Exfoliation Syndrome in Black South Africans

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Background: Data on exfoliation syndrome (XFS) in Africans are scarce.

Objective: To determine the prevalence and clinical features of XFS among black South Africans.

Design: Random cross-sectional samples of the black population aged 40 years or older from 2 districts in South Africa: Hlabisa, in northern KwaZulu-Natal Province, and Temba, North West Province.

Methods: Standardized examination, including slit-lamp biomicroscopy with pupil dilatation, gonioscopy, pachymetry, tonometry, binocular indirect ophthalmoscopy, and visual field testing.

Results: Among 1840 participants, the prevalence of XFS was 7.7% (95% confidence interval, 5.4%-10.5%) in Hlabisa and 6.0% (95% confidence interval, 4.1%-8.4%) in Temba. The prevalence increased with age, with 18.9% (Hlabisa) and 16.5% (Temba) of those 70 or older affected. The clinical appearance was similar to that reported in other ethnic groups. Exfoliative glaucoma accounted for approximately one fourth of open-angle glaucoma cases (OAG). Open-angle glaucoma was associated with XFS; the age-adjusted and sex-adjusted odds ratios were 2.3 (95% confidence interval, 1.0-5.2) and 2.8 (95% confidence interval, 1.2-6.3) for Hlabisa and Temba, respectively. The relationship with OAG was absent when adjusting for intraocular pressure. Exfoliative glaucoma was characterized in this predominantly untreated population by high intraocular pressure and severe visual loss. Among subjects with XFS and OAG, 16 of 18 were blind in 1 or both eyes.

Conclusions: Exfoliation syndrome occurs at a high prevalence among black South Africans and incurs a moderate increase in risk of glaucoma. In this untreated population, this increased risk was dependent on raised intraocular pressure. Open-angle glaucoma in association with XFS appears to be associated with a poor prognosis.

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EXFOLIATION SYNDROME (XFS) is said to be the single most common identifiable cause of open-angle glaucoma (OAG).1 However, it is a condition that remains poorly understood, and among the black population of Africa and their descendants, our knowledge of it is particularly scanty. A recent collaborative review2 of the existing knowledge of XFS aimed at directing future research concluded that there is a lack of epidemiological data from African populations.

Previous clinical studies have identified XFS as a prevalent condition in South Africa's indigenous Bantu population,3 but the only population-based study to date did not use a representative sample.4,5 To our knowledge, there are also no published descriptions of the distribution of clinical features of XFS, nor estimates of the effect of XFS on the risk of developing glaucoma in a black population.

In this article, we report the prevalence and clinical appearance of XFS and estimate the strength of association with glaucoma in 2 cross-sectional samples of the black population of South Africa.

METHODS

Setting

Two indigenous black communities were sampled for this study. Details of the sampling and examination protocols are published in detail elsewhere.6,7 The setting for the first study was Hlabisa, a typical rural Zulu land district in KwaZulu-Natal Province. The population is almost exclusively Zulu, an anthropologically homogeneous Bantu tribe, who constitute the largest single ethnic group in South Africa. The second study was performed in the health district of Temba, a suburban township in North West Province. Residents are drawn from a variety of Bantu groups from across the country, principally Tswana.
Northern Sotho, Ndebele, and Tsonga. Being Southern Bantu, all the participants in this study share a common East African ancestry but can be grouped on the basis of linguistic differences into Nguni (Zulu, Ndebele, and Tsonga) and Sotho (Tswana and Northern Sotho). For the purposes of this study, ethnicity was defined on the basis of the language spoken in the home.

According to the 1996 census, 17% of the population of Hlabisa and 22% in Temba were aged 40 years or older.

**SAMPLING AND EXAMINATION**

A cluster-based random sampling method was used in both studies to select 1115 residents of Hlabisa and 1120 residents of Temba aged 40 years or older. Subjects were invited to undergo a detailed ophthalmic examination. In both studies, this included visual acuity assessment with a tumbling-E Snellen chart, and in every eye with a mean visual acuity of 20/200 (6/60) or better, testing of the central 25° visual field using the Henson CFA 3000 (Tinsley Precision Instruments, Croydon, England) computerized field analyzer was performed.

