

Decreased Risk of Intracerebral Hemorrhage Among Patients With Milder Allergic Rhinitis

Running title: Allergic Rhinitis and Ischemic Stroke

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These authors' individual contributions were as follows: Chun-Hung Tseng and Chia-Hung Kao designed the study. Cheng-Li Lin carried out the statistical analysis. All authors drafted the manuscript. Chia-Hung Kao revised the manuscript. All authors approved the final version submitted for publication.

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All authors have no conflicts of interest to declare

Abstract

Background: This study investigated whether allergic rhinitis (AR) increases the risk of intracerebral hemorrhage (ICH).

Methods: Using Taiwanese insurance outpatient claims data, 52 870 patients with new diagnoses of AR between 2000 and 2010 were identified, and 105 5680 age- and sex-frequency matched people without AR were chosen randomly as controls. Risks of ICH were correlated with AR and comorbidities, such as diabetes, hypertension, coronary artery disease, hyperlipidemia, disease and chronic kidney disease, and were estimated by the end of 2011.

Results: The risk of ICH was lower in the AR cohort than in the comparison cohort, with an adjusted hazard ratio (aHR) of 0.58 (95% confidence interval [CI] = 0.50-0.66), assessed using the multivariable Cox model. Age-specific analysis demonstrated that the aHR for ICH in the AR patients increased with age, with an aHR of 0.53 (95% CI = 0.39-0.71) in the ≤ 49 -year age group, which increased to 0.72 (95% CI = 0.59-0.89) in the elderly age group. The risk of ICH increased with the severity of AR, from an aHR of 0.47 (95% CI = 0.40-0.56) in mild AR patients to 2.55 (95% CI = 1.88-3.47) in severe ones. For patients without comorbidities, the risk of ICH was 0.46 times (95% CI = 0.34-0.63) lower in the AR cohort than in the comparison cohort.

Conclusion: This study showed for the first time that milder AR is correlated with a reduction in the risk of ICH, particularly for elderly patients.

Keywords: Inflammatory disease; allergic rhinitis (AR); intracerebral hemorrhage (ICH); Taiwanese insurance claims data; Cox proportional hazard regression models

Introduction

Stroke (ie, ischemic stroke or hemorrhagic stroke) is one of the leading causes of disability and death in adults.¹⁻³ In addition to the increased risk of disability for patients with intracerebral hemorrhage (ICH) compared with those who have experienced ischemic stroke, greater economic and health care burdens exist for patients with ICH, which accounts for 10%–25% of total strokes¹⁻³ and is connected with several pathological changes in cerebral arterioles, such as the proliferation and death of smooth muscle cells in the arteriolar walls, arteriolar ectasia with succeeding microaneurysm formation,³ and the rupture of arteriolar microaneurysm.¹⁻³ These pathological changes can be caused by several traditional cardiovascular risk factors for ICH, such as hypertension,¹⁻⁷ diabetes²⁻⁷ hyperlipidemia,⁴⁻⁶ coronary artery disease (CAD)^{5,8,9} and chronic kidney disease (CKD).^{7,10} Nevertheless, in approximately 10%–25% of patients with ICH, the risk factors are unknown,^{4,11} particularly in younger patients.^{1,4,11}

Numerous studies have provided strong evidence that chronic inflammation can cause arterial ectasia, followed by the formation of a microaneurysm in the coronary artery.¹²⁻¹⁴ Previous studies have combined ICH with several chronic inflammatory processes in cerebral arterioles caused by viral infections of human immunodeficiency virus (HIV)^{15,16} and varicella-zoster virus (VZV),^{16,17} and by autoimmune disorders

such as systemic lupus erythematosus (SLE)^{18,19} and rheumatoid arthritis (RA).^{19,20}

Nevertheless, the precise mechanisms associating inflammation with arteriolar ectasia and the subsequent formation and rupture of microaneurysms remain unclear.

Allergic rhinitis (AR), a common atopic disease, is in most cases considered to be a disorder associated with IgE-mediated chronic inflammation that affects nasal mucosa and causes rhinorrhea, sneezing, pruritus, and nasal congestion.²¹⁻²³ As shown by previous research, T-helper 2 cells (Th2) with anti-inflammatory properties²⁴⁻²⁶ play a crucial role in the modulation of IgE-associated inflammation in AR.²¹⁻²³ However, it remains unclear whether AR, a Th2-modulated inflammatory disorder, can enhance the risk of ICH. Through access to the health records of the large population enrolled in Taiwan's National Health Insurance (NHI) program, the present investigation used the NHI claims database to evaluate the association between AR and ICH in a 12-year follow-up period.

Methods

Data Source

This retrospective cohort study used the Longitudinal Health Insurance Database (LHID) that comprises 1 million enrollees from 2000 to 2011, obtained from the

beneficiary list of the National Health Insurance Research Database (NHIRD).^{27,28}

The NHIRD was established on the basis of the Taiwanese NHI program that was implemented in 1995, and covers more than 98% of the total population of Taiwan.

The information in the LHID includes the medical facilities where patients were registered, demographic statuses, and the types of care supplied. Access to inpatient and outpatient registries in the LHID requires the approval of the insurance authority.

The patients' identification numbers used to link data files were scrambled before the files were released to users to ensure patient privacy. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Diagnoses of diseases were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes.

Study Patients

Based on the LHID, extracted from the NHIRD, enrollees who had newly diagnosed AR (ICD-9-CM code 477) from January 1, 2000 to December 31, 2010 and had no previous medical history of stroke (ICD-9-CM codes 430-438) were placed into the AR cohort. The entry date was defined as the first date of AR diagnosis. The comparison cohort comprised patients who numbered double the amount of the AR cohort, and who were randomly selected with age, sex, comorbidities of hypertension,

diabetes, hyperlipidemia, CAD, and CKD frequency matched from patients with no AR or previous indication of stroke.

Outcome and Relevant Variables

The AR and the comparison cohorts were followed until the end of 2011 to assess the incident cases with a diagnosis of ICH (ICD-9-CM code 431). Variables relevant to ICH were age, sex, and comorbidities such as hypertension (ICD-9-CM codes 401-405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM codes 272), CAD (ICD-9-CM codes 410.00-410.92, 411.0, 412, 411.1, 411.81, 411.89, 413.0, 413.1, 413.9, 414.00-414.05, 414.8, 414.9), and CKD (ICD-9-CM code 585). Incident cases of ICH were also evaluated in connection with these factors.

Statistical Analysis

The *t* test and chi-square test were used to estimate the distributions of continuous and discrete variables, respectively, between the AