Primary Open-Angle Glaucoma Risk Factors

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Abstract

Purpose: The objective of this study was to identify possible risk factors associated with primary open-angle glaucoma (POAG).

Methods: A case-control study included patients seen at Rasoul-Akram Hospital ophthalmology clinic. Cases were consecutive patients with confirmed unilateral or bilateral POAG presented during the study period. Controls were a random sample of all other patients aged 30 or more, seen in the same department in the same period who were randomly selected if they fulfilled the inclusion criteria and then matched with the cases by age and sex. Data on demographic, anthropometric as well as medical characteristics were collected from 191 subjects, by interview and medical examination.

Results: Sixty consecutive patients with POAG and 131 controls were chosen. Odds ratios (OR) are calculated for the relation between POAG and family history of glaucoma, body mass index, hypertension, diabetes mellitus, cigarette smoking, migraine, and refractive error. Chi-square and student t tests were used. Results indicated the following: family history of glaucoma: OR: 35, 95% CI: 4.57-282.43, P<0.0001, hyperopia: OR: 0.432, 95% CI: 0.209-0.893, P=0.021, hypertension: OR: 1.46, 95% CI: 0.78-2.73, P=0.223, body mass index: P=0.378 (student t test) , migraine: OR: 0.46, 95% CI: 0.098-2.23, P=0.507, and cigarette smoking: OR, 1.81; 95% CI, 0.747-4.41; P= 0.184.

Conclusion: This study replicated the finding that family history is a major risk factor for POAG (when adjusting for age and sex), while it failed to show that hypertension, diabetes mellitus, myopia, cigarette smoking, migraine, and body mass index to be associated with POAG. It also suggested a protective role for hyperopia in POAG.

Keywords: Primary Open-Angle Glaucoma, Risk Factors

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Introduction

Increased IOP, advancing age, a family history of glaucoma, decreased corneal thickness, and race have been reported as being risk factors for open-angle glaucoma (OAG).[1,2] Surveys in black populations suggest that racial factors may affect glaucoma prevalence.[2,3] Data also support diabetes and myopia as risk factors but these data are generally less convincing. The relevance of sex and of various systemic factors, such as systemic hypertension and arteriosclerosis and ischemic vascular disease to glaucoma risk has been widely debated and currently available data are inconclusive. The purpose of this study was to further investigate the association of POAG and possible determinants such as family history of glaucoma, body mass index, hypertension, diabetes mellitus, cigarette smoking, migraine and refractive error in an Iranian sample, using a case-control design. This could either confirm or refute the hypothesis. It also could determine whether a confirmed relation can be explained by the presence of effect modifiers or confounders. The acquisition of more knowledge regarding risk factors of open angle glaucoma is important not only for individual patient care, but also for public health planning.

Methods

Study was done between July 2003 and January 2004 at the Department of Ophthalmology, *Rasoul-Akram* Hospital and at a private ophthalmologic practice in the city of Tehran, Iran.

Cases

All consecutive patients with confirmed bilateral or unilateral POAG presenting during the study period were included as cases in the study. All patients were aged 30 years or older (range 30-80 years). The criteria considered for the diagnosis of POAG were: intraocular pressure>21 mm Hg, vertical cup-to-disc ratio>0.5, and a characteristic visual field defect.[4] The diagnosis of POAG for confirmation was based on at least two of the three criteria in at least one eye. Additionally patients presented with an open anterior chamber angle. Intraocular pressure was measured three times in each eye, with the median value chosen as the pressure in that

eye. Intraocular pressure for a person was defined as the highest of the pressures in the two eyes. Cup-to-disc ratios were evaluated initially by direct ophthalmoscopy and by indirect ophthalmoscopy after dilatation of the pupils with a Volk 78 lens during the slit-lamp examination and computed for vertical and horizontal meridians of each eye. The vertical ratio was chosen for these analyses. The disc was compared with nine standard drawings labeled 2 to 10, corresponding to a vertical cup-to-disc ratio shown (0.2-1.0).

