

Allergic rhinitis is associated with open-angle glaucoma: A population-based case-control study

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ABSTRACT

Background: Despite many reports linking allergic rhinitis (AR) to problems of the eye, the relationship between AR and open-angle glaucoma (OAG) has not been studied. The purpose of this epidemiology study was to provide an estimation of the association of OAG with AR by using a population-based data set in Taiwan.

Methods: We retrieved our study sample for this case-control study from the Longitudinal Health Insurance Database 2000. We extracted 7063 subjects with OAG as cases and 21,189 matched controls (three controls per case). We used conditional logistic regression analyses to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) to describe the association between OAG and having previously been diagnosed with AR.

Results: A chi-squared test showed that there was a significant difference in the prevalence of prior AR between cases and controls (28.8% versus 22.3%; $p < 0.001$). A conditional logistic regression analysis suggested that the OR of having previously been diagnosed with AR for cases was 1.40 (95% CI, 1.31–1.48; $p < 0.001$) compared with controls after adjusting for monthly income, geographic region, urbanization level, hypertension, diabetes, asthma, coronary heart disease, hyperlipidemia, and hypothyroidism. It also revealed that OAG was consistently and significantly associated with prior AR across all age groups. In particular, subjects aged 50–59 years had the highest OR for prior AR among cases compared with controls (OR, 1.77; 95% CI, 1.53–2.06; $p < 0.001$).

Conclusion: This outcome research found that there was an association between AR and OAG.

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Allergic rhinitis (AR) is a common disease that affects 10–30% of children and adults in the United States and other industrialized countries.^{1–3} It is characterized by paroxysms of sneezing, rhinorrhea, and nasal obstruction, often accompanied by itching of the eyes, nose, and palate. Postnasal drip, coughing, irritability, and fatigue are other common symptoms.^{4,5} The condition is also especially common in southern Asian countries with a climate of high humidity suitable for the development of various allergens.⁶

AR was shown to be comorbid with many diseases such as allergic conjunctivitis, rhinosinusitis, asthma, and otitis media.^{7–11} It has long been known that patients with AR often develop dark circles under the eye called “allergic shiners.”¹² The circle phenomenon was believed to result from infraorbital edema, and the darkening was caused by subcutaneous venodilation. Periorbital hyperpigmentation was shown to be predominantly of the vascular type, especially among Chinese populations.¹³ Despite many reports linking AR to problems of the eye, the relationship between AR and open-angle glaucoma (OAG) has not been studied. Being a neighboring structure, it is reasonable to suspect that the eye itself would be affected by circulation disturbances caused by AR. Moreover, it was shown that AR likely induces localized hypoxia by blocking the middle meatus and ostium because of allergic swelling of the nasal mucosa, and hypoxia was shown to be a factor leading to retinal ganglion cell damage.^{14,15}

The purpose of this study was to provide an estimation of the association of OAG with AR by using a case-control design with a population-based data set in Taiwan.

METHODS

Database

We retrieved the study sample for this case-control study from the Longitudinal Health Insurance Database 2000 (LHID2000). Taiwan began its National Health Insurance (NHI) program in 1995, and the coverage rate has been maintained at >96% since its implementation. The LHID2000, which is released by the Taiwan National Health Research Institute, consists of all medical claims and registration files for 1,000,000 enrollees in the NHI program. These 1,000,000 enrollees are randomly selected from all enrollees listed in the 2000 Registry of Beneficiaries ($n = 23.72$ million) under the NHI program. The Taiwan National Health Research Institutes and some researchers have shown the high validity of data from the NHI program.^{16,17}

Selection of Cases and Controls

As for selection of cases, we first identified 7063 subjects ≥ 18 years old who had received a first-time diagnosis of diagnosis of OAG (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 365.1 or 365.11) between January 1, 2002 and December 31, 2011. We assigned the date of receiving their first-time OAG diagnosis as the index date. Because administrative data sets are criticized for poor diagnostic validity, we only included OAG cases who received treatment with topical antiglaucoma medication to increase the validity of the OAG diagnoses sourced from the data set.

As for the selection of controls, we likewise selected them from the LHID2000. In total, 21,189 controls (three controls per case) were randomly selected and matched with cases in terms of sex, age group (18–30, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and ≥ 65 years), and index year. Although for cases, the year of the index date was the year in which the cases received their first OAG diagnosis, for controls, the year of the index date was simply a matched year in which controls had an ambulatory care visit. We further indicated the first ambulatory care visit that occurred in the index year as the index date for controls.

