Family History Of Glaucoma And Disease Severity

Mohannad Q. Albdour MD*Khiem T. Vu, BS*Nathan L. Markel, BS*Kisan Parikh, BS*Xilong Li, PhD**Beverley Adams-Huet, MS**Karanjit S. Kooner, MD*

ABSTRACT

Objectives: To determine if a positive family history of glaucoma, overtime, translates to a more severe form of the disease.

Methods: A retrospective chart review of 359 consecutive patients diagnosed with primary open-angle glaucoma (POAG) and normal tension glaucoma was performed. Family history of glaucoma, age, gender, race, cup/disk (C/D) ratio, visual field (VF) defects, intraocular pressure (IOP), central corneal thickness (CCT), and current glaucoma medications were recorded. Characteristics of patients with positive family history (Group A) and negative family history (Group B) were compared using Fisher’s Exact and Wilcoxon Rank sum tests for categorical and continuous variables, respectively.

Results: There were 144 (40.1%) patients in Group A and 215 (59.9%) patients in Group B. Racially, both groups were similar, p= 0.44. Patients in Group A were younger at diagnosis, (61.9 ± 13.5 years vs 65.2 ± 12.5; p=0.02), had greater percentage of females (50.7% vs 37.7%; p= 0.02), had thicker CCT, µm, (546 ± 58.1 vs 532.7 ± 40.2; p=0.02), higher IOP (16.6 ± 3.9 vs 1.6 ± 3.9; p=0.02), advanced (C/D ≥ 0.9) cupping (32.2% vs 22.4%; p=0.05) and higher prevalence of moderate to severe VF defects (66.2% vs 54.8%, p= 0.04), compared with normal to mild VF defects.

Conclusion: Our study has suggested that a positive family history of glaucoma may be associated with higher IOP, as well as greater prevalence of advanced cupping and moderate to severe VF defects. Vigilance and aggressive treatment are warranted for these patients.

Key words: Family history of glaucoma, glaucoma severity, central corneal thickness

JRMS Dec 2016; 23(4):36-40/DOI:10.12816/0032199

Introduction

One of the leading causes of blindness in the world, primary open-angle glaucoma (POAG) is a chronic, multifactorial disease characterized by an insidious onset of progressive vision loss secondary to optic nerve degeneration. It is associated with open iridocorneal angle, inappropriately high IOP, though not invariably, thin CCT, and a higher (C/D) ratio in affected eye(s). Cross-sectional studies have suggested that a positive family history increases the risk factor for developing POAG across populations but the association between family history of glaucoma and severity of glucomatous damage is not well understood. Moreover, Landers et al have reported that in patients with a family history of glaucoma, age at diagnosis was important: those under 50 years had less visual field (VF) damage than those who were older than 50 years. Therefore, the purpose of this study was to determine, whether a positive family history of glaucoma also predisposes these patients, over time, to a more severe form of the disease. We hypothesized that patients with a...
family history of glaucoma would show more damage from glaucoma over the course of the disease.

**Methods**

We carried out a retrospective cross-section chart review approved by the Institutional Review Board (IRB) at the University of Texas Southwestern Medical Center (UTSW). Using electronic medical records, we collected patient information from 359 qualified consecutive patients diagnosed with POAG and normal tension glaucoma between February 2010 and December 2013 at UTSW and associated clinics. Normal-tension glaucoma was defined as a form of open-angle glaucoma characterized by glaucomatous optic neuropathy in patients with IOP measurements consistently lower than 21 mmHg. Glaucoma suspects, patients with narrow-angle glaucoma, pigmentary glaucoma, pseudoexfoliation glaucoma, secondary glaucoma, unknown family history of glaucoma and those with incomplete data, including those scheduled for surgery or who were recovering from surgery were excluded till they were deemed stable. Positive family history was defined by first degree (parents, siblings, and off springs), second degree (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) or third degree (first-cousins, great-grandparents or great-grandchildren) relatives affected and comprised Group A. Patients with a negative family history were referred to as Group B. We adhered to the revised tenets of the Declaration of Helsinki.

