The Relationship Between Glaucoma and Pseudoexfoliation

The Blue Mountains Eye Study

Paul Mitchell, MD, FRACO, FRCOphth; Jie Jin Wang, MBBS, MMed(Clin Epi); Fleur Hourihan, BSc, MPH

Objective: To quantify the relationship between pseudoexfoliation (PXF) and open-angle glaucoma, ocular hypertension, and intraocular pressure (IOP) in a defined older population.

Methods: A cross-sectional study of 3654 people aged 49 to 97 years identified subjects with PXF during slitlamp examination. The IOP was measured by applanation tonometry. Glaucoma was diagnosed from characteristic visual field loss combined with optic disc cupping and rim thinning, without reference to IOP. Ocular hypertension was diagnosed if IOP was greater than 21 mm Hg in either eye, without field and disc changes. General estimating equation models were used to assess associations between eyes with PXF and glaucoma or ocular hypertension.

Results: Pseudoexfoliation was diagnosed in 2.3% of subjects, and both prevalence and bilaterality increased with age. Glaucomatous damage was present in 14.2% of eyes with PXF compared with 1.7% of eyes without PXF (age- and sex-adjusted odds ratio (OR), 5.0; 95% confidence interval (CI), 2.6-9.6). This was almost unchanged (OR, 4.8) after adjustment for glaucoma risk factors and was also relatively unaffected by IOP adjustment (OR, 3.7; 95% CI, 1.8-7.6). For subjects with PXF, the relationship with glaucoma persisted, but was weaker (OR, 2.3; 95% CI, 1.0-5.0) in the multivariate model. However, the population attributable risk from PXF was only 2.7%. Ocular hypertension was also more frequent in eyes with PXF (9.3%) than in eyes without PXF (3.1%) but was of borderline significance in the multivariate model (OR, 2.3; 95% CI, 0.9-5.7).

Conclusions: This study confirmed the strong relationship between glaucoma and PXF. Subjects with PXF had an increased risk of glaucoma, while eyes with PXF had a higher risk, which was independent of other glaucoma risk factors, including IOP.


PSEUDOEXFOLIATION (PXF), also known as the exfoliation syndrome, is the most common identifiable precursor of open-angle glaucoma worldwide.1 An extensive body of literature has documented marked geographic variations in the population distribution of PXF,2-6 despite some studies that used the same examiner.7 These different rates may reflect true racial or ethnic differences, but they could also result from use of different clinical or diagnostic criteria, ability of the examiner to detect early cases, or the examination technique.8 Most of the literature devoted to PXF has examined its well-known association with glaucoma, sometimes referred to as “capsular glaucoma” or “glaucoma capsulare.”9 Pseudoexfoliation manifests clinically as characteristic fibrillar protein deposits in the anterior segment of the eye.10 This material is associated with elastic microfibrillar-associated glycoproteins, including fibrillin, amyloid P, elastin, and tropoelastin.11 Electron microscopy demonstrates amyloidlike material consisting of cross-banded fibrils and filamentous subunits with an amorphous ground substance.8

In the eye, exfoliative material is produced by the lens, iris, and ciliary epithelia and is also found in the conjunctiva.12 Recent studies, however, have disclosed the systemic nature of PXF. Typical exfoliative material has now been found widely distributed in the body, including heart, lung, liver, gallbladder, kidney, and meninges, suggesting aberrant connective-tissue metabolism.13-15 Skin biopsy specimens in patients with classic PXF have shown a fibrillopathy closely resembling that in the eye,16 and this is thought to be a form of elastosis.17 Indeed, site-specific elastosis of the lamina cribrosa of the optic nerve has now been demonstrated in patients with PXF and glaucoma. This could explain why glaucomatous optic...
SUBJECTS AND METHODS

The Blue Mountains Eye Study was a population-based study of the prevalence and causes of age-related vision loss, conducted in 2 urban postal code areas of the Blue Mountains region, near Sydney, Australia. The study population and methods have been previously described. Briefly, after a private census of the region, all permanent residents aged 49 years or older were invited to participate. Of 4433 age-eligible residents, 3654 people (82.4%) aged 49 to 97 years participated in the study during 1992 through 1994, including 2072 women and 1582 men (mean age, 66 years). Ethical approval for the study was obtained from the Western Sydney Area Human Ethics Committee, and written, informed consent was obtained from all subjects.

