Frequency and Risk Factors of Narrow Angles in Patients with Pseudoexfoliation: A Case-Control Study

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Abstract

Purpose To determine the frequency and risk factors of narrow angles in pseudoexfoliation (PXF) patients.

Methods A prospective case-control study was conducted during the period from March 2017 to December 2020. Adult patients (above 40 years) presenting with PXF were consecutively enrolled (study group). Cases were matched with individuals above 40 years presenting to a comprehensive ophthalmology clinic without evidence of PXF (control group).

Results We enrolled 196 PXF patients and 98 controls. The occurrence of narrow angles was 25% in the PXF group and 5.1% in the control group (P = 0.0001). Compared to controls, PXF patients were older (72.6 ± 9.6 vs. 64.4 ± 8.5, P < 0.0001) and had a lower mean ACD (2.79 ± 0.4 vs. 3.05 ± 0.4, P < 0.0001). There was no difference in AL measurements between both groups (23.3 ± 1.4 vs. 23.7 ± 1.0, P = 0.0714). After stratification by age group and gender, the risk of narrow angles was higher in PXF patients above 60 years (OR, 5.71; 95% CI, 1.01-32.27; P, 0.048). There was no gender difference in the risk of developing narrow angles.

Conclusion Narrow angles are more frequently encountered in PXF patients compared to controls. Advanced age (> 60 years) is significantly associated with an increased likelihood of developing narrow angles.

Introduction

Pseudoexfoliation syndrome (PXF) is a systemic disorder characterized by the production of abnormal basement membrane material from an aging extracellular matrix[1]. The deposition of this material inside the eye leads to secondary glaucoma [2].

Pseudoexfoliation glaucoma (PXG) is characterized by elevated intraocular pressure (IOP) and progressive optic neuropathy associated with the presence of pesudoexfoliative material in the anterior chamber [3]. Gonioscopic evaluation of patients with PXG typically reveals an open angle with a hyperpigmented trabecular meshwork and deposition of pigments anterior to Schwalbe's line, hence, PXG is commonly regarded as a secondary open angle glaucoma and the degree of IOP elevation was correlated in some studies with the extent of angle pigmentation [4]. This was further supported by the fact that patients with unilateral PXF have a higher mean IOP in the affected eye [5]. Nonetheless, clinical studies looking into the angle status of patients with PXF have demonstrated that some patients may have narrow anterior chamber angles [6]. Moreover, it has also been reported that some patients with PXG may have angle closure, rather than open angle glaucoma [7].

It remains unknown whether the occurrence of narrow angles in PXF patients is higher than the general population. Moreover, limited information is available on factors that may lead to narrow angles in

patients with PXF. Therefore, the aim of our study was to report the frequency of narrow angles in a serial cohort of PXF patients and to determine the risk factors associated with narrow angles in PXF.

Materials And Methods

This was a prospective case-control study conducted at a tertiary care eye center in Riyadh, Saudi Arabia, and approved by the local Institutional Review Board. Patient evaluation took place during the period from March 2017 to December 2020. New patients presenting to both the glaucoma and comprehensive clinic that were above 40 years and had evidence of pseudoexfoliation on clinical examination were enrolled sequentially (study group). The control cohort comprised individuals above 40 years presenting to the comprehensive eye clinic for various reasons. The exclusion criteria were: (1) prior history of intraocular surgery; (2) prior history of any laser procedure (e.g. laser peripheral iridotomy); (3) history of uveitis; (4) posterior segment disease that may affect angle status.

For each patient, a comprehensive ocular examination was performed including visual acuity assessment, slit lamp examination, gonioscopy, and measurements of anterior chamber depth (ACD) and axial length (AL).

Gonioscopy was performed by glaucoma specialists and ophthalmologists competent in performing gonioscopy in a standardized fashion. The testing was done in a dark room using a Volk G-6 gonioscopy lens (Volk Opticals, Mentor, OH). Gonioscopy was performed for each eye individually with the patient maintaining the primary position of gaze. Each quadrant was evaluated and graded separately by moving the slit beam of light from one mirror to the other. In patients with narrow angles, slight indentation on the cornea was performed to diagnose appositional closure and to identify peripheral anterior synechiae. Grading of the anterior chamber angle was recorded using the Shaffer angle grading system (0: no visible structures, 1: Schwalbe's line seen, 2: posterior pigmented trabecular meshwork seen, 3: scleral spur seen, 4: ciliary body band seen) [8].

