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Pseudoexfoliation syndrome at a Singapore eye clinic

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Background: The purpose of this study was to investigate the demographics of pseudoexfoliation syndrome (PXF) and pseudoexfoliative glaucoma (PXG) in a Singapore hospital eye outpatient clinic.

Methods: A retrospective study of 93 consecutive patients (146 eyes) with PXF was undertaken by a single ophthalmologist over a period of 37 months (July 1, 2006, to July 31, 2009).

Results: Ninety-three (2.8%) of 3,297 patients seen during the study period were diagnosed with PXF. Forty-three (46.2%) of the 93 PXF patients were male. Indians were 5.04 times more likely to develop PXF than Chinese ($P<0.001$, 95% confidence interval 3.05–8.33), while Malays were 2.22 times more likely to develop PXF as compared with Chinese ($P=0.029$, 95% CI 1.08–4.55). Twenty-two (23.7%) of the 93 PXF patients had PXG at the time of diagnosis. There was no statistically significant difference in mean age between PXF and PXG patients. There was a larger proportion of males with PXG than females ($P<0.001$).

Conclusion: PXF is not infrequent in elderly Singapore eye clinic patients, and is more likely to occur in Indians than in Chinese. In the Singapore eye clinic setting, males may be more likely to develop PXG, although larger studies will be required to confirm this.

Keywords: exfoliation syndrome, pseudoexfoliation syndrome, exfoliation glaucoma, glaucoma capsulare

Introduction

Pseudoexfoliation syndrome (PXF) is thought to be an ocular manifestation of a systemic extracellular matrix disorder characterized by accumulation of fibrillar material in tissues, including ocular tissues.[1–5] It is characterized by the presence of small, white pseudoexfoliative material in the anterior segment, predominantly on the pupillary margin and anterior lens capsule.[6]

The association between PXF and glaucoma is well recognized.[3,7] In fact, PXF has been described as the most common identifiable cause of open-angle glaucoma worldwide.[8] Studies have also shown that glaucomatous damage progresses more rapidly in patients with PXF and glaucoma when compared with those having chronic open-angle glaucoma.[9–14] Visual field defects have also been shown to be more severe at the time of diagnosis in patients with pseudoexfoliative glaucoma (PXG)[11,15] and to deteriorate more rapidly when compared with chronic open-angle glaucoma.[16] Cataracts have been reported to be more common in PXF patients,[17,18] and PXF has also been shown to be associated with zonulysis during cataract surgery as well as postoperative lens dislocation.[8,19]

PXF is an age-related disease with significant geographic and racial variations in prevalence.[20–23] Population-based studies have reported prevalence rates of PXF worldwide varying from 0%[24] to over 40%.[20,21,24] The prevalence of PXF has been reported in various parts of the world, including Europe, the Middle East, and Australia.[25–41]

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Singapore is a multiracial country, comprising predominantly Chinese, Malay, and Indian populations. To date, there have only been two studies looking at the prevalence of PXF in the Singapore population, and both targeted specific ethnic groups.[42,43] Therefore, this study was conducted to provide further insight into the demographics of PXF and PXG across all ethnic groups in Singapore.

Materials and methods

All patients aged 40 years or older seen by a single ophthalmologist over a period of 37 months (July 1, 2006, to July 31, 2009) at the general ophthalmology clinic of a tertiary hospital in Singapore were recruited into the study. Patients diagnosed with PXF were identified, and a retrospective case review of their case sheets was performed. Appropriate ethics approval was obtained from the National Healthcare Group Domain Specific Review Board.

All patients underwent a comprehensive ophthalmological assessment including visual acuity assessment, Goldmann applanation tonometry, slit-lamp examination before and after dilation of pupils, and dilated fundus examination. The anterior lens surface and pupillary ruff were inspected under high magnification. All eyes were also retroilluminated to detect the presence of a hoarfrost ring.

PXF was diagnosed if typical pseudoexfoliative material was present on the anterior lens capsule and/or pupillary margin in either one or both eyes. PXG was defined as the presence of typical pseudoexfoliative material in combination with a raised intraocular pressure of >21 mmHg and a reproducible visual field loss with optic disc cupping and neuroretinal rim thinning, with no evidence of other secondary causes of glaucoma.

The medical records of patients diagnosed with PXF and PXG were reviewed for demographic characteristics, including age, sex, and ethnic origin. Ethnic origin was ascertained based on the patients' registration information sheet.