Exposure Assessment

This study identified AR cases based on ICD-9-CM code 477 or 477.0–477.9. This study only counted AR cases if they had received at

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least two diagnoses of AR before the index date to increase the validity of the AR diagnoses. Furthermore, AR cases had to have received at least one diagnosis of AR from a certified otolaryngologist.

Statistical Analysis

We used the SAS system (SAS System for Windows, Version 8.2; SAS Institute, Cary, NC) for data analysis in this study. The χ^2 -tests were performed to compare differences in monthly income, urbanization level, geographic location (northern, central, eastern, and southern Taiwan), and selected medical comorbidities (hypertension, diabetes, coronary heart disease [CHD], hyperlipidemia, obesity, asthma, renal disease, and hypothyroidism). We also conducted conditional logistic regression analyses (conditioned on sex, age group, and index year) to calculate the odds ratio (OR) and the corresponding 95% confidence interval (CI) to describe the association between OAG and having previously been diagnosed with AR. Furthermore, we computed the OR for having been previously diagnosed with AR stratified by age group. We used the conventional $p \leq 0.05$ for statistical significance in this study.

RESULTS

Of the 28,252-person study sample, the mean age was 56.5 (± 17.4 years) years; the mean age was 56.6 years among cases and was 56.5 years among controls ($p = 0.726$). The distributions of demographic characteristics and medical comorbidities between cases and controls are presented in Table 1. After matching for sex, age group, and index year, cases were more likely to reside in the northern part of Taiwan ($p < 0.001$) and the most urbanized areas ($p < 0.001$) and have monthly incomes of $\geq \$25,000$ in New Taiwan currency ($p < 0.001$) than controls. As for medical comorbidities, cases had a higher prevalence of hyperlipidemia (30.7% versus 22.7%; $p < 0.001$), diabetes (26.1% versus 17.3%; $p < 0.001$), hypertension (44.6% versus 37.4%; $p < 0.001$), CHD (19.8% versus 14.9%; $p < 0.001$), asthma (6.3% versus 5.7%; $p = 0.049$), and hypothyroidism (0.8% versus 0.5%; $p < 0.001$) compared with controls.

Table 2 presents the prevalence and ORs of prior AR between cases and controls. A total of 24.0% of the 28,252-person study sample had been diagnosed with AR before the index date. The χ^2 -test showed that there was a significant difference in the prevalence of prior AR between cases and controls (28.8% versus 22.3%; $p < 0.001$). The conditional logistic regression analysis (conditioned on sex, age group, and index year) suggested that the OR of having previously been diagnosed with AR for cases was 1.41 (95% CI, 1.33~1.50; $p < 0.001$) compared with controls. Furthermore, after adjusting for monthly income, geographic region, urbanization level, hypertension, diabetes, asthma, CHD, hyperlipidemia, and hypothyroidism, the OR of having previously been diagnosed with AR for cases was 1.40 (95% CI, 1.31~1.48; $p < 0.001$) compared with controls.

Table 3 further shows the ORs for prior AR stratified by age group. It reveals that OAG was consistently and significantly associated with prior AR across all age groups. In particular, subjects aged 50~59 years had the highest ORs for prior AR among cases compared with controls (OR, 1.77; 95% CI, 1.53~2.06; $p < 0.001$).

DISCUSSION

In our study, we revealed a possible relationship between AR and OAG. Our findings suggest the possibility that underlying AR should be considered in patients with OAG. We believe that this is the first study to use a nationwide population-based data set to examine the association between AR and the development of OAG.

AR is a heterogeneous disease with a complicated pathophysiology.¹⁸ It is known that people with AR are at greater risk of suffering from asthma, rhinosinusitis, other related upper airway conditions, and even allergic conjunctivitis.^{7,19} In our previous study, we showed

Table 1 Demographic characteristics of subjects with OAG and controls in Taiwan ($n = 28,252$)

