Risk factors for progression to blindness in high tension primary open angle glaucoma: Comparison of blind and nonblind subjects

Karanjit S Kooner1
Mohannad AlBdoor1
Byung J Cho3
Beverley Adams-Huet2

1Department of Ophthalmology, University of Texas Southwestern Medical Center, Dallas, Texas, USA; 2Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA; 3Konkuk University Hospital, Seoul, Korea

Aims: To determine which risk factors for blindness were most critical in patients diagnosed with high tension primary open angle glaucoma (POAG) in a large ethnically diverse population managed with a uniform treatment strategy.

Methods: A longitudinal observational study was designed to follow 487 patients (974 eyes) with POAG for an average of 5.5 ± 3.6 years. Detailed ocular and systemic information was collected on each patient and updated every six months. For this study, blindness was defined as visual acuity of 20/200 or worse and/or visual field less than 20° in either eye. Known risk factors were compared between patients with blindness in at least one eye versus nonblind patients.

Results: The patients with blindness had on average: higher intraocular pressure (IOP, mmHg): (24.2 ± 11.2 vs. 22.1 ± 7.7, p = 0.03), wide variation of IOP in the follow-up period (5.9 vs. 4.1 mmHg, p = 0.031), late detection (p = 0.006), poor control of IOP (p < 0.0001), and noncompliance (p < 0.0003). Other known risk factors such as race, age, myopia, family history of glaucoma, history of ocular trauma, hypertension, diabetes, vascular disease, smoking, alcohol abuse, dysthyroidism, and steroid use were not significant.

Conclusions: The most critical factors associated with the development of blindness among our patients were: elevated initial IOP, wide variations and poor control of IOP, late detection of glaucoma, and noncompliance with therapy.

Keywords: primary open angle glaucoma, blindness, intraocular pressure, risk factors, and noncompliance

Introduction


However, it is not clear which of these factors are most important and which are influenced by variables such as fewer patients, short follow up, and ethnically non-diverse patient population. To determine risk factors for progression to blindness,
we followed a large ethnically diverse patient population with high tension glaucoma over a long time frame. The primary outcome variable was the average percent of eyes that developed glaucoma-related blindness in either eye. Secondary outcome variables include sustained decrease of vision, progression of the disease, poor control, noncompliance, late detection, and level of intraocular pressure (IOP).

Features of patients who developed blindness were compared with those who did not. The underlying hypothesis was that certain risk factors in such a diverse study population were not significant over the long term allowing us to identify the most critical clinical factors.

**Materials and methods**

Our cohort was selected from the patient population at an academic center, a county hospital, and a Veterans Affairs Hospital.

Legal blindness is defined in the US as visual acuity of 20/200 or worse and/or visual field less than 20° in the better eye (Social Security Act 2006). Since this study was designed to follow individual eyes, this definition of blindness was modified to refer to either eye rather than the better eye. The diagnosis of POAG included glaucomatous optic nerve cupping with corresponding VF defects, IOP ≥21 mmHg and open irido-corneal angle (Klein et al 1992; Dielemans et al 1994). Nine patients were blind in one eye at the start of the study. They were included because adequate long term information on the study variables were available. The exclusion criteria were: normal tension glaucoma (IOP < 21 mmHg), secondary glaucoma, inability to maintain follow up for 3 months, eye conditions such as opaque media, macular degeneration, and vascular accidents that preclude diagnosis of glaucoma, and patients who were unable to perform ocular tests reliably. All eligible patients were examined and treated by the first author or by the eye residents and glaucoma fellows under direct supervision. The study protocol was approved by the appropriate Institutional Review Boards/Ethics Committees of the three clinics and adhered to the Declaration of Helsinki.

In all, 487 eligible patients (974 eyes) with POAG were enrolled in the study. The academic center (231 patients, 462 eyes) is a private patient facility attached to the University of Texas Southwestern Medical Center at Dallas. Parkland Memorial Hospital is a county hospital (98 patients, 196 eyes). The Dallas Veterans Affairs Hospital (158 patients, 316 eyes) is a federal government facility for United States veterans.

Measured continuous and categorical variables at the conclusion of the study are summarized in Table 2.

