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Open-Angle Glaucoma and the Risk of Stroke Development
A 5-Year Population-Based Follow-Up Study

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Background and Purpose—Although open-angle glaucoma (OAG) is associated with some of the risk factors of stroke development, there is still no published study addressing whether OAG increases the risk of stroke development. We investigated the risk of stroke development after a diagnosis of OAG.

Methods—Data were retrospectively collected from the Taiwan National Health Insurance Research Database, which is comprised of 1 073 891 random subjects from among Taiwan's 23 million residents. The study cohort comprised all patients with a diagnosis of OAG (International Classification of Diseases, 9th Revision, Clinical Modification code 365.1 to 365.11) in 2001 (n=4032). The comparison cohort was comprised of randomly selected patients (5 for every patient with OAG, n=20 160) matched with the study group in terms of age, gender, geographic location, and comorbid medical disorders. Patients were tracked from their index visits for 5 years. Cox proportional hazard regression was used to compute the 5-year stroke-free survival rate after adjusting for possible confounding factors.

Results—Stroke developed in 14.9% of patients with OAG and 9.5% of patients in the comparison cohort during the 5-year follow-up period. Patients with OAG had significantly lower 5-year stroke-free survival rates than patients in the comparison cohort. After adjusting for patients' demographic characteristics and selected comorbidities, patients with OAG were found to have a 1.52-fold (95% CI, 1.40 to 1.72) higher risk of having a stroke than the matched comparison cohort.

Conclusions—Patients with OAG demonstrated a significantly increased risk of stroke development during the 5-year follow-up period. **(*Stroke*. 2009;40:2685-2690.)**

Key Words: epidemiology ■ open-angle glaucoma ■ risk factors ■ stroke

Glaucoma is one of the leading causes of blindness worldwide[1,2] and one of the most prevalent forms of glaucoma is open-angle glaucoma (OAG).[3] The systemic risk factors associated with OAG include old age,[4] diabetes mellitus,[5] and hypertension,[6] although there is conflicting evidence as to some of these (ie, diabetes and hypertension).[7, 8] In addition, it has been shown that dynamic cerebral autoregulation is impaired in patients with OAG patients.[9] All of these risk factors are associated with the development of stroke, which is the most common cause of serious disability in adults.[10] Therefore, it would be of clinical relevance to investigate whether OAG is a predictor for the future development of stroke.

In an observational cross-sectional study involving 50 patients with a diagnosis of primary OAG (POAG) and 50 patients without POAG, an association was found between POAG and stroke.[11] In a study of patients with diabetes, neither glaucoma nor OAG was associated with an increased risk of stroke mortality.[12] However, to the best of our knowledge, there is still no published study comparing the rate of stroke development in patients diagnosed as having OAG with a control cohort. Using a population-based data set from Taiwan, this study investigated the relationship between OAG and the risk of future stroke development.

Methods

Database

This study used a subdata set from the National Health Insurance Research Database released by the Taiwan National Health Research Institute in 2006. Taiwan initiated its National Health Insurance program in 1995, and there are currently over 22 million enrollees in the National Health Insurance program representing approximately 98% of the island's population. This subdata set consists of 1 073 891 randomly selected subjects, approximately 5% of all enrollees in the National Health Insurance program. This data set was created by the Taiwan National Health Research Institute using a systematic method to randomly select a representative database from the entire set of enrollees. It was reported that there were no statistically significant differences in age, gender, or healthcare costs between the sample group and all enrollees. Therefore, this subdata set provides a unique opportunity to identify the risk of stroke development occurring among patients with OAG.

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Table 1. Demographic Characteristics and Comorbid Medical Disorders for Patients With OAG and Patients in a Comparison Cohort in Taiwan, 2001 (N=24 192)

	Patients With OAG		Comparison Cohort		
Variable	Total No.	Column, %	Total No.	Column, %	*P* Value
Gender					1.000
Male	1984	49.2	9919	49.2	
Female	2048	50.8	10 241	50.8	
Age, years, mean (SD)	60.2 (17.8)		60.2 (17.8)		1.000
Hypertension					1.000
Yes	1968	48.8	9838	48.8	
No	2064	51.2	10 322	51.2	
Diabetes					1.000
Yes	1043	25.9	5221	25.9	
No	2989	74.1	14 939	74.1	
Hyperlipidemia					1.000
Yes	746	18.5	3730	18.5	
No	3286	81.5	16 430	81.5	
CHD					1.000
Yes	896	22.2	4476	22.2	
No	3136	77.8	15 684	77.8	
Geographic region					1.000
Northern	2715	67.3	13 568	67.3	
Central	470	11.7	2359	11.7	
Southern	799	19.8	3992	19.8	
Eastern	48	1.2	241	1.2	

