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CLINICAL STUDY

Association between open-angle glaucoma and neovascular age-related macular degeneration: a case-control study

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Abstract

Purpose **To investigate the relationship between previously diagnosed open-angle glaucoma (OAG) and neovascular age-related macular degeneration (AMD) using a routine insurance dataset.**

Methods **This study retrieved data from the Taiwan Longitudinal Health Insurance Database 2005. We found 3282 patients with neovascular AMD as cases and 13 128 sex- and age-matched subjects without neovascular AMD as controls. Conditional logistic regressions were performed to evaluate the association of neovascular AMD with previously diagnosed OAG among the sampled patients.**

Results **Of the 16 410 sampled patients, 2.55% had previously diagnosed OAG, 5.06 and 1.92% for the cases and controls, respectively. The logistic regression analysis showed that the odds ratio (OR) of previously diagnosed OAG for cases was 2.45 (OR: 2.45; 95% confidence interval: 1.99–3.01) compared with the controls after adjusting for potential confounders. In addition, the adjusted ORs for previously diagnosed OAG were similar for patients with AMD in both genders (with an adjusted OR of 2.49 for males and 2.39 for females). Furthermore, it shows that OAG was significantly associated with neovascular AMD regardless of sex even after adjusting for monthly income, geographic region, urbanisation level, and comorbidities (with adjusted ORs of 2.49 for males and 2.39 for females).**

Conclusions **This study demonstrated that patients with neovascular AMD had a higher odds of previously diagnosed OAG compared with those patients without neovascular AMD regardless of sex.**

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Introduction

Neovascular age-related macular degeneration (AMD) is a prevalent degenerative disease of the central retina in elderly populations, and it affects >8 million individuals in the United States.[1–4] Although the exact pathophysiology of neovascular AMD is still under discussion, this disease is thought to be associated with multifactorial etiologies, including genetic, environmental, metabolic and functional factors.[5,6] Recently, increasing evidence has supported a vascular pathogenesis of neovascular AMD.[7–10] Abnormal choroidal perfusion was suggested to be a risk factor for the development of choroidal neovascularization which is a frequent cause of neovascular AMD.[7,9,11]

Glaucoma is a major cause of irreversible visual impairment, and this disease affected ~64 million people in 2013 worldwide.[12] Open-angle glaucoma (OAG) is the most common type of glaucoma in all populations, and it is a multifactorial chronic optic neuropathy which is characterised by the progressive death of retinal ganglion cells and may subsequently lead to loss of the visual field.[12–14] To date, even though the actual pathway of OAG still remains unclear, many recent studies have observed relationships between OAG and certain vascular factors, such as abnormally narrow retinal vessels and a lack of blood perfusion to retinal blood vessels.[13,15–17]

However, even if both OAG and neovascular AMD have similar vascular pathophysiological mechanisms, according to our knowledge, no prior studies have attempted to examine the association between these two diseases. Therefore, this case-control study aimed to explore the relationship between prior OAG and neovascular AMD using a large dataset in Taiwan.

Methods

Database

We retrieved the sampled subjects and relevant medical records from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The LHID2005 includes longitudinal data on medical claims for 1 000 000 enrollees randomly selected from the 2005 Registry of Beneficiaries ($n=25.68$ million) of the National Health Insurance (NHI) program in Taiwan. The NHI program was founded in 1995, and it provides affordable, accessible and comprehensive medical services for almost all (over 98%) Taiwanese citizens. To date, many studies have been published in international peer-reviewed journals using data from the NHI program.

Selection of cases and controls

This study was designed to include cases and controls. To select cases for this study, we initially found 3569 patients who received a first-time diagnosis of neovascular AMD (ICD-9-CM codes 362.42, 362.43, 362.52 or 362.53) during an ambulatory care visit (outpatient visit) between January 2001 and December 2013. In addition, we excluded 287 patients under 40 years of age, because this age group has a very low prevalence of neovascular AMD. Ultimately, 3282 patients with neovascular AMD were identified as cases in this study.

This study identified the patients without neovascular AMD as the controls. In order to decrease the potential selection bias which frequently occurred in case-control study, we have recruited the controls by matching. The matched controls ($n=13\,128$) (four controls per patient with neovascular AMD) were derived from residual beneficiaries of the LHID2005. Controls were matched by sex, age group (40–49, 50–59, 60–69, 70–79 and ≥ 80 years), and year of the index date. As for cases, the year of the index date for cases was the year in which the cases received their first neovascular AMD diagnosis. As for controls, the date of their first use of outpatient services during the matched year was defined as the index date. We also assured that all selected controls had at least one ophthalmologic ambulatory care visit (ophthalmologic outpatient visit) during the study period in order to avoid the potential bias. In addition, we guaranteed that none of the selected controls had received a neovascular AMD diagnosis since the beginning of the Taiwan NHI program in 1995.

Variables of interest

In this study, we attempted to calculate the odds of prior OAG in patients with neovascular AMD compared with those without neovascular AMD. We defined OAG based on ICD-9-CM codes 365.1, 365.10 or 365.11 and patients who were newly diagnosed with OAG before the index date were identified as OAG cases in this study. In Taiwan, OAG is frequently diagnosed by ophthalmologists. This study only involved the patients who had received two or more OAG diagnoses prior to the index date, with at least one being made by an ophthalmologist in order to elevate the validity of the OAG diagnoses and further decrease the measurement error.

Statistical analysis

All analyses were conducted using the SAS system (SAS System for Windows, vers. 9.2, SAS Institute, Cary, NC). Chi-square tests were performed to compare differences between the cases and controls in terms of monthly income, geographic location, urbanisation level (five levels, with one being the most urbanised and five being the least), and medical comorbidities. The medical comorbidities, such as diabetes (ICD-9-CM codes 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272.0–272.4), stroke (ICD-9-CM codes 430–438) and ischaemic heart disease (ICD-9-CM codes 410–414 or 429.2), were only included if they had been diagnosed before the index date. These factors were all recognised as risk factors for developing neovascular AMD and might potentially confound the relationship between prior OAG and neovascular AMD.[1,18] We then performed conditional logistic regressions (stratified on sex, age group and year of the index date) to estimate the relationship between prior OAG and neovascular AMD. We displayed odds ratios (ORs) along with 95% confidence intervals (CIs). Statistical significance was set as a two-sided $P<0.05$.

Results

This study included 3282 patients with neovascular AMD as cases and 13 128 matched subjects without neovascular AMD as controls. Of the 16 410 total subjects, the mean age was 66.7 years with a SD of 12.1 years. In addition, the mean ages for cases and controls were 66.9 and 66.6 years, respectively ($P=0.229$). Demographic characteristics of patients with and those without neovascular AMD are presented in Table 1.

After matching for sex, age group and index year, the cases in this study had a higher prevalence of comorbidities of diabetes (36.3 *vs* 21.6%, $P<0.001$), hypertension (51.9 *vs* 48.0%, $P<0.001$) and hyperlipidemia (30.6 *vs* 24.2%, $P<0.001$) than controls. Additionally, cases were more likely to have monthly incomes of $<$NT\$15 841 ($P<0.001$), to reside in communities located in the northern part of Taiwan ($P<0.001$), and to live in the most urbanised locations of

Taiwan ($P<0.001$) than controls. However, there was no difference in the prevalence of stroke or ischemic heart disease between cases and controls.

Table 2 shows the proportions of prior OAG between cases and controls. The findings revealed that 418 (2.55%) of the total sampled patients had OAG prior to the index date. In addition, OAG was found in 166 (5.06%) cases and 252 (1.92%) controls. The conditional logistic regression analysis (stratified by sex, age group and index year) further showed that the crude OR of prior OAG for cases was 2.73 (95% CI: 2.24–3.34) compared with controls. After adjusting for monthly income, geographic region, urbanisation level, and comorbidities, patients with neovascular AMD were more likely to have been previously diagnosed with OAG (OR: 2.45; 95% CI: 1.99–3.01) compared with those without neovascular AMD.

