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Circumferential iris trans-illumination defects in exfoliation syndrome

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Abstract

Purpose—We identified a pattern of concentric circular transillumination defects in a few patients with exfoliation syndrome using an infrared detection system. This pattern of iris abnormality has also been observed in a mouse model of exfoliation syndrome. The objective of the current study is to determine if concentric iris transillumination defects are specific to exfoliation syndrome and may have some diagnostic utility for identifying early cases of disease.

Materials and Methods—A total of 68 volunteers from the University of Iowa Glaucoma Clinic with normal eyes (n=21) or diagnoses of either exfoliation syndrome (n=12), pigment dispersion syndrome (n=8), or primary open angle glaucoma (n=27) were enrolled in the study. The irides of these subjects were each examined by four ophthalmologists masked to their diagnosis, using infrared videography. The presence of concentric, circular transillumination defects on the videos was graded as none (grade 0), possible (grade 1), definite (grade 2), or prominent (grade 3) by four examiners. We searched for an association between the presence of concentric bands of trans-illumination and the diagnosis of exfoliation syndrome after removing the effect of different raters was evaluated using the Cochran-Mantel-Haenszel test. We performed the same analysis for pigment dispersion syndrome and for primary open angle glaucoma.

Results—The presence of any concentric, circular iris trans-illumination defects (grades 1–3) was detected in a mean of 38% normal subjects, 35% POAG patients, 53% pigment dispersion syndrome patients, and 77% of exfoliation syndrome patients. When the frequency of concentric, circular iris transillumination (grades 1–3 pooled) was compared between each of the patient groups and normal controls, a significant difference was detected between exfoliation syndrome patients and controls (p-value = 0.000019). No significant difference was detected between POAG and controls (p=0.64) or between pigment dispersion syndrome and controls (p=0.20). Furthermore, prominent concentric, circular iris trans-illumination (grade 3) was only observed in exfoliation syndrome.

Conclusion—Detection of concentric, circular iris transillumination defects with an infrared system is easy, inexpensive, rapid, and relatively specific in exfoliation syndrome. Future larger studies will be needed to confirm the findings of this small pilot study. Furthermore, this examination technique has the potential to help physicians to make earlier diagnoses of exfoliation syndrome and to better plan for future surgeries to minimize risk of complication.

Keywords

exfoliation syndrome; iris transillumination defects; diagnostic sign

Exfoliation syndrome (XFS) is a systemic disease which is characterized by deposits of fibrillar material within the eye as well as in many other organs. Although there may be some increased risk of vascular disease,¹ the most prominent pathologic features of XFS are ocular and include: ocular hypertension, secondary glaucoma (exfoliation glaucoma), and zonular weakness that can lead to phacodonesis and challenging cataract surgery. The clinical features of exfoliation syndrome include exfoliative material on the lens capsule, corneal endothelium, zonules, and in the iridocorneal angle. Iris signs of exfoliation include atrophy with a characteristic “moth eaten” appearance of the pupillary margin.²

Exfoliation syndrome has a strong genetic basis. In 2007, Thorleifsson and coworkers discovered that common variations in the lysyl oxidase like 1 (*LOXLI*) gene are strong risk factors for the development of XFS in patients from Iceland and Sweden.³ Subsequent studies of additional cohorts from United States,^{4–8} Europe,^{7, 9} Australia,¹⁰ India,¹¹ Japan,^{12, 13} Saudi Arabia,¹⁴ and South Africa¹⁵ have confirmed an association between variations in the *LOXLI* gene and XFS. However, it remains unclear which variations in the *LOXLI* gene are the source of risk for XFS. Recent data suggests that variations in the *LOXLI* promoter that alter its expression¹⁶ are associated with XFS and may be the source of some risk for XFS.¹⁷

The genetics of XFS has also been studied using mouse resources. Trantow and coworkers recently showed that mutations in the *Lyst* gene cause a phenotype in the mouse eye that closely resembles XFS.¹⁸ Mice with the *beige* mutation in the *Lyst* gene have fibrillar deposits in their eyes and pigment dispersion. Furthermore, the iris pigment epithelium cells of the *Lyst^{beige}* mice have an abnormal saw-tooth morphology that leads to concentric, circular transillumination defects of the iris. This distinct pattern of transillumination has also been anecdotally observed in human patients with XFS,¹⁸ (personal communication, Dr. H. Stanley Thompson). Here we report a prospective, masked case controls study to determine if concentric transillumination is a specific sign for XFS.

MATERIALS AND METHODS

Patient Cohorts

The study was approved by the University of Iowa’s Institutional Review Board and informed consent was obtained from study participants.