Interviewer-administered questions covered demography, medication use, vision, and medical history, including diabetes, hypertension, and typical migraine. Subjects underwent a detailed eye examination, including applanation tonometry, automated perimetry, slitlamp examination, and subjective refraction. The Humphrey 76-point suprathreshold visual field test (Allergan Humphrey, San Leandro, Calif) was performed in 3241 participants (88.7%), of whom 352 persons (9.6%) were classified as glaucoma suspects, either from defects on the 76-point test or because optic disc signs suggested glaucoma. All were asked to return for Humphrey full-threshold 30-2 visual fields, of whom 336 (9.2%) completed the test. Stereo optic disc photographs of both eyes (30°) were performed in 97.1% of subjects.

ASSESSMENT OF PXF

After pupil dilatation, a detailed high-magnification slit-lamp assessment of the anterior segment was performed by means of a narrowed slit beam, by 1 observer (P.M.), on all participants. The anterior lens surface from each eye was scanned from left to right, looking specifically for early signs of PXF, including pregranal radial lines as well as established granular deposits. Presence of specific anterior segment abnormalities was recorded, including the presence of exfoliative material on the anterior lens surface or iris margin. Pseudoexfoliation was diagnosed by the presence of typical layered white deposits on the anterior lens surface, often in different zones. The density of these deposits was graded on a 3-level scale. Slitlamp photographs of the lens were taken with a photo-slitlamp camera (model SL-7e; Topcon Optical Co, Tokyo, Japan). Retroillumination photographs of the anterior and posterior lens surface were taken with a cataract camera (model CT-R; Neitz Instrument Co, Tokyo, Japan). Estimates of PXF prevalence were made before and after exclusion of subjects with bilateral aphakia or pseudophakia.

ASSESSMENT OF GLAUCOMA AND OCULAR HYPERTENSION

Open-angle glaucoma (here termed glaucoma) was diagnosed by the presence of matching optic disc cupping with rim thinning (cup-disc ratio, ≥0.7, or cup-disc asymmetry, ≥0.3) plus characteristic visual field loss on automated perimetry, after excluding rubeotic, angle-closure, or secondary glaucoma (other than from PXF) with gonioscopy. The diagnosis of glaucoma was made without reference to IOP. Characteristic glaucomatous field loss was defined as an abnormal result on the Humphrey 30-2 test, (Humphrey-Zeiss Inc, San Leandro, Calif) with 1 or more of the following defects, not explained by ocular or neurologic causes: (1) arcuate or paracentral scotoma, at least 4 contiguous points on the pattern deviation plot depressed at $P<.05$ level; (2) nasal step at least 2 horizontal points in width (10°) on the pattern deviation plot depressed at $P<.05$ level; or (3) advanced glaucomatous field loss. Ocular hypertension (OH) was defined as an IOP greater than 21 mm Hg in either eye, but without diagnostic visual field and optic disc signs, after exclusion of people with open-angle or other forms of glaucoma.

POTENTIAL CONFOUNDERS

Diabetes was diagnosed from history or an elevated fasting blood glucose level of 7.8 mmol/L (140 mg/dL) or more. Persons with no history of diabetes who did not return for blood tests were treated as nondiabetic in this study. We defined hypertension as a history of hypertension with current use of antihypertensive medication or elevated blood pressure (systolic, ≥160 mm Hg, or diastolic, ≥95 mm Hg). The questionnaire assessed first-degree family history of glaucoma (parents or siblings), typical migraine history, and history of inhaled or systemic corticosteroid use. Myopia was considered to be present if spherical equivalent refraction of an eye was ≤−1.00 diopters or greater.

STATISTICAL METHODS

Associations between glaucoma and PXF were assessed for individual eyes, because of the asymmetry of PXF, glaucomatous damage, or IOP in many subjects. We used the generalized estimating equation method of Liang and Zeger as this allows use of data from both eyes while accounting for the correlation between the 2 eyes in a single subject. Analyses by subject were also performed with logistic regression. Age and IOP were used as continuous variables, while other variables were categorical. SAS (Statistical Analysis System V6.12, SAS Institute, Cary, NC) was used for all statistical analyses, including generalized estimating equation analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. $P$ values less than .05 have been taken to indicate statistical significance.

nerve damage is more likely in people with elevated intraocular pressure (IOP) who also have PXF and the increased frequency of optic disc hemorrhages found in the present study among subjects with PXF. In another report from the present study, the possibility of an increased vascular risk associated with PXF was explored, on the basis that elastosis may also involve the walls of blood vessels.

Although the prevalence of PXF has been examined previously in many populations and its association with glaucoma examined in a number of large case series, few recent population-based studies have examined the role of PXF as a risk factor for glaucoma, while controlling for other known factors. We aimed in this report to describe the prevalence of PXF and to examine its contribution to the attributable risk of glaucoma in an older Australian population.
RESULTS

PREVALENCE OF PXF

Because of potential difficulties in making a definitive diagnosis of PXF after cataract surgery, 111 subjects with bilateral aphakia (or pseudophakia) were excluded. Phakic eyes of subjects with unilateral aphakia were included in analyses by eye. Pseudoexfoliation was graded present in 1 or both eyes of 81 participants during the clinical examination, a prevalence of 2.3% (95% CI, 1.8%-2.8%). In many cases, pseudoexfoliative material was also visible when the Neitz retroillumination photographs of the anterior lens were graded (Figure 1). Of 81 subjects with PXF, 42 (52%) had PXF deposits visible in only 1 eye and 39 (48%) had signs in both eyes, totaling 120 affected eyes. The age and sex distribution of eyes with PXF is shown in Table 1. Involvement with PXF of right (n = 62) and left (n = 58) eyes was similar. The proportion of subjects with bilateral involvement increased markedly with age, from 0% of subjects aged younger than 60 years to 75% of subjects aged 80 years or older ($\chi^2$ trend = 7.2; $P = .007$), as shown in Figure 2. There was a nonsignificant trend for the density of graded pseudoexfoliative deposits to also increase with age.

Pseudoexfoliation involved 1 or both eyes in 0.5% of persons aged younger than 60 years, 1.4% of those aged 60 to 69 years, 4.6% of those aged 70 to 79 years, and 5.0% of persons aged 80 years or older, a significant age-related increase ($\chi^2$ trend = 45.7; $P < .001$). The prevalence increase per year was 1.08% (95% CI, 1.06%-1.11%), using logistic regression. Pseudoexfoliation was more frequent in women (2.6%) than men (1.8%), particularly after age 70 years (Figure 3). However, this difference was not statistically significant after age-adjustment (OR, 1.46; 95% CI, 0.91-2.34).

Most members of this population were white, with northern European origin. There were too few participants from individual ethnic groups to examine PXF prevalence by ethnicity.

PREVALENCE OF GLAUCOMA AND OH

Definite or probable glaucoma was diagnosed in 108 people (3.0%) from congruous visual field and optic disc signs. Glaucoma prevalence increased exponentially with age, and the age-adjusted rate was higher in women than men. Among subjects with glaucoma, 72 (66.7%) had typical glaucomatous field loss in the right eye and 88 (81.5%) had field loss in the left eye (totaling 160 eyes). After excluding nonphakic eyes, a total of 126 eyes had diagnostic glaucomatous field loss and were used for the analyses by eye. Ocular hypertension was diagnosed in 135 participants (3.7%), but there was no statistically significant age-related increase and also no sex difference. Among persons with OH, 124 (91.9%) had elevated IOP in the right eye and 109 (80.7%) had elevated IOP in the left eye (total, 233 eyes). After excluding nonphakic eyes, a total of 211 eyes had OH and were used for the analyses by eye.

![Figure 1. Neitz retroillumination photograph of a left eye showing typical well-established pseudoexfoliation deposits and early cataract.](image1)

![Figure 2. Bilaterality of pseudoexfoliation deposits by age.](image2)

![Figure 3. Prevalence of pseudoexfoliation by age and sex.](image3)

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No. (%) of Eyes With PXF</th>
<th>Women (4012 Eyes)</th>
<th>Men (3072 Eyes)</th>
<th>Total (7084 Eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>3 (0.3)</td>
<td>2 (0.2)</td>
<td>5 (0.2)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>16 (1.1)</td>
<td>10 (1.1)</td>
<td>26 (1.0)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>40 (3.7)</td>
<td>21 (3.7)</td>
<td>61 (3.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>23 (6.0)</td>
<td>5 (2.0)</td>
<td>28 (4.4)</td>
<td></td>
</tr>
<tr>
<td>All Ages</td>
<td>82 (2.0)</td>
<td>38 (1.2)</td>
<td>120 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>

$P$ for trend <.001 <.001 <.001

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A strong association was found between PXF and glaucoma in the analyses by eye (Table 2). Glaucoma was around 8 times as frequent in eyes with PXF (14.2%) than in eyes without PXF (1.7%) (OR, 5.0; 95% CI, 2.6-9.6) after adjustment for age and sex. This relationship was unchanged when other known glaucoma risk factors (age, sex, family history of glaucoma, diabetes, hypertension, myopia, and typical migraine) were simultaneously adjusted for (OR, 4.8; 95% CI, 2.5-9.2). As no cases of glaucoma with PXF were younger than 70 years, Table 2 also shows the effect of stratifying into age groups younger and older than this age. There was very little change in the ORs when only the older group of subjects was considered.

Pseudoexfoliation was present in 1 or both eyes of 13.4% of subjects with glaucoma, compared with 1.9% of subjects without glaucoma (age- and sex-adjusted OR, 3.6; 95% CI, 1.7-7.2). A multivariate model was constructed, controlling for all known glaucoma risk factors, as above. Pseudoexfoliation remained statistically significantly associated with glaucoma in the subject-level analyses, but at a lower magnitude (OR, 2.3; 95% CI, 1.0-5.7) with adjustment for age and sex, and the association was unchanged after adjustment for known glaucoma risk factors. The relationship with OH was similar in older and younger ages, but not statistically significant for either stratified group.

Because of its low prevalence in our study, the population attributable risk for glaucoma from PXF was only 2.7%. However, among persons with PXF, 55.9% of the glaucoma was caused by this condition.

Table 4 shows that, after exclusion of subjects with glaucoma, only a borderline nonsignificant relationship was also found between PXF and OH. Ocular hypertension was 3 times more frequent in eyes with signs of PXF (9.3%) than in eyes without PXF (3.1%) (OR, 2.3; 95% CI, 1.0-5.7) with adjustment for age and sex, and the association was unchanged after adjustment for known glaucoma risk factors. The relationship with OH was similar in older and younger ages, but not statistically significant for either stratified group.

ASSOCIATIONS BETWEEN PXF AND GLAUCOMA OR OH

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This population-based study of an Australian population has demonstrated a strong relationship between signs of PXF in the anterior segment and features of open-angle glaucoma. The strength of this finding, after adjustment for other known glaucoma risk factors, and its consistency in analyses by eye or by subject support the role of PXF as a risk factor for glaucoma. Nevertheless, the relatively low prevalence of PXF in this population translates to a low attributable risk for glaucoma from this sign.