All statistical analyses were performed using IBM SPSS Statistics (version 19, IBM Corp, Armonk, NY, USA) and R (version 2.15.2, The R Foundation for Statistical Computing, Vienna, Austria). The mean ± standard deviation for age and frequencies of other demographic and clinical characteristics were calculated. The mean age was compared between groups using the independent-samples *t*-test, while categorical data, such as sex, race, and laterality, were compared using the Pearson chi-square test or Fisher's Exact test if expected counts within a category were less than 5 for more than 20% of cells. Logistic regression was performed to calculate the odds ratio of likelihood of having PXF, with the 95% confidence interval (CI) for each demographic factor. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Table 1 Population with and without pseudoexfoliation syndrome based on age groups

Age (years)	Non-PXF, n (%)	PXF, n (%)	All patients, n (%)
40–49	340 (10.6)	1 (1.1)	341 (10.3)
50–59	806 (25.2)	3 (3.2)	809 (24.5)
60–69	984 (30.7)	32 (34.4)	1,016 (30.8)
70–79	735 (22.9)	41 (44.1)	776 (23.5)
≥80	339 (10.6)	16 (17.2)	355 (10.8)
Total	3,204	93	3,297

Abbreviation: PXF, pseudoexfoliation syndrome.

Results

Overall demographics

A total of 3,297 patients were identified, of whom 1,459 (44.3%) were male and 1,838 (55.7%) were female. The ethnic distribution of the patients included 2,779 (84.3%) Chinese, 199 (6.0%) Malays, 237 (7.2%) Indians, and 82 (2.5%) from other races.

Pseudoexfoliation syndrome

Ninety-three patients (2.8%, 146 eyes) were identified as having PXF, of whom 46.2% were male. PXF was bilateral in 53 patients (57.0%). The mean age of patients with PXF was 72.2±8.7 (range 44–94) years, with the majority (95.7%) being 60 years or older (Table 1). We found no significant sex predilection in the patients with PXF whether we analyzed the data as a cohort or in separate ethnic groups. The sex distribution of the patients with PXF according to ethnicity is summarized in Table 2.

The major ethnic groups among the 93 PXF patients were Chinese, Malay, and Indian (Table 3). In the Chinese population, 2.1% were found to have PXF. About twice the

Table 2 Sex distribution based on ethnicity in patients with pseudoexfoliation syndrome

	Sex		Total
	Male	Female	
Ethnicity n (%)			
Chinese	22 (51.2)	36 (72.0)	58 (62.4)
Malay	5 (11.6)	4 (8.0)	9 (9.7)
Indian	15 (34.9)	8 (16.0)	23 (24.7)
Others	1 (2.3)	2 (4.0)	3 (3.2)
Total	43	50	93

Table 3 Age, ethnicity, and sex of patients with pseudoexfoliation syndrome

	Non-PXF population	PXF population	Unadjusted OR	95% CI	*P*-value	Adjusted OR (full model)	95% CI	*P*-value
Age (years)								
Mean ± SD	64.3±11.6	72.2±8.7	1.06	1.04–1.08	<0.001	1.07	1.05–1.09	<0.001
Ethnicity n (%)								
Chinese	2,721 (84.9)	58 (62.4)	Ref	–	–	Ref	–	–
Malay	190 (5.9)	9 (9.7)	2.22	1.08–4.55	0.029	2.49	1.20–5.15	0.014
Indian	214 (6.7)	23 (24.7)	5.04	3.05–8.33	<0.001	6.00	3.57–10.09	<0.001
Others	79 (2.5)	3 (3.2)	1.78	0.55–5.81	0.338	1.71	0.51–5.67	0.381
Sex n (%)								
Female	1,788 (55.8)	50 (53.8)	Ref	–	–	Ref	–	–
Male	1,416 (44.2)	43 (46.2)	1.09	0.72–1.64	0.696	1.08	0.70–1.64	0.734

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; PXF, pseudoexfoliation syndrome; Ref, reference.

percentage of Malays (4.5%) was found to have PXF. The Indian population were found to have the highest percentage of PXF (9.7%) among the three major races.

Indians were found to be 5.04 times more likely to develop PXF than Chinese ($P<0.001$, 95% CI 3.05–8.33), while Malays were 2.22 times more likely to develop PXF than Chinese ($P=0.029$, 95% CI 1.08–4.55). The relationship between sex and likelihood of developing PXF was not statistically significant ($P=0.696$). The results were similar in the full model (Table 3). Our study found no statistically significant relationship between laterality and age, sex, or ethnicity (Table 4).

Pseudoexfoliative glaucoma

Of the 93 patients with PXF, 22 (23.7%) were identified as having PXG, among whom almost three quarters of cases were bilateral (16 patients, 72.7%). The mean age of patients with PXG was 73.1±9.1 years. There was no statistically significant difference in mean age between patients with PXG and those with PXF only ($P=0.390$; Table 5). Eighteen (81.8%) of the 22 patients were male. There was a significantly larger proportion of males with PXG than without PXG ($P<0.001$; Table 5).

