Accuracy and Implications of a Reported Family History of Glaucoma

Experience From the Glaucoma Inheritance Study in Tasmania

Andrew I. McNaught, MD, FRCOphth; Jennifer G. Allen, BMedSci; Danielle L. Healey, BSc; Paul J. McCartney, MBBS, FRACO, FRACS; Michael A. Coote, MBBS, FRACO; Tiffany L. Wong, BAppSci; Jamie E. Craig, MBBS, DPhil; Catherine M. Green, MBChB; Julian L. Rait, MBBS, FRACO, FRACS; David A. Mackey, MD, FRACO, FRACS

Objectives: To ascertain the prevalence of previously undiagnosed primary open-angle glaucoma (POAG) within 5 large POAG pedigrees and to evaluate the reliability of a reported family history of glaucoma within these pedigrees.

Methods: The Glaucoma Inheritance Study in Tasmania (GIST) identified several large adult POAG pedigrees. Intraocular pressure (IOP), optic disc stereophotography, and automated perimetry were performed on all adult pedigree members. Participants were classified as normal (IOP < 22 mm Hg and normal optic disc and field); glaucoma suspect (normal field, but an IOP ≥ 22 mm Hg and/or suspicious optic disc); or POAG (field defect and glaucomatous optic disc). Some individuals with POAG had been previously diagnosed by their local ophthalmologist; others were diagnosed as a result of the GIST project. Family members with a prior diagnosis of POAG were asked to report if they were aware of any relatives with POAG. This reported family history was then directly compared with the actual pedigree (before the diagnosis of new cases) to calculate agreement.

Main Outcome Measure: The rate of glaucoma in pedigrees and percentage of previously diagnosed glaucoma cases who were aware of the positive family history of POAG.

Results: Four hundred forty-two subjects (mean age, 54 years [range, 13-97 years]) from 5 pedigrees were examined: 316 subjects (71%) were normal, 47 (11%) were previously diagnosed with POAG, and 8 (2%) were previously diagnosed glaucoma suspects; 30 cases (7%) of POAG and 41 suspects (9%) were newly diagnosed as a direct result of the GIST examination. Of the 47 previously diagnosed POAG cases, 41 were questioned about their prior knowledge of any family history and 11 (27%) were unaware of their family history of POAG.

Conclusions: Examination of all adult subjects from POAG families yields new cases. Even in large POAG pedigrees, 27% of previously diagnosed POAG patients were unaware of their positive family history. These findings suggest that a higher percentage of adult POAG may be inherited than hitherto reported.


PRIMARY open-angle glaucoma (POAG) has long been recognized as having a familial tendency. Recent discoveries of POAG pedigrees, in which linkage has been demonstrated to specific gene loci, contribute to the understanding of the underlying mechanisms of this disease. In 1993, Sheffield et al. published the first report of a relevant genetic locus of POAG in an American family with juvenile open-angle glaucoma (glaucoma 1, open angle α [GLC1A]). The gene was subsequently recognized as being the trabecular meshwork–induced glucocorticoid response protein (TIGR), which had also been identified in the retina as myocilin (MYOC). Later reports have confirmed that mutations in TIGR/MYOC (GLC1A) are also responsible for some cases of adult POAG. The population prevalence of POAG linked to the GLC1A mutations accounts for fewer than 5% of the cases of adult POAG. Other groups have recently reported different loci linked to adult POAG. The contribution of these other loci in population samples of adult POAG remains to be determined, as the specific genes have not yet been isolated.

Cross-sectional epidemiological studies have shown that 10% to 50% of POAG patients report a family history of glaucoma. Furthermore, a declared family history of glaucoma is a risk factor for progression of ocular hypertension into POAG. Importantly, the accuracy of this declared family history is unknown. This body of epidemiological and genetic evidence suggests an inherited risk
factor for the development of adult POAG; however, a more complete knowledge of the actual, rather than the reported, familial tendency of POAG would allow a more accurate assessment of the likely magnitude of this effect.

The Rotterdam Eye Study investigated the familial aggregation of POAG by examining the first-degree relatives (siblings and children) of 45 of the 48 cases of glaucoma identified, as well as a matched set of controls. Glaucoma was found in 10.4% of siblings and 1.1% of children. Lifetime risk of elevated intraocular pressure (IOP) was 42.5% (6.7% in controls), of enlarged cup-disc ratio was 62.2% (16.6% in controls), and of glaucoma was 22.0% (2.3% in controls). This thorough piece of work could underestimate the genetic component of glaucoma, especially if the children examined were too young to manifest the disease. More extensive assessment of the glaucoma status in the extended family (uncles, aunts, and cousins) may have revealed an even stronger component of familial aggregation.

The Glaucome Inheritance Study in Tasmania (GIST) is a large-scale study based in Tasmania and other states in Australia. The primary aim has been to recruit large Australian POAG pedigrees to allow identification of POAG genes. Pedigree members have undergone systematic examination of optic disc, visual field, and IOP. In the course of studying this large, well-documented cohort, previously undiagnosed cases of POAG and glaucoma-suspect status have been identified. Consequently, it is possible to calculate the relative prevalence of previously diagnosed against newly diagnosed (by study examination) cases of POAG and glaucoma suspects. Interviewing previously diagnosed POAG patients has allowed investigation of the relationship between a reported family history of POAG and the actual family history, as ascertained by GIST investigation.

Through systematic review of the clinical data of the POAG families identified and most completely documented by GIST, we proposed to determine: (1) The total POAG and glaucoma-suspect prevalence within the pedigrees (ie, how many additional new [and suspected] POAG cases were discovered after systematic examination of all adult members of the pedigree as part of the GIST project. (2) The accuracy of a reported family history of POAG by comparing the subjects' reported family history of POAG with the actual family history at the outset of the study (ie, before the addition of new cases diagnosed by the study) as determined by GIST investigation.

Subjects examined were classified as normal (optic disc, HFA, IOP <22 mm Hg); POAG (glaucomatous disc and glaucomatous field defect and/or IOP ≥22 mm Hg); or suspect (normal HFA, but an IOP ≥22 and/or suspicious, but not unequivocally glaucomatous, disc appearance). The timing of diagnosis was noted (ie, whether diagnosis was made before, or as a direct result of, the GIST examination visit).

To determine the accuracy of reported family history, 41 of 47 patients with a previous diagnosis of POAG were questioned (3 had died since initial examination, 2 had POAG but married into the pedigree, and 1 was unable to be contacted). Patients were asked to describe their personal knowledge of their family history of POAG before the GIST intervention: “Before your involvement in the GIST study, were you aware of any history of glaucoma or ‘raised pressure in the eye’ among members of your family, specifically parents, siblings, aunts/uncles, or cousins?”

The patients with a previous diagnosis of glaucoma were asked about their family history at various points during the GIST team’s ascertainment of the actual pedigree (ie, some were among the first members of the pedigree examined, while others were questioned at a time when the pedigree was almost complete). The ascertainment process was, of necessity, piecemeal. Some subjects were questioned prospectively as the first member of that pedigree seen by the GIST team. However, most were questioned retrospectively, as the pedigree was almost completely documented before they were actually seen.

The accuracy of the details of this reported family history was compared with the actual pedigree of those diagnosed before the GIST study (specific relatives reported to have glaucoma/actual diagnosis of same relatives: expressed as the true positive rate, or sensitivity, in percentage). “Don’t know” responses were included in the “no family history” group.

