Disease Severity of Familial Glaucoma Compared With Sporadic Glaucoma

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Objective: To determine whether there is a difference in disease severity between familial and sporadic primary open-angle glaucoma (POAG).

Methods: A cross-sectional study design compared the distribution of Glaucoma Inheritance Study in Tasmania (GIST) severity scores of patients with genealogically confirmed familial POAG and those with sporadic POAG. The GIST severity scores provide a combined weighting of glaucoma severity based on findings from visual field defects and optic disc analysis, with and without intraocular pressure. A Poisson regression analysis, t test, and $\chi^2$ tests were performed.

Results: One thousand twelve (59.5%) of 1700 subjects had familial glaucoma. The mean±SD age at examination was greater in the sporadic POAG group compared with the familial group (72.6±10.3 years vs 70.6±12.6 years; $P=.001$). The family group was significantly younger at diagnosis than the sporadic group (mean±SD, 61.4±13.0 years vs 64.0±12.6 years; $P<.001$). The GIST severity scores were significantly skewed toward greater disease severity in the familial group compared with the sporadic group ($P<.001$).

Conclusion: Identifying individuals at risk of severe POAG will be more successful if screening programs are developed with appropriate weighting toward those with a positive family history of the disease.

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Glaucoma is the second most common cause of blindness worldwide.1,2 Primary open-angle glaucoma (POAG) constitutes the largest subset of all the glaucomas. Primary open-angle glaucoma is often but not invariably associated with an elevated intraocular pressure (IOP). In more than 20% of cases, IOP elevation is absent and a diagnosis of normal-tension glaucoma can be made.3,4 Given this discrepancy in IOP findings, a scheme for classifying POAG that incorporates the optic nerve head appearance with a corresponding visual field deficit has been advocated.5,6,7

Even in developed countries, more than half of those with POAG remain undiagnosed.3,6,7 Population-based studies have revealed the prevalence of POAG in Australia to be between 2.3% and 3.7%.6,7 Strategies to reduce glaucoma blindness must be aimed at identifying individuals at risk. Identification of risk factors allows early diagnosis and treatment prior to loss of visual function. Cross-sectional studies have suggested that more than 50% of all glaucoma is familial and a positive family history of glaucoma conveys up to a 3-fold increase in risk of developing POAG.7,8,9

Population studies examining the risk of family history of POAG support the view that there is an increased prevalence of POAG among first-degree relatives of patients with the disease.10,11 The risk ratio of developing POAG for people with a positive family history is approximately 9.2.10 However, there is often a poor knowledge of such a family history.12 Interestingly, though prone to considerable recall bias, results from the Ocular Hypertension Treatment Study suggested that family history was not a significant risk factor influencing progression from ocular hypertension to glaucoma.13 Although subject to the same biases, a clinic-based investigation concluded that a positive family history of POAG did not influence disease severity at the time of diagnosis.14 Given the significant risk of developing POAG in the presence of a positive family history, our cross-sectional study was specifically established to determine whether there is a difference in disease severity between familial and sporadic cases.
STUDY POPULATION AND DESIGN

Separate audits of patients with glaucoma attending all ophthalmologic practices in the Australian state of Tasmania between 1994 and 1996 were conducted. Surveys inviting patients with glaucoma (index cases) to participate in the study were directly mailed to more than 3800 Tasmanian patients who had been investigated or treated for glaucoma during the preceding 15 years. To ensure maximal subject ascertainment, ophthalmologists, optometrists, family medicine doctors, glaucoma support groups, and pharmacies distributed additional surveys. Community awareness was increased through advertisements in local newspapers, radio, and television media.

Pedigrees were extended by connecting index cases and examining consenting family members older than 10 years. Given the substantial overlap of glaucoma pedigrees, in many cases both the maternal and paternal sides of the family were reviewed.15 A research genealogist reconstructed 309 pedigrees from the family history surveys and through accessing computerized databases. The accuracy of individuals recalling their family history of glaucoma on the questionnaire and at interview was assessed through comparison with genealogic data and, in many cases, by direct examination of relatives. Familial glaucoma was defined as the presence of a fourth-degree (ie, second cousins or great-great-grandparents) or closer relative affected by POAG.

Written informed consent was obtained from each participant in the Glaucoma Inheritance Study in Tasmania (GIST). The GIST was approved by the relevant ethics committees of the following institutions, The University of Tasmania (Hobart), the Royal Hobart Hospital (Hobart), and the Royal Victorian Eye and Ear Hospital (Melbourne), and was conducted in accordance with the revised Declaration of Helsinki.