Non-contact ocular biometry was performed using IOL Master 500 (Carl Zeiss Meditec AG, Jena, Germany). Recorded measurements of ACD and AL were included. For each patient, five serial measurements were taken and their average was provided by the device.

Patients were classified as open angle if they had a Shaffer grade 3 or 4 in at least three quadrants, whereas those with a Shaffer grade 2 or less were classified as narrow angle. In patients with unilateral PXF, measurements of the affected eye were used to report ACD and AL values, and in the remainder of the participants measurements of the right eye were used.

The sample size was calculated based on the assumption that the proportion of PXF patients with narrow anterior chamber angle is 9.3% [6]. In order to detect such a difference in the proportion of patients between cases and controls with a 85% power at an alpha error probability of 5% with an allocation ratio of 2:1, the required number of participants was 294 (196 cases and 98 controls).

Statistical analysis was performed using R (R Studio version 1.1.463 Mac, RStudio Inc., Boston, MA). Continuous variables were reported as mean ± standard deviation and categorical variables were reported as frequency and percentage. The unpaired t-test was used to compare numerical variables, whereas the chi-square and Fisher's exact tests were used to compare categorical variables. Binary logistic regression analysis was used to assess variables associated with the incidence of narrow angles in patients with PXF. Statistical significance was set at a P value of less than 0.05.

Results

The study group included 196 PXF patients and the control group included 98 consecutively matched patients without PXF. Table 1 outlines the baseline characteristics of the cohort. Overall, a narrow angle was documented in 25% of patients in the PXF group and 5.1% of patients in the control group (P = 0.0001). Compared to the control group, patients with PXF were older and had a lower mean ACD. AL measurements were comparable between both groups (P = 0.0713).

Table. 1	Baseline Characteristics				
	PXF group		Control group		P
Number	196		98		
Age					
Mean (SD)	72.6 (9.6)		64.4 (8.5)		< 0.0001
Range	52–100		41–93		
	n	%	n	%	
Gender					
Male	111	56.6	50	51.0	0.4688
Female	85	43.4	48	49.0	
Angle Status					
Open	147	75.0	93	94.9	0.0001
Narrow	49	25.0	5	5.1	
ACD					< 0.0001
Mean (SD)	2.79 (0.4)		3.05 (0.4)		
Range	1.99–3.75		2.17–3.83		
AL					
Mean (SD)	23.3 (1.4)		23.7 (1.0)		0.0714
Range	20.8–31.3		21.1–27.0		
PXF, pseudoexfoliation; SD, standard deviation; n, number; ACD, anterior chamber depth; AL, axial length					

The mean ACD in PXF patients with an open angle was 2.89 ± 0.35 mm compared to 2.49 ± 0.31 mm in PXF patients with a narrow angle (P < 0.0001) (Fig. 1). Furthermore, the mean AL in PXF patients with an open angle was 23.47 ± 1.5 mm compared to 22.68 ± 0.96 mm in PXF patients with a narrow angle (P = 0.0001) (Fig. 2).

Unilateral PXF was documented in 49 (25%) patients, of which 15 (30.6%) had a narrow angle in the affected eye. Out of these 15 patients, 9 (60%) had a narrow angle in the contralateral eye too, whereas the other eye had an open angle in 6 (40%) patients.

After stratification by age group and gender, an increased risk of narrow angle was noted in PXF patients that were above 60 years (OR, 5.71; 95% CI, 1.01–32.27; P, 0.048) (Table 2).

