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 χ² 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) composes 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 Even in developed countries, more than half of those with POAG remain undiagnosed.3,6,7 Large population-based epidemiological 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.7-9 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.
METHODS

STUDY POPULATION AND DESIGN

Separate audits of patients with glaucoma attending all ophthalmic 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.13 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 acuity. 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, falsenegative 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 peripapillary 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,3 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, rheboitic 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 anterior segment dysgenesis; and 68 subjects were un-

<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>.71</td>
</tr>
<tr>
<td>Female/male, No.</td>
<td>580/432</td>
<td>380/300</td>
<td>.14</td>
</tr>
<tr>
<td>Age at review, y</td>
<td>70.6 ± 12.6</td>
<td>72.6 ± 10.3</td>
<td>.01</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>

Table 1. Composition of the Study Groups*

Abbreviations: GIST, Glaucoma Inheritance Study in Tasmania; IOP, intraocular pressure; POAG, primary open-angle glaucoma.

*Values are expressed as mean ± SD unless otherwise indicated.

Intragroup Proportion of Subjects, %

Figure. Distribution of raw Glaucoma Inheritance Study in Tasmania (GIST) severity scores for all subjects with primary open-angle glaucoma (POAG). The \( \chi^2 \) test for difference between each group’s proportion of subjects in the mild and very severe categories is displayed.

Supporting previous investigations, approximately 60% (1014/1700) of subjects in our cohort were classified into the familial POAG group.11 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

### COMMENT
findings are merely a reflection of IOP factors. Visual field findings circumvents any suggestion that our\njusted analysis weighting severity only on optic disc and\ndisease likelihood, which must also account for the ran-
severity score was initially developed for subject intrapedi-
masked fashion avoiding bias in diagnosis. Clinical feature of glaucoma was assessed separately in a
lection was possible with a relatively low attrition rate. Each
referral centers or subspecialty clinics. Thorough data col-
logic information and the examination of many relatives. Thorough ascertainment. Although reporting of family his-
tomy is subject to recall bias and unawareness, this was mini-

There are some limitations to this study. The GIST se-
verity score was initially developed for subject intrapedi-
consideration. This pedigree probability is not a true
disease likelihood, which must also account for the ran-
mon occurrence of glaucoma (approximately 3% in Aus-
tion of family members without the mutation in question
ning that there was a greater proportion of POAG sub-
duction in the differences of systemic glaucoma-

The advance of molecular technologies and the iden-
tification of disease-causing alterations in genes allow for
diagnostic genetic testing in some instances. Several glau-
related genes have been identified, with mutations in myocilin and optineurin accounting for 3% to 5% and
and 0.1% of unselected 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 pa-
tients are screened for the mutation. We have recently dem-
strated that genetic testing in “myocilin glaucoma” is per-
cieved to be appropriate and desirable by both patients and
their families. Following mutation screening, a propor-
tion of family members without the mutation in question
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


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