The proportions of prior OAG between patients with neovascular AMD and those without neovascular AMD stratified by sex is shown in Table 3. It shows that OAG was significantly associated with neovascular AMD regardless of sex even after adjusting for monthly income, geographic region, urbanisation level, and comorbidities (with adjusted ORs of 2.49 for males and 2.39 for females).

Table 4 presents the covariate-adjusted ORs and 95% CIs for neovascular AMD among sampled subjects. The results displayed that prior OAG, monthly income, and geographic region were significantly associated with neovascular AMD. Additionally, it was noteworthy that the diabetes (adjusted OR = 2.03, 95% CI = 1.86–2.23) was significantly associated with neovascular AMD.

Table 1 Demographic characteristics of subjects with neovascular age-related macular degeneration (NV AMD) and controls in Taiwan ($n = 16\ 410$)

Variables	*Patients with NV AMD* (n = *3 282*)		*Controls* (n = *13 128*)		P *value*
	Total no.	*%*	*Total no.*	*%*	
Age (years)					1.000
40–49	312	9.5	1248	9.5	
50–59	606	18.5	2424	18.5	
60–69	885	27.0	3540	27.0	
70–79	985	30.0	3940	30.0	
≥80	494	15.1	1976	15.1	
Sex					1.000
Female	1440	43.9	5760	43.9	
Male	1842	56.1	7368	56.1	
Monthly Income					<0.001
≤NT$15 840	1726	52.6	5991	45.6	
NT$15 841–25 000	1027	31.3	5105	38.9	
≥NT$25 001	529	16.1	2032	15.5	
Geographic region					
Northern	1717	52.3	5113	39.0	<0.001
Central	593	18.1	3490	26.6	
Southern	848	25.8	4093	31.2	
Eastern	124	3.8	432	3.3	
Urbanisation level					<0.001
1 (most urbanised)	1014	30.9	3408	26.0	
2	959	29.2	3456	26.3	
3	450	13.7	2 022	15.4	
4	458	14.0	2 270	17.3	
5 (least urbanised)	401	12.2	1972	15.0	
Comorbidities					
Diabetes	1190	36.3	2841	21.6	<0.001
Hypertension	1704	51.9	6306	48.0	<0.001
Hyperlipidemia	1004	30.6	3179	24.2	<0.001
Stroke	447	13.6	1639	12.5	0.081
Ischemic heart disease	73	2.2	329	2.5	0.350

The average exchange rate in 2012 was US$1≈New Taiwan (NT)$30.

Discussion

This case-control study observed that patients with neovascular AMD were 2.45-times more likely to have been diagnosed with prior OAG than those patients without neovascular AMD even after adjusting for monthly income, geographic region, urbanisation level, and comorbidities. Additionally, both males and females with neovascular AMD had a higher prior odds of OAG compared with those without neovascular AMD.

To date, only a few studies have mentioned the issue of an association between glaucoma and retinal diseases.[19,20] One prior study which included 5154 patients with glaucoma in the United States showed that glaucoma is frequently accompanied by retinal comorbidities.[20] In addition, patients with primary OAG (15.7%) had

Table 2 Proportions, crude odds ratios (ORs), and 95% confidence intervals (CIs) for open-angle glaucoma among sampled subjects

Presence of open-angle glaucoma	*Total* (n = *16 410*) *n*, %		*Patients with NV AMD* (n = *3282*) *n*, %		*Controls* (n = *13 128*) *n*, %	
Yes	418	2.55	166	5.06	252	1.92
No	15 992	97.45	3116	94.94	12 876	98.08
Crude OR (95% CI)	—		2.73*** (2.24–3.34)		1.00	
Adjusted OR[a] (95% CI)	—		2.45*** (1.99–3.01)		1.00	

Abbreviation: NV AMD, neovascular age-related macular degeneration. The OR was calculated by a conditional logistic regression stratified by sex, age group and index year. [a]Adjusted for monthly income, geographical region, urbanisation level, diabetes, hypertension, and hyperlipidemia. ***$P<0.001$.