EXAMINATION PROTOCOL

Examiners masked to overall POAG severity each assessed 1 clinical facet according to a standard examination protocol. One examiner obtained written informed consent, a medical history, measured refraction, and then the subject’s best-corrected Snellen visual acuities. A detailed questionnaire covering knowledge of family history, demographic data, and medical history of systemic disorders, such as hypertension, diabetes mellitus, migraine, corticosteroid use, and systemic vascular disease, was administered. Questions related to past ocular disease and treatment, as well as ocular symptoms, were also included. Responses were cross-checked with patients’ medication lists and medical summaries.

Humphrey automated perimetry (Humphrey, Inc, San Leandro, Calif) using a 24-2 array, a size III target, and full-threshold test system was performed. Results were reviewed for reliability using fixation losses, false-positive errors, false-negative errors, and short-term fluctuations. Defects were detected using pattern deviation analysis with the GIST visual field severity criteria, which is based on the Advanced Glaucoma Intervention Study locations.16 Seated IOP was taken using the standard calibrated Goldmann applanation tonometer (Haag Streit AG, Bern, Switzerland), and gonioscopy was performed. All optic discs were scored independently by at least 2 ophthalmologists who were masked to the patients’ supplementary clinical findings. Simultaneous stereophotographs of the optic discs were taken with a Nidek 3-Dx camera (Nidek, Gamagori, Japan). The vertical and horizontal cup-disc ratio as judged on contour as well as the size of the scleral canal were recorded. The presence of neuroretinal rim thinning, pallor, and focal defects; nerve fiber layer defects; Drance-type nerve fiber layer hemorrhages; bayoneting of emerging nerve head vasculature; and peri-papillary changes to retinal pigment epithelium and choroidal vasculature were also noted. If there was a discrepancy, consensus between the graders was reached through open discussion.

GLAUCOMA DEFINITION AND GIST SEVERITY SCORE

Disease severity in this study was defined by the GIST severity score, which was initially developed to provide a probability score of a glaucoma diagnosis.16 As described previously, the GIST severity score assigns a value to the findings of optic disc assessment, visual field deficit, and elevated IOP.16 The eye with the highest raw score is used in the calculation. A maximum of 3 points can be summed from the 3 points allocated to glaucomatous disc changes, 2 points for elevated IOP, and 2 points for visual field changes consistent with glaucoma. These summate to a “raw score,” which is then translated into the pedigree probability or the GIST score as it increases from 0.5 at intervals of 0.1 by each raw score point to a maximum of 1.0.16 For example, a cup-disc ratio of 0.7 scores 1 point, 0.3 scores 2 points, and 0.9 or more scores 3 points. A moderate field defect (category C16) with 3 or more adjacent points significantly depressed on a Humphrey 24-2 Hemifeld test scores 1 point, while a severe field defect (category D16) with extensive field loss and pattern deviation highly consistent with glaucoma scores 2 points. An IOP of 22 mm Hg or higher scores 1 point, and an IOP of 28 mm Hg or higher scores 2 points. Hence, the GIST score correlates positively with the severity level of glaucoma. In general, for the purpose of understanding the severity scale, scores of 0.7, 0.8, 0.9, and 1.0 confer disease of mild, moderate, severe, and very severe phenotype, respectively. Given the recent de-emphasis of IOP as a diagnostic criterion,5 GIST severity scores for each individual were also calculated with the IOP points removed.

In the majority of cases, treating ophthalmologists made the diagnosis and patients were reviewed as part of GIST to verify diagnostic subclassification. For inclusion into this study, subjects were required to have a GIST severity score of 0.7 or higher and clinical features necessitating antiglaucoma therapy. Subjects were excluded if there was evidence of congenital glaucoma or secondary glaucoma including traumatic glaucoma, rubeotic glaucoma, aphakic glaucoma, anterior segment dysgenesis, angle-closure glaucoma, pseudoexfoliative glaucoma, pigment dispersion syndrome, or steroid-induced glaucoma.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Subjects were stratified into familial and sporadic POAG groups. Subjects in the familial group were further subcategorized according to whether their closest affected relative was first, second, third, or fourth degree. Subjects with first-degree affected relatives (ie, parent, offspring, or sibling) were compared with those who had second-degree or more distant affected relatives. To avoid the confounding bias introduced by the age at diagnosis, the intrafamilial groups were further subdivided according to age at the time of examination (<75 years and ≥75 years).