The date of birth, date of diagnosis, gender, family history, race, C/D ratio, VF defects, IOP (mm Hg), CCT (μm), and current glaucoma medications of each patient were recorded onto a custom paper data collection form and then transferred to Microsoft Access database. The IOPs were calculated as an average of the three most recent measurements obtained by Goldman applanation tonometry (Haag Streit AG, Berne, Switzerland). The C/D for each eye was calculated as an average of the three most recent measurements obtained from patient medical record. Visual fields were performed using Humphrey automated perimetry (Humphrey, Inc., San Leandro, CA, USA). Visual field defects, if present, were categorized as mild (mean deviation MD = 0 to -6 dB), moderate (MD -0.01 to -12 dB) or severe (MD ≥ -12 dB) modified from Hodapp, Parish and Anderson classification.9 These deficits were only considered if deemed attributable to POAG, thereby excluding the effects of other comorbidities such as lid ptosis, macular degeneration, media opacities, or ocular trauma. A field was considered unreliable if false –positive or false –negative errors were more than 30% and fixation losses were more than 25%. The CCT was recorded as the most recent measurement obtained by the Corneo-Gage Plus pachymeter (Sonogage, Inc., Cleveland, OH).

**Statistical Analyses**

The statistical analysis was performed using SAS 9.4 (SAS, NC, USA). Descriptive statistical analysis was done to characterize clinical and functional data. Groups A and B were compared using Fisher’s Exact and Wilcoxon Rank sum tests for categorical and continuous variables, respectively. Counting information for number of medicines was analyzed by Poisson Model. For measurements made on both eyes, one eye was chosen at random for statistical comparisons. A p-value less than or equal to 0.05 was deemed clinically significant.

**Results**

From a total list of 456 patients, 97 (21.27%) were excluded (32 due to insufficient data, 43 due to unknown family history or lineage and 22 due to other ocular conditions interfering with VF results). The remainder 359 patients were divided into two categories: 144(40.1%) in Group A (positive family history) and 215 (59.9%) in Group B (negative family history). In Group A, 112 (77.7%) had a first–degree relative affected, 31 (21.5%) had a second-degree relative affected and 1 (0.7%) had a third-degree relative affected. There were 3 (2.08%) patients with NTG in Group A and 5 (2.33%) in Group B, the rest all had POAG. Among the 144 patients in Group A, the mean follow-up time after glaucoma diagnosis was 3.53 ± 4.13 years while for Group B, the follow up time was 4.05 ± 3.48 years.
Table I highlights comparisons of the various variables among the two groups. As shown, the main distinguishing characteristics of Group A patients compared to Group B were: younger age at diagnosis, (61.9 ± 13.5 years vs 65.2 ± 12.5; p=0.02), higher percentage of females (50.7% vs 37.7%; p= 0.02), thicker CCT µm (546 ± 58.1 vs 532.7 ± 40.2; p=0.02) elevated IOP, mm Hg ( 16.6 ± 3.9 vs 15.6 ± 3.9; p= 0.02), advanced (C/D ≥ 0.9) cupping (32.5% vs 22.4%; p=0.05), and higher prevalence of moderate to severe VF defects, compared with normal to mild (66.2% vs 54.8%; p= 0.04) was observed. However, VF defects were not statistically different based on the four VF categories of normal, mild, moderate, severe p= 0.07. No significant differences were noticed in terms of race, mean C/D ratio or the number of glaucoma medications per patient.

Table I: Comparison between patients with positive family history of glaucoma (Group A) and those with a negative family history (Group B).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>144 (40.1)</td>
<td>215 (59.9)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>61.9 ± 13.5</td>
<td>65.2 ± 12.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71 (49.3)</td>
<td>134 (62.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>73 (50.7)</td>
<td>81 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>58 (40.3)</td>
<td>90 (41.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Black</td>
<td>66 (45.8)</td>
<td>86 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (13.9)</td>
<td>39 (18.1)</td>
<td></td>
</tr>
<tr>
<td>VF defects*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10 (7.2)</td>
<td>29 (14.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mild</td>
<td>37 (26.6)</td>
<td>61 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>36 (25.9)</td>
<td>36 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>56 (40.3)</td>
<td>73 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Cup/disk</td>
<td>0.72 ± 0.21</td>
<td>0.71 ± 0.19</td>
<td>0.58</td>
</tr>
<tr>
<td>Cup/disk ≥ 0.9</td>
<td>46 (32.2)</td>
<td>46 (22.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>546 ± 58.1</td>
<td>532.7 ± 40.2</td>
<td>0.02</td>
</tr>
<tr>
<td>IOP (mm Hg)‡</td>
<td>16.6 ± 3.9</td>
<td>15.6 ± 3.9</td>
<td>0.02</td>
</tr>
<tr>
<td># of glaucoma medications</td>
<td>2.0 [1, 3]</td>
<td>2.0 [1, 3]</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Results are presented as n (%) or mean ± standard deviation unless otherwise specified. Number of medications was reported as median [IQR]. Legend: VF = visual field, CCT = central corneal thickness, IOP = intraocular pressure.

