Manuscript type: Original Article: Clinical Report

Title: Pseudoexfoliation in a Rural Burmese Population: The Meiktila Eye Study

Keywords: pseudoexfoliation syndrome, glaucoma, blindness, cataract, occludable angle.

Authors: Anmar M.A. Rahman, FRANZCO¹, RJ Casson DPhil, FRANZCO², HS Newland, MPH, FRANZCO², J Muecke FRANZCO², S McGovern FRANZCO², TH Aung MB,BS, M.Med Sc,³ D Selva FRANZCO², T Aung MD³.

¹Department of Ophthalmology, Middlemore Hospital, Auckland, New Zealand.
²South Australian Institute of Ophthalmology, Adelaide, South Australia
³Yangon Eye Hospital, Yangon, Myanmar

Address for correspondence:
Corresponding Author: Anmar M Abdul-Rahman
Mailing address: Department of Ophthalmology, Manukau SuperClinic, Private Bag 98743, South Auckland Mail Centre, Auckland, New Zealand.
Tel.0064-9-277 1660
Fax. 0064-9-277 1600
Email: anmar_rahman@hotmail.com

Manuscript word count: 2492
Abstract Word count: 200
Number of references: 22
Number of tables: 4
Licence for Publication:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in British Journal of Ophthalmology editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence.

Competing Interest: None declared.
Abstract

Aims:
To report the prevalence and correlates of pseudoexfoliation syndrome (PXF) in a rural Burmese population.

Methods:
A cross-sectional, population-based survey of the inhabitants 40 years of age and over in the Meiktila District. Ophthalmic examination included Snellen visual acuity, slit lamp examination, tonometry, gonioscopy, dilated fundus examination and Frequency Doubling Perimetry.

Results:
In a population of 2076 subjects (4016 eyes) the prevalence of PXF was 3.4% (95% Confidence interval (CI) 2.14 - 4.67%; 78 eyes). Twelve eyes with PXF were blind. In the univariate analysis, PXF was associated with: increasing age, blindness (odds ratio (OR) 4, 95% CI 1.84 - 8.68, p<0.0004), increasing intraocular pressure (IOP) (OR 1.08, 95% CI 1.04 - 1.11, p<0.00001), nuclear cataract (OR 6.92, 95% CI 2.89-16.59, p<0.00001), cortical cataract (OR 4.78, 95% CI 2.37 - 9.65, p<0.00001), and the presence of an occludable angle (OR 3.05, 95% CI 1.52 – 6.13, p<0.002). In the multivariate analysis, only increasing age and IOP remained significantly associated with PXF.

Conclusions:
The prevalence of PXF in the Burmese population is greater than previously reported in other East Asian populations. Increasing age and IOP are the strongest predictors of PXF, and it is associated with cataract, occludable angles and blindness.
Introduction

Pseudoexfoliation (PXF) is a disease characterised by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues [1]. PXF has a worldwide distribution and its prevalence increases universally with age [2-13], but age-specific prevalences vary widely between populations, and reports of some associations, including gender and sunlight exposure are often conflicting, suggesting a complex mix of genetic and environmental causation.

The prevalence of PXF in Chinese eyes (< 0.5% in those 40 years of age and over) is the lowest reported for any population [13]. Recent population-based studies from southern India have reported higher rates in these populations and have highlighted its association with cataract, glaucoma and blindness in these populations. Prevalence data from other Asian regions, particularly Southeast Asia are scarce [11, 12, 14].

Central, rural Myanmar (formerly Burma) has one of the highest reported blindness rates in the world, with cataract and glaucoma, particularly angle-closure glaucoma (ACG), accounting for the majority of the burden [15]. However, the prevalence of PXF in this population was considered low. The known association of PXF with cataract, glaucoma (especially angle-closure glaucoma) and complicated cataract surgery makes an understanding of the prevalence of PXF and its correlates in this population particularly important. We present data relating to the prevalence, clinical correlates and biometric parameters associated with PXF in a rural population of central Myanmar.
Materials and Methods
The Meiktila Eye study (MES) was a population-based cross-sectional ophthalmic survey of the inhabitants of rural villages in central Myanmar who were 40 years of age or older. The study was conducted within the Mandalay Division, an area encompassing 34253 km² divided into seven second-order administrative districts of approximately equal size. The sampling frame for this study consisted of a sample of six rural zones that together comprise the Meiktila District.

Participants were selected using a stratified random cluster sampling process. A sampling frame consisting of the list of all villages in the Meiktila District with their populations obtained from the Ministry of Health (MOH). For logistical reasons, sampling was restricted to villages within 3 hours drive from Meiktila (an area encompassing approximately 80% of the District).

Data Collection
Data collection occurred in November 2005 until February 2006. A single survey team conducted the entire study. All equipment and personnel were transported to each village, and the data collection occurred on site. Those with treatable disease were offered referral to Kandy hospital.

There were six geographical zones within the Meiktila district, which constituted the strata. Medical and ophthalmic history were obtained from each patient in their own language by qualified health care workers. Each participant then received a comprehensive eye examination, including Snellen acuity, Goldmann tonometry, and slit lamp examination of the anterior segment; the presence or absence of PXF material on the lens, iris or pupil margin was recorded. The undilated slit lamp examination and gonioscopy were performed by two experienced ophthalmologists (RJC and SM). Static gonioscopy was performed using a Sussman goniolens; each quadrant was graded using the Scheie classification. If > 90 degrees of posterior trabecular meshwork (posterior TM) was visible the pupil was dilated with tropicamide 1% and phenylephrine 2.5%. Eyes with ≤ 90 degrees of posterior TM visible were deemed “occludable” and dilated with tropicamide 0.5% only and kept under observation for 4 hours. After dilation, lens opacities were recorded using a Lens Opacity Classification System (LOCS) III grading system and a further assessment for PXF on the anterior lens capsule was made by two experienced ophthalmologists (HSN and JM) who then performed optic disc and retinal examination using a 78D lens and reference to standard disc images. The vertical cup/disc ratio (CDR) and the presence of focal notching were recorded. The agreement between the 2 ophthalmologists was good for grading the occludability [kappa] = 0.78 and for determining the CDR [kappa] = 0.72.

Eyes with VA > 6/60 and which fulfilled Category 1 optic disc criteria (table 1) underwent Frequency Doubling Perimetry (FDP; Zeiss Humphrey Systems, Dublin, Calif) using C-20 strategy. The criteria for the diagnosis of glaucoma by FDT were those outlined by Ferreras et al. The optimum criteria for glaucoma diagnosis are the presence of five or more altered points with p < 5% and/or two
or more altered points with $p < 2\%$ and/or at least one altered point with $p < 1\%$
at any location [16].

Axial length, anterior chamber depth, lens thickness, and vitreous chamber length were measured by ultrasonographic biometry with a soft-touch A-scan hand held probe (Ocuscan; Alcon,. Fort Worth, TX). At least 10 scans were obtained per individual; each scan was interpreted by experienced biometrists and the average of the 3 optimal scans was recorded.

**Ethics**

The MES was approved by the MOH in Myanmar and had ethical approval from the Royal Adelaide Hospital Ethics Committee. Consent for participation was obtained from the head of each village prior to commencement of the survey; and written, informed consent, in the participants own language, was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

**Definitions**

PXF syndrome was defined as the presence of dandruff like material on the pupillary margin (undilated examination), on the anterior lens capsule (dilated examination) and or the trabecular meshwork (on gonioscopy), the presence of a pigmented angle or Sampaolesi line was considered insufficient to diagnose PXF.

Open-angle glaucoma (OAG) was diagnosed if criteria for Category 1-3 were met (table 1) and > 90 degrees of posterior TM was visible with static gonioscopy [17].

Angle-closure glaucoma (ACG) was diagnosed if criteria for Category 1-3 (table 1) were met and $\leq 90$ degrees of posterior TM was visible with static gonioscopy. PXF glaucoma was defined as the presence of PXF and the presence of criteria 1-3 (table 1), these cases were subdivided into open angle and angle closure glaucoma according to the criteria mentioned above.

Best-corrected visual acuities were used in all analyses. Blindness was defined as unaided VA (or with spectacles if worn) $< 3/60$ in the better eye.

Nuclear cataracts were defined as a lens nuclear opalescence with LOCS III score of $\geq 4$. Posterior subcapsular cataract (PSCC) and cortical cataracts were defined by scores of $\geq 2$ in their respective categories.

Those describing themselves as farmers or labourers were considered to have outdoor occupations.

**Statistics**

The prevalence of PXF in one or more eyes was calculated as a ratio estimate incorporating weights for each of the sampled villages. The variance of the prevalence of PXF was calculated using the bootstrap method. Non-parametric bootstrapping involving 1000 replications was used to overcome the problem of variance estimation in clusters where only the one primary sampling unit (village) was selected. All prevalence estimates were performed using SAS Version 9.1
(SAS Institute Inc., Cary, NC, USA). Villages were randomly selected; hence, point prevalences are unbiased.