Table 2
Risk of narrow angle in patients with PXF

	n	%	OR	95% CI	P
Total	49	25			
Age			5.71	(1.01–32.27)	**0.048**
< 60y	1	0.5			
> 60y	48	24.5			
Sex			1.73	(1.03–2.90)	0.827
Male	23	11.7			
Female	26	13.3			
PXF, pseudoexfoliation; n, number; OR, odds ratio; CI, confidence interval; y, years					

Discussion

In the current study, we report a high frequency of narrow angles in PXF patients compared to the serially examined control patients (25.1% vs. 5%). The Middle Eastern region lacks population-based studies on the prevalence of narrow angles in the adult population for comparison, however, data from other ethnic groups suggests that it ranges from 2.2% in Whites [9] to 15.9% in Asians [10]. A higher rate of narrow angle detection in PXF patients in the study population suggests that there is an association between PXF and clinically evident narrow anterior chamber angle.

Two prior studies have described the incidence of narrow angles in PXF patients. Out of 74 PXF patients, Roth M et al [11] found 3 (4.1%) cases of angle closure. Moreover, Gross FJ et al [6] reported five cases with a narrow angle (Shaffer grade two or less) in a review of 54 PXF patients (an incidence of 9.3%). The higher occurrence of narrow angles in our cohort (25.1%) compared to the reports by Roth M et al and Gross FJ et al might be explained by the racial difference between our patient population and theirs.

Several factors have been cited as causes of a narrow angle in PXF patients. First, laxity or degeneration of lens zonules may lead to decreased tension and subsequently a forward displacement of the lens [12]. Secondly, several studies have suggested that certain ocular biometric characteristics (e.g. corneal thickness, AL, and ACD) in PXF patients may differ compared to healthy individuals [13, 14], thus, such difference may anatomically predispose to narrow angles. Finally, as it is well known from previous studies that the incidence of PXF increases with age [15] and that the anterior chamber angle is narrower in older individuals [16], it is possible that the high rate of PXF is attributed to the older age of affected patients.

The mean ACD in PXF patients was lower compared to the control group in our study (2.79 ± 0.4 vs. 3.05 ± 0.4, P < 0.0001), whereas the mean AL was comparable between both groups (23.3 ± 1.4 vs. 23.7 ± 1.0, P = 0.0714). This suggests that the anatomical difference between healthy eyes and eyes with PXF is at the level of the anterior segment and that PXF patients do not have shorter eyes compared to normal subjects. Therefore, the higher rate of narrow angles in PXF patients is possibly related to a larger or anteriorly displaced crystalline lens that may occur secondary to PXF-related zonular weakness. Another factor that is important to consider is the mean age of the PXF group in our study. PXF patients were older compared to the control group (72.6 ± 9.6 vs. 64.4 ± 8.5, P < 0.0001); thus, it is possible that crystalline lens enlargement occurring at a higher rate with advancing age contributed to a narrower angle which may explain the higher frequency of narrow angles in the older PXF group compared to the younger control group. Measurement of lens thickness in PXF patients is required to substantiate this hypothesis.

In binary logistic regression analysis of our data, PXF patients above 60 years were more likely to have narrow angles compared to younger patients (OR, 5.71; 95% CI, 1.01–32.27; P, 0.048). A finding that is consistent with previously published data correlating narrow angles with advanced age in normal individuals [16]. Furthermore, we did not find a gender difference in the risk of narrow angles among PXF patients, which is in contrary with studies on healthy subjects that report a higher prevalence of angle narrowing among female patients [17].

The findings of our study must be carefully interpreted within the context of the following limitations. First, we recruited PXF patients from a tertiary care glaucoma clinic. This might have led to a referral bias, in that patients with narrow angles were most likely to be referred for further glaucoma workup. Secondly, the study sample constitutes a cohort of patients from the Saudi population, thus, findings cannot be directly extrapolated to other populations. Finally, due to machine unavailability, lens thickness measurements were not performed. Greater lens thickness is an important anatomical trait that is known to be a risk factor in the development of angle closure glaucoma [18]. Thus, future studies documenting lens thickness measurements are required to further improve our understanding of the correlation between narrow angles and PXF.

In summary, narrow angles were more frequently encountered in PXF patients compared to controls. The higher frequency of narrow angles is most probably attributed to ocular biometric changes in the anterior segment of PXF eyes. Advanced age (> 60 years) was significantly associated with an increased likelihood of narrow angles.

Declarations

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Consent to participate: All subjects have signed a consent to participate in this research project.