Discussion

This study was designed to determine if patients with a positive family history of glaucoma experience a severe form of the disease. We observed that approximately 40% of patients who gave a family history of glaucoma had been diagnosed earlier, had thicker CCT, higher IOPs, and greater prevalence of severe (C/D ≥ 0.9) optic nerve cupping as well as moderate to severe VF defects than those without a family history of glaucoma. There were no differences in terms of race, mean C/D ratio or the number of anti-glaucoma medications.

A family history of glaucoma is a well-recognized risk factor for developing the disease and both Mendelian and non-Mendelian forms of glaucoma have been identified.1-7 Forty percent of our patients gave a positive family history of glaucoma which is in agreement with previous reports of 13% to 60% in the literature.3-8, 10-12 Moreover, 77% of our patients reported a first-degree relative affected with glaucoma as reported by others.4-6,11-14 We did not specifically look for which relative(s) among the first degree category were affected. There were gender differences in both groups. There was a greater percentage of females (50.7%)
in Group A than in Group B (37.7%). While most studies have pointed family history more towards female siblings and mothers but in the Barbados Family Study, family history was more prevalent in males. The argument that female patients with glaucoma were significantly more likely to report a positive family history is without strong explanation, but could very well represent a form of gender-dependent reporting bias. Our results also support findings of prior studies that patients with a positive history of glaucoma may present earlier than those without such a history and tend to be younger with advanced damage at diagnosis. One could imply that seeing or hearing about a family member with glaucoma and its associated visual disability, prompts family members to seek help for early diagnosis and treatment. We also noticed that patients in Group A had thicker CCT µm (546 ± 58.1 vs 532.7 ± 40.2; p=0.02). This may have contributed to early detection of glaucoma because thick CCT is associated with high IOP. In our study, a large proportion(66%) of Group A patients showed moderate to severe VF loss and 32% had associated severe (C/D ≥0.9) optic nerve cupping. These findings are in agreement with results of Wu et al. In contrast, Gramer et al did not show a significant association between family history of glaucoma and VF defects or an increased risk to develop a more severe VF defect. This disparity may be the result of different definitions of VF damage used by investigators or because our patients were derived from a specialty glaucoma clinic.

Our study has corroborated the importance and critical role of family history of glaucoma in the disease management. There is a wide spread thrust from governments and other health care organizations to target the issue of blindness locally and internationally. Specifically, United Kingdom has initiated a free National Health Service sight test for people with a family history of glaucoma. The general population needs to be educated regarding the need for glaucoma screening in all adults especially those with a known family history of glaucoma. This may aid in early diagnosis and prompt treatment of glaucoma.

**Conclusion**

Determination of family history of glaucoma is essential in patients with glaucoma. The family history of glaucoma is more common in females. In addition, these patients present early, show poor intra-ocular pressure control, more optic nerve cupping and visual field defects. Overall, our results suggest an association between a more severe form of the disease for patients with a family history of glaucoma, despite being treated and monitored at a younger age. We recommend more aggressive treatment and careful follow-up in patients with a family history of glaucoma. The implication that patients with affected relatives were more likely to be females, merits further study into the possible heritability of predisposing sex-specific factors in the pathogenesis of POAG.

**Limitations of study**

Besides the inherent weaknesses of a retrospective study, the major limitation of our study is that the determination of a family history was based on patient’s memory recall. Many patients may not be aware of a positive family history of glaucoma or they may be confusing glaucoma with other eye diseases such as cataract or macular degeneration. Glaucoma Inheritance Study in Tasmania has reported that 27% of patients with POAG were unaware of their positive family history. Another limitation of our study is that UTSW and associated clinics are large, tertiary referral teaching centers and our patients may have presented late and with greater VF damage. Thus our results are subject to typical clinic-based selection biases and cannot be generalized. The magnitude of misinformation and the effect on observed associations in this study are unknown. Nevertheless the strength of our study lies in the fact that our patients were well represented based on race and gender. They also received uniform glaucoma care under the guidance of university based glaucoma specialists.

**Acknowledgement**

Supported in part by unrestricted grant from the Research to Prevent Blindness New York, NY, Visual Science Core Grant EY 020799 and NIH CTSA Grant UL1-RR024982
References