Because the National Health Insurance Research Database consists of deidentified secondary data released to the public for research purposes, the study was exempt from full review by the Internal Review Board after consulting with the Director of the Internal Review Board of our university.

Study Sample

We identified 4687 patients who had ambulatory care visits for treatment of OAG (International Classification of Diseases, 9th Revision, Clinical Modification codes 365.1 to 365.11) between January 1 and December 31, 2001. Because the diagnostic validity of administrative data sets is often questioned, we only included patients who had at least 3 consensus OAG diagnoses in the study sample (n=4657) to assure the validity and reliability of the diagnoses. In addition, we limited our study sample to those patients who had received antiglaucoma medications for >1 year or had undergone glaucoma surgery (n=4126). Patients who had been diagnosed with stroke (International Classification of Diseases, 9th Revision, Clinical Modification codes 430 to 438) in the preceding 5 years (1996 to 2000) were also excluded (n=94). Ultimately, our study cohort included 4032 patients with OAG.

Our comparison cohort was extracted from the remaining patients in the subdata set. We excluded patients who had ever been diagnosed as having any type of glaucoma. Again, we excluded patients who had been diagnosed with stroke in the preceding 5 years. We then randomly selected 20 160 subjects (5 for every patient with OAG) matched with the study cohort in terms of age (as a continuous variable), gender, the geographical location of the community in which the patient resided (northern, central, eastern, and southern Taiwan), and whether they had hypertension, diabetes, coronary heart disease (CHD), or hyperlipidemia. Past studies have established the positive associations between occurrence of stroke and hypertension, diabetes, CHD, and hyperlipidemia. These comorbidities therefore were taken into account in this study. Medical comorbidities were identified by the diagnosis codes from the medical records 6 months before and after the index ambulatory care visits. There were no significant differences in age, gender, geographical region, hypertension, diabetes, CHD, or hyperlipidemia between the study and comparison cohorts.

Statistical Analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the analyses in this study. Each patient was individually tracked for a 5-year period from their index ambulatory care visits in 2001 to the end of 2006 to distinguish all patients who had developed any type of stroke during the follow-up period. Pearson χ^2 tests were performed to examine differences between the 2 cohorts in terms of sociodemographic characteristics, selected comorbid medical disorders, and the risk of developing a stroke. Thereafter, the 5-year stroke-free survival rate was calculated by the Kaplan-Meier method using the log rank test to examine differences in the risk of stroke occurrence between the 2 cohorts. Cox proportional hazard regressions were also performed to compute the adjusted 5-year survival rate after adjusting for sociodemographic characteristics and selected comorbid medical disorders. Finally, we present hazard ratios (HRs) along with 95% CIs. A 2-sided probability value of 0.05 was used to indicate statistical significance.

Results

The distributions of demographic characteristics and selected comorbid medical disorders for these 2 cohorts are presented in Table 1. The mean age of patients with OAG was 60.2 years with a SD of 17.8 years. Slightly more than half (50.8%) of the sampled patients were female. In total, 48.8%, 25.9%, 18.5%, and 22.2% of sampled patients had hypertension, diabetes, hyperlipidemia, and CHD, respectively.

Table 2. Stroke Occurrence Among Patients With OAG and Patients in the Comparison Cohort in Taiwan During the 5-Year Follow-Up Period (N=24 192)

	Stroke Occurrence			
Variable	Yes, Row n (%)	No, Row n (%)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Cohort				
OAG	599 (14.9)	3433 (85.1)	1.65† (1.50–1.83)	1.52† (1.40–1.72)
Comparison	1924 (9.5)	18 236 (90.5)	1.00	1.00

*Adjusted for gender, age, hypertension, diabetes, hyperlipidemia, CHD, and geographic region.
†$P<0.001$.