Consent for publication: Not applicable.

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Figures

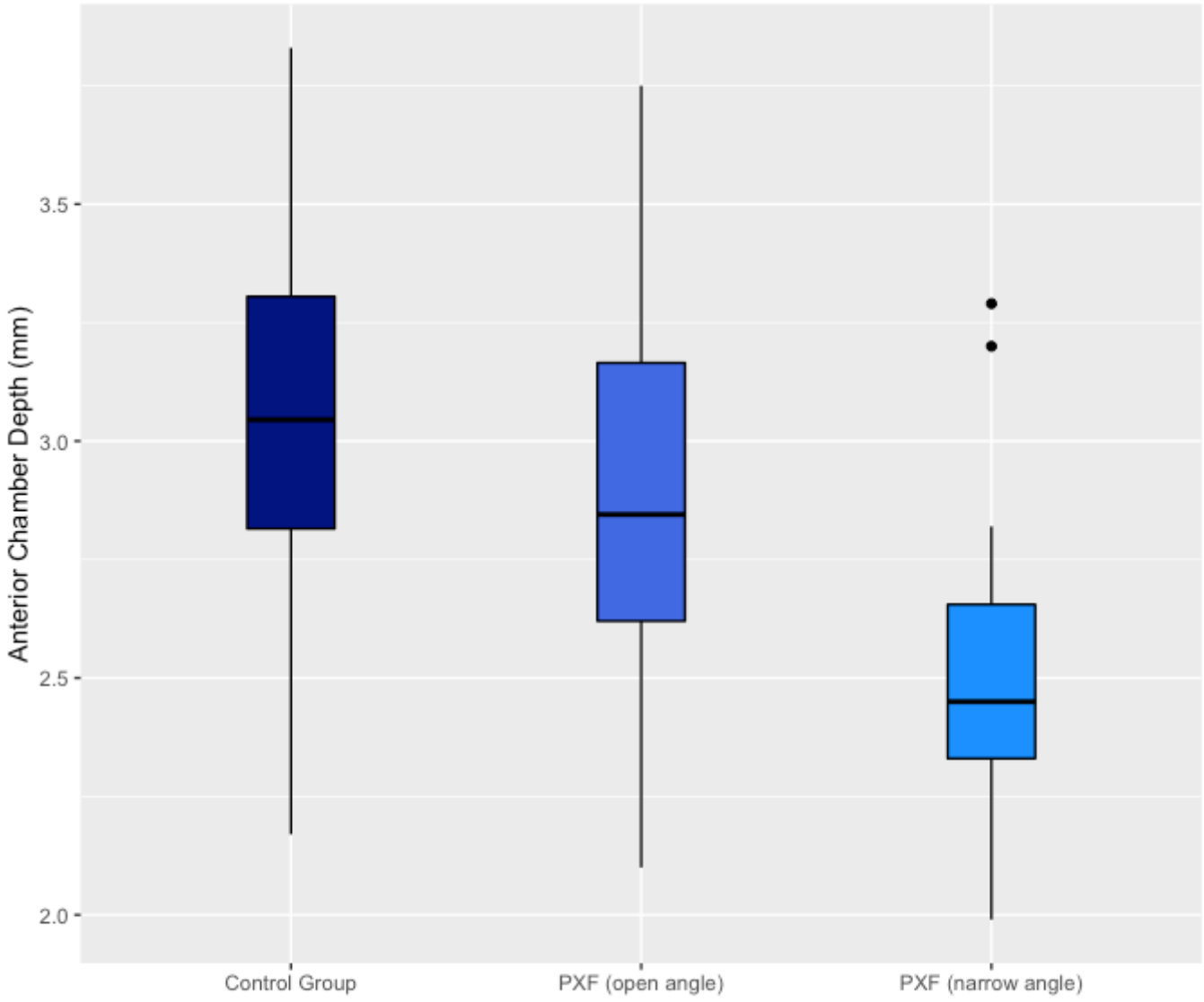

Figure 1

Boxplots showing the distribution of the mean anterior chamber depth (in mm) in the control group, pseudoexfoliation patients with open angle, and pseudoexfoliation patients with narrow angle.