Variable	Subjects with OAG ($n = 7063$)		Controls ($n = 21,189$)		p Value
	Total No.	%	Total No.	%	
Sex					1.000
Male	3662	51.9	10986	51.9	
Female	3401	48.1	10203	48.1	
Age (yr)					1.000
18~29	608	8.6	1824	8.6	
30~34	318	4.5	954	4.5	
34~39	380	5.4	1140	5.4	
40~44	499	7.1	1497	7.1	
45~49	585	8.3	1755	8.3	
50~54	647	9.2	1941	9.2	
55~59	694	9.8	2082	9.8	
60~64	674	9.5	2022	9.5	
≥ 65	2658	37.6	7974	37.6	
Urbanization level					<0.001
1 (most urbanized)	2510	35.5	6417	30.3	
2	1939	27.4	5727	27.0	
3	895	12.7	3066	14.4	
4	908	12.9	3104	14.7	
5 (least urbanized)	811	11.5	2875	13.6	
Monthly income*					<0.001
NT\$0~15,840	3296	46.7	9072	42.8	
NT\$15,841~25,000	2069	29.3	7734	36.5	
$\geq$ NT\$25,001	1698	24.0	4383	20.7	
Geographic region					<0.001
Northern	3725	52.7	9735	45.9	
Central	1279	18.1	4955	23.4	
Southern	1924	27.2	5952	28.1	
Eastern	135	1.9	547	2.6	
Hypertension	3150	44.6	7931	37.4	<0.001
Diabetes	1846	26.1	3675	17.3	<0.001
Hyperlipidemia	2170	30.7	4802	22.7	<0.001
CHD	1400	19.8	3156	14.9	<0.001
Asthma	446	6.3	1204	5.7	0.049
Hypothyroidism	59	0.8	96	0.5	<0.001

*The average exchange rate in 2010 was US\$1.00 $\approx$ New Taiwan (NT)\$29. OAG = open-angle glaucoma; CHD = coronary heart disease; NT = New Taiwan.

that patients with AR were more likely to develop nasopharyngeal carcinoma.²⁰ It is therefore suggested that AR should no longer be regarded as a localized disease but instead one that interacts with many other systems in the human body.^{21,22}

It is already known that intraocular pressure plays a critical role in the development and/or progression of glaucoma. It is possible that disturbed blood circulation might also result in a disturbance in regulating intraocular pressure. It was proposed that glaucomatous optic neuropathy is a consequence of an insufficient blood supply, and the vast majority of published studies dealing with blood flow reported reduced ocular perfusion in glaucoma patients compared with normal subjects.²³ It is believed that the major cause of this reduction is not atherosclerosis, but rather vascular dysregulation, leading to both low perfusion pressures and insufficient autoregulation. A recent study by Lan *et al.* found that patients with AR may have poor sympathetic modulation in the sitting position, and the autonomic dysfunction may therefore play a role in the pathophysiology of AR-related glaucoma.²⁴

It is also possible that nitric oxide may play a pathophysiological role in both AR and OAG. The evidence of high levels of nitric oxide

Table 2 Prevalence rate, crude and adjusted ORs, and 95% CIs for AR among the sampled patients

Presence of prior allergic rhinitis	Total (n = 28,252)		Subjects with OAG (n = 7063)		Controls (n = 21,189)	
	No.	%	No.	%	No.	%
Yes	6765	24.0	2035	28.8	4730	22.3
OR# (95% CI)	—		1.41*** (1.33~1.50)		1.00	
Adjusted§ OR (95% CI)	—		1.40*** (1.31~1.48)		1.00	

*** $p < 0.001$.

#ORs were calculated using a conditional logistic regression (conditioned on sex, age group, and year of the index date).

§Adjusted for patient's monthly income, geographic region, urbanization level, hypertension, diabetes, CHD, asthma, hyperlipidemia, and hypothyroidism.

AR = allergic rhinitis; CIs = confidence intervals; ORs = odds ratios; OAG = open-angle glaucoma; CHD = coronary heart disease.

present in patients with allergies might possibly provide some explanation for the relationship of AR with glaucoma.^{25,26}

There are several limitations of our study. First, like much research that analyzes a health insurance database, there is the possibility of surveillance bias because patients with AR are more likely to have frequent evaluations and thus more OAG would be detected, and *vice versa*. However, our study included only patients receiving AR and OAG diagnoses made by certified otolaryngologists and ophthalmologists. Under these circumstances, patients with AR are unlikely to be referred to an ophthalmologist unless they had obvious eye complaints.