Four different cohorts of subjects from Iowa were consecutively enrolled for this study: XFS n=12; primary open angle glaucoma (POAG) n=27; pigment dispersion syndrome (PDS) n=8; and normal control subjects n= 21. Each of the 68 subjects was examined by four board-certified ophthalmologists, three of whom were fellowship-trained glaucoma specialists, the fourth was a glaucoma fellow. Subjects received complete ophthalmic examinations (including gonioscopy, standardized visual field testing, and stereoscopic optic nerve examination). Subjects were diagnosed with XFS when characteristic exfoliation material was observed on slit-lamp exam of the lens or other structures of the eye. Ten of the 12 subjects with XFS had exfoliative glaucoma, while the remaining two patients had ocular hypertension (IOP >21 mm Hg) but no exfoliative glaucoma. Subjects were diagnosed with POAG when characteristic optic nerve damage and corresponding visual field defects were detected in at least one eye and the maximum IOP was greater than 21 mm Hg as previously described.¹⁹ Subjects were diagnosed with PDS when classic signs were observed including

pigment deposits on the corneal endothelium (Krukenburg spindle), radial iris transillumination defects, and heavy pigmentation of the trabecular meshwork on gonioscopy. Seven of the 8 subjects with PDS had pigmentary glaucoma, while the remaining patient had ocular hypertension but no pigmentary glaucoma. Normal subjects had no evidence of XFS, or PDS or glaucomatous optic nerve damage and had IOP ≤ 21 mm Hg.

Infrared Videography

Patients were examined for concentric, circular transillumination by one of the authors using infrared videography as previously described.²⁰ The examiner and ophthalmologists that served as video graders were masked to the patients' diagnoses. Briefly, patients were seated with their brow resting against a headrest. A black and white digital camera that is sensitive to infrared light (RCA TC77011/u, RCA Inc., Lancaster, PA) was focused on the patient's iris using a macro/zoom lens (Javelin 99035 J, 18-108 mm, f2.5, Javelin Electronics Inc., Torrance, CA). Next, a halogen light source (Finhoff transilluminator, Welch Allyn, Skaneateles Falls, NY) was positioned against the lower eyelid and gently pressed posteriorly to illuminate the retina through the lid with both visible and infrared light. Once an image of the iris was obtained, the magnification and focus were adjusted to produce a sharp image of the iris that filled the camera field which was recorded with a digital video tape machine (JVC BR-DV3000, Wayne, NJ). Video was edited (for length only) using the software package iMovie (Apple, Cupertino, CA). Transillumination observed on the videos was then graded using a scale of 0 to 3 (Figure 1). "Grade 0" indicates no concentric bands of transillumination were observed. "Grade 1" indicates that possible concentric bands of iris transillumination were seen. "Grade 2" indicates that definite concentric bands of iris transillumination were observed, while a "Grade 3" indicates that prominent concentric bands of iris transillumination were detected. Still photos for a characteristic video of each Grade (0–3) were exported from iMovie to Photoshop (Adobe, San Jose, CA). The background illumination for each of these example images were matched to each other using the "exposure" setting in Photoshop.

Statistical Analysis

A power analysis showed that a cohort of 10 XFS subjects and 20 control subjects would have have 80% power to detect an 49% difference in the frequency of concentric iris TIDS (grade 1–3) between the groups given significance level 0.05. The association of any concentric bands of transillumination (Grade 1–3) with disease was investigated in a cohort of exfoliation syndrome patients and controls using Cochran-Mantel-Haenszel test. Exact p-values were obtained using the R statistical computing software package, which is available at www.r-project.org/. The same analyses were performed for pigment dispersion syndrome and primary open angle glaucoma subjects.

RESULTS

A cohort of exfoliation syndrome patients (n=12), pigment dispersion syndrome patients (n=8), POAG patients (n=27) and controls (n=21) was examined with infrared iris transillumination videography by four ophthalmologists that were masked to their diagnosis. The presence of concentric bands of iris transillumination defects (TIDs) was scored using a 4-step scale of grade 0 (absent); grade 1 (possible), grade 2 (definite), and grade 3 (prominent). Still photo examples of each grade are shown in Figure 1. We detected the presence of concentric, circular iris transillumination defects (grades 1–3) in a mean of 38% normal subjects, 35% POAG patients, 53% pigment dispersion syndrome patients, and 77% of exfoliation syndrome patients.

We compared the frequency of concentric TIDs between each category of eye disease (exfoliation syndrome, pigment dispersion syndrome, or POAG) and controls to search for a statistically significant association using the Cochran-Mantel-Haenszel test (Table 1). Exfoliation syndrome was found to be significantly associated with the presence of concentric bands of iris trans-illumination defects ($p=1.9\times 10^{-5}$) while no association was detected with pigment dispersion syndrome ($p=0.20$) or with POAG ($p=0.64$). The association of these transillumination bands remains highly significant after Bonferroni correction for the three tests that were conducted ($p=5.7\times 10^{-5}$). Furthermore, prominent concentric bands of iris TIDs were only observed in exfoliation syndrome patients and were never seen in the pigment dispersion syndrome patients, POAG patients, or in controls.