The age-specific PXF prevalence rates in this study are similar to those in reports from many other largely white populations. All have shown a marked age-related increase in prevalence, with PXF prevalence typically less.
than 1% in persons younger than 60 years, rising to rates of 5% or higher among subjects aged 80 years or older. However, the considerable geographic variations that have been reported, particularly in certain Scandinavian countries, such as Iceland, and in certain nonwhite races, remain to be explained. The majority of studies have also suggested by Ritch, that some cases of glaucoma may be caused gested by Ritch, that some cases of glaucoma may be caused to the stages of the syndrome. It remains a possibility, as also sug-

The possibility of misclassification of PXF status is also likely to have been minimized or at least reduced, as the dilated examinations of all 3654 participants were performed by a single experienced ophthalmologist (P.M.), who made a specific search for signs of PXF on the anterior lens capsule and iris. Ritch pointed out that PXF may be an environmental disease, induced by solar radiation, because of a relationship found to latitude and global radiation levels as well as to male sex in a survey of Australian aboriginals. This hypothesis was used to explain the relatively high rate of PXF found in Spanish-American residents of New Mexico. Although we were not able to examine this theory, as we did not collect detailed data on sunlight exposure, the higher prevalence among women in our study may argue against it.

None of the recent large population-based eye studies providing glaucoma prevalence data (in Baltimore, Md, Beaver Dam, Wis, Rotterdam, the Netherlands, Roscommon, Ireland, or Barbados) has reported a detailed assessment of the relationship between PXF and open-angle glaucoma, while controlling for other known glaucoma risk factors. Our findings are therefore relevant at this time, and the population-based design of our study is likely to have minimized the potential effects of selection bias.

Table 3. Factors Associated With Open-angle Glaucoma (n = 108) in Final Multivariate (Logistic) Model* 

<table>
<thead>
<tr>
<th>Factors</th>
<th>Prevalence (p), %</th>
<th>Multivariate-adjusted OR (95% CI)</th>
<th>PAR, † %</th>
<th>AR, ‡%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>NA</td>
<td>1.10 (1.08-1.13)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Maximum IOP of 2 eyes (per mm HG)</td>
<td>NA</td>
<td>1.17 (1.12-1.22)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Glaucoma family history</td>
<td>8.8</td>
<td>3.18 (1.82-5.56)</td>
<td>16.1</td>
<td>68.6</td>
</tr>
<tr>
<td>Myopia</td>
<td>12.5</td>
<td>2.37 (1.46-3.85)</td>
<td>14.6</td>
<td>57.8</td>
</tr>
<tr>
<td>PXF</td>
<td>2.2</td>
<td>2.27 (1.03-5.02)</td>
<td>2.7</td>
<td>55.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.9</td>
<td>1.91 (1.02-3.59)</td>
<td>5.9</td>
<td>47.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45.7</td>
<td>1.64 (1.06-2.52)</td>
<td>22.6</td>
<td>39.0</td>
</tr>
</tbody>
</table>

*All variables in the table were included in the model (adjusted R² for model = 0.22). OR indicates odds ratio; CI, confidence interval; PAR, population attributable risk; AR, attributable risk; NA, not applicable; IOP, intraocular pressure; and PXF, pseudoexfoliation.
†Population attributable risk (the proportion of cases in the population attributable to the risk factor) obtained with formula: p (OR − 1)/[1 + p (OR − 1)].
‡Attributable risk among exposed (the proportion of risk in exposed group attributable to the risk factor) obtained with formula: (OR − 1)/OR.

