کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاریبردی در تدوین و چاپ مقاله
Clinical and Optical Coherence Tomography Features in Unilateral versus Bilateral Pseudoexfoliation Syndrome

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Purpose: To compare clinical findings and peripapillary retinal nerve fiber layer (RNFL) thickness using optical coherence tomography (OCT) in affected and fellow eyes of patients with unilateral pseudoexfoliation (PXF) syndrome with that of bilateral cases. Methods: This cross-sectional study enrolled 91 subjects with PXF including 32 unilateral and 59 bilateral cases. Subjects with elevated intraocular pressure or findings suggestive of glaucoma were excluded. RNFL thickness and optic nerve head profile were studied in all eyes using the RNFL and optic nerve head analysis OCT protocol. Clinical and OCT features were compared in affected and unaffected eyes of unilateral PXF subjects to bilateral cases. Results: Bilateral cases with PXF were older (P<0.01) and had thinner RNFL (P=0.04) than unilateral cases. From a total of 32 unilateral PXF cases, 7 subjects demonstrated RNFL thinning in the clinically normal fellow eye; all of these eyes had evidence of pupillary ruff atrophy on slit lamp examination in the absence of evident exfoliation material in the eye. Similar ruff atrophy with RNFL thinning was seen in 38 of 59 bilateral and in 16 of 32 unilateral cases. Pupillary ruff atrophy predicted RNFL thinning with sensitivity of 88.9% (95% CI, 73-96.7%) and 79.2% (95% CI, 74-84.5%) in bilateral and unilateral cases respectively, with low specificity of 45.8% (95% CI, 33.9-51.7%) and 45.5% (95% CI, 22.9-68.8%) in the same order. Conclusion: Patients with bilateral PXF have significantly thinner RNFL as compared to unilateral cases. Iris sphincter abnormality, clinically detected as pupillary ruff atrophy, may reflect early glaucomatous damage; however the specificity of this sign for predicting RNFL thinning is low. Keywords: Pseudoexfoliation Syndrome; Exfoliative Glaucoma; Optical Coherence Tomography

INTRODUCTION

Several studies have defined the clinical characteristics of manifest pseudoexfoliation (PXF) syndrome and more recent studies have focused on its pathogenesis.1,2,5 Identifying PXF glaucoma and appropriate treatment is important to prevent progressive damage. Conversion from clinically unilateral to asymmetric bilateral PXF or pseudoexfoliation glaucoma (PXFG), has already been reported.2-4 Herein we compare clinical findings and retinal nerve fiber layer (RNFL) thickness in unilateral and bilateral PXF cases in order to identify predictors of early
glaucomatous damage on optical coherence tomography (OCT).

METHODS

Consecutive patients, 40 years of age and older, attending our outpatient services unit or referred to our glaucoma clinic were screened and those with unilateral or bilateral PXF were identified. There was no hospital ethics committee at the study location which is a private practice setting, however written informed consent was obtained from all patients enrolled in this cross sectional non-interventional study. The study conformed to the tenets of the Declaration of Helsinki.

All participants underwent a detailed ophthalmologic examination including best corrected visual acuity, slit lamp examination, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, gonioscopy and +90 diopter fundus examination. A detailed slit lamp evaluation of the anterior segment in all eyes addressed changes in the cornea, iris, pupil and lens. Gonioscopy, employing the Zeiss four-mirror goniolens under standard conditions, and +90 diopter fundus examination were performed by one examiner (AR). Manipulative and indentation gonioscopy were performed to visualize the angle and the angle recess; trabecular pigmentation was noted and open angle and primary angle closure suspects were defined according to the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) classification.

The clinical definition for pseudoexfoliation included any of the following features or any combination of them: the presence of white fluffy dandruff-like material on the pupillary border, the lens capsule (after dilatation) or the angle; poor iris dilation; and crystalline lens subluxation. The right eye in bilateral cases and the affected eye in unilateral cases were selected for analysis. Eyes were classified as clinically normal if there was no evidence of exfoliation material on the pupil, lens or angle together with the absence of glaucomatous optic disc changes or visual field defects.

Patients with corneal or posterior segment pathologies, IOP >21mmHg, significant cataracts precluding clear fundus viewing, clinically detectable glaucomatous disc changes such as cupping with focal notching, disc hemorrhage or RNFL defects, previous glaucoma surgery or laser photocoagulation, history of trauma, systemic diseases such as diabetes or hypertension, and refractive errors exceeding 3 diopters were excluded from the study.

Standard achromatic automated perimetry was performed using the Humphrey visual field analyzer with the 30-2 SITA standard program (San Leandro, CA, USA, version 2) in all patients. Minimal criteria for labeling a glaucomatous visual field defect were as follows: glaucoma hemifield test (GHT) outside normal limits, abnormal pattern standard deviation (PSD) with P value <5%, or a cluster of three or more points in the pattern deviation plot in a single hemifield with P values <5%, one of which must have a P value <1%. Any one of the preceding criteria, if reconfirmed on repeat testing on two tests within one month, was considered sufficient evidence of a glaucomatous visual field defect. Patients with visual field defects at presentation reproducible over at least 3 visual fields were excluded.

OCT measurements were performed using OCT (OCT-3, Stratus, Zeiss Humphrey, Dublin, CA, USA) in both eyes in all subjects. Scans were acquired after dilation, the retinal nerve fiber layer (RNFL) thickness and fast optic nerve head protocols were used for the study. Only high quality images with signal to noise ratio >7 were selected for the study. OCT and clinical profiles of unilateral and bilateral PXF patients were compared.

Statistical analysis was performed using SPSS software 10. Differences between unilateral and bilateral PXF cases were analyzed using the student t-test and Mann-Whitney test for non-parametric variables, while chi-square test was used for analysis of differences among proportions; statistical significance was set at 0.05. Correlation among parameters was studied using Pearson’s correlation coefficient.

RESULTS

Initially, 2052 patients aged 40 years and older attending our outpatient services were screened,
out of which 203 patients (9.8%) with unilateral or bilateral exfoliation syndrome were identified and selected for the study. From a total of 203 patients, 106 cases with significant cataracts were excluded from the study and 6 patients refused to undergo OCT imaging; eventually 91 patients fulfilling all inclusion criteria were selected for the study. These included 54 male and 37 female subjects (Table 1). No significant difference was observed in clinical variables between the two genders.

Mean patient age was 52±7.1 years and mean baseline best corrected visual acuity ranged from 20/20 to 20/60. Bilateral cases were significantly older (P=0.03) and had larger cup disc ratio (P<0.01) than unilateral cases at presentation, but no significant difference was present in IOP or proportion of open and closed angles between unilateral and bilateral PXF cases (Tables 1 and 2).

Examination revealed a predominance of iris changes in the form of pupillary ruff atrophy and depigmentation patches in addition to poor dilation (Fig. 1). Some affected unilateral (1 of 32) and bilateral cases (8 of 59) had evidence of patchy iris depigmentation. Pupillary ruff atrophy was present in 48 of 59 bilateral subjects, 18 of 32 unilaterally affected cases, and also in 7 clinically normal fellow eyes of patients with unilateral PXF.

Significant RNFL thinning (flagged red in the OCT printouts) in 1 or 2 quadrants was seen in 48 of 59 bilateral PXF and in 18 of 32 unilateral PXF eyes (Table 2). Average, superior and inferior RNFL thicknesses were significantly lower in bilateral cases than unilateral cases, with the former having smaller discs (P<0.01) as demonstrated in Table 2.

All 7 contralateral normal fellow eyes of patients with unilateral PXF and pupillary ruff atrophy had borderline RNFL thickness in one quadrant as detected by OCT. None of these eyes had evident exfoliation material or other features suggestive of exfoliation syndrome. Ruff atrophy as a predictor of RNFL thinning in these eyes had a high sensitivity of 0.80% (95%CI, 0.5-0.9%) but low specificity of 0.41 (95%CI, 0.2-0.4). We compared the utility of this clinical sign in signposting RNFL thinning on OCT in bilateral versus unilateral PXF and obtained similar results with high sensitivity, 88.9% (95% CI, 73-96.7%) versus 79.2% (95% CI, 74-84.5%) but low specificity, 45.8% (95% CI, 33.9-51.7%) versus 45.5% (95% CI, 22.9-68.8%), respectively.

**DISCUSSION**

Based on the results of our study, patients with

### Table 1. Demographic and clinical characteristics of patients with unilateral and bilateral pseudoexfoliation syndrome

| Variable                  | Unilateral (n=32) (Mean±SD) | Bilateral (n=59) (Mean±SD) | P-Value |
|---------------------------|-----------------------------|----------------------------|---------|
| Age (years)               | 49±3.4                      | 57±2.1                     | 0.03    |
| Male: Female              | 18:14                       | 36:23                      | 0.6     |
| IOP (mmHg)                | 18±3.4                      | 20±1.2                     | 0.4     |
| Cup/Disc Ratio            | 0.5±0.2                     | 0.7±0.2                    | <0.01   |

SD, standard deviation; IOP, intraocular pressure

### Table 2. Optic nerve head characteristics in unilateral and bilateral pseudoexfoliation syndrome by optical coherence tomography

| Variable                              | Unilateral (n=32) (Mean±SD) | Bilateral (n=59) (Mean±SD) | P-value |
|---------------------------------------|-----------------------------|----------------------------|---------|
| Average RNFL Thickness (microns)      | 100±12.1                    | 78±10.1                    | 0.04    |
| Disc Diameter (mm)                    | 1.83±0.6                    | 1.42±0.8                   | <0.01   |
| Smax (microns)                        | 142±14.7                    | 117±15.6                   | 0.02    |
| Imax (microns)                        | 138±16.2                    | 108±12.1                   | 0.01    |
| Rim Area (mm²)                        | 1±0.8                       | 0.6±0.8                    | 0.4     |
| Total Pupillary Ruff Atrophy          | 18 (56%)                    | 48 (81%)                   | 0.08    |
| With RNFL Thinning                    | 16 (88%)                    | 38 (79%)                   |         |
| Without RNFL Thinning                 | 2 (12%)                     | 10 (21%)                   |         |
| No Ruff Atrophy/RNFL Defect          | 14 (44%)                    | 11 (19%)                   |         |
| Open: Narrow Angles                   | 18:14                       | 28:33                      | 0.07    |

RNFL, retinal nerve fiber layer; Smax, superior maximum; Imax, inferior maximum
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bilateral PXF had smaller discs, larger cup to disc ratios and thinner RNFL at presentation than their unilateral counterparts despite comparable baseline IOP. This may reflect that bilateral PXF cases may have already sustained glaucomatous damage at presentation mandating early treatment in eyes with borderline IOP.

According to current knowledge, PXF represents a continuum from unilateral to bilateral disease, with or without raised IOP, optic nerve damage and visual field defects. The spectrum between unilateral and bilateral disease and that between PXF syndrome and PXF glaucoma, remains largely unexplored. This study included more bilateral subjects (65%) than unilateral cases (35%). Bilateral cases were older than unilateral cases; this may be attributed to age related degenerative changes or represent greater ongoing glaucomatous damage due to PXF. Different results on the prevalence and proportion of unilateral and bilateral cases have been reported earlier. Puska and associates have observed 32% conversion from unilateral to bilateral PXF, and direct conversion of the unaffected fellow eye to PXF glaucoma in 38% of eyes. Vesti et al stated that the condition is never strictly unilateral and that the non-exfoliative fellow eye demonstrates exfoliative material on immunohistochemical study.

Pupillary ruff atrophy with RNFL thinning on OCT was present in 38 eyes of 59 bilateral and 16 eyes of 32 unilateral PXF cases in the current study as well as in 7 clinically normal fellow eyes of unilateral PXF. If clinically unmanifest

Figure 1. Slit lamp photographs of a patient with unilateral exfoliation syndrome: note exfoliative material in the pupillary area (left upper image); slit lamp photograph of the clinically normal fellow eye shows pupillary ruff atrophy (right upper image). Slit lamp photograph of unilateral exfoliation syndrome with exfoliative material in the pupillary area (left lower image); slit lamp photograph of the clinically normal fellow eye demonstrates pupillary ruff atrophy (right lower image).
PXF is to be considered as a separate entity, as observed in this study and concurring with previous reports, the classification of exfoliation syndrome may require revision with possible inclusion of a new category defined as PXF suspects.

RNFL thinning, an indicator of early glaucoma, can be detected with various imaging devices including OCT. In this study, 7 fellow eyes of patients with unilateral PXF showed significant RNFL thinning in the absence of exfoliation material anywhere in the eye and only the presence of pupillary ruff abnormality, however the specificity of this finding as a predictor of optic nerve damage in PXF was low. While the predictive value of sphincter abnormalities in diagnosing PXF suspects is not established from this study, a randomized controlled trial with masked observers and a larger sample size may further explore this possibility.

Well established pathogenic mechanisms exist for primary open angle and closed angle glaucoma. Iris atrophy and/or trabecular pigmentation signifies repeated ischemic episodes in an eye with a closed angle and also foretells possible angle closure attacks in a patient with a narrow or occludable angle. Yet, little correlation has been found between the amount of trabecular pigmentation and the extent of glaucomatous damage in PXF glaucoma. Pupil ruff atrophy in PXF may be caused by silent ischemic attacks or mechanical disruption due to iridolenticular contact despite the absence of clinically evident exfoliative material, thereby presumably signposting “PXF suspects” or early glaucomatous damage in unilateral cases.

The pathogenesis of pseudoexfoliation has been the subject of interest only in recent years. Ruff atrophy and patchy iris depigmentation was seen in eyes with open angles in our study which excluded eyes with high IOP or clinical glaucomatous damage. This suggests alternate and IOP-independent pathogenic mechanisms for ischemic optic nerve damage in PXF. We are not sure if these ischemic episodes in pseudoexfoliation syndrome and the resultant glaucomatous damage are the result of primary vascular involvement or due to blockage of vessels with exfoliative material.

Electron microscopy and ultrastructural studies have confirmed the presence of exfoliation material in the clinically normal fellow eye of unilateral cases as well as in other organs. Similar investigations in eyes showing RNFL loss and/or ruff atrophy could confirm our findings.

One study has reported thinner RNFL in nonglaucomatous PXF eyes compared to age matched normal subjects and non-PXF fellow eyes, also commenting that the relation between RNFL loss and glaucoma needs clarification. We understand that the relation between RNFL thinning and possible glaucoma in these eyes can only be confirmed with long term follow up.

To conclude, bilateral PXF differed from unilateral cases in terms of clinical and OCT characteristics. Pupillary ruff atrophy may be an indicator of RNFL thinning on OCT imaging reflecting early glaucomatous damage, however the specificity of this finding was low. A combination of other clinical features therefore needs to be sought which may help predict optic nerve damage in manifest and unmanifest PXF syndrome.

Conflicts of Interest
None.

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