Glaucomatous visual field defects detected using Humphrey automated perimetry included an arcuate scotoma continuous with the blind spot, a paracentral scotoma larger than 50, a nasal step larger than 100, or an advanced glaucomatous visual field loss. Only patients with POAG were included in the study and patients with pseudoexfoliation or pigmentary or other forms of secondary glaucoma and any previous ocular surgery were excluded from the study.

Controls

A hundred and thirty-one patients as control patients were selected from patients aged 30 years or older (range, 30-80 years) who were seen in the same practices during this period. Systematic sampling was chosen to select controls. Patients with acute infections, ocular trauma, or orbital tumors were excluded from the control group. The most common disease (eye condition) in controls was presbyopia seen in 108 patients (82%), and cataract (52 patients, 39%). Other eye diseases included the following: refractive errors (88 patients, 67%), retinal disorders with or without cataract (11 patients, 8%), and opacity of vitreous with cataract (2 patient, 1.5%), lacrimal drainage disorders (4 patient, 3%), corneal leukoma with cataract (2 patient, 1.5%), pterygium (5 patient, 4%). In remaining patients (21%), no abnormality was found.

Risk factors

Data concerning demographic and anthropometric variables, medical characteristics and ocular variables were obtained through interviews, medical and ocular examinations. Demographic and anthropometric variables included: age, sex,

body mass index (defined as body weight in kilograms divided by square height in meters).

Medical characteristics were based on the following signs, symptoms and history variables: systolic and diastolic pressure, presence of non-treated hypertension, presence of diabetes, blood glucose level and recent smoking. Hypertension was defined as a mean systolic blood pressure of 140 mm Hg or more, and/or a mean diastolic blood pressure of 90 mm Hg or more, and/or a history of hypertension with use of antihypertensive medication at the time of the examination. The mean systolic blood pressure was the average of the two systolic blood pressure measurements, and the mean diastolic blood pressure was the average of the two diastolic blood pressure measurements. Tobacco use (smoking) was defined as any current use or use within a five-year period of the reference date. Ocular characteristics included intraocular pressure, refraction, presence of cataract, history of glaucoma, other eye disease or ocular surgery; and use of ocular medication. All categorical variables were dichotomized.

Ocular examination

An ocular examination was performed in all cases and controls and included the following tests: measurement of visual acuity, inspection of adnexa, refraction examination, examination of the visual field using the Humphrey automated perimeter, applanation tonometry by means of a Goldman tonometer, slit-lamp examination of the anterior segment and gonioscopy, and evaluation of the optic disc by means of direct and indirect ophthalmoscopy with pharmacologic mydriasis. An objective refraction with a retinoscopy and manual subjective refraction were performed in all patients. Because of the age of the study population, cycloplegia was not used. All refractive errors were converted to the sphere by adding the spherical component of refraction to half of the cylindrical component. For this report, myopia was defined as a refractive error less than -0.50 D (refractive error of worse than -0.50 D); hyperopia was defined as a refractive error greater than +0.50 D and

emmetropia was defined as a refractive error between +0.50 D and -0.50 D.

Statistical analysis

Chi-square value or Fisher exact test, as appropriate, were calculated to test for significance of a relation between dichotomous variables. The Student's t-test was used to compare between means or ordered variables.

The data of patients who were diagnosed as having POAG were compared with controls. Ophthalmological parameters were analyzed by SPSS, taking the value in the worse eye for each parameter. Refractive error was defined as the spherical equivalent power in the eye with the higher absolute value. The results are presented as odds ratios (OR) and their 95% confidence interval (CI) for the association of each possible determinant with POAG. All variables were first evaluated bivariately for their association with POAG. Variables with $P<0.05$ were considered as significant. SPSS software (version 13) was used for data analysis.

Results

We identified 60 patients with POAG (cases) and 131 controls. Of 60 patients with POAG, 46 (76.6%) had bilateral OAG. Table 1 shows the characteristics of both cases and controls. The mean age (±SD) was 64 years (±12) for cases and 63 years (±11) for controls ($P>0.05$).

