Jpn J Ophthalmol (2012) 56:324–329
DOI 10.1007/s10384-012-0153-4

CLINICAL INVESTIGATION

Risk factors for primary open-angle glaucoma in South Korea: the Namil study

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Received: 15 October 2011 / Accepted: 13 March 2012 / Published online: 5 June 2012

Abstract
Purpose To investigate the risk factors for primary open-angle glaucoma (POAG) in the Namil study population.
Methods A cross-sectional, population-based epidemiological study of residents aged ≥40 years from Namil-myon, South Korea, was conducted. Fifty-five subjects with POAG and 1,409 controls were enrolled in this study. Univariate and multivariate logistic regression analyses were performed to identify ocular and systemic factors associated with POAG.
Results Multivariate logistic regression analysis demonstrated that older age, a history of thyroid disease and higher IOP were associated with an increased risk of POAG. Subgroup analysis showed that older age (OR 1.033, 95 % CI 1.003–1.063 per year), a history of thyroid disease (OR 7.373, 95 % CI 1.407–38.636) and higher IOP (OR 1.132, 95 % CI 1.011–1.268 per mmHg) were risk factors for normal tension glaucoma (NTG, POAG with IOP ≤21 mmHg).
Conclusions In the Namil study, higher IOP, older age and a history of thyroid disease were significant risk factors for POAG.

Keywords Open angle glaucoma · Normal tension glaucoma · Risk factor · Epidemiology

Introduction

Glaucoma is a significant cause of irreversible blindness worldwide [1]. Primary open-angle glaucoma (POAG) is the most common type, particularly in populations of European and African ancestry [2], and those of East Asia, including Korea [3] and Japan [4].

A number of epidemiologic studies sought to identify risk factors for POAG. Elevated intraocular pressure (IOP), older age [5, 6] and African ancestry [2] have been shown to be strongly associated with POAG. A number of other risk factors, including myopia [6, 7], a family history of POAG [8, 9], a thinner central cornea [9, 10], smoking [11] and a history of thyroid disease [12, 13], are suggested to be risk factors. However, the studies are not consistent in their findings. Moreover, few studies have been performed to evaluate the risk factors for normal tension glaucoma (NTG) in a population.

A recent population-based epidemiologic study in Korea (the Namil study) demonstrates that 77 % of POAG patients (prevalence of POAG, 3.5 %) had an IOP ≤21 mmHg at screening [3]. A high proportion of NTG has also been previously demonstrated in Japan. The Tajimi study shows that 92 % of patients with POAG (prevalence of POAG, 3.9 %) had an IOP ≤21 mmHg [6].

For the Namil Study Group, the Korean Glaucoma Society.

The members of Namil Study Group, the Korean Glaucoma Society, are given in the Appendix.

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These data together suggest that NTG is a major health problem in these regions.

The purpose of the present study was to investigate the ocular and systemic risk factors for POAG, as revealed by the Namil study. In addition, we performed subgroup analysis to determine the risk factors for NTG, identified as the most common form of glaucoma in Korea.

Materials and methods

The detailed protocol of the Namil study is reported elsewhere [3]. The study was a population-based cross-sectional survey conducted at Namil-myon, a 47.14-km^2 area in central South Korea. The study was carried out in accordance with the Declaration of Helsinki and the municipal laws of the Province of Chungcheongnam-do, and was approved by the Institutional Review Board of Chungnam National University Hospital.

Local residents aged 40 years or older ($n = 2{,}027$), were selected for the study. Of these, 20 died during the screening period, and 79 moved from the area or could not be located in Namil-myon at the end of the survey (28 February 2008). Of the remaining 1,928 eligible subjects, 1,532 (887 women and 645 men) received eye examinations, corresponding to an overall response rate of 79.5 %.