In order to identify risk factors for PXF, logistic generalized estimation equation (GEE) regression models incorporating weights from the sampled villages were fitted to the data. The GEE portion of the model was used to adjust variance estimates for the dependence in outcomes between eyes of the same patient. Odds ratios and 95% confidence intervals for each of the predictor variables were calculated in univariate analyses. A multivariate regression model including gender, age, blindness and IOP was also fitted to the data to assess the independent influence of these variables on PXF (these variables were chosen based on biological plausibility and/or previous evidence).

Table 1

<table>
<thead>
<tr>
<th>Category 1 diagnosis (structural and functional evidence):</th>
<th>Eyes with a CDR &gt; 97.5th percentile for the normal (non-glaucomatous) population (CDR ≥ 0.7 was used based on data from previous studies in the region) or a CDR ≥ 0.6 in the presence of asymmetry ≥ 0.3 or a neuretinal rim width reduced to &lt; 0.1 CDR (between 11 to 1 o’clock or 5 to 7 o’clock) plus a definite visual field defect consistent with glaucoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2 diagnosis (advanced structural damage with unproved field loss):</td>
<td>If the subject could not satisfactorily complete visual field testing but had a CDR &gt; 99.5th percentile for the normal (non-glaucomatous) population (CDR ≥ 0.8 was used based on data from the normal population in this study) glaucoma was diagnosed solely on the structural evidence.</td>
</tr>
<tr>
<td>Category 3 diagnosis (Optic disc not seen. Field test impossible):</td>
<td>If it was not possible to examine the optic disc, glaucoma was diagnosed if: (A) The visual acuity was &lt; 3/60 and the IOP &gt; 99.5th percentile or (B) The visual acuity was &lt; 3/60 and the eye showed evidence of glaucoma filtering surgery.</td>
</tr>
</tbody>
</table>

Legend for table 1: Criteria for the diagnosis of glaucoma (based on Foster’s criteria for epidemiological studies) [17]. CDR = cup/disc ratio.
Results
A total of 2076 subjects were examined (1240 females, 836 males), 4016 eyes (2416 females, 1600 males) had sufficient data to be included in the final analysis. The overall participation rate was 83.7%. The mean population age was 56.2 years (range 40-87 ± 11.6) and 100% of the participants were self-identified as belonging to the Burman ethnic group. Of the total eligible population the prevalence of PXF was estimated to be 3.4% (95% CI 2.14 - 4.67%; 78 eyes). PXF was bilateral in 24 subjects. The prevalence of PXF increased with age (Table 2). The mean age of those with PXF was 68 years (range 41-87 ± 11.4), while the mean age of those without PXF was 56 years (range 40-91 ± 11.5). There was a statistically insignificant gender difference in the prevalence of PXF (p<0.8) (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eyes with PXF</th>
<th>Eyes without PXF</th>
<th>Age/Gender Adjusted prevalence (%)</th>
<th>95% CI Total Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>2</td>
<td>1256</td>
<td>0.16</td>
<td>0.29-0.31</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>1153</td>
<td>0.77</td>
<td>0.69-0.79</td>
</tr>
<tr>
<td>60-69</td>
<td>18</td>
<td>860</td>
<td>2.0</td>
<td>1.97-2.03</td>
</tr>
<tr>
<td>70+</td>
<td>49</td>
<td>665</td>
<td>6.9</td>
<td>6.88-6.92</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>2369</td>
<td>1.9</td>
<td>1.89-1.91</td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>1567</td>
<td>2.0</td>
<td>1.99-2.01</td>
</tr>
</tbody>
</table>

Legend for table 2: Age and gender adjusted prevalence of PXF in the Burmese population by demographic characteristics.

The mean IOP in the PXF population was 19.5 mmHg (range 8-48 ± 9.4), in comparison with a mean IOP in the population without PXF of 15.2mmHg (range 7-70 ± 4.7). The mean difference of 4.3mmHg between the 2 populations was statistically significant (95% CI 3.2 - 5.4 p<0.0001).

An IOP > 21 mmHg was present in 38% of PXF eyes compared with 5.2% of eyes without PXF (P <0.001). The prevalence of glaucoma of any category in at least one eye was 4.9% (95% CI 4.1 - 5.7). The overall prevalence of primary angle closure glaucoma (PACG) was 2.5% (95% CI 1.5 - 3.5) and of primary open-angle glaucoma (POAG) was 2.0% (95% CI 0.9 - 3.1). There were 10 (0.5%) participants with secondary glaucoma in at least one eye, 3 with uveitic, 2 with neovascular and 5 with PXF glaucoma in at least one eye (0.2% of the total population, and 9.2% of the population with PXF). Three participants with PXF had chronic ACG (0.14%) in the affected eye; the remaining two cases (0.11%)
had chronic OAG. A further 10 (12.8%) had an occludable angle. There were no cases of ACG as a result of pupillary dilation. Peripheral anterior synechiae were present in 176 in 11 (0.3%) eyes with PXF and in 165 (4.1%) eyes without PXF. In those eyes with PXF, only 13% had a visual acuity $\geq 6/12$ compared with 21% in the population without PXF ($P < 0.01$). In those subjects with unilateral PXF, the affected eye had $\geq 3$ lines of visual impairment in 67% of cases when compared with the uninvolved fellow eye ($P < 0.001$). Of the 78 eyes with PXF, 38 were blind (48.7%), and 10 of the participants with bilateral PXF were blind (41.7%). Blindness was caused by dense nuclear or cortical cataract in the majority of eyes and chronic ACG in 3 eyes. In the univariate analysis a number of variables were significantly associated with the presence of PXF (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Label</th>
<th>Odds ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2.8976</td>
<td>0.6035</td>
<td>13.9120</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60-69</td>
<td>6.2889</td>
<td>1.5564</td>
<td>25.4124</td>
<td>0.00986</td>
</tr>
<tr>
<td>70+</td>
<td>27.3875</td>
<td>7.4869</td>
<td>100.1847</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.3804</td>
<td>0.6364</td>
<td>2.9940</td>
<td>0.41452</td>
</tr>
<tr>
<td>Blindness</td>
<td>4.0055</td>
<td>1.8469</td>
<td>8.6870</td>
<td>0.00044</td>
</tr>
<tr>
<td>IOP</td>
<td>1.0829</td>
<td>1.0491</td>
<td>1.1177</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Nuclear opacity</td>
<td>6.9257</td>
<td>2.8903</td>
<td>16.5950</td>
<td>0.00001</td>
</tr>
<tr>
<td>Cortical opacity</td>
<td>4.7859</td>
<td>2.3718</td>
<td>9.6573</td>
<td>0.00001</td>
</tr>
<tr>
<td>Occludable angle</td>
<td>3.0538</td>
<td>1.5207</td>
<td>6.1324</td>
<td>0.00170</td>
</tr>
<tr>
<td>PSCC</td>
<td>1.2493</td>
<td>0.3879</td>
<td>4.0236</td>
<td>0.70915</td>
</tr>
<tr>
<td>Occupation</td>
<td>0.4581</td>
<td>0.2004</td>
<td>1.0471</td>
<td>0.06420</td>
</tr>
<tr>
<td>Biometry Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axial length</td>
<td>1.0410</td>
<td>0.7887</td>
<td>1.3739</td>
<td>0.77678</td>
</tr>
<tr>
<td>ACD</td>
<td>0.2328</td>
<td>0.0778</td>
<td>0.6966</td>
<td>0.00915</td>
</tr>
<tr>
<td>Lens Thickness</td>
<td>1.4381</td>
<td>0.5878</td>
<td>3.5181</td>
<td>0.42609</td>
</tr>
<tr>
<td>PCD</td>
<td>1.2045</td>
<td>0.8819</td>
<td>1.6451</td>
<td>0.24206</td>
</tr>
</tbody>
</table>

Legend for table 3: Univariate analysis of factors associated with the diagnosis of PXF in the Burmese population. PSCC=posterior subcapsular cataract, ACD=Anterior chamber depth, PCD= Posterior chamber depth.
Age in the category of 60 years and over, blindness, the presence of nuclear or cortical cataract and an occludable angle, decrease in ACD and IOP were significantly associated with PXF. Neither PSCC nor axial length was significantly associated with PXF.

In the multivariate analysis, only increasing age and IOP were significantly associated with PXF (Table 4). Lens thickness, IOP and ACD were tested for linear association with PXF and the Pearson’s correlates were 0.05 (p<0.002), 0.12 (p<0.001) and -0.28(p<0.09) for the three factors respectively, indicating a statistically significant positive correlation with IOP, a poor correlation with lens thickness and correlation failed to reach statistical significance for ACD.