The GIST severity scores were treated as a continuous variable. Poisson regression analysis was used to test for the hypothesis of an inverse relationship between decreasing proportion of subjects in either the familial or sporadic glaucoma group and increasing GIST severity scores. To determine if the distribution of GIST scores differed between the familial and sporadic groups, the 2-tailed Kolmogorov-Smirnov test was used. This test is preferred to the Mann-Whitney test because it is...
sensitive to any type of difference, including 2 frequency distributions. Difference in age and sex proportions between the familial and sporadic groups was assessed by either the t test or the \chi^2 test. The parametric data of the number of affected relatives were analyzed using the 1-way analysis of variance. Statistical analyses were performed using Intercooled Stata 7.0 (StataCorp, College Station, Tex).

### RESULTS

Of approximately 3800 potential POAG cases, many had died during the 15-year period or could not be located. Others declined or were too elderly or infirm to participate. In total, 2062 subjects were examined. Three hundred sixty-two subjects were excluded: 241 were found to have glaucoma other than POAG; 27 had a visual field defect or optic disc abnormality not related to POAG, thereby invalidating their GIST severity scores; 26 had a GIST severity score equal to 1.0, very severe disease \((P<.001)\), or greater than 0.8, moderate disease \((P<.001)\), compared with the sporadic glaucoma group. When the IOP score was removed from the raw GIST severity score, there were statistically significantly more familial than sporadic subjects with an adjusted GIST severity score greater than 0.8, moderate disease \((P<.001)\), although not with an adjusted GIST severity score equal to 1.0, very severe disease \((P=.97)\).

For all POAG subjects older than 75 years at the time of examination, a stepwise increase in severity was noted between the sporadic group, the familial subset with a second-degree or more distant POAG-affected relative, and those with a first-degree affected relative (Table 2). This stepwise increase in severity was not noted in subjects older than 75 years. In the older subset, the odds ratio of having a raw GIST severity score worse than 0.9 for the subgroup with an affected first-degree relative compared with the sporadic group was 3.24 (95% confidence interval, 2.01-5.29) \((P<.001)\). The odds ratio for having a raw GIST severity score worse than 0.9 for those with a POAG-affected first-degree relative against those with a second-degree or more distant affected relative was 1.66 (95% confidence interval, 0.99-2.83) \((P=.04)\).

Supporting previous investigations, approximately 60% (1014/1700) of subjects in our cohort were classified into the familial POAG group.\(^1\)\(^1\) Given that the prevalence of POAG in Australia is between 2.3% and 3.7%, the estimated number of people in our study population with POAG is approximately 3600.\(^5\)\(^7\)\(^17\) In our cross-sectional study of 1700 cases, which achieved almost total ascertainment of diagnosed POAG, subjects with familial POAG were more likely to have worse GIST severity scores than those with sporadic POAG \((P<.001)\). This finding was upheld on analysis of adjusted GIST scores, after the IOP weighting had been removed. Cases with familial glaucoma were seen and diagnosed at a significantly younger age than sporadic cases. This could reflect either genuine earlier onset of

### Table 1. Composition of the Study Groups*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Familial POAG</th>
<th>Sporadic POAG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>1012</td>
<td>688</td>
<td></td>
</tr>
<tr>
<td>Female/male, No.</td>
<td>580/432</td>
<td>388/300</td>
<td>.71</td>
</tr>
<tr>
<td>Age at review, y</td>
<td>70.6 ± 12.6</td>
<td>72.6 ± 10.3</td>
<td>.001</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>61.4 ± 13.0 (n = 780)</td>
<td>64.0 ± 12.6 (n = 575)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Raw GIST severity scores</td>
<td>0.82 ± 0.11</td>
<td>0.79 ± 0.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GIST severity scores with IOP score removed</td>
<td>0.71 ± 0.11</td>
<td>0.68 ± 0.11</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: GIST, Glaucoma Inheritance Study in Tasmania; IOP, intraocular pressure; POAG, primary open-angle glaucoma. *Values are expressed as mean ± SD unless otherwise indicated.
findings are merely a reflection of IOP factors. Visual field findings circumvents any suggestion that our adjusted analysis weighting severity only on optic disc and visual field findings underscores the importance of this study’s finding.

The primary strengths of this study are the objective examination and grading of POAG, our large sample size, and thorough ascertainment. Although reporting of family history is subject to recall bias and unawareness, this was minimized through direct comparison with extensive genetic-logic information and the examination of many relatives. Selection biases were minimized through the recruitment of patients from the community-based practices rather than referral centers or subspecialty clinics. Thorough data collection was possible with a relatively low attrition rate. Each examination and grading of POAG, our large sample size, and hence tendency to be screened and treated. The latter has occurred to a limited extent in our study, resulting in new diagnoses of glaucoma in additional family members of affected cases. This could lead to a bias toward earlier age at diagnosis and hence lesser severity of disease in the familial group. The fact that our results indicate increased severity of glaucoma in the familial cases underscores the importance of this study’s finding.