The ethnic distribution of the patients with PXG included 12 Chinese (55.5%), three Malays (13.6%), and seven Indians (31.8%). There was no statistically significant difference in ethnic distribution of PXG patients when compared with non-PXG patients ($P=0.531$, Table 5). Subgroup analysis also revealed no sex predilection in the various ethnic groups. Our study found a larger proportion of bilateral eye involvement of PXF in the PXG group when compared with the non-PXG group, although the difference did not reach statistical significance ($P=0.088$).

Table 4 Association of laterality with age, sex, and ethnicity of patients in PXF population

	Unilateral	Bilateral	*P*-value
Patients, n (%)	40 (43.0)	53 (57.0)	
Age (years)			
Mean ± SD	70.9±7.9	73.1±9.1	0.237*
Ethnicity n (%)			0.937***
Chinese	26 (65.0)	32 (60.4)	
Malay	3 (7.5)	6 (11.3)	
Indian	10 (25.0)	13 (24.5)	
Others	1 (2.5)	2 (3.8)	
Sex, n (%)			0.530**
Male	17 (42.5)	26 (49.1)	
Female	23 (57.5)	27 (50.9)	

Notes: *Independent samples *t*-test; **Pearson chi-square test; ***Fisher's Exact test.
Abbreviations: SD, standard deviation; PXF, pseudoexfoliation syndrome.

Discussion

PXF has been shown in previous studies to be associated with increasing age, typically being more common after the age of 60 years. Forsius et al[20] found that the incidence of PXF doubled every decade after the age of 50 years. Our study observed a similar trend. However, we also observed a decrease in the number of patients with PXF from the age of 80 years onwards. There are two possible explanations for this observation. The average life expectancy of

Table 5 Age, ethnicity, and sex of PXG patients

	Non-PXG population	PXG population
Age (years)		
Mean ± SD	70.9±7.9	73.1±9.1
Ethnicity n (%)		
Chinese	46 (64.8)	12 (54.5)
Malay	6 (8.5)	3 (13.6)
Indian	16 (22.5)	7 (31.8)
Others	3 (4.2)	0 (0.0)
Sex, n (%)		
Female	46 (64.8)	4 (18.2)
Male	25 (35.2)	18 (81.8)

Abbreviations: PXG, pseudoexfoliative glaucoma; SD, standard deviation.

Singapore's population around the time of data collection was 81.4 years,[44] so the decrease in numbers of patients aged over 80 years could be attributed to a higher death rate in that age group. Another possible explanation could be that more people over 80 years of age are pseudophakic, and mild underlying PXF may have been undetected after surgery. Various studies have shown conflicting results for sex predisposition.[25,28,40,45] However, our present study found no significant sex predilection.

The prevalence of PXF has been shown to vary significantly between populations[7,25,26,28–30,32–37,39–43,45–55] (Table 6). The underlying reason for the large demographic variation in PXF is still undetermined. However, factors including genetics[56–58] and environmental influences such as living in lower latitudes,[21] sun exposure,[20,46] dietary factors,[50] altitude,[53] and even iris color[59] have been postulated.

Data from previous studies have shown that the prevalence of PXF in East Asians is low when compared with Europeans.[25,28,29,40–43] It has been postulated that this may be the result of both genetic composition and environmental influences.

Table 6 Prevalence of PXF in populations around the world

Country	Age (years)	Prevalence (%)
Australia (Central Australia)[46]	≥61	16.3
Australia (Blue Mountains)[7]	49–97	2.3
Australia (Victoria)[33]	≥40	0.98
People's Republic of China[41]	≥50	2.38
Finland[17]	≥70	22.1
France[49]	>50	5.5
Greece (Epirus)[51]	≥50	24.3
Greece (Crete)[53]	≥40	16.1
Greenland[50]	≥70	4.5
Hong Kong[45]	≥60	0.4
Iceland[28]	≥50	10.7
India (South India)[29]	≥40	3.8
India (Tamil Nadu)[32]	≥40	6.0
India (Andhra Pradesh)[40]	≥40	3.01
India (Central India)[55]	≥30	0.95
Iran[35]	≥50	13.1
Japan[34]	≥50	3.4
Jordan[26]	40–90	9.1
Myanmar[25]	≥40	3.4
Nepal (Gurungs)[37]	≥30	8.2
Nepal (Tamangs)[37]	≥30	0.3
Nigeria[54]	30–90	2.7
Norway[48]	>65	16.9
Pakistan[36]	≥45	6.45
Singapore (Chinese)[42]	≥40	0.2
Singapore (Malay)[43]	40–80	0.46
Turkey[52]	≥50	7.2
USA (Framingham)[47]	52–85	1.8
USA (Southeastern USA)[30]	≥60	3.2

Notes: Current study: Chinese 2.1%; Malays 4.5%; Indians 9.7%.
Abbreviation: PXF, pseudoexfoliation syndrome.