PATIENTS AND METHODS

Written informed consent was obtained from patients involved in the GIST, which was approved by the relevant ethics committees of the following institutions: The Royal Victorian Eye and Ear Hospital (Melbourne, Victoria), the University of Tasmania (Hobart), and the Royal Hobart Hospital (Hobart, Tasmania). This study was conducted in accordance with the Declaration of Helsinki and subsequent revisions. The 5 largest and most completely documented GIST families were chosen for analysis. The following clinical examination protocol was followed for all family members: (1) Use of applanation tonometry and clinical slitlamp examination, including gonioscopy. (2) Use of automated perimetry (Humphrey Field Analysis [HFA] 24-2 Full Threshold Field; Humphrey Inc, San Leandro, Calif), which classified individual fields as normal or glaucomatous using the GIST field score24 and the Glaucoma Hemifield Test (GHT) (Humphrey Inc).25 (3) Classification of optic disc appearance by 2 clinicians according to the GIST scoring protocol at the time of examination: discs were classified as normal, suspicious, and frankly glaucomatous by using disc size–adjusted cup-disc ratios (≥0.7) and by the presence of qualitative signs (focal neuroretinal rim thinning, retinal nerve fiber layer defects, disc hemorrhages, right/left asymmetry, and bared circumpapillary vessels).24 Disc stereo photographs (Nidek Co Ltd, Gamagori, Japan) were also reviewed using the same criteria; if there was disagreement, a consensus between the ophthalmologists was reached. (4) Interview to determine knowledge of family history (known pedigrees were annotated and updated as each new member was examined). (5) Use of venipuncture (blood was obtained for DNA extraction).
RESULTS

Four hundred forty-two individuals (243 women and 199 men) from 5 pedigrees with a strong positive family history of POAG were examined. The mean age of all examined subjects was 54 years (range, 13-97 years). The number of individuals included from each pedigree is listed as follows:

<table>
<thead>
<tr>
<th>Pedigree*</th>
<th>No. of Individuals Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTas2</td>
<td>132</td>
</tr>
<tr>
<td>GTas6</td>
<td>113</td>
</tr>
<tr>
<td>GTas1</td>
<td>89</td>
</tr>
<tr>
<td>GMc1</td>
<td>59</td>
</tr>
<tr>
<td>GTas37</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>442</td>
</tr>
</tbody>
</table>

* Tas indicates a pedigree from Tasmania; Vic, Victoria.

The results of diagnosis are as follows:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%) of Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>316 (71)</td>
</tr>
<tr>
<td>Previously diagnosed POAG</td>
<td>47 (11)</td>
</tr>
<tr>
<td>Previously diagnosed suspect</td>
<td>8 (2)</td>
</tr>
<tr>
<td>GIST-diagnosed POAG</td>
<td>30 (7)</td>
</tr>
<tr>
<td>GIST-diagnosed suspect</td>
<td>41 (9)</td>
</tr>
</tbody>
</table>

The breakdown of diagnoses within each pedigree is shown in the Figure. Forty-one of the 47 previously diagnosed POAG patients were asked to detail those relatives whom they thought had glaucoma. Overall, 11 (27%) of 41 were previously unaware of any family history of POAG. The accuracy (specific relatives thought to have glaucoma/actual diagnosis of same relatives) of the details of the reported family history was compared with the actual (GIST-ascertained) pedigree (Table 1). The agreement between reported and actual diagnoses is also expressed using the κ statistic. The recollection of the glaucoma status of more distant relatives (eg, cousins or grandparents), was sometimes not a particular individual. If the description of the position of that individual within the pedigree was approximately correct, this response was recorded as a correct recollection of the actual relative with glaucoma within that “class” of relative: greater precision being impractical. Some pedigrees demonstrated more than 1 glaucoma-affected individual within a given class of relative. A correct recollection of one of these individuals was documented as a correct recollection of glaucoma in that particular class of relative. Unsurprisingly, closer relatives were usually identified by name, and could be precisely compared with the named individual in the ascertained pedigree.

The accuracy was highest for first-degree relatives (mother/father, sister/brother, daughter/son) and lower for second-degree relatives (grandparents, aunt/uncle) or third-degree relatives (great-grandparents, great aunt/uncle, first cousins) (Table 1).

The GVic1 family is a rural Victorian pedigree recently found to have a GLC1A mutation (THR377MET). All 8 POAG patients questioned reported some (at least 1 affected relative) family history of glaucoma. In this pedigree, the prevalence of POAG is high, the mean age of diagnosis is low (fourth decade of life), and all patients questioned did indeed have at least 1 close (first- or second-degree) relative with POAG (Table 2). The accuracy and κ statistics therefore indicate the completeness of each questioned individual’s knowledge (ie, could they recall all those relatives with the disease). In contrast, the family GTas6 (who had normal-tension glaucoma that was usually diagnosed in the sixth decade of life) had a lower reported positive family history.