Crude data analysis

The results of the bivariate analysis are summarized in Table 2, which reveals that family history of glaucoma was significantly associated with POAG. On the other hand, patients with hyperopic refractive error had significantly lower rate of POAG compared to patients without it. The distribution of refraction between patients in POAG cases and controls was as follows: 12 (20%) cases had hyperopia compared with 48 (36%) among control patients. In study group 16 (26.6%) of patients had myopia compared with 36 (27.4%) of patients in the control group. In the remaining patients refraction was plano.

Table 1. Demographics and clinical characteristics of 60 cases of POAG and 131 controls

Variables	No. of cases of POAG (n=60)	No. of controls (n=131)
Age group (years)		
30-51	3 (5%)	7 (5.3%)
51-70	33 (55%)	72 (54.9%)
>70	24 (40%)	52 (39.6%)
Gender		
Male	33 (55%)	66 (51%)
Female	27 (45%)	65 (49%)
Family history of glaucoma (Yes)	13 (21%)	1 (0.7%)
Diabetes mellitus (Yes)	15 (25%)	19 (14%)
Smoking, tobacco use (Yes)	10 (16%)	13 (9%)
Hypertension (Yes)	26 (43%)	45 (34%)
Refraction (Hyperopia)	12 (20%)	48 (36%)
Refraction (Myopia)	16 (26.6%)	36 (27.4%)
Cataract (Yes)	18 (30%)	52 (39%)
Migraine	2 (3%)	9 (6%)
Age, years (Mean±SD)	64.68±12.22	63.06±11.54
Body mass index (Mean±SD)	27.2±5.06	26.56±4.4
Cup-to-disc ratio (Mean±SD)	0.6±0.3	0.3±0.2
IOP, mm Hg (Mean±SD)	29.6±11.9	15.07±2.33
IOP range	21-62	10-21

POAG: primary open-angle glaucoma, IOP: intraocular pressure, SD: standard deviation

Table 2. Results of bivariate analysis of 60 cases of POAG and 131 controls

Variables	Odds ratio	95% Confidence Interval	P value
Diabetes mellitus (Yes)	1.94	0.91-4.19	0.83
Smoking, tobacco use (Yes)	1.81	0.74-4.41	0.184
Hypertension (Yes)	1.46	0.78-2.73	0.233
Refraction (hyperopia)	0.432	0.20-0.89	0.021
Migraine	0.46	0.098-2.23	0.507
Body mass index (student *t* test)	N/A	N/A	0.378

POAG: primary open-angle glaucoma

Discussion

In this case-control study, we investigated the risk factors associated with POAG among our patients. Many studies around the glaucoma risk factors have been performed in the world. The results of these studies have confirmed that age, positive family history, high IOP, high cup-to-disc ratio and corneal pachymetry are related with glaucoma, but about the other risk factors such as diabetes mellitus, refraction, hypertension, sex, smoking, migraine, alcohol, and body mass index data are inconclusive. Since the age has been confirmed in most of these studies as risk factor we matched our study groups based on age to decrease the role of confounding factors. The results of the study showed that family history of glaucoma was associated with POAG, and hyperopia acts as a protective role, so that patients with hyperopia had significantly lower rate of POAG.

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A family history of glaucoma is generally accepted as a risk factor for the disease. Positive family histories have been reported in 13% to 25% of cases.[5,6] *Shin* et al[7] report that up to 50% of POAG patients and 43% of ocular hypertensive cases in their study presented with a positive family history of glaucoma. Consistent results were obtained from the *Barbados* Family Study of Open-angle Glaucoma (BFSG), in which 39% of the recruited probands had one or more family members affected with POAG.[8] In the Rotterdam, Netherlands, study,[9] the lifetime absolute risk of glaucoma at age 80 years was nearly 10 times higher for individuals having relatives with glaucoma than for control patients (22.0% vs. 2.4%; relative risk=9.2; 95% CI: 1.2, 73.9; P<0.001). Extrapolating from these data, a "family score," derived by compiling data from family members, was a strong predictor of POAG independent of IOP.[10] The higher prevalence of POAG within certain families may be attributed to either genetic or environmental factors, or to a combination of both.[11] However, it is now clear that genetic factors directly account for at least a proportion of POAG inheritance.[12] Because black heritage is also a risk factor to develop POAG,[13] blacks with a family history of glaucoma should be closely monitored.