The remainder of the examination was performed by a single ophthalmologist in Hlabisa (A.P.R.) and 1 of 4 (including A.P.R., J.F.K., and P.R.) experienced ophthalmologists in Temba. Both eyes of all subjects were examined with a slitlamp biomicroscope before pupil dilatation for signs of XFS in the anterior segment, including granular deposits at the pupillary margin, pigment deposition on the corneal endothelium, and iris transillumination defects.

Intraocular pressure (IOP) was measured using Goldmann and Tono-Pen XL (Mentor Ophthalmics, Santa Barbara, Calif) instruments.

Gonioscop was performed using a Goldmann 2-mirror lens in each subject in Hlabisa. In Temba, this procedure was reserved for those with (1) limbal anterior chamber depth (ACD) grading of 25% or less, (2) IOP of 21 mm Hg or higher, or (3) glaucoma, as well as in every fifth subject. Indentation gonioscopy was performed if necessary to examine the trabecular meshwork and to detect peripheral synchiae. Signs of granular deposits of exfoliative material in the drainage angle and pigment deposition in the trabecular meshwork and anterior to the Schwalbe line (Sampaolesi line) were noted.

Using a slitlamp-mounted optical pachymeter (devices 1 and 2; Haag-Streit, Bern, Switzerland), central corneal thickness and ACD were measured in accord with the instructions in the Haag-Streit manual in all phakic eyes. The subject was instructed to maintain gaze in the primary position. A bright, narrow slitlamp beam was centered in the pupil using the pupil margins for reference. The central corneal thickness was determined by measuring the distance between the anterior corneal epithelial surface and the posterior endothelial surface using device 1 at ×1.6 magnification. The “touch technique” (in which the posterior surface of the endothelium in the upper image just touches the anterior surface of the epithelial surface in the lower image) was used. The distance between the anterior corneal epithelial surface and the anterior lens capsule epithelium was measured using device 2 at ×1.1 magnification, and the ACD (corneal endothelium to the anterior lens capsule) was calculated by subtracting the first reading from the second. In this way, the central corneal thickness was estimated to the nearest 0.01 mm and the ACD to the nearest 0.05 mm. Single readings were taken because repeatability has been shown to be high using this instrument.

If the drainage angle was judged to be not occludable (as defined in the next subsection), the pupils were dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride to allow examination of the lens and to facilitate binocular funduscopic examination.

The anterior surface of the lens capsule was subsequently examined with the slitlamp biomicroscope for the presence of exfoliative material. In aphakic and pseudophakic eyes, the anterior vitreous, posterior capsule, and intraocular lens were examined for the presence of exfoliative material.

The optic disc was examined stereoscopically using a Volk 78 diopter lens (Volk Optical Inc, Mentor, Ohio). The vertical cup-disc ratio (CDR) was assessed, recording the largest value between the clock hours of 11 to 1 and 5 to 7.

**DEFINITIONS**

For the purposes of this study, XFS was diagnosed based on the presence of granular deposits of exfoliative material on the anterior lens capsule or the pupillary margin in either eye. This has been the predominant, but not exclusive, definition in epidemiological studies of XFS. It precludes diagnosis on the basis of signs related to pigment dispersion alone to avoid confusion with pigment dispersion syndrome. Pregranular changes, which may represent an early form of the syndrome, were not included in the definition. If the presence of XFS could not be excluded because of corneal opacification, the subject was not included in the analysis.

The diagnosis of glaucoma was based on a scheme proposed by the Working Group for Defining Glaucoma of the International Society of Geographical and Epidemiological Ophthalmology that was developed specifically for cross-sectional prevalence surveys. An eye was diagnosed as glaucomatous if it fell into one of the following categories: (1) a definite and reliable glaucomatous visual field defect was found in the presence of a CDR of 0.7 or higher or CDR asymmetry between fellow eyes of 0.2 or higher; (2) threshold visual field testing was incomplete or inconclusive, but the CDR was 0.9 or higher or CDR asymmetry was 0.3 or higher; (3) optic disc assessment was not possible because of media opacity, but the visual acuity was light perception or worse, with an IOP of 30 mm Hg or higher.

Visual field criteria were previously reported. Glaucomatous eyes were categorized as having OAG or angle-closure glaucoma (ACG) on the basis of findings on gonioscopy. A drainage angle was defined as narrow (occludable) when pigmented trabecular meshwork was visible on gonioscopy with the eye in the primary position for less than 90° of the circumference without indentation. Blindness was defined according to World Health Organization criteria as a mean visual acuity less than 20/400 (3/60) or complete loss of sensitivity within 10° of fixation.