Table 4

<table>
<thead>
<tr>
<th>Label</th>
<th>Odds ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59 vs. 40-49</td>
<td>2.7914</td>
<td>0.5536</td>
<td>14.0751</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60-69 vs. 40-49</td>
<td>6.0122</td>
<td>1.3620</td>
<td>26.5406</td>
<td>0.01790</td>
</tr>
<tr>
<td>70+ vs. 40-49</td>
<td>24.8391</td>
<td>6.2399</td>
<td>98.8764</td>
<td>0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.4856</td>
<td>0.6574</td>
<td>3.3574</td>
<td>0.34130</td>
</tr>
<tr>
<td>IOP</td>
<td>1.0788</td>
<td>1.0449</td>
<td>1.1138</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Occludable angle</td>
<td>1.7849</td>
<td>0.8623</td>
<td>3.6948</td>
<td>0.11858</td>
</tr>
</tbody>
</table>

Legend for table 4: Multivariate analyses of factors associated with the diagnosis of PXF in the population (age, blindness, IOP= intraocular pressure, nuclear and cortical cataract and occludable angle).
Discussion

Limited data indicate that the prevalence of PXF in people of East Asian extraction, including Inuit [2, 13, 18], is low compared with European [10] or African ancestry [19, 20]. These data suggest both genetic and environmental influence. Foster et al, in a population-based study, recently reported that the prevalence of PXF in Chinese Singaporeans 40 years of age and over was 0.2% (95% CI: 0.0 to 0.4) [13]. Although Myanmar borders China, and southerly migrations from northeast Asia contributed to the population of this region, there is considerable genetic diversity within the southeast Asian region [21] and in the current study, the prevalence of PXF 3.4% (95% CI 2.14 - 4.67%) is considerably higher than in Inuit [4], Chinese [13] or Mongolian eyes [18], and approaches estimates for those 40 years of age or older from two recent studies in southern India: 3.8% in the state of Tamil Nadu [11] and 3.01% (95% CI: 2.45 - 3.80) in the state of Andhra Pradesh [14]. However, in a third study from southern India, the prevalence of PXF in the same age group was 6.0% [12]. Rates of approximately 3.0% have been reported in white Australians [10]. The comparison of the prevalence of PXF amongst studies remains difficult due to differences in definitions and examination techniques; however, it appears that the prevalence in Burmese eyes is probably higher than in Chinese eyes.

There are conflicting reports regarding a gender association with PXF; we found no significant association in this population. Similarly, although a possible association with sunlight exposure has been suggested, particularly in Australian Aborigines [3], reports from other populations are conflicting [10] and although we did not attempt to obtain a robust account of sunlight exposure, we found no association with outdoor occupation.

Recent studies from India have highlighted the association between PXF and visual morbidity [11, 14]. Similarly, in the current study, blindness was strongly associated with the presence of PXF in the univariate analysis. Blindness was due to dense nuclear cataract, mature cortical cataract or chronic ACG. As PXF glaucoma occurred in only 5 patients, no statistically significant conclusion could be drawn on the difference in prevalence of OAG and ACG in this population. The association of PXF with narrow angles is a well-recognized clinical entity [22], possibly relating to forward movement of the crystalline lens due to increasing zonular laxity. Arvind et al in a recent population-based study from southern India reported that occludable angles (pigmented trabecular meshwork not visible for > 180 degrees) were present in 14.8% of eyes with PXF and that on univariate analysis PXF was associated with a two-fold risk of occludability (p= 0.002); however, a multivariate analysis was not reported [11]. We found an occludable angle (pigmented trabecular meshwork not visible for > 270 degrees) in 12.8% of eyes with PXF. A shallow anterior chamber was also significantly associated with PXF, but neither axial length nor lens thickness were associated, suggesting that the occludable angles may have been secondary to anterior movement of the lens. However, occludable angles were not a significant predictor of PXF in the multivariate logistic regression analysis. In this model, only age and IOP were significant predictors for the presence of PXF.
Although the participation rate was reasonable (83%), we have no knowledge about the demographics or visual status of the non-participants. Anecdotally, (according to the village chiefs), the principal reasons for non-participation were occupation related. Hence, it is likely that none were blind and given the association of PXF with blindness, the PXF prevalence estimates from this study may be slightly higher than the target population prevalence of PXF [11, 14].

In conclusion, the prevalence of PXF in Burmese eyes appears greater than that reported in other people of East Asian extraction, including the Chinese and Inuit. PXF is strongly associated with blindness in this population. Increasing age and IOP are strong predictors for the presence of PXF. A high degree of suspicion should be maintained for the presence of PXF during routine ophthalmic examination, particularly in the elderly with high intraocular pressures.
References