Also in our study a strong association was found between a positive family history of glaucoma and the disease resulting in an odds ratio of 35.95 (95% CI, 4.57-282.43). This strong association could be explained by our definition of open glaucoma; we included IOP and cup-to-disc ratio in our definitions. These two physiologic or anatomic characteristics are, themselves, at least in part, genetically determined.[14,15] Additionally, the increase of POAG with age is well known[16,17] although we did not evaluated this factor in our study.

In several studies a higher prevalence of POAG has also been identified in males,[18-20] while other investigators found an equal prevalence of POAG in both sexes[21] and even a higher prevalence in females.[22] In our study, to resolve this problem we matched both groups based on sex and age.

Several reports have shown an association between POAG and cardiovascular disease, although this finding has not been consistent.[23] In our data, only risk factors for cardiovascular disease were studied. Body mass index was not related to POAG in contrast to *Kaimbo* et al study.[24] The recently described absence of a relation between smoking and POAG[25] was confirmed and also no independent relation was found between POAG and hypertension.

Most previously published studies have supported the notion of a relation between diabetes mellitus and POAG. Several studies have shown a high prevalence of diabetes mellitus in patients with POAG, as well as a high prevalence of POAG in patients with diabetes.[26-29] More recently, most large population-based studies have supported the linkage between diabetes mellitus and POAG.[29-31] However, no association between diabetes and POAG was observed in Afro-Caribbeans living in the *United Kingdom*.[32] Another important exception is the Baltimore Eye Survey, in which no relationship was established.[33] In our study the OR between POAG and diabetes is 1.94 and this supports the data of the study noted.

Surprisingly, we found hyperopia to be lower frequently present in POAG patients compared to controls. In previous reports, myopia has been associated with POAG.[34-36] Both an increased incidence of myopia among patients who have POAG[19] and an increased prevalence of POAG among myopes[36] have been described. Conversely, hyperopia has been associated with a lower risk of glaucoma.[19] In glaucoma suspects, the absence of hyperopia was found to be a strong prognostic indicator for developing visual field defects.[37] However, two studies[38,39] have found that blacks were more hyperopic than whites. In both the Glaucoma Laser Trial and the Advanced Glaucoma Intervention Study, have found a greater hyperopic mean refractive error in blacks than in whites. Authors in the Advanced Glaucoma Intervention Study thought that perhaps the influence of refractive error becomes less important with age. In our study, There were marked differences in the distribution of hyperopia between patients in POAG cases and controls: 12 (20%) cases had hyperopia in the POAG cases, compared with 48 (36%) among control patients. (P=0.021). We cannot easily explain the relation between POAG and hyperopia in our study. It suggests that

hyperopia may be a protective factor for POAG.

Our study had some limitations that seems some of them be due to nature of such studies in patients with diseases such as glaucoma; First, we could not completely match patients in study group with patients in control group; Second, observational studies dictates some problems that may be impossible to solve them and reach the best and expected aims; third, in this study we did not include some factors that can affect on our results. For example, we did not performed pachymetry to detect effect of corneal pachymetry on IOP. Authors of this study recommend a large study to refine risk factors of POAG and establish findings of this study.

Conclusion

The excess risk of POAG was seen in patients with a family history of POAG (bearing an OR of 35.95 for patients with a positive family history compared to patients without family history, adjusting for age and sex). Our study failed to show that hypertension, diabetes mellitus, myopia, cigarette smoking, migraine, and body mass index to be associated with POAG. It also suggested a protective role for hyperopia in POAG.

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