Table 3 Proportions, odds ratios (ORs), and 95% confidence intervals (CIs) for open-angle glaucoma among sampled patients according to sex

Presence of open-angle glaucoma	*Males* (n = *9210)*		*Females* (n = *7200)*	
	Patients with NV AMD (n = *1842)* *n*, %	*Controls* (n = *7368)* *n*, %	*Patients with NV AMD* (n = *1440)* *n*, %	*Controls* (n = *5760)* *n*, %
Yes	96 (5.21)	144 (1.95)	70 (4.86)	108 (1.88)
No	1746 (94.79)	7224 (98.05)	1370 (95.14)	5652 (98.13)
Crude OR (95% CI)	2.77*** (2.13–3.61)	1.00	2.68*** (1.97–3.64)	1.00
Adjusted OR[a] (95% CI)	2.49*** (1.90–3.26)	1.00	2.39*** (1.74–3.27)	1.00

Abbreviation: NV AMD, neovascular age-related macular degeneration. The OR was calculated by a conditional logistic regression stratified by age group, and index year. [a]Adjusted for monthly income, geographical region, urbanisation level, diabetes, hypertension, and hyperlipidemia. ***$P<0.001$.

Table 4 Covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for neovascular AMD among sampled subjects ($n=16\,410$)

Variables	*Presence of neovascular AMD*	
	Adjusted OR	*95% CI*
Prior OAG	2.45***	1.99–3.01
Monthly income		
≤NT$15 840	1.18***	1.07–1.31
NT$15 841–25 000 (reference group)	1.00	
≥NT$25 001	1.09	0.96–1.24
Urbanisation level		
1 (reference group)	1.00	
2	1.09	0.99–1.22
3	0.95	0.83–1.08
4	0.97	0.85–1.11
5	0.96	0.83–1.11
Geographic region		
Northern	1.83***	1.64–2.06
Central (reference group)	1.00	
Southern	1.17**	1.04–1.32
Eastern	1.74***	1.39–2.17
Comorbidities		
Hypertension	1.00	0.92–1.09
Diabetes	2.03***	1.86–2.23
Hyperlipidemia	1.05	0.96–1.16

**$P<0.01$, ***$P<0.001$.

significantly higher prevalences of retinal comorbidities compared with those patients with other types of glaucoma, including low-tension OAG, pseudoexfoliation glaucoma, or pigmentary OAG.[20] However, no previous literature has investigated the association between OAG and neovascular AMD to date, although these two diseases may share similar pathophysiological mechanisms.

The positive association between prior OAG and neovascular AMD which was reported in this study might be explained by the vascular pathogenesis. Increasing evidence suggests that vascular factors may play key roles in the incidence and progression of neovascular AMD.[7–11] Some previous studies indicated that patients with neovascular AMD have decreased choroidal and retinal blood flow.[21–24] The ischaemia and hypoxia due to abnormal choroidal perfusion are thought to activate the development of angiogenesis.[7,11] Additionally, angiogenesis would contribute to the formation of choroidal neovascularization which is a frequent rationale for neovascular AMD and usually induces visual loss by disturbing normal macular function.[9,11]

As for OAG, the actual pathophysiological mechanism is still unclear, and prior studies reported a mechanical and a vascular theory for the pathogenesis of this disease.[25] The mechanical theory of glaucoma generally considers that glaucomatous optic neuropathy is directly induced by elevated IOP.[26] The vascular theory supposes that increased IOP or some other factors associated with reduced ocular blood flow may affect blood perfusion in retinal blood vessels and further lead to glaucomatous optic neuropathy.[26,27] Recently, many studies highlighted the importance of a vascular pathogenesis. Increasing evidence has shown associations between glaucoma and many vascular factors, including an abnormal narrowing of retinal vessels and perfusion deficits of the optic nerve head, retina, or choroid.[13,16,17,27,28] Accordingly, it is plausible that OAG may be associated with neovascular AMD, because these two diseases share similar underlying vascular pathophysiological pathways.