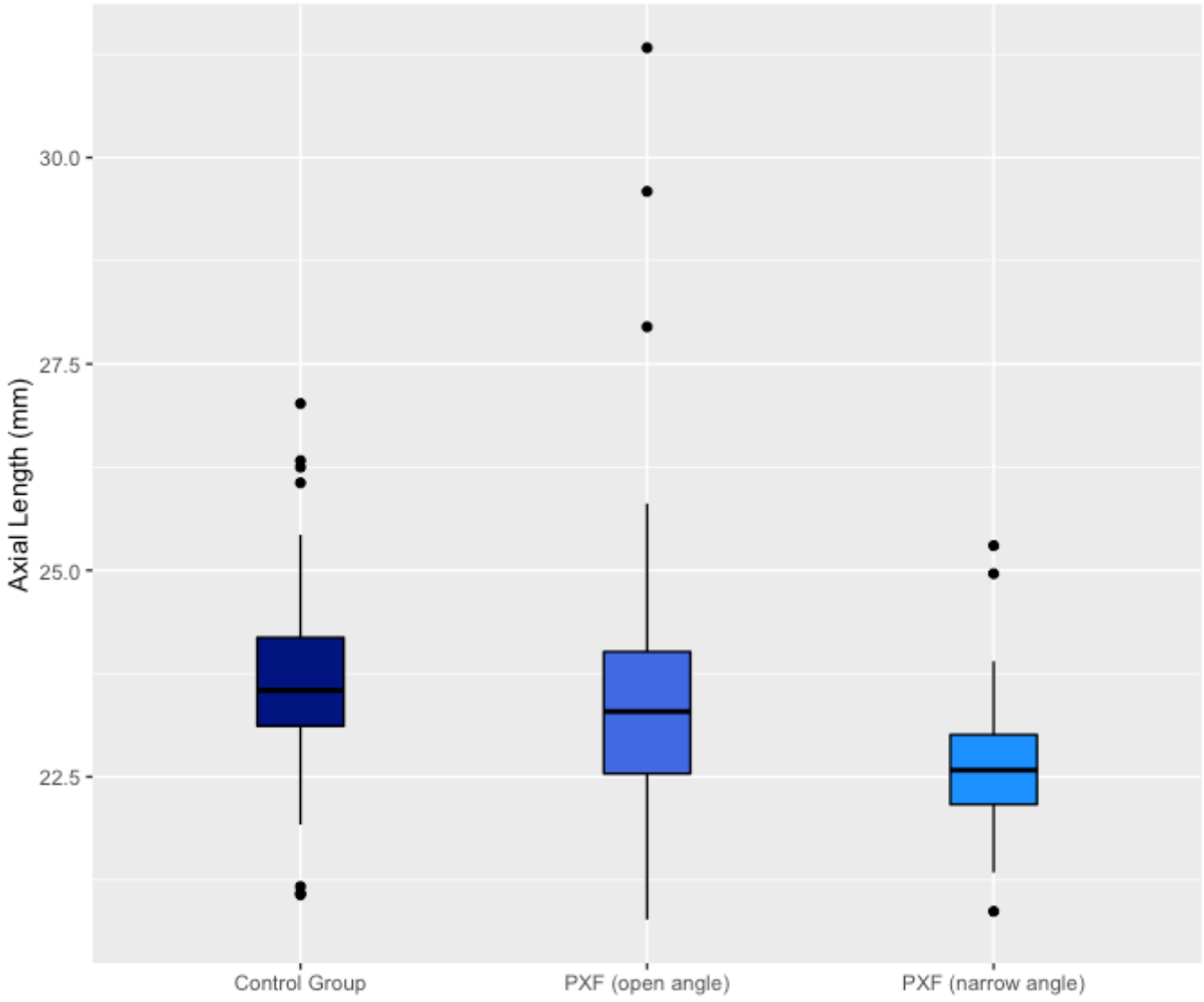

Figure 2

Boxplots showing the distribution of the axial length (in mm) in the control group, pseudoexfoliation patients with open angle, and pseudoexfoliation patients with narrow angle.