
10. Ritch R. Exfoliation syndrome-the most common identifiable cause of open-angle glaucoma. J Glaucoma. 1994;3(2):176-7.
11. Puska P, Vesti E, Tomita G, Ishida K, Raitta C. Optic disc changes in normotensive persons with unilateral exfoliation syndrome: a 3-year follow-up study. Graefes Arch Clin Exp Ophthalmol. 1999;237:457-62. doi: 10.1007/s004170050261.
12. Yarangümeli A, Davutluoglu B, Kőz OG, Elhan AH, Yaylaci M, Kural G. Glaucomatous damage in normotensive fellow eyes of patients with unilateral hypertensive pseudoexfoliation glaucoma: normotensive pseudoexfoliation glaucoma? Clin Exp Ophthalmol. 2006 Jan-Feb;34(1):15-9. doi: 10.1111/j.1442-9071.2006.01140.x.
13. Rao O. Clinical and Optical Coherence Tomography Features in Unilateral versus Bilateral Pseudoexfoliation Syndrome. J Ophthalmic Vis Res. 2012;7(3):197-202. PubMed PMID: 23264861.
14. Puska PM. Unilateral Exfoliation Syndrome: Conversion to Bilateral Exfoliation and to Glaucoma: A Prospective 10-year Follow-up Study. J Glaucoma. 2002;11(6):517-24. doi: 10.1097/00061198-200212000-00012.
15. Tarkanen A, Kivelä T. Cumulative Incidence of Converting from Clinically Unilateral to Bilateral Exfoliation Syndrome. J Glaucoma. 2004;13(3):181-4. doi: 10.1097/00061198-200406000-00001.
16. Puska P, Harju M. Optic nerve head topography in nonglaucomatous, normotensive patients with unilateral exfoliation syndrome. Graefes Arch Clin Exp Ophthalmol. 2009;247:1111-7. doi: 10.1007/s00417-009-1057-y.
17. Vesti E, Kivelä T. Exfoliation syndrome and exfoliation glaucoma. Prog Retin Eye Res. 2000;19(3):345-68. doi: 10.1016/s1350-9462(99)00019-1.
18. Schlőtzer-Schrehardt U, Küchle M, Naumann GOH. Electron-microscopic Identification of Pseudoexfoliation Material in Extrabulbar Tissue. Arch Ophthalmol. 1991;109(4):565-70. doi:10.1001/archopht.1991.01080040133044.

Sažetak

KORELACIJA OSJETLJIVOSTI VIDNOG POLJA I DEBLJINE SLOJA MREŽNIČNIH ŽIVČANIH VLAKANA U JEDNOSTRANOM EKSFOLIJATIVNOM SINDROMU

M. Šimić Prskalo, *Z. Prskalo*, *Ž. Tomić* i *T. Tomić*

Cilj je ove studije bio ispitati debljinu mrežničnog sloja ganglijskih stanica kod jednostranog eksfolijativnog sindroma pomoću optičke koherentne tomografije (*optical coherence tomography*, OCT). Ova prospektivna studija uključila je 90 ispitanika s jednostranim eksfolijativnim sindromom. Ispitanici s povišenim intraokularnim tlakom, kao i s nalazima koji upućuju na glaukom te oni s promjenama vidnog živca isključeni su iz ispitivanja. Nalazi OCT-a uspoređivani su u obje grupe – zahvaćenog i nezahvaćenog oka.

Rezultati studije pokazali su da stanjenje prosječne debljine mrežničnog sloja ganglijskih stanica, osobito onog u inferiornom i superiornom kvadrantu, nije rezultiralo oštećenjem vidnog polja u ovoj grupi ispitanika. U grupi očiju bez eksfolijativnog sindroma bilo je 85.55% onih s referentnim vrijednostima debljine donjeg kvadranta i 91.11% s referentnim vrijednostima debljine gornjeg kvadranta. U grupi očiju s manifestnim eksfolijativnim sindromom bilo je 82.22% onih s referentnim vrijednostima debljine donjeg kvadranta i 88.88% očiju s referentnim vrijednostima debljine gornjeg kvadranta. Većina ispitanika obje grupe imala je normalnu prosječnu debljinu sloja mrežničnih živčanih vlakana (72.22%).

Stanjenje mrežničnog sloja živčanih vlakana važan je znak u oba oka kod klinički jednostranog eksfolijativnog sindroma, čak prije obostrane pojave eksfolijacija i prije nego što se pojavi povišeni očni tlak.

Ključne riječi: *Sloj mrežničnih živčanih vlakana*; *Eksfolijacija*