There are some limitations to this study. The GIST severity score was initially developed for subject intrapedigree consideration. This pedigree probability is not a true disease likelihood, which must also account for the random occurrence of glaucoma (approximately 3% in Australia) as well as the increased probability of more distant relatives being affected. The GIST severity score was designed for genotype-phenotype analysis rather than including or excluding people based on the presence of a single clinical feature. It should only be interpreted as an indirect measurement of clinical severity of POAG. Additionally, patients with normal-tension glaucoma tend to have lower raw GIST severity scores given that IOP was included in the calculation of the score. However, when the GIST score was recalculated without the IOP contribution, the results were unchanged.

The study design and data collection preceded the current understanding of the impact of central corneal thickness on IOP and our own recent findings of the familial nature of central corneal thickness. Once again, the adjusted analysis weighting severity only on optic disc and visual field findings circumvents any suggestion that our findings are merely a reflection of IOP factors. In both the familial and sporadic glaucoma groups, the proportion of subjects with a particular GIST score declined with increasing GIST severity scores, reflecting that there was a greater proportion of POAG subjects clustered in the less severe end of the disease spectrum. This may reflect that POAG is an age-related, slowly progressive disease or that comorbidities are associated with more severe glaucoma types. Further investigation into the differences in systemic glaucoma-associated risk factors between sporadic and familial POAG cases is required.

A stepwise increase in severity between the sporadic group, the familial subset with a second-degree or more distant POAG-affected relative, and those with a first-degree affected relative was not found in subjects 75 years or younger. Such a finding could have been confounded by the younger age at examination and diagnosis in the familial group.

Although there is no universally accepted screening strategy for POAG, any targeted screening programs must include family history. The Rotterdam Eye Study found that the prevalence of POAG in siblings of patients with POAG was 10.4%, which is somewhat lower than the 64.7% reported by Nguyen et al. Such a discrepancy may reflect racial differences. A study conducted in the United Kingdom has revealed a substantial yield for diagnosing new cases through comprehensive examination of first-degree relatives. Interstudy differences in definition of disease and, in particular, family history could account for some differences in findings.

The advance of molecular technologies and the identification of disease-causing alterations in genes allow for diagnostic genetic testing in some instances. Several glaucoma-related genes have been identified, with mutations in myocilin and optineurin accounting for 3% to 5% and 0.1% of selected cases, respectively. However, a number of other genes remain to be identified. Although population-based screening is not currently cost-effective, it is possible to perform cascade screening, where the offspring and siblings of index mutation-carrying patients are screened for the mutation. We have recently demonstrated that genetic testing in “myocilin glaucoma” is perceived to be appropriate and desirable by both patients and their families. Following mutation screening, a proportion of family members without the mutation in question

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First-Degree Affected Relative (Familial POAG)</th>
<th>Second-Degree or More Distant Affected Relative (Familial POAG)</th>
<th>No Affected Relative (Sporadic POAG)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>256</td>
<td>147</td>
<td>297</td>
<td>.55</td>
</tr>
<tr>
<td>Female/male, No.</td>
<td>160/96</td>
<td>84/63</td>
<td>177/20</td>
<td>.44</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>69.5 ± 10.4 (n = 194)</td>
<td>70.3 ± 10.5 (n = 116)</td>
<td>72.3 ± 9.7 (n = 250)</td>
<td>.01</td>
</tr>
<tr>
<td>Raw GIST severity score</td>
<td>0.85 ± 0.11</td>
<td>0.83 ± 0.11</td>
<td>0.80 ± 0.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GIST severity scores with IOP score removed</td>
<td>0.75 ± 0.11</td>
<td>0.72 ± 0.11</td>
<td>0.69 ± 0.11</td>
<td>&lt;.001</td>
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</table>

Abbreviations: See Table 1. *Values are expressed as mean ± SD unless otherwise indicated.
would be identified who do not require frequent screening. The incorporation of cascade screening into clinical practice should consequently reduce the cost of “unnecessary screening.” It is also envisaged that with a treatable disease such as glaucoma, early diagnosis of individuals at risk of severe disease will reduce later costs of blindness.

Our results suggest that patients with familial POAG have a greater disease severity and an earlier onset age at diagnosis compared with patients with sporadic disease. This finding underscores the importance of further understanding the genetics of POAG. The nature of appropriate screening strategies for individuals with and without a family history of POAG requires further study. Targeted screening strategies for POAG should take the importance of family history into account.

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REFERENCES