In retrospect, we further noted that the irides of some exfoliation syndrome patients had peri-pupillary iris trans-illumination defects consistent with a “moth-eaten” pupillary margin that is a classic sign of exfoliation syndrome (Figure 1D).

DISCUSSION

The hallmarks of exfoliation syndrome include exfoliative material on the lens capsule and in the iridocorneal angle and iris atrophy particularly at the pupillary margin. Other important signs of exfoliation syndrome include zonular dehiscence and small pupils, which can complicate cataract extraction and artificial lens implantation. A recent report of an inbred mouse model of exfoliation syndrome (*Lyst^{beige}*) displayed classic signs of the human disease as well an unusual pattern of concentric circles of iris trans-illumination defects.¹⁸ Here we showed that concentric bands of trans-illumination are strongly associated with exfoliation syndrome in man ($p=0.000069$) and are not associated with other forms of glaucoma ($p>0.05$). Not only does the *Lyst^{beige}* mouse exhibit classic signs of human disease, deposits of exfoliation material on the iris and in the aqueous humor, but this mouse also has a typical pattern of iris defects that are statistically more common in exfoliation syndrome patients than controls. These data further support the *Lyst^{beige}* mouse¹⁸ as a model of human exfoliation syndrome.

The source of the transillumination defect is abnormal morphology of the iris pigment epithelial cells. In both the eyes of *Lyst^{beige}* mice and human patients with exfoliation syndrome, the iris pigment epithelial cells take on a sawtooth-like conformation in which the periodicity of the “teeth” matches the periodicity of the iris trans-illumination defects.¹⁸ The mechanism that leads to the saw-tooth conformation of the iris pigment epithelial cells is unknown, but may involve a loss of adhesion between neighboring iris pigment epithelial cells.

The equipment cost and the examination time necessary to search for concentric bands of trans-illumination defects are modest. As a result, testing for iris trans-illumination may have some clinical utility in the early identification of those with exfoliation syndrome to allow careful surveillance for the development of ocular hypertension or exfoliation glaucoma. Additionally, this screening test may also be valuable in surgical planning for cataracts by alerting surgeons of potential risk for zonular dehiscence and the small pupils that are also hallmarks of exfoliation syndrome. However, among the four examiners in our study, iris trans-illumination had an average sensitivity of 77% (range 67–83%) and an average specificity of 62% (range 38–74%) for detecting XFS. The relatively low specificity may limit the utility of this examination in screening, however, it is important to note that prominent concentric bands of transillumination were only seen in patients with exfoliation syndrome, suggesting that pronounced concentric trans-illumination may be very predictive of exfoliation syndrome. However, the ability of infra-red iris trans-illumination to facilitate

early diagnosis of XFS is hypothetical and future prospective studies are warranted to explore its clinical utility.

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FIGURE 1. EXAMPLES OF CONCENTRIC IRIS TRANS-ILLUMINATION DEFECTS

The presence of a pattern of concentric iris trans-illumination defects was graded on a 4-step scale, Grade 0: No sign of concentric iris trans-illumination defect (Figure 1A). Grade 1: Possible concentric iris trans-illumination defect (Figure 1B). Grade 2: Definite concentric iris transillumination (Figure 1C). Grade 3: Prominent concentric iris trans-illumination defect (Figure 1D). The iris defects are indicated with arrows.

Table 1

Group	Rater	Rating Score					p-value
		0	1	2	3	1-3	
XFS N = 12	1	2 (18%)	3 (27%)	4 (36%)	2 (18%)	9 (82%)	0.000019
	2	4 (33%)	2 (17%)	2 (17%)	4 (33%)	8 (67%)	
	3	2 (17%)	2 (17%)	4 (33%)	4 (33%)	10 (83%)	
	4	3 (25%)	1 (8.3%)	3 (25%)	5 (42%)	9 (75%)	
PDS N = 8	1	4 (50%)	3 (38%)	1 (13%)	0	4 (50%)	0.20
	2	5 (63%)	0	3 (38%)	0	3 (38%)	
	3	4 (50%)	2 (25%)	2 (25%)	0	4 (50%)	
	4	2 (25%)	2 (25%)	4 (50%)	0	6 (75%)	
POAG N = 27	1	18 (69%)	7 (27%)	1 (3.8%)	0	8 (31%)	0.64
	2	23 (85%)	4 (15%)	0	0	4 (15%)	
	3	11 (41%)	14 (52%)	2 (7.4%)	0	16 (59%)	
	4	18 (67%)	8 (30%)	1 (3.8%)	0	9 (33%)	
NL = 21	1	14 (67%)	7 (33%)	0	0	7 (33%)	-
	2	14 (74%)	4 (21%)	1 (5.3%)	0	5 (26%)	
	3	8 (38%)	9 (43%)	4 (19%)	0	13 (62%)	
	4	14 (70%)	4 (20%)	2 (10%)	0	6 (30%)	