Second, many would question the findings of our study as a result of corticosteroid use although we considered whether or not a patient had asthma in the regression models to minimize the influence of systemic or inhaled steroid therapy. It is known that both systemic and inhaled corticosteroids may induce the development of glaucoma.^{27–29} However, on the other hand, the effects of intranasal corticosteroids on the development of glaucoma remain controversial.³⁰ Many prior studies failed to establish a link between nasal steroids and intraocular pressure.^{31,32} In addition, in Taiwan, dust mites are major allergens for AR, and many patients are encouraged to control their environment without taking medications, which appears to be very effective. Furthermore, after analyzing our data, we found that <3% of AR patients had ever been prescribed nasal steroids. Of the AR patients who were prescribed nasal steroids, >90% of the medications were taken for <3 days. It is difficult to determine an association of OAG with the use of nasal steroids for such a short period. Therefore, we did not further evaluate AR patients who received treatment with topical steroids versus without topical steroids in this study.

Third, treatment information of the AR group was unknown in this study. In this database study, it was difficult to evaluate how these patients were managed. Therefore, there might have been some patients whose AR had been adequately treated but were still included in the AR group. This could potentially affect the accuracy of our data interpretation. However, we believe this potential bias would have little effect on our conclusions. If many well-treated AR subjects were included in the AR group, the results would theoretically tend toward the null hypothesis. Because the results of our study all reached statistically significant differences, we believe this limitation remains fairly acceptable.

Fourth, some factors including intraocular pressure, racial background, and family history, which may have had an influence on the development of OAG, were not available in our insurance-based database, and this might have contributed to a certain bias in comparisons with the selected control group.³³

Finally, it was difficult to determine how long a subject was affected by AR before subsequently developing OAG. In our study, we might have universally included patients with relatively long as well as short intervals between a diagnosis of AR and one of OAG. Therefore, it is difficult to determine the cause–effect relationships

because of variable exposure periods because of the underlying genetic nature of AR, because the interval between the diagnoses of AR and OAG could not be regarded as exposure time to define cause–effect relationships. Moreover, because both the disorders being studied are relatively common, it is possible that the association found in our study might not be causative but rather spurious. Although we tried to adjust the results for confounding factors and separate these data according to age groups, it is still possible that a certain bias does exist in our retrospective data and a prospective cohort study design would be more favorable.

Despite these limitations, we found that patients with AR had a significantly higher risk of developing OAG compared with patients without AR. Even after adjustments, the OR for OAG was 1.4-times greater in cases than comparison subjects. According to our current data, increased study to reveal the true relationship between the AR and the OAG is warranted.

CONCLUSIONS

This study showed an association between AR and OAG. Although the true relationship between AR and OAG remains to be further investigated, we recommend that physicians and AR patients keep this potential risk in mind.

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Table 3 ORs and 95% CIs for AR among subjects with OAG and controls by age group

Presence of prior AR	Age Group (yr)									
	18~29		30~39		40~49		50~59		60~69	
	Subjects with OAG n, %	Controls n, %	Subjects with OAG n, %	Controls n, %	Subjects with OAG n, %	Controls n, %	Subjects with OAG n, %	Controls n, %	Subjects with OAG n, %	Controls n, %
Yes	235 (38.7)	534 (29.3)	231 (33.1)	606 (28.9)	338 (31.2)	821 (25.2)	384 (28.6)	750 (18.6)	482 (25.1)	1069 (19.5)
OR ^a (95% CI)	1.52*** (1.26~1.85)	1.00	1.21* (1.01~1.46)	1.00	1.34*** (1.16~1.56)	1.00	1.75*** (1.52~2.02)	1.00	1.39*** (1.23~1.57)	1.00
Adjusted ^b OR (95% CI)	1.52*** (1.25~1.86)	1.00	1.25* (1.03~1.51)	1.00	1.31*** (1.12~1.54)	1.00	1.77*** (1.53~2.06)	1.00	1.32*** (1.17~1.50)	1.00

*p < 0.05, **p < 0.01, and ***p < 0.001.

#ORs were calculated using a conditional logistic regression (conditioned on sex, age group, and year of the index date).

\$Adjusted for patient's monthly income, geographic region, urbanization level, hypertension, diabetes, asthma, CHD, hyperlipidemia, and hypothyroidism.

AR = allergic rhinitis; CIs = confidence intervals; ORs = odds ratios; OAG = open-angle glaucoma; CHD = coronary heart disease.

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