Of the total sample of 24 192 patients, 2523 patients (10.4%) developed stroke during the 5-year follow-up period, including 599 (14.9% of the patients with OAG) from the study cohort and 1924 (9.5% of the comparison patients) from the comparison cohort (Table 2). The regression showed that the HR of developing stroke during the 5-year follow-up period for patients with OAG was 1.65 (95% CI, 1.50 to 1.83; $P<0.001$) compared with that for patients in the comparison cohort. The log rank test also indicated that patients with OAG had significantly lower 5-year stroke-free survival rates than patients in the comparison cohort ($P<0.001$; Figure).

After adjusting for patients' gender, age, hypertension, diabetes, hyperlipidemia, and CHD, the hazard of developing stroke during the 5-year follow-up period was 1.52 (95% CI, 1.40 to 1.72; $P<0.001$) times greater for patients with OAG compared with patients in the comparison cohort (Table 2). As expected, patients with hypertension (HR, 3.22; 95% CI, 2.78 to 4.32; $P<0.001$), diabetes (HR, 2.25; 95% CI, 2.04 to 2.48; $P<0.001$), hyperlipidemia (HR, 1.15; 95% CI, 1.02 to 1.29; $P<0.001$), and CHD (HR, 2.23; 95% CI, 1.72 to 2.89; $P<0.001$) had a greater likelihood of developing stroke. Among patients with OAG, 146 (3.62% of all patients with POAG) received glaucoma surgery from 2000 to 2006. Of these patients, 18 (12.3%) developed a stroke during the 5-year follow-up period. However, among patients with POAG who did not receive glaucoma surgery, 581 (15.0%) developed a stroke during the 5-year follow-up period. There was no difference in the hazard of developing stroke between these 2 cohorts ($P=0.382$).

Table 3 reveals results from further analyses stratified by hypertension and diabetes. Among individuals with and without hypertension, the adjusted hazard of stroke during the 5-year follow-up was 1.23 (95% CI, 1.02 to 1.52; $P=0.032$) and 2.05 (95% CI, 1.73 to 2.42; $P<0.001$) for patients with OAG compared with patients in the comparison cohort. Compared with patients in the comparison cohort, patients with OAG both with and without diabetes had an increased risk of stroke (HR, 1.20; 95% CI, 1.01 to 1.43; $P=0.028$ and HR, 1.60; 95% CI, 1.42 to 1.81; $P<0.001$, respectively).

Discussion

In this study, in which data on 4032 patients with OAG were analyzed, we found that patients with OAG had a significantly higher risk of stroke development in the 5-year follow-up period. After adjusting for age, gender, geographic region, and comorbid medical disorders (hypertension, diabetes, hyperlipidemia, and CHD), OAG remained a significant predictor for the development of stroke. In stratified analyses, these associations were present in people with and without hypertension and in people with and without diabetes.

Belzunce and Casellas' study reported an association between POAG and stroke. It was an observational cross-sectional study (prevalence ratio, 2.16; 95% CI, 1.02 to 2.20).[11] In that report, the study group was comprised of 50 patients with POAG who had been admitted to a tertiary hospital for any reason and which were selected by consecutive sampling. The comparison group was comprised of 50 patients admitted to the same hospital without a POAG

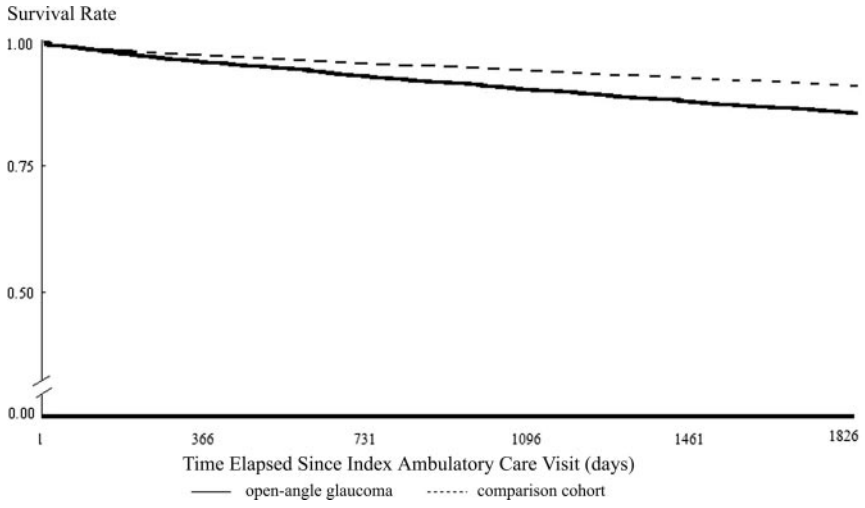

Figure. Stroke-free survival rates for patients with OAG and patients in the comparison cohort in Taiwan, 2001 to 2006.

Table 3. Adjusted HR for Stroke During the 5-Year Follow-Up Period for Patients With OAG as Compared With Patients in the Comparison Cohort, Stratified by Hypertension and Diabetes

	Stroke			
Variables	Patients With Hypertension Adjusted HR* (95% CI)	Patients Without Hypertension Adjusted HR* (95% CI)	Patients Without Diabetes Adjusted HR† (95% CI)	Patients Without Diabetes Adjusted HR† (95% CI)
Cohort				
OAG	1.23‡ (1.02–1.52)	2.05§ (1.73–2.42)	1.20‡ (1.01–1.43)	1.60§ (1.42–1.81)
Comparison	1.00	1.00	1.00	1.00

*Adjusted for gender, age, diabetes, hyperlipidemia, CHD, and geographic region.
†Adjusted for gender, age, hypertension, hyperlipidemia, CHD, and geographic region.
‡$P<0.05$.
§$P<0.001$.

diagnosis in the same period of time. When interpreting the results of that study, several points of the methodology must be noted. First, Belzunce and Casellas' study relied on data from a single hospital, which might not have been sufficiently representative to draw unequivocal conclusions. Second, their study did not match for age, gender, or comorbid medical disorders when selecting the comparison group. Third, they calculated the stroke prevalence only (not the incidence of stroke after a diagnosis of POAG was made) because it was a cross-sectional study, in contrast to the longitudinal design in our study. Fourth, they did not adjust for confounding factors when making the comparison between the study and comparison groups.

In a population-based cohort study on patients with diabetes, it was found that neither glaucoma nor OAG at the baseline was associated with an increased risk of stroke mortality during the 16-year follow-up period after controlling for other confounding factors.[12] It must be noted that that study included only patients with diabetes, and stroke mortality was not equal to stroke development in interpreting the results of that study.

Glaucoma is characterized by progressive optic neuropathy resulting in optic nerve head damage and visual field loss. The pathogenesis of glaucoma may be multifactorial and still generates a lot of discussion and great research efforts. Intraocular pressure is considered a major risk factor, but only one of many. On the other hand, impaired vascular function may play a role in the pathophysiology of glaucoma. According to the vascular theory of glaucoma, blood vessel disease leads to vascular dysregulation and defective autoregulation of ocular blood flow, resulting in ischemic optic nerve damage and glaucomatous optic neuropathy.[13] There is evidence that blood perfusion to the optic nerve is reduced in OAG.[14] It was also demonstrated that ocular blood flow reduction was a predictor for future progression of glaucomatous optic nerve damage.[15] Although secondary reduction of ocular blood flow can be observed in glaucoma, there is a component of ocular blood flow reduction that is independent of optic nerve damage and intraocular pressure.[16,17] In addition, upregulation of the hypoxia-inducible factor 1-α was observed in the optic nerve head of patients with glaucoma.[18] It was also shown that the reduced blood flow was not limited to the eye.[19] At least 3 population-based studies, including 2 among Asians, demonstrated that retinal arteriolar narrowing is related to POAG.[20–22] Furthermore, it is now known that retinal arteriolar narrowing is related to risk factors for stroke such as chronic hypertension,[23] carotid artery stiffness,[24] and aortic distensibility.[25] It has also been shown that retinal arteriolar narrowing predicts both subclinical cerebral infarcts[26] and clinical stroke events.[27,28] The optic nerve and retina are extensions of the diencephalons. Blood vessels in the optic nerve and retina share similar anatomic, physiological, and embryological characteristics as cerebral vessels. The circulation in the optic nerve head and retina is similar to that in brain vessels.[13,29] Pathological changes in the vessels of the optic nerve may reflect similar changes in cerebral vessels. For example, it has also been demonstrated that the ability of the cerebral vascular bed to compensate for changes in perfusion pressure was impaired in POAG.[11] Our result of a significantly increased risk of stroke development in patients with OAG is compatible with the results of those studies and seems to strengthen the hypothesis that glaucoma might be a manifestation of a more widespread disease.[30]

We analyzed our data to examine the association between primary angle-closure glaucoma and the risk of stroke. We found that 8.9% of patients with primary angle-closure glaucoma developed a stroke during the 5-year follow-up period. There was no difference in the hazard of stroke between patients with primary angle-closure glaucoma and the comparison cohort ($P=0.672$). This result provides further support for the vascular theory of OAG.