**DATA MANAGEMENT**

The statistical analysis was performed using Stata 6 (Stata Corporation, College Station, Tex) software. Confidence intervals for prevalence were derived using the binomial distribution, and an allowance for the design effect was included (ie, the excess variability of the estimates under the cluster-based selection procedure was used, instead of simple random sampling). Summary odds ratios (ORs) were derived using fixed-effects weighted means of log ORs (Woolf method). Adjusted figures were derived by direct age and sex standardization to the local indigenous population structure from the 1996 national census for Hlabisa and Temba. Right and left eyes were analyzed separately.

One thousand five subjects were examined in Hlabisa and 839 in Temba, yielding recruitment rates of 90.1% and 74.9%, respectively. Among those 60 or older (ie, the group expected to be most at risk of XFS), recruitment rates were higher (93.8% and 90.5%, respectively). In Hlabisa, the presence or absence of XFS in at least 1 eye could not be...
adequately determined in 4 subjects because of corneal opacification, and these were excluded from the analysis.

The age distribution of the 2 samples was similar, with mean values for Hlabisa and Temba of 59.4 and 60.6 years, respectively. In both, there was a low proportion of male participants (27.8% in Hlabisa and 33.4% in Temba). The recruitment rate and demographic details are published elsewhere.6,7

### PREVALENCE OF XFS

The crude prevalence of XFS was 9.4% (95% CI, 6.9%-12.5%) (94/1001) in Hlabisa and 7.7% (95% CI, 5.6%-10.4%) (65/839) in Temba. The figures adjusted for age and sex were 7.7% (95% CI, 5.4%-10.5%) and 6.0% (95% CI, 4.1%-8.4%), respectively. The difference between the adjusted prevalences of the 2 populations was not significant (P=.30, χ² test).

There was no significant sex difference in the crude or age-adjusted prevalence for either population.

Age-specific prevalence rates are given in Table 1.

A strong tendency toward increasing prevalence with age was found in both samples (P<.001, χ² test). The prevalence increased from 1.1% (Temba) and 2.0% (Hlabisa) among subjects in their fifth decade to 16.5% (Temba) and 18.9% (Hlabisa) among those 70 or older. Among subjects 50 or older, the mean increased risk of XFS increased with age in a linear manner at a rate of 6.4% per year (95% CI, 4.1%-8.7%) in Temba and 6.1% (95% CI, 3.7%-8.6%) in Hlabisa. The youngest subject found to have XFS was aged 45 in both samples. In subjects 60 or older (the age group used in the comparison with other populations that is summarized in Table 2), the prevalences were 16.1% (11.4%-21.8%) and 12.5% (9.1%-16.6%) for Hlabisa and Temba, respectively.

### Table 1. Crude and Adjusted Prevalence of Exfoliation Syndrome (XFS) by Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Hlabisa</th>
<th>Temba</th>
<th>Hlabisa</th>
<th>Temba</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>254 (5)</td>
<td>181 (2)</td>
<td>2.0</td>
<td>1.1</td>
</tr>
<tr>
<td>50-59</td>
<td>269 (12)</td>
<td>211 (7)</td>
<td>4.5</td>
<td>3.3</td>
</tr>
<tr>
<td>60-69</td>
<td>245 (33)</td>
<td>241 (22)</td>
<td>13.5</td>
<td>9.1</td>
</tr>
<tr>
<td>≥70</td>
<td>233 (44)</td>
<td>206 (34)</td>
<td>18.9</td>
<td>16.5</td>
</tr>
<tr>
<td>Crude Total</td>
<td>1001 (94)</td>
<td>839 (65)</td>
<td>9.4 (6.9-12.5%)</td>
<td>7.8 (5.6-10.4%)</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>...</td>
<td>...</td>
<td>7.7 (5.4-10.5%)</td>
<td>6.0 (4.1-8.4%)</td>
</tr>
</tbody>
</table>

### Table 2. Prevalence of Exfoliation Syndrome (XFS) and the Proportion of Open-Angle Glaucoma (OAG) Associated With XFS in Population-Based Studies of Subjects 60 Years and Older (Except Where Stated) in Order of Prevalence*

<table>
<thead>
<tr>
<th>Nation</th>
<th>No./Total With XFS</th>
<th>Prevalence, %</th>
<th>% of OAG</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland12</td>
<td>69/328</td>
<td>21.0</td>
<td>NA</td>
<td>Kuusamo, ≥65 y</td>
</tr>
<tr>
<td>Crete13</td>
<td>124/627</td>
<td>19.8</td>
<td>NA</td>
<td>National sample</td>
</tr>
<tr>
<td>Iran14</td>
<td>41/222</td>
<td>18.5</td>
<td>12.5†‡§</td>
<td>Falavarjan, central Iran</td>
</tr>
<tr>
<td>Sweden15</td>
<td>138/760</td>
<td>18.2</td>
<td>35.5</td>
<td>Tierp, northern Uppland, 65-74 y</td>
</tr>
<tr>
<td>Saudi Arabia16</td>
<td>25/147</td>
<td>17.0</td>
<td>33.3†‡§</td>
<td>National sample</td>
</tr>
<tr>
<td>Norway17</td>
<td>318/1887</td>
<td>16.9</td>
<td>59.6</td>
<td>Holtaalen, Rennebu, Hitra, ≥65 y</td>
</tr>
<tr>
<td>Australia18</td>
<td>30/184</td>
<td>16.1</td>
<td>NA</td>
<td>Aborigines, pupils not dilated</td>
</tr>
<tr>
<td>South Africa</td>
<td>77/478</td>
<td>16.1</td>
<td>24.3†</td>
<td>Hlabisa, Zululand, present study</td>
</tr>
<tr>
<td>South Africa</td>
<td>56/447</td>
<td>12.5</td>
<td>23.1†</td>
<td>Temba, North West, present study</td>
</tr>
<tr>
<td>South Africa4</td>
<td>82/854</td>
<td>9.6</td>
<td>50.0†</td>
<td>Pondoland, Eastern Cape Province</td>
</tr>
<tr>
<td>Australia19</td>
<td>81/3543</td>
<td>2.3</td>
<td>13.4</td>
<td>Blue Mountains, ≥49 y</td>
</tr>
<tr>
<td>United States20</td>
<td>34/1906</td>
<td>1.8</td>
<td>0.0</td>
<td>Framingham, ≥52 y</td>
</tr>
<tr>
<td>Australia21</td>
<td>42/4457</td>
<td>0.9</td>
<td>6.9†</td>
<td>Victoria, ≥40 y</td>
</tr>
<tr>
<td>Singapore</td>
<td>2/542</td>
<td>0.4</td>
<td>0.0</td>
<td>Chinese, Foster’s</td>
</tr>
<tr>
<td>Cook Islands22,23</td>
<td>3/986</td>
<td>0.3</td>
<td>NA</td>
<td>Polynesians in Raratonga</td>
</tr>
<tr>
<td>United Kingdom24</td>
<td>10/4231</td>
<td>0.2</td>
<td>NA</td>
<td>Fernside, Wales, ≥40 y</td>
</tr>
<tr>
<td>South Africa25</td>
<td>2/987</td>
<td>0.2</td>
<td>0.0</td>
<td>Mamre, Cape Colored, ≥40 y</td>
</tr>
<tr>
<td>Thailand</td>
<td>1/495</td>
<td>0.2</td>
<td>0.0</td>
<td>Bangkok, Bourne</td>
</tr>
<tr>
<td>Nigeria</td>
<td>0/128</td>
<td>0.0</td>
<td>0.0</td>
<td>Kaduna State, Murdoch</td>
</tr>
<tr>
<td>Greenland</td>
<td>0/146</td>
<td>0.0</td>
<td>0.0</td>
<td>Umanaq, Inuit, Alsbirk26</td>
</tr>
<tr>
<td>Alaska</td>
<td>0/267</td>
<td>0.0</td>
<td>0.0</td>
<td>Inuit, ≥50 y, Arkell26</td>
</tr>
<tr>
<td>Tanzania25</td>
<td>0/914</td>
<td>0.0</td>
<td>0.0</td>
<td>Kongwa</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
*Samples drawn exclusively from patients in homes for the elderly or in which a large proportion were examined without pupil dilatation were excluded.
†Aged ≥40 y.
‡Refers to eyes with glaucoma, not cases.
§No automated visual field testing.
| Personal communication of unpublished data.

