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Family History Is a Strong Risk Factor for Prevalent Angle Closure in a South Indian Population

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Purpose: To compare the prevalence of angle closure among siblings of patients with open angles (OAs), suspect angle closure (PACS), and either primary angle closure (PAC) or PAC glaucoma (PACG).

Design: Cross-sectional, clinical study.

Participants: A total of 303 South Indian sibling pairs, including 81 OA probands, 143 PACS probands, and 79 PAC/PACG probands.

Methods: Probands and siblings underwent a clinical examination, including gonioscopy by a masked grader, applanation tonometry, slit-lamp biomicroscopy, optic nerve evaluation, and A-scan ultrasonography. Probands and siblings were classified into 1 of 3 groups based on the phenotype of the more severely affected eye: OA, PACS, or PAC/PACG. Multivariable regression models were used to estimate the odds of prevalent angle closure in PACS or PAC/PACG siblings compared with OA siblings.

Main Outcome Measures: Prevalence and relative prevalence of angle closure and PAC/PACG among OA, PACS, and PAC/PACG siblings.

Results: Mean sibling age was 49.7±8.7 years, and 56.6% of siblings were females. Angle closure was more prevalent in both PACS siblings (35.0%) and PAC/PACG siblings (36.7%) compared with OA siblings (3.7%; $P < 0.001$). There was PAC/PACG present in 11.4% of PAC/PACG siblings compared with 4.9% of PACS siblings ($P = 0.07$) and 0% of OA siblings ($P = 0.002$). In multivariable models adjusting for sibling age and sex, the odds of angle closure was 13.6 times greater in angle closure (PACS or PAC/PACG) siblings compared with OA siblings (95% confidence interval [CI], 4.1−45.0; $P < 0.001$). Sibling angle-closure risk was also greater in female (odds ratio [OR], 2.3; 95% CI, 1.3−4.0; $P = 0.005$) and older siblings (OR, 1.5 per 10-year increment; 95% CI, 1.1−2.0; $P = 0.02$). Siblings of PAC/PACG probands had a 2.3-fold greater odds (95% CI, 0.8−6.5) of having PAC/PACG compared with siblings of PACS probands, although the association was not significant ($P = 0.13$).

Conclusions: In the South Indian population screened, siblings of angle-closure patients had a >1 in 3 risk of prevalent angle closure, whereas siblings of PAC/PACG patients had a >10% risk of prevalent PAC/PACG. Screening siblings of angle-closure patients is likely to be of high yield in finding undetected angle closure. *Ophthalmology 2014;121:2091-2097 © 2014 by the American Academy of Ophthalmology.*

Glaucoma is the second leading cause of blindness worldwide,[1] and primary angle-closure glaucoma (PACG) accounts for nearly half of glaucoma-related blindness, despite being significantly less prevalent than primary open-angle glaucoma. By 2020, it is estimated that there will be 5.3 million people who are blind from PACG,[2] with the majority of this blindness occurring in Asian populations.[3] South Indians have a high prevalence of PACG (4.3% of adults >40 years old)[4] and the vast majority do not have routine access to eye care to prevent PACG-related vision loss.[5,6]

Angle-closure glaucoma is a model disease in which to take a preventive approach because early diagnosis and therapy may prevent progression to more advanced stages of disease. For example, laser peripheral iridotomy in the contralateral eyes of patients presenting with an acute angle crisis largely prevents vision loss from PACG.[7−9] Furthermore, the majority of primary angle-closure suspect (PACS) eyes treated with laser peripheral iridotomy have no residual iridotrabecular contact,[7−9] suggesting that early treatment of these eyes may prevent future progression to PACG.

Finding and treating undiagnosed cases of angle closure on the basis of demographic or ocular risk factors is challenging. Demographic risk factors of angle closure (age, ethnicity, female sex) cannot by themselves identify persons at sufficiently high risk to merit screening, whereas other risk factors consist of ocular features that cannot be identified without an eye examination or imaging. However, a positive family history is known to predispose siblings to PACG.[10−12] Roughly 50% of Singapore Chinese[13] and Indian[14] adult family members of individuals with primary angle closure (PAC) or PACG have narrow angles. However, no previous studies have prospectively examined siblings of individuals with suspect PAC (PACS). Additionally, prior studies of Indian populations[14] contained no comparison

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population, leaving the increased risk of angle closure attributable to family history unknown.

Herein we have compared the risk of prevalent angle closure in siblings of South Indian probands with open angles (OAs), PACS, and either PAC or PACG. Unique features of the study included the use of masked gonioscopic graders and the study of >300 total sibling pairs, making it the largest study of family history of angle closure to date.

Methods

This study complied with the tenets of the Declaration of Helsinki, and ethics approval was received from the institutional review boards of the Aravind Eye Hospital (AEH) and Johns Hopkins University. All study participants (probands and enrolled siblings) gave written informed consent before entering the study.