For this study, VF changes were recorded as stages: 1 = normal; 2 = relative scotoma outside 20°; 3 = absolute scotoma outside 20°; 4 = relative/absolute scotoma within 20°–10°; 5 = relative/absolute scotoma within 10°–5°; 6 = relative/absolute scotoma within 5° in 1–3 quadrants, 7 = relative/absolute scotoma within 5° in all quadrants (Jay and Murray 1988). The criteria for VF abnormality on Humphrey

**Table 1 Risk factors for blindness in glaucoma**

<table>
<thead>
<tr>
<th>IOP</th>
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</thead>
<tbody>
<tr>
<td>Large diurnal variations (The AGIS Investigators 2000; Oliver et al 2002).</td>
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<tr>
<td>Poor control of IOP (Oliver et al 2002).</td>
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<tr>
<td>Mean IOP in the better eye (King et al 2000).</td>
</tr>
<tr>
<td>Advanced VF damage at diagnosis (Harrington 1959; Kolker 1977; Grant and Burke 1982; Leski 1983; Quigley et al 1994; Oliver et al 2002; Chen 2003).</td>
</tr>
<tr>
<td>Longer duration of disease (Grant and Burke 1982).</td>
</tr>
<tr>
<td>Noncompliance (Spaeth 1971; Grant and Burke 1982; Chen 2003).</td>
</tr>
<tr>
<td>Frequent disc hemorrhage (Drance et al 1981).</td>
</tr>
<tr>
<td>Late detection (Spaeth 1971; Perkins 1978; Grant and Burke 1982; Fraser et al 1999).</td>
</tr>
<tr>
<td>Worse vision (Grant and Burke 1982).</td>
</tr>
<tr>
<td>Vascular insufficiency (Reese and McGavic 1942; Spaeth 1971; Drance et al 1978; Grant and Burke 1982; Gherghel et al 2000).</td>
</tr>
<tr>
<td>Family history of glaucoma (Drance et al 1978).</td>
</tr>
<tr>
<td>Greater number of antiglaucoma medications (Kwan et al 2001).</td>
</tr>
<tr>
<td>Glaucoma surgery (Kwan et al 2001).</td>
</tr>
<tr>
<td>Higher socioeconomic class (King et al 2000).</td>
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<tr>
<td>VF loss in the worse eye (King et al 2000).</td>
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</tbody>
</table>

**Abbreviations:** IOP, intraocular pressure; VF, visual field.
program 30-2 full threshold strategy were a cluster of two or more adjacent points of 5-decibels (dB) or greater loss, and at least one of the points showing more than 10 dB loss according to the age corrected total deviation values. Every patient received one or more VF tests yearly. Optic nerve cupping was noted and drawn at baseline exam and at each visit. No photographs were taken. Any progression was flagged and reconfirmed by KSK or the glaucoma fellow. Features of optic disk progression were; progression of C/D ratio by \( \geq 0.2 \), rim notching and thinning from baseline, and disk hemorrhage. Noncompliance was based on documented nonadherence to therapy/surgery or from two or more missed clinic appointments during the observation period. Poor control of glaucoma was based on the following features: use of three or more medications, requirement of laser or incisional surgery, progression of C/D ratio by \( \geq 0.2 \), or progression of VF from one stage to the next. Late detection was defined as C/D disparity of \( \geq 0.2 \) or VF loss of stage \( \geq 3 \) in one or both eyes at initial presentation.

Categorical variables (such as gender, procedures, medications) of blindness and no-blindness groups were compared with the Fisher’s Exact Test or Chi-square statistics. Continuous variables (such as age, C/D ratio) were compared between groups with two-sample t-tests or Wilcoxon Rank Sum tests if normality assumptions were not met. Logistic regression models were used to assess multiple risk factors simultaneously. Data management was performed using Microsoft Access 97 and 2000 (Microsoft Corp. Redmond, WA). For statistical analysis, SAS version 8.0 (SAS Institute, Cary, NC) was used.

**Results**

At the end of the study, there were 282 (57.9%) nonblind patients and 205 (42.1%) blind patients. Of the total number of patients, 195 were diagnosed initially at one of the three study clinics. In the blind group, 120 (58.5%) had bilateral blindness while 85 (41.5%) had unilateral blindness. Table 2 lists the main characteristics of the groups.

### Table 2 Demographics and characteristics of composite patient population: No blindness versus blindness

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No blindness n (%) 282</th>
<th>Blindness n (%) 205</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, yr (mean ± SD, median, range)</td>
<td>59.0 ± 12.6, 59.4, 21.2–86.9</td>
<td>59.3 ± 13.2, 61.1, 28.8–90.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Follow-up, yr (mean ± SD, median, range)</td>
<td>5.1 ± 3.1, 4.2, 1.0–18.1</td>
<td>6.1 ± 4.0, 5.2, 0.3–23.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>151 (53.5)</td>
<td>139 (67.8)</td>
<td>( p &lt; 0.002 )</td>
</tr>
<tr>
<td>Female</td>
<td>131 (46.4)</td>
<td>66 (32.2)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>124 (44.0)</td>
<td>69 (33.7)</td>
<td></td>
</tr>
<tr>
<td>Black American</td>
<td>134 (47.4)</td>
<td>119 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>12 (4.3)</td>
<td>7 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Other ethnicities</td>
<td>12 (4.3)</td>
<td>10 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Ocular surgeries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>52 (18.4)</td>
<td>48 (23.4)</td>
<td>0.211</td>
</tr>
<tr>
<td>ALT</td>
<td>92 (32.6)</td>
<td>89 (43.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>LPI</td>
<td>29 (10.3)</td>
<td>31 (15.2)</td>
<td>0.124</td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td>28 (9.9)</td>
<td>60 (29.3)</td>
<td>(&lt; 0.0001)</td>
</tr>
<tr>
<td>Combined</td>
<td>22 (7.8)</td>
<td>18 (8.8)</td>
<td>0.740</td>
</tr>
<tr>
<td>Cyclodestruction</td>
<td>0 (0.0)</td>
<td>9 (4.4)</td>
<td>(&lt; 0.0004)</td>
</tr>
<tr>
<td>Others</td>
<td>14 (5.0)</td>
<td>16 (7.8)</td>
<td>0.252</td>
</tr>
<tr>
<td>Visual acuity Deteriorization</td>
<td>36 (12.7)</td>
<td>82 (40.0)</td>
<td>(&lt; 0.0001)</td>
</tr>
<tr>
<td>VF progression</td>
<td>46 (16.3)</td>
<td>47 (22.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>IOP mmHg (mean ± SD, median, range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial visit</td>
<td>22.1 ± 7.7, 21.0, 2.0–70</td>
<td>24.2 ± 11.2, 21.0, 2.0–70.0</td>
<td>0.030</td>
</tr>
<tr>
<td>Final visit</td>
<td>18.1 ± 2.4, 18.0, 10.0–26.0</td>
<td>17.7 ± 4.8, 18.0, 0.0–46.0</td>
<td>0.153</td>
</tr>
<tr>
<td>C/D ratio progression</td>
<td>92 (32.6)</td>
<td>55 (26.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>131 (46.4)</td>
<td>129 (63.0)</td>
<td>(&lt; 0.0003)</td>
</tr>
<tr>
<td>Poor control</td>
<td>207 (73.4)</td>
<td>196 (95.6)</td>
<td>(&lt; 0.0001)</td>
</tr>
<tr>
<td>Late detection</td>
<td>248 (87.9)</td>
<td>195 (95.1)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Notes:** Blindness was defined as visual acuity of 20/200 or worse and/or visual field less than 20° in either eye.

**Abbreviations:** ALT, argon laser trabeculoplasty; LPI, laser peripheral iridotomy; CF, count fingers; HM, hand motion; LP, light perception; NLP, no light perception; VF, visual field; IOP, intraocular pressure; C/D, cup-to-disc; CAI, carbonic anhydrase inhibitor.
At baseline, the blind group had statistically significant higher IOP than the nonblind group (24.2 vs. 22.1 mmHg; \( p = 0.03 \)). They also showed wide fluctuations (maximum to minimum IOP) over the course of the study (5.9 mmHg vs. 4.1 mmHg, \( p = 0.031 \)). The mean IOP for each patient in both groups is shown in Figure 1.

At pressure of 17 mmHg or less, 54 (26.3%) patients were blind. Pressure levels gradually decreased in both groups over time, but the standard deviation of individual IOP was still higher in the blind group (4.8 vs. 2.4 mmHg, \( p = 0.02 \)).

Blind patients required more laser (43.4%), trabeculectomy (29.3%), and cyclodestruction (4.4%) procedures. Their vision at initial visit was also worse, with 76 (37%) recording vision \( \leq 20/200 \) and only 93 (45.4%) showing vision of \( >20/40 \) compared with 261 (92.5%) of the nonblind group. By the last visit, 82 (40%) of blind subjects experienced deterioration of vision and 115 (56%) had dropped to \( \leq 20/200 \). In comparison, only 36 (12.7%) of the nonblind group showed progression.