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In the ethnically heterogeneous population of Temba, there was no significant variation in the prevalence of XFS by ethnic group.

Bilateral involvement was apparent in 56.9% (37/65) in Temba and in 45.7% (43/94) in Hlabisa. There was no significant age difference between cases with unilateral or bilateral disease ($P_{\text{Temba}}=.26$, and $P_{\text{Hlabisa}}=.20$; $t$ test).

FEATURES OF XFS

Description of the clinical features of XFS is restricted to the 137 affected eyes of 94 individuals in the Hlabisa sample because of the more complete examination in this group. Furthermore, the examination in Hlabisa was performed by one investigator, thereby eliminating a source of bias. The findings were not, however, significantly different in the 2 samples.

The mean IOP (SD) in right eyes with XFS was 18.1 (12.4) mm Hg compared with 14.1 (4.1) mm Hg in non-exfoliative eyes. The values for left eyes were 17.1 (9.4) mm Hg and 14.1 (3.7) mm Hg, respectively ($P<.001$ for both, Mann-Whitney test). The distribution of IOP in eyes with and without XFS is shown in Figure 1. Among those with XFS, the appearance had a greater skew to the right. This results from an excess of high-tension glaucoma and ocular hypertension in cases with XFS. Among nonglaucomatous subjects with XFS in whom IOP was recorded, 15.7% (13/83) had ocular hypertension (IOP of >21 mm Hg in either eye in the absence of glaucoma) compared with 5.3% (46/866) among cases without XFS ($P=.001$, $\chi^2$ test), giving an age-adjusted and sex-adjusted OR of 3.4 (95% CI, 2.0-5.9). At normal pressures, however, the distribution in eyes with and without XFS was remarkably similar, and some eyes with signs of XFS had IOP as low as 8 mm Hg.

The features of the drainage angle were typical of those reported in XFS in other populations. Results are given for right eyes, but the findings in left eyes were not significantly different. A typical Sampaolesi line, consisting of a wavy line of pigment anterior to the Schwalbe line, was present in 34.8% (24/69) of right eyes with XFS compared with 5.5% (51/932) of those without XFS (age-adjusted $P<.001$). This sign is, therefore, characteristic of XFS in Zulus, as it is in other populations. (Scheie grade 3) assessed at the 12-o’clock position was also a common feature, being found in 34.8% (24/69) of right eyes with XFS compared with 4.1% (38/932) of those without XFS (age-adjusted $P<.001$). Pigmentation was typically blotchy and diffuse and more prominent inferio. There was a strong but incomplete correlation between heavy pigmentation of the trabecular meshwork and the presence of a Sampaolesi line. Dense pigmentation was found in 33% of eyes with a Sampaolesi line. A line was found in 40% of those with heavy trabecular pigmentation. The concordance was higher in subjects with XFS, however, with 67% agreement in either direction. Neither sign was associated with raised IOP in patients with XFS.

The appearance of the anterior lens surface demonstrated the classic pattern of white material in a central disc and a peripheral zone, separated by a clear intermediate ring. The central disc was not invariably present. It typically demonstrated a homogeneous ground-glass appearance, often with overlying deposits of exfoliative granules and a clear line of demarcation from the surrounding clear zone. Diffuse pigment granule deposition on the lens surface of this axial zone was present in 55.2% (37/67) of phakic right eyes with XFS compared with 6.2% (57/921) of those without XFS (age-adjusted $P<.001$). The peripheral zone had a frosted or granular appearance. Its anterior border consisted of a continuous wavy line of deposited material or had a dentate appearance. Radial clefts or striae in the peripheral zone matched the topography of the posterior surface of the iris. The posterior border, when visible, also had a radial pattern. Some of the typical features of XFS seen in this population are illustrated in Figure 2.
Exfoliated material was commonly seen at the pupil margin and was therefore visible before mydriasis. However, this sign was present in only 43 (62.3%) of 69 right eyes, despite careful examination. Deposits of pigment on the corneal endothelium, typically on the inferior third, were a further common finding, present in 29.0% (20/69) of exfoliative right eyes and in 1.5% (14/932) of normal eyes. The iris around the pupil margin was commonly moth-eaten in appearance, but iris transillumination defects were not found.

The distribution of the drainage angle width for eyes with and without XFS is given in Figure 3. A Shaffer grade of 2 or less was found in 19.7% (13/66) of exfoliative right eyes compared with 12.7% (113/889) without XFS. After adjusting for the confounding effect of age on the narrowing of the drainage angle, there was no significant association between XFS and angle width (P = .38).

The anterior chamber depth was measured in at least 1 eye (94.0%) of 941 Hlabisa subjects. The mean values decreased with increasing age and were lower in women and in left eyes in the exfoliative and nonexfoliative groups. After adjusting for age and sex by linear regression, the mean ACD was lower in those with XFS by 0.10 mm (95% CI, 0.03-0.17) and 0.09 mm (95% CI, 0.02-0.16) for the right and left eyes, respectively (Table 3). Although statistically significant, these differences amount to only 3.8% and 3.4% of the mean ACDs for the right and left eyes, respectively.

### XFS AND GLAUCOMA

In both samples, XFS was the most frequently associated secondary cause of glaucoma, accounting for 24.3% (9/37) and 23.1% (9/39) of cases of OAG in Hlabisa and Temba, respectively. In Hlabisa, 9.6% (9/94) of subjects with XFS had evidence of glaucoma with open angles in the same or in both eyes compared with 3.1% (28/907) of those without XFS, giving a crude OR of 3.3 (95% CI, 1.5-7.3). In Temba, 13.8% (9/65) of subjects with XFS in the same or in both eyes had OAG compared with 3.9% (30/774) of those without XFS, giving a crude OR of 4.0 (95% CI, 1.7-9.3). The age-adjusted and sex-adjusted ORs were 2.3 (95% CI, 1.0-5.2) and 2.8 (95% CI, 1.2-6.3) for Hlabisa and Temba, respectively (Table 4). The difference in OR was not significant (P = .48, χ² test for homogeneity), and a combined summary OR was estimated as 2.5 (95% CI, 1.4-4.5).

Using the adjusted OR, the proportion of the risk of OAG attributable to XFS among those with XFS (the attributable risk in the exposed) was 56.5% in Hlabisa and 63.5% in Temba, assuming a causal effect. In the whole population, the proportion of OAG attributable to XFS (the population attributable risk fraction) was 9.1% in Hlabisa and 9.5% in Temba (Table 4).

Glaucoma of the chronic angle-closure type was found in association with XFS in an additional 2 subjects, both in Hlabisa.

### FEATURES OF EXFOLIATION-RELATED GLAUCOMA

The role of IOP in the relationship between XFS and OAG was examined by adjusting for the mean IOP as a continuous variable, in addition to age and sex, by logistic regression. In this model, the association between XFS and OAG was markedly reduced (ORHlabisa, 0.98; 95% CI, 0.4-2.8; and ORTemba, 1.3; 95% CI, 0.4-4.2). Although these results do not distinguish between whether high IOP is the result of
the cause, it suggests that the effect of XFS on the risk of glaucoma is almost restricted to those with raised IOP.

A prior diagnosis was uncommon for XFS-related and primary OAG in both populations, with 3 of 37 cases in Hlabisa and 4 of 39 cases in Temba having received any form of treatment to reduce IOP.

The degree of visual loss was high in cases with exfoliative glaucoma. In Temba, 9 of 9 subjects with exfoliative glaucoma were blind in at least 1 affected eye, as were 7 of 9 in Hlabisa. These proportions of blind subjects were higher than those for primary OAG (15/30 [50.0%] in Temba, and 9/28 [32.1%] in Hlabisa), and these differences were significant ($P_{Temba}=.007$, and $P_{Hlabisa}=.02$; Fisher exact $\chi^2$). Exfoliative glaucoma overall accounted for 40.0% (16/40) of eyes blind as a result of OAG.

**COMMENT**

This study confirms the high prevalence of XFS across several different Bantu tribal groups in South Africa. The rates of 16.1% and 12.5% for those 60 or older in Hlabisa and Temba, respectively, are not far below the highest published figures from Scandinavia, where the syndrome was first reported (Table 2). Despite their being drawn from 2 of the country’s major linguistic groups (Nguni and Sotho), there was no significant ethnic variation in the prevalence in our samples.

The prevalence has previously been reported to be low among African Americans. Grizzle and Sugar reported seeing only 2 cases among black Americans in their clinic in Chicago, Ill, and in a series of 500 patients with OAG in south Louisiana, XFS was present in only 0.4% of black patients compared with 2.7% among white patients. Among indigenous African populations, the prevalence of XFS varies widely. In a population from Nigeria in the west, from where the majority of African Americans derive, prevalence was found to be very low (I. E. Murdoch, MD, unpublished data, 1993). In contrast, XFS is reportedly not uncommon in Chad and was found in one third of a sample of clinic patients in Somalia (G.J.J., unpublished data). In East Africa, a population-based survey in rural Tanzania yielded no cases of XFS among a sample of 3268 people older than 40. This is surprising because the Bantu population of South Africa that we have examined is thought to have derived by migration from East Africa.

Earlier clinic-based work in South Africa led us to believe that XFS was common in the indigenous Bantu population. Bartholomew reported finding XFS in 5.2% of 625 new eye clinic patients older than 30 from a mix of tribal groups in Johannesburg, South Africa, and Luntz found that 20% of black patients referred to a glaucoma clinic in another Johannesburg hospital had XFS, compared with only 1.4% of white patients. In a community-based sample in the South African region of Pondoland, a prevalence of 5.4% among persons 40 or older (9.6% among those 60 or older) was reported. However, this was a volunteer as opposed to a randomly selected sample, so it may be misleading to compare the results with those of our surveys.

Among the Cape Colored population of Western Cape Province of South Africa, XFS is uncommon. This population has Southeast Asian, as well as indigenous Khoisan ancestry, and the low prevalence of XFS typifies that found from cross-sectional work in Thai, Singapore, and Inuit populations who share Sinomongoloid lineage (R. R. Bourne, FRCOphth [2001], and P. J. Foster, FRCOphth [2000], unpublished data). Exceptions within this group include the Japanese and Navajo, in whom XFS is a common finding. This heterogeneity is also typical in white populations, and significant variation has been shown between different regions of an ethnically homogeneous country.

Based on findings in white populations, it is often stated that XFS is the most common identifiable cause of glaucoma. We confirm that XFS also increases the risk of having OAG in our population. Nearly one fourth of cases of OAG were associated with XFS in Hlabisa and Temba. Of 159 examined subjects with XFS, 18 (11.3%) had OAG, yielding a summary OR, adjusted for age and sex, of 2.5 (95% CI, 1.4-4.5).

Before the present study, a measure of risk of glaucoma in XFS adjusted for age had been reported in few population-based studies. In Australian aborigines, 3 (8.3%) cases of glaucoma were diagnosed among 36 subjects with XFS older than 40, although this study (and other population-based studies) lacked automated visual field testing data in the definition of glaucoma.

Among studies that included visual field analysis in the definition of glaucoma, a study from New South Wales, in Australia, reported an OR of 2.3 (95% CI, 1.0-5.0) for the increase in likelihood of OAG among 81 subjects with XFS, adjusted for multiple risk factors. Also in Australia, the OR for glaucoma, adjusted for significant variables (age and cataract) in 42 subjects with XFS was reported as 3.8 (95% CI, 1.7-8.3). Also similar to our findings, we calculated a crude OR of 2.7 (95% CI, 1.4-5.3) from a cross-sectional survey of subjects aged 65 to 74 in Sweden. Incidence figures from the follow-up of the same cohort yielded a crude OR of 15.8. However, this figure was based on only 3 incident cases of OAG. A relatively high figure was also calculated from data reported among subjects older than 64 years in Norway (crude OR, 10.1; 95% CI, 7.0-14.6). This high measure of effect may be because, according to their definition, either field loss or an IOP of 25 mm Hg or higher was sufficient for a diagnosis of glaucoma. Cases of ocular hypertension, which was highly prevalent among patients with XFS, may have been classified as glaucoma-tous, which would have resulted in an overestimation of the effect of XFS on OAG. For the earlier South African study in Pondoland, we also calculated a much higher OR for the association between XFS and OAG than that found in Temba or Hlabisa (age-adjusted OR, 15.4; 95% CI, 8.6-30.1; Mantel-Haenszel test). However, the volunteer study sample probably led to overrepresentation of symptomatic eye disease. Therefore, recruitment of excess cases of glaucoma associated with XFS is to be expected because, as in our surveys, these patients had significantly more advanced disease than patients with primary OAG. If the latter 2 studies are excluded because of these differences in methods, the cross-sectional studies in Sweden and Australia and our studies show remarkable homogeneity in results (P=.90, $\chi^2$...
test) and yield a fixed-effects summary OR of 2.7 (95% CI, 1.9-3.9). Therefore, there is a clear positive association between XFS and OAG, although the degree of increased risk may be less than previously appreciated.