The specific strength of this study is the use of a routine insurance database which is representative of the entire Taiwanese population. Features of the LHID2005 can provide a sufficient sample size to investigate the association between prior OAG and neovascular AMD. These characteristics could elevate the statistical power of this study. Additionally, we restricted patients aged over 40 years and selected controls by matching sex and age group. These two strategies were considered to eliminate

a selection bias for the findings. Furthermore, the LHID2005 contains detailed records regarding all physicians' diagnoses and relevant medical services since the individuals were included in the NHI system in Taiwan. Thus, a recall bias was avoided in this case-control study.

Nevertheless, several limitations in this study should be considered. First, the LHID2005 provides no lifestyle or individual information, including cigarette smoking, the body-mass index, or a family history of neovascular AMD which are all recognised as risk factors for developing neovascular AMD and might potentially confound the association between prior OAG and neovascular AMD.[29,30] Second, a surveillance bias might have occurred in this study because many researchers consider that patients with neovascular AMD are more likely to receive ophthalmologic examinations and thus more OAG would be detected. However, we selected subjects who had at least one ophthalmologic ambulatory care visit during the study period as controls in this case-control study in order to eliminate the potential effect of a surveillance bias. Third, some investigators also suspected that measurement error and diagnostic bias might affect the association between prior OAG and neovascular AMD in this study. However, in order to elevate the AMD diagnostic accuracy, avoid misclassification, and eliminate measurement error, we limited our study cases only to those patients with neovascular AMD. Neovascular AMD is frequently along with rapid worsening of central vision and the clinical signs of this disease permit different ophthalmologists to make direct and accurate diagnoses. Fourth, the diagnoses of OAG and neovascular AMD were based on the ICD-9-CM codes which might be less accurate than some studies which used standardised diagnostic examinations. Nevertheless, the NHI administration of Taiwan preserved a routine cross-checking system with scrutiny and evaluation of the medical records from every hospital and clinic, followed by penalties if inconsistencies or cases of malpractice are discovered, in order to prevent miscoding or inaccurate medical records and to confirm diagnostic validity. Additionally, the LHID2005 which used in this study might not include all patients with neovascular AMD and OAG in Taiwan. Some patients in the beginning of neovascular AMD or OAG might not immediately seek medical services which are covered by the NHI program, because they might think that the relevant treatments for these diseases were unnecessary. Therefore, the selection bias might still occur in this case-control study, even though we have used a large database and two strategies, including restriction and matching, to selected controls in this study. Finally, most subjects recruited in this study were of Chinese ethnicity. Consequently, the ability to generalise the findings to other ethnic groups is not assured.

In conclusion, this case-control study showed significant differences in the odds of prior OAG between patients with neovascular AMD and those without neovascular AMD regardless of sex. Therefore, we recommend that physicians should provide periodic ophthalmologic examinations for patients with OAG in order to detect neovascular AMD at an early stage. In addition, physicians can provide instructions for patients with OAG and advise them to visit an ophthalmologist regularly. Nevertheless, further experimental studies are still required to identify the actual pathways for the relationship between prior OAG and neovascular AMD.

Summary

What was known before

- Recently, increasing evidence has supported a vascular pathogenesis of neovascular AMD.
- Many recent studies have observed relationships between OAG and certain vascular factors.

What this study adds

- Of the sampled patients, 2.55% had prior OAG, 5.06% and 1.92% for patients with and without neovascular AMD, respectively.
- Patients with neovascular AMD had a higher odds of prior OAG compared with controls.

Conflict of interest

The authors declare no conflict of interest.

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