Table 4. Associations Between OH and PXF* 

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>No. (%</th>
<th>OR (95% CI)</th>
<th>OR in Eyes With PXF (n = 120)</th>
<th>OR in Eyes Without PXF (n = 6847)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>1 (3.2)</td>
<td>131 (2.9)</td>
<td>2.7 (0.6-11.8)</td>
<td>2.6 (0.6-12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>10 (11.5)</td>
<td>74 (3.2)</td>
<td>2.4 (0.8-7.3)</td>
<td>2.5 (0.8-7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Ages</td>
<td>11 (9.3)</td>
<td>205 (3.0)</td>
<td>2.3 (1.0-5.7)</td>
<td>2.3 (0.9-5.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Stratified by age group and adjusted for confounders, after exclusion of nonphakic eyes (general estimating equation model). OH indicates ocular hypertension; PXF, pseudoexfoliation; OR, odds ratio; and CI, confidence interval.
† Adjusted for age, sex, glaucoma family history, diabetes, hypertension, myopia, typical migraine history, and corticosteroid use.

Table 5. Mean Intraocular Pressure of Right and Left Phakic Eyes With and Without Pseudoexfoliation (PXF), Before and After Multivariate Adjustment

<table>
<thead>
<tr>
<th>Mean ± SE Intraocular Pressure, mm Hg</th>
<th>Right eyes (n = 3438)</th>
<th>Right eyes* (n = 3415)</th>
<th>Left eyes (n = 3448)</th>
<th>Left eyes* (n = 3432)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PXF Present</td>
<td>17.78 ± 0.37</td>
<td>17.87 ± 0.36</td>
<td>17.20 ± 0.36</td>
<td>17.21 ± 0.36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PXF Absent</td>
<td>16.12 ± 0.05</td>
<td>16.13 ± 0.05</td>
<td>16.03 ± 0.05</td>
<td>16.02 ± 0.05</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, diabetes, systolic blood pressure, and myopia.

Figure 5. Distribution of intraocular pressure (IOP) in phakic eyes with and without pseudoexfoliation (PXF).

Taylor speculated that PXF may be an environmental disease, induced by solar radiation, because of a relationship found to latitude and global radiation levels as well as to male sex in a survey of Australian aboriginals. This hypothesis was used to explain the relatively high rate of PXF found in Spanish-American residents of New Mexico. Although we were not able to examine this theory, as we did not collect detailed data on sunlight exposure, the higher prevalence among women in our study may argue against it.

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by PXF, in the absence of clinically visible exfoliative deposits on the lens, but in which exfoliation material is demonstrated on conjunctival biopsy.

It is also likely that, although clinically visible in only 1 eye, many PXF cases have exfoliative material present histologically in both eyes, so that it is more often asymmetric than truly monocular.66 However, we found stronger associations with glaucoma in the eye-level rather than subject-level analyses. This suggests a possible relationship between the amount of exfoliative material and its effect in causing glaucoma in some individuals.

Could our findings of a strong association between open-angle glaucoma and PXF be confounded by misclassification of the glaucoma status of persons in this population, leading to an overestimation of any relationship between the 2 conditions? The overall age-specific glaucoma prevalence rate reported from our study (3.0%)22 is slightly higher than in most other recent prevalence studies. However, the diagnosis of open-angle glaucoma in our study was based on the presence of congruous glaucomatous visual field and optic disc changes, without any reference to IOP. Furthermore, the demonstration that the relationship between PXF and glaucoma was almost unchanged after adjusting for IOP in the multivariate model suggests a possible nonpressure effect in causing glaucoma in some individuals.

In summary, data from this study have confirmed the strong relationship between glaucoma and PXF in an older, largely white population sample. Subjects with PXF had a 2- to 3-fold increased risk of glaucoma, and eyes with PXF had a 5-fold increased risk. This risk was independent of other known glaucoma risk factors. Pseudoexfoliation was associated with only a modest increase in IOP, and its relationship with glaucoma was relatively independent of IOP.18

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Corresponding author: Paul Mitchell, MD, FRACO, FRCOphth, Department of Ophthalmology, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, New South Wales, Australia 2145 (e-mail: paulmi@westmed.wahs.edu.au).

REFERENCES