Subjects

Probands were recruited from patients visiting the AEH in Pondicherry, located in the South Indian state of Tamil Nadu. Individuals were eligible to be recruited as proband subjects if they were ≥30 years old and had ≥1 sibling who was (1) >30 years old, (2) shared the same mother and father as the proband (by proband report), and (3) were able to visit the AEH in Pondicherry for an eye examination. Individuals were not eligible for recruitment as probands or siblings if they (1) were bilaterally pseudophakic, (2) had prior iridotomy, iridoplasty, or incisional glaucoma surgery in either eye, or (3) had signs or symptoms consistent with acute angle closure (probands only). Probands with PACS and PAC/PACG were recruited from the Glaucoma Clinic; control probands with OAs were recruited from among patients without eye disease presenting for routine eye examinations.

Clinical Assessment

An initial interview was conducted to collect demographic data and relevant ocular history. All subjects then underwent a comprehensive ophthalmic examination. Trained technicians measured visual acuity (VA) and performed refraction, A-scan ultrasonography, and pachymetry. Three designated glaucoma-trained ophthalmologists completed slit-lamp biomicroscopy, Goldmann applanation tonometry (GAT), and gonioscopy on all subjects. For all examinations, the ophthalmologist was masked to the subject's diagnosis and proband/sibling status.

Evaluation of Vision

Presenting VA was evaluated for each eye with subjects wearing their presenting correction using Snellen charts. Automated refraction, followed by subjective refraction, was then performed to obtain refractive error and best-corrected VA for each eye. All VA scores were converted to a logarithm of the minimum angle of resolution scale, as previously described.[15]

A-Scan and Pachymetry

A-scan ultrasonography (Sonomed Escalon, Lake Success, NY) was performed in both eyes. Five consecutive machine readings were taken and averaged to assess axial length, anterior chamber depth, and lens thickness. Measurements were repeated if the axial length standard deviation was >0.13 mm.

Ultrasound pachymetry (PACSCAN 300P, Sonomed Escalon) was used to obtain the central corneal thickness (CCT) in both eyes. Five measurements were taken and averaged to obtain CCT. If the standard deviation of CCT was >10 μm, all measurements were repeated.

Slit-Lamp Biomicroscopy

A slit-lamp examination of the anterior segment was performed, and those with suspected secondary causes of angle closure were excluded from the study. A dilated fundoscopic examination was performed in all eyes to assess vertical cup-to-disc ratio (CDR) and document the presence/absence of other glaucomatous changes including notching, nerve fiber layer defects, or optic disk hemorrhage. When laser iridotomy was performed, dilated fundus examinations were completed after iridotomy.

Intraocular pressure (IOP) was measured in a masked manner in both eyes using GAT before pupillary dilation. Before measuring the IOP, a technician adjusted the GAT dial to an arbitrary number between 5 and 25. The ophthalmologist looking through the slit lamp then adjusted the dial to the appropriate IOP measure while a technician recorded the result. The IOP measures were taken until 2 consecutive readings differing by <2 mmHg were obtained or until a maximum of 4 measurements were taken. The IOP was calculated as the average GAT value of all measurements. Ophthalmologists were also unaware of the study participant's diagnosis and their proband/sibling status.

Gonioscopy was performed in a dimly illuminated room using a 1×1-mm slit beam. The most posterior structure in each quadrant was initially identified using a 2-mirror Goldmann-type gonioscopy lens (Volk Optical, Mentor, Ohio) in primary gaze. Indentation gonioscopy was performed with a Zeiss 4-mirror gonioscopy lens when necessary to distinguish uncomplicated iridotrabecular contact from iridotrabecular contact complicated by peripheral anterior synechiae (PAS). For each quadrant in which the posterior trabecular meshwork (TM) was not visible, PAS were noted to be either present or absent.

Diagnosis

Probands were classified into 1 of 3 groups based on findings of the ophthalmic examination in the more severely affected eye: (1) OA controls, (2) PACS, or (3) PAC/PACG. One sibling of each proband was also classified as either OA, PACS, or PAC/PACG based on the phenotype of the more severely affected eye. If >1 sibling was recruited for any proband, data from the sibling closest in age to the proband was used for all analyses.

Stages of angle closure were defined based on International Society of Geographical and Epidemiological Ophthalmology classification guidelines, modified to collapse PAC and PACG into a single category (PAC/PACG), reflecting angle closure with either manifest disease or a significant risk of future disease.[16] We defined PACS as having 1 or both eyes with ≥2 quadrants of iridotrabecular contact without visible pigmented TM. Subjects were classified as PAC/PACG if, in addition to 2 full quadrants of appositional angle closure, they also had any 1 of the following: IOP >21 mmHg, evidence of PAS, abnormal trabecular pigmentation consistent with PAC/PACG, CDR ≥0.7, or other evidence of glaucomatous optic neuropathy on dilated fundoscopic examination (notching, nerve fiber layer defects, optic nerve hemorrhage, or vertical cup/disc asymmetry >0.2). We considered PAC and PACG as a single category because reliable visual field data enabling us to distinguish PAC and PACG were not available for many subjects. Probands were classified as OA if both eyes had (1) no quadrants in which posterior TM was not visible, (2) IOP ≤21, (3) no PAS, and (4) no evidence of glaucomatous optic neuropathy.

Probands (and their siblings) who did not meet the requirements for any of these 3 groups in either eye were excluded from the