COMMENT

Four hundred forty-two subjects from 5 large, well-documented Australian POAG pedigrees were examined: 13% had a prior diagnosis of POAG or glaucoma-suspect status, and 16% were newly diagnosed by the GIST study examination as POAG or glaucoma suspects. No previous study has examined entire glaucoma families in such detail, including both affected and unaffected family members. Therefore, within these large, extended pedigrees, even an accurately reported family history of POAG will underestimate the true prevalence of disease, as a percentage of those thought to be unaf-
affected are in fact affected. Interestingly, the ratio of prior diagnosis of disease to new diagnosis by study examination is similar to that reported for unrelated, population-based samples of glaucoma prevalence. However, most new diagnoses in our study were glaucoma-suspect cases.

In the second part of this study, the accuracy of pedigree members’ prior knowledge of their own family history was evaluated. Twenty-seven percent of POAG patients with a true family history of POAG were previously completely unaware of this. When the accuracy of family history collection was stratified according to the specific familial relationship, POAG affecting a parent was most accurately recalled. This is unsurprising, as is the finding that the knowledge of the status of more distant relatives was less accurate than knowledge of first-degree relatives. It is important to note that, in this study, we assessed the patients’ recollection of relatives known to have POAG before the GIST examination. Thus, those individuals diagnosed subsequently as a direct result of the study were unknown to both the patient and the investigators. Given that there are many new cases diagnosed by such a study, the underreporting of a family history of POAG is larger than 27%, in proportion to the ratio of previously diagnosed POAG to the study-diagnosed POAG. This factor will vary between pedigrees depending on the proportion of the total POAG patients who were diagnosed before the study examination.

Patients with POAG from the Victorian pedigree GVic1, which has a GLC1A mutation, demonstrated the most accurate knowledge of other relatives with the disease. This may reflect the younger age of onset (mean age of diagnosis was in the fourth decade of life compared with the sixth decade for the other pedigrees) and more severe form of glaucoma (frequently requiring drainage surgery) suffered by members of this family. The fact that most members of this family live in close proximity in a region of rural Victoria may also be important. Because of these factors, the overall inaccuracy of family history knowledge shown by the combined pedigrees would be higher than 27% if the GVic1 pedigree was excluded from the analysis.

It is noteworthy that this study is based on the 5 pedigrees with the strongest family histories. The POAG patients with a smaller number of affected relatives (ie, a weak positive family history) are likely to demonstrate a lower accuracy of reported family history, although this interpretation ignores potentially important family communication dynamics within some, or all, of these 5 pedigrees.

These findings imply that inherited POAG may be more frequent than previously suggested in studies using reported family history data only. This apparent inaccuracy of reported family history data is also well described in the more general medical literature, and it is suggested that attempts should be made to validate the accuracy of reported family history data before these are reported as indicative of the actual population prevalence.

In contrast to the lack of knowledge of affected family history, there were no affected members who incorrectly said unaffected members were affected, although they were not specifically asked about every unaffected family member. From the more than 2000 affected members of other smaller families seen by GIST but not included in this study, there have been occasional cases of affected status being incorrectly assigned to unaffected family members. In other families with glaucoma, there are also some patients with glaucoma and taking glaucoma medication who deny that they have glaucoma.

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Corresponding author: David A. Mackey, MD, FRACO, FRACS, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, 32 Gisborne St, East Melbourne, 3002 Victoria, Australia (e-mail: D.Mackey@utas.edu.au).

REFERENCES


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From the Archives of the Archives

A look at the past...

In 1936 I performed the first keratoplasty in a case of advanced keratoconus, with resulting pronounced improvement of vision and seemingly lasting cure. Encourage by the first trials, I proceeded to treat other patients with advanced keratoconus by corneal transplantation. The results have been most encouraging.