PXF has been described as being rare in the Chinese population. Lee et al[60] showed that the G allele of rs3825942 within LOXL1 confers a tenfold increase in risk for PXF/PXG in the Chinese population. However, they found a similar allelic architecture between Chinese and other Caucasian populations, and went on to postulate that there might be other genetic and/or strong environmental factors that could be modulating the phenotypic expression of PXF in the Chinese population, resulting in a lower prevalence of the disease.

In this study, we observed that approximately 2.1% of the Chinese population had PXF. This value was similar to that reported by the Beijing Eye Study,[41] which found an overall prevalence of definite PXF in a Northern Chinese population of 2.38%, but this is much higher than that reported by the Tanjong Pagar survey[42] or a hospital-based cohort study in Hong Kong. The Tanjong Pagar survey looked specifically at Chinese Singaporean adults aged 40 years and older and observed a prevalence of 0.2% that rose to 0.7% in those over 60 years of age. Young et al[45] investigated a hospital-based cohort of Chinese in Hong Kong and observed a prevalence of 0.4%.

In our study, 9.7% of Indians were found to have PXF. Krishnadas et al,[32] Arvind et al,[29] and Thomas et al[40] looked at the South Indian populations and reported prevalences of 6.0%, 3.8%, and 3.01%, respectively, in individuals over the age of 40 years. Jonas et al[55] looked at Central Indian populations aged 30 and above and reported the prevalence of PXF to be 0.95%.

Data on the prevalence of pseudoexfoliation in the Malay ethnic group is very limited. The Singapore Malay Eye Study[43] is the only research that has looked at the prevalence of PXF in the Malay population aged 40–80 years, and reported the prevalence of PXF in Malays to be 0.46%. Our study observed a much higher percentage, with 4.5% of Malays having PXF.

The higher proportion of PXF found in all ethnic groups in our study could be attributed to the fact that our research was hospital-based. PXF has been described to be more prevalent in patients with ocular conditions such as cataracts and glaucoma,[3] and determining prevalence in a hospital-based cohort would have resulted in some degree of selection bias.

Another explanation could be that the prevalence of PXF is in fact higher in the general population and that we may be underdiagnosing the condition. Making a diagnosis of

PXF requires a careful slit-lamp examination[3] after pupillary dilatation, and the condition may be underdiagnosed in the community.

When comparing the three ethnic groups in our present study, we observed that Indians were five times more likely to have PXF than Chinese, whereas Malays were about twice as likely to have PXF when compared with Chinese. This is consistent with the available data on the prevalence of PXF in these three races.[29,32,40,42,43,45]

Almost one in four (23.6%) PXF patients in our study had glaucoma. Studies that have looked at PXG in PXF patients have reported variable percentages. The Andhra Pradesh Eye Disease study[40] reported that 5.5% of PXF patients had glaucoma. In the Aravind Comprehensive Eye Survey,[32] 23 (7.5%) of 308 patients had definite glaucoma, while the Blue Mountain Eye Study[7] reported a 14.2% incidence of glaucoma. A possible explanation for this variation in the percentage of glaucoma could be due to genetic as well as environmental differences. Previously mentioned studies had focused on Indian or Caucasian populations; our present study, however, focused on a predominantly Chinese population in a hospital clinic setting where ocular diseases are expected to be encountered more frequently. Our study also found a significantly larger proportion of males than female with PXG. Nevertheless, the reliability of this finding may be limited given the small sample size.

Our current study is one of the largest of its kind to address PXF among the Chinese and Malay populations living in Southeast Asia. It is also the first study to make direct comparisons between PXF sufferers in the Chinese, Malay, and Indian populations within the unique multiracial setting of Singapore. There was also consistency in clinical examinations, as all were performed by the same ophthalmologist.

The limitations of the present study include its retrospective design, and its hospital-based nature, which may have possibly resulted in selection bias. A larger prospective study looking at the prevalence of PXF in the local community would be helpful to decipher the unique epidemiology of PXF in our local population. In conclusion, PXF is not infrequently encountered in elderly Singapore eye clinic patients, and is more likely to occur in Indians and less likely in Chinese. In the Singapore clinic setting, males may be more likely to develop PXG, although larger studies will be required to confirm this.

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Disclosure

The authors report no conflicts of interest in this work.

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