The Blue Mountains Eye Study showed that OAG was associated with increased cardiovascular mortality in the <75-year age group. Cardiovascular mortality was higher among those also treated with topical timolol.[31] The Barbados Eye Study similarly found a positive association between cardiovascular mortality and timolol-treated POAG ($P=0.04$).[32] However, a recent meta-analysis of 9 cohort studies did not demonstrate an association between POAG and all-cause or cardiovascular mortality.[33] Because all personal identifiers in the data set (National Health Insurance Research Database) were encrypted before release to the researchers, we could not link the National Health Insurance Research Database and the Cause of Death file. Thus, we could not examine the association between the timolol use in patients with OAG and cardiovascular mortality. However, we found that patients with OAG who received timolol did not have higher hazard of stroke than patients with OAG receiving other types of antiglaucoma medication ($P=0.572$).

The findings of this study need to be interpreted in the context of the following limitations. First, diagnoses of OAG, stroke, or any other comorbid medical conditions that are totally dependent on International Classification of Diseases codes may be less accurate than those obtained through a standardized procedure. Information about glaucomatous optic neuropathy and visual field defects were not available in the National Health Insurance Research Database. This is a major limitation of this study compared with studies that use standardized examinations of patients. However, the National Health Insurance Bureau of Taiwan randomly samples a fixed percentage of claims from every hospital and randomly interviews patients and reviews charts each year to verify the diagnosis validity and quality of care. Any hospital with outlier charges or outlier practice patterns or which is suspected of malpractice faces the risk of an audit and subsequent heavy penalties by the National Health Insurance Bureau when discrepancies, overcharging, and malpractice are discovered. To ensure the validity of the OAG diagnosis in this study, we ensured that all of the study cohort patients had at least 3 consensus diagnoses of OAG. In addition, we limited our study sample to those patients who had received antiglaucoma medications for >1 year or who had undergone glaucoma surgery. Second, data on some variables such as smoking, dietary habits, and body mass index, which might contribute to stroke development, are not available in this database. In addition, data of blood pressure and blood glucose levels are also not available. Simply including hypertension and diabetes in the model might not adequately adjust for the confounding effects of blood pressure and blood glucose levels. These factors may have compromised our findings. Third, it has been shown in most studies that approximately 50% of glaucoma cases are undetected.[34] In recent years, there have been several well-conducted studies on the epidemiology of glaucoma in Asian people indicating that the prevalence of glaucoma ranges from 2.1% to 5.0%.[35] Inferring from these data, it is estimated that approximately 1.05% to 2.5% of the population has undetected glaucoma. This small number of patients with undetected glaucoma would be categorized as nonglaucoma and would have a small chance of being selected as part of the comparison cohort. The number of these patients with undetected glaucoma would dilute or mask any real difference in the stroke incidence between the study and comparison cohorts. In our study, patients with OAG showed a significantly higher risk of stroke development. Therefore, our observation of an increased stroke incidence in patients with OAG is a real phenomenon. Fourth, most of the residents in Taiwan are of Chinese ethnicity. The ability to generalize the results to other racial/ethnic groups is unclear given that strokes in Chinese/Asians might not be completely similar to strokes in other ethnic groups. Finally, our data only allowed us to trace the medical history of the sampled patients back to the year 1996. We cannot be certain that patients in the study and comparison group had no glaucoma or stroke before 5 years before the study baseline date. This could have compromised our findings.

In summary, this population-based study has demonstrated that OAG is a significant predictor for the development of stroke after adjusting for possible confounding factors. Further studies will be conducted to see if our data can be replicated and help clarify the underlying pathophysiological mechanisms of OAG and their associations with stroke development.

Disclosures

None.

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