After informed written consent was obtained, each participant was interviewed and completed a questionnaire exploring the occurrence of systemic diseases such as hypertension, diabetes mellitus, thyroid disease and stroke. Subjective symptoms such as migraine and cold extremities, any family history of glaucoma and smoking history were also explored in the questionnaire. After interviews, ophthalmic examinations were conducted by trained technicians. Each examination included measurement of visual acuity, refractive status, anterior segment dimensions using IOL Master® (Carl Zeiss Meditec, Oberkochen, Germany) and central corneal thickness (CCT) employing IOPac® (Heidelberg Engineering, Heidelberg, Germany). Slit-lamp biomicroscopic examination, IOP measurement by Goldmann applanation tonometry and gonioscopy were performed by a glaucoma specialist. A screening visual field test using frequency doubling technology (N30-1 screening, Humphrey Matrix; Carl Zeiss Meditec Inc., Dublin, CA, USA) and fundus photography (TRC-NW200; Topcon, Tokyo, Japan) were also performed.

Subjects with suspected glaucoma were referred for definitive examination. Visual field testing was performed using the Humphrey Field Analyzer SITA Standard 30-2 program (HFA II 720i; Carl Zeiss Meditec Inc.). When an abnormal result was found or when the data were of poor reliability, retinal nerve fiber layer analysis was performed using either optical coherence tomography (Stratus OCT; Carl Zeiss Meditec) or scanning laser polarimetry (GDxVCC; Carl Zeiss Meditec). Any definitive test yielding suspicious or abnormal results was repeated on either the same or the following day.

Two separate evaluation committees, each composed of four glaucoma specialists from four different institutes, made the diagnosis of glaucoma based on IOP levels, anterior chamber depth, gonioscopic results, appearance of the optic disc and retinal nerve fiber layer, and perimetric results, in accordance with the criteria of the International Society for Geographical and Epidemiological Ophthalmology [14]. The decisions of the two committees were re-evaluated by a third committee that discussed any discrepancies between the first two results and then made the final diagnosis [3].

Ophthalmologic and systemic data on all patients diagnosed with POAG in the Namil study were analyzed in the present work. Nonglaucomatous eyes of the Namil study were used as a control group. Such eyes were defined by excluding eyes with any type of glaucoma or that were glaucoma-suspect, but not those with ocular hypertension (IOP >21 mmHg). When both eyes were eligible, one eye was randomly selected and used for the analyses.

Data analysis

The demographic and systemic parameters included in the analysis were age, gender, history or presence of any of the following: diabetes mellitus, hypertension, thyroid disease or stroke, migraine or cold extremities, smoking habit and any family history of glaucoma. Smoking status was evaluated as non-smoker, ex-smoker or current smoker. Of the ocular parameters, IOP, spherical equivalent (SE), CCT, axial length (AL) and anterior chamber depth (ACD) were included in the analysis. When ocular parameters such as SE, ACD and AL were analyzed, pseudophakic or aphakic eyes were excluded, because cataract surgery could change these parameters [6, 7, 15]. When the analysis involved IOP, eyes with a history of glaucoma surgery or under current medication for glaucoma were excluded.

Univariate and multivariate logistic regression analyses were performed to identify risk factors for POAG. In the multivariate analysis, variables that retained significance at $P < 0.2$ in the univariate analysis were included. Subgroup analysis was performed to determine the risk factors for NTG, defined as POAG with IOP $\leq$21 mmHg. Statistical significance in logistic regression analysis was defined as a probability value <5 %.

Results

In the Namil study, 55 subjects were diagnosed with POAG. Of the 55 eyes of these subjects, 43 eyes had IOP

≤21 mmHg [3]. A total of 1,409 eyes, including normal eyes (1,400 eyes) and eyes with ocular hypertension (9 eyes), were used as a control group. Four eyes of four glaucoma patients who either received antiglaucoma medication or underwent glaucoma surgery were excluded from the analysis involving IOP. In addition, a total of 141 eyes, which were either pseudophakic or aphakic, were also excluded from the analysis whenever it involved SE, AL or ACD.

Comparisons of ocular and systemic parameters between the POAG and control subjects are summarized in Table 1. No statistically significant difference was evident between the POAG patients and the controls in regard to smoking history, history of stroke, symptoms including migraine and cold extremities, CCT, SE, AL or ACD, ($P = 0.04$). The history or presence of systemic hypertension ($P = 0.026$), and IOP ($P < 0.001$) differed significantly between POAG patients and controls. The history or presence of diabetes mellitus and thyroid disease were of marginal significance.

Multivariate logistic regression analysis demonstrated that older age [odds ratio (OR) 1.047, 95 % confidence interval (CI) 1.020–1.074], a history of thyroid disease (OR 8.386, 95 % CI 1.539–45.685) and higher IOP (OR 1.286, 95 % CI 1.182–1.398) were associated with an increased risk of POAG (Table 2).

Risk factors for normal tension glaucoma

Table 3 shows the results of the subgroup, univariate and multivariate logistic regression analyses where only subjects with IOP ≤21 mmHg were included among the POAG patients. Univariate analysis revealed that older age, a history or presence of diabetes mellitus, systemic hypertension or thyroid disease, and higher IOP were all significantly associated with NTG. Of these parameters, older age (OR 1.033, 95 % CI 1.003–1.063), a history or presence of thyroid disease (OR 7.373, 95 % CI 1.407–38.636) and higher IOP (OR 1.132, 95 % CI 1.011–1.268) remained significant upon multivariate analysis.

Table 1 Differences between POAG eyes and Controls

Parameter	POAG ($n = 55$)	Control ($n = 1,409$)	P value
Systemic			
Age (years; mean ± SD)	68.4 ± 10.1	63.5 ± 11.6	0.004
Gender (male)	51.0 %	42.1 %	0.196
Diabetes mellitus	18.2 %	10.2 %	0.059
Hypertension	41.8 %	28.0 %	0.026
Thyroid disease	3.6 %	0.6 %	0.051
Stroke	1.8 %	1.1 %	0.480
Smoking			0.443
Ex-smoker	18.5 %	14.9 %	
Current smoker	27.8 %	22.9 %	
Family history of glaucoma	3.6 %	1.5 %	0.215
Migraine	30.9 %	29.6 %	0.834
Cold hand	41.8 %	42.9 %	0.877
Ocular			
Intraocular pressure (mmHg)[a] (mean ± SD)	15.7 ± 4.7	13.4 ± 2.8	<0.001
Central corneal thickness (μm)[a] (mean ± SD)	529.6 ± 29.1	530.5 ± 31.3	0.564
Spherical equivalent (diopters)[b] (mean ± SD)	0.3 ± 2.2	0.2 ± 2.0	0.904
Axial length (mm)[b] (mean ± SD)	23.3 ± 0.9	23.3 ± 1.0	0.769
Anterior chamber depth (mm)[b] (mean ± SD)	3.1 ± 0.4	3.0 ± 0.3	0.529

POAG primary open-angle glaucoma, *SD* standard deviation

[a] Eyes with a history of glaucoma treatment or refractive surgery were excluded from analysis

[b] Eyes with pseudophakia or aphakia were excluded from analysis

Table 2 Multivariate analysis of risk factors associated with primary open-angle glaucoma

Parameter	Odds ratio (95 % CI)	P value
Age	1.047 (1.020–1.074)	<0.001
Gender (male)	1.514 (0.854–2.682)	0.156
Diabetes mellitus	1.645 (0.764–3.543)	0.203
Hypertension	1.242 (0.678–2.272)	0.483
Thyroid disease	8.386 (1.539–45.685)	0.014
Family history of glaucoma	2.961 (0.642–13.660)	0.164
Intraocular pressure (mmHg)	1.286 (1.182–1.398)	<0.001

Discussion

The Namil study was the first population-based survey to examine the prevalence of and risk factors for glaucoma in Korea. As with the Tajimi study in Japan [4], the most common type of glaucoma was POAG, and the majority of the patients (77 %) diagnosed with POAG had IOP ≤21 mmHg [3].

As in most other epidemiologic surveys, the present study identified higher IOP as a risk factor for POAG [5, 6, 9, 10, 15]. It is notable that this was also true in the subgroup analysis in which only NTG patients were included. This is consistent with the results of the Tajimi study, where IOP was identified as a risk factor for POAG, despite the fact that most (92 %) of the POAG patients had an IOP ≤21 mmHg [6]. These data together suggest that the IOP plays an important role in the pathogenesis

Table 3 Univariate and multivariate analysis of risk factors associated with normal-tension glaucoma

Parameter	Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value
Age	1.032 (1.004–1.061)	0.025	1.033 (1.003–1.063)	0.031
Gender (male)	0.999 (0.5540–1.848)	0.997		
Diabetes mellitus	2.369 (1.113–5.042)	0.025	2.010 (0.901–4.481)	0.088
Hypertension	2.269 (1.232–4.178)	0.009	1.522 (0.784–2.954)	0.215
Thyroid disease	8.445 (1.739–41.014)	0.008	7.373 (1.407–38.636)	0.018
Stroke	–	–		
Smoking				
Ex-smoker	1.359 (0.604–3.057)	0.459		
Current smoker	0.973 (0.449–2.107)	0.944		
Family history of glaucoma	3.166 (0.718–13.955)	0.128	3.397 (0.743–15.529)	0.115
Migraine	1.546 (0.830–2.880)	0.170		
Cold hand	0.859 (0.462–1.598)	0.632		
Intraocular pressure (mmHg)	1.118 (1.000–1.251)	0.050	1.132 (1.011–1.268)	0.032
Central corneal thickness (μm)	0.998 (0.988–1.008)	0.719		
Spherical equivalent (diopters)	1.119 (0.934–1.341)	0.221		
Axial length (mm)	1.027 (0.749–1.407)	0.869		
Anterior chamber depth (mm)	1.663 (0.811–3.409)	0.165		

of glaucoma even when it is within the normal range. In addition, older age was also identified as a risk factor for POAG, consistent with the results of previous reports [6, 9, 15].

A history of thyroid disease was a risk factor for the overall POAG and NTG. This is consistent with a finding of the Blue Mountains study, which showed an association between thyroid disease and POAG [13]. The cited work also found more lower than high-tension glaucoma patients among POAG patients with thyroid disease. The association of thyroid disease and glaucoma may be explained immunologically. Thyroid disease has an immunological basis, and it is acknowledged that the development of autoimmunity may also be linked to glaucoma pathogenesis [16, 17]. It is possible that an autoimmune response to a sensitizing antigen may damage either the retinal ganglion cells or the optic nerve vasculature, leading to increased optic nerve head susceptibility to glaucomatous damage.

Myopia was not a risk factor for POAG in the present study. This is contradictory to some of the other reports [6, 7, 18]. Although we do not have a definitive explanation for this observation, it is possible that the age of the population in this study affected our results. In any analysis of myopia prevalence, pseudophakic or aphakic eyes should be excluded, because cataract surgery changes the refractive error. In the present work, the mean patient age was 64.1 ± 11.5 years, older than that of the subjects of other epidemiologic studies, and 9.7 % of the eyes were excluded from SE analysis because of a history of cataract surgery. This relatively high exclusion rate may have affected the outcome.

A thin cornea was not a significant risk factor in the present work, unlike that found in the Ocular Hypertension Treatment Study (OHTS), where a low CCT was a significant risk factor for conversion to POAG [19]. The Barbados study also found that a thinner CCT was associated with POAG [9, 20]. In the Tajimi study, however, as in the present work, CCT was not a significant risk factor for POAG [6]. We speculate that ethnic differences may partly explain these discrepancies. In addition, IOP differences among reports may be relevant. The IOPs of our subjects and of those in the Tajimi study were much lower than those of the subjects in the OHTS and Barbados surveys. This finding suggests that the relevance of CCT to the risk of developing POAG may differ depending on the IOP levels.

Some known risk factors, including a family history of glaucoma, migraine and cold hands, were not identified by the Namil study. The absence of such factors should be interpreted with caution because the relevant information here was obtained solely by interview.

There were several limitations to the present study. First, as mentioned above, the information on family history and systemic diseases was obtained by interview without a biochemical examination. A future, population-based study where systemic and ophthalmologic parameters are more deliberately selected and estimated is warranted. Second, about 10 % of the subjects were excluded from the analysis involving IOP or biometric parameters because of a history of either glaucoma treatment or cataract surgery. This should be considered in interpreting the data of the IOP and biometric parameters. Third, because of the relatively small

number of patients with high-tension POAG, subgroup analysis for these patients was not performed. Further work with a larger study population is needed.

In conclusion, the Namil study found that higher IOP, older age and the presence of thyroid disease were significant risk factors for POAG.

Acknowledgments The authors thank Soo Hee Kang, Medical Research Collaborating Center, Seoul National University Hospital, for assistance with statistical analysis. This study was supported by Alcon Korea, Merck Korea, Pfizer Korea, Taejoon Pharmaceutical, Zeiss Korea and the Korean Ophthalmological Society.

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