Despite the high prevalence of XFS in South Africa, this risk factor was estimated to be responsible for only 9% to 10% of cases of OAG (assuming a causal effect for XFS). The underlying cause for most OAG remains unclear.

The severity and prognosis of OAG are generally believed to be worse in eyes with XFS, as manifested by higher IOP and more rapid field loss. This could be a result of the greater resistance to treatment that is reported in exfoliative glaucoma, rather than a more severe natural course, and the distinction is difficult to make in clinic populations undergoing treatment. The natural history can be observed in populations in which glaucoma is undiagnosed. In our effectively untreated groups, the proportion with advanced visual field loss was high among all patients with glaucoma but was significantly higher for glaucoma associated with XFS.

We also found that the added risk of glaucoma in association with XFS was dependent on IOP. This is in contrast to a recent study20 from Australia suggesting that the relationship was independent of IOP and that a nonpressure mechanism in the pathogenesis of XFS-related optic nerve damage might exist. However, this apparent contradiction might be a reflection of the high proportion of subjects previously diagnosed and given treatment aimed at reducing IOP in Australia.20 Whether raised IOP is the mechanism by which glaucoma is caused or is a secondary effect in our population remains an important question that could only be answered by a longitudinal study.

The features of XFS found in this population-based study were largely in agreement with findings of clinic-based studies. The absence of granular deposits at the pupillary margin in 38% of subjects, despite careful examination, emphasizes the importance of dilating the pupil in the detection of XFS.26,39 A Sampaoli line and heavy trabecular meshwork pigmentation were found in some affected cases. Neither was associated with raised IOP in this study, despite several studies26,29,40 suggesting that there is a positive relationship between increased angle pigmentation and raised IOP or glaucoma in XFS. Loss of the pupillary ruff was a common feature, but peripheral iris transillumination defects, which are seen in white populations, were not found. This may be a reflection of a thick iris pigment layer in this population.

There is debate as to whether ACG is more common among subjects with XFS, compared with the general population.1,41,42 Most studies31-34,41-43 mention only sporadic cases of association, suggesting that these may be coincidental. In several series of patients with XFS, most of whom had glaucoma, ACG was found in 2.6% to 4.0%.34,39,44,46 In series of patients with ACG, XFS has rarely been reported. In Australia, Lowe45 found XFS in 2.8% (7/230) of patients with ACG, which was a proportion similar to that in the general population. It is surprising, therefore, that several authors report narrow drainage angles in as many as 20% or more of eyes with XFS in uncontrolled clinic-based groups,29,39,41,42 and in a series of patients with occludable angles, 25% had XFS.37 In our studies, there were 9 cases with ACG, 2 of whom had XFS. This is insufficient to draw any conclusions about the relationship between ACG and XFS. However, there was no association between the width of the drainage angle and XFS after controlling for the confounding effect of age. Likewise, although ACDs were statistically significantly shallower in eyes with XFS in both our samples, the magnitude of the differences was small.48 They were considerably deeper on average than in age-matched populations that are at high risk of developing ACG, such as Mongols and Inuit.23

Eyes with XFS do not generally appear to have the anatomical features of shallow anterior chambers and narrow drainage angles that predispose to angle closure. If there is a tendency toward angle closure in XFS, a different mechanism, such as zonular weakening, iris rigidity, or posterior synechiae, predisposing to pupil block must be responsible. A longitudinal study of nonglaucomatous exfoliative eyes is needed to look for changes in ACD and the drainage angle to resolve this issue.

This population-based study demonstrates a high prevalence of XFS among black South Africans. We found that XFS is a moderate risk factor for glaucoma (summary OR, 2.5; 95% CI, 1.4-4.5), which is in line with results found in several population-based studies among white populations. The relationship between XFS and OAG appears to be dependent on IOP. Exfoliative glaucoma accounts for approximately one fourth of OAG, making it the most frequently associated secondary cause of OAG in this population. It appears in its untreated form to be associated with a poor prognosis among subjects with XFS-associated OAG, demonstrating a higher rate of visual loss than that found among subjects with OAG not associated with XFS.

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