In blind individuals, the VF status at initial visit was: mild damage (stage 1 and 2) in 29 (14.2%); moderate damage (stage 3 and 4) in 49 (23.9%); and severe damage (stage 5 to 7) in 127 (61.9%). At the final visit the values were 17 (8.3%), 41 (20.0%), and 147 (71.7%), respectively. VF deterioration occurred in 46 (16.3%) of nonblind group and 47 (22.9%) of blind group.

As expected, optic nerve appearance was worse in the blind group at first visit, with 154 (75%) of patients showing C/D of \( >0.7 \) compared with 102 (36.2%) in the nonblind group. This figure reached 175 (85.4%) and 132 (46.8%) at the last visit, respectively. Both groups exhibited deterioration of optic nerve features. Similarly, noncompliance, inadequate control and late detection were higher in blind subjects. Baseline IOP, female gender, and baseline VF were significant risk factors for blindness (Table 3).

Other risk factors such as race, age, history of hypertension, diabetes, vascular disease, family history of glaucoma, smoking, alcohol abuse, systemic or topical steroids dysthyroidism, ocular trauma (all variables obtained by history) and myopia, were not significant.

**Discussion**

Our findings support the widely held belief that IOP is still of paramount importance in management of glaucoma (Harbin et al 1976; Kolker 1977; Anderson 1989; O’Brien et al 1991; Araie et al 1994; Quigley et al 1994; Gherghel et al 2000; King et al 2000; Stewart et al 2000; The AGIS Investigators 2000; Kwan et al 2001; Oliver et al 2002). Blind patients in
our study had higher level of initial IOP, more fluctuations in pressure, and were difficult to control. Blindness and progression of glaucoma was evident at all pressure levels (Figure 1). This finding is in contrast to the Advanced Glaucoma Intervention Study (AGIS) where progression was minimal in patients with IOP less than 18 mmHg. The AGIS investigators found that VF progression was less if a patient had advanced glaucoma based on medical therapy maintained IOP of less than 18 mmHg at each visit, but their progression of glaucoma was evident at all pressure levels (The AGIS Investigators 2000). The progressive nature of POAG was evidenced by VF deterioration. Both noncompliance to treatment and inadequate control were more prevalent in blind patients. The significance of noncompliance with treatment has been stressed by several investigators (Dranche et al 1978; Kostas et al 2000). One weakness of the study is that the central corneal thickness was not measured because of the unavailability of measuring devices at the three centers. The authors understand the pivotal role of IOP reduction. Central corneal thickness may play in the development and progression of glaucoma (Gordon et al 2002).

In conclusion, we followed 487 ethnically diverse patients with high tension POAG in a single metropolitan area and with a uniform management strategy for over 5 years. Risk factors for blindness were mainly pressure-related: elevated initial IOP, wide variations and poor control of IOP, late detection of glaucoma, and noncompliance with therapy. Other known factors such as older age (Quigley et al 1994; Hattenhauer et al 1998; Stewart et al 2000), black American (Sommer et al 1991a; Hiller and Kahn 1975), vascular insufficiency (Reese and McGavic 1942; Spaeth 1971; Drance et al 1978; Grant and Burke 1982; Gherghel et al 2000), or family history of glaucoma (Dranche et al 1978) were not significant. Our results suggest that further studies with larger diverse populations and longer follow are required to verify these findings and to better understand the dynamics of glaucoma progression.

Table 3 Multiple logistic regression analysis of the various variables and their effect on progression to blindness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% confidence limit for odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.008</td>
<td>0.993–1.024</td>
<td>0.281</td>
</tr>
<tr>
<td>Race</td>
<td>1.148</td>
<td>0.919–1.435</td>
<td>0.224</td>
</tr>
<tr>
<td>Baseline IOP (&gt;22 mmHg vs. &lt;22 mmHg)</td>
<td>1.54</td>
<td>1.05–2.268</td>
<td>0.028</td>
</tr>
<tr>
<td>Clinic</td>
<td>1.157</td>
<td>0.905–1.478</td>
<td>0.244</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>0.601</td>
<td>0.383–0.943</td>
<td>0.0268</td>
</tr>
<tr>
<td>Baseline VF (1 scotoma or worse vs. normal)</td>
<td>13.698</td>
<td>4.863–38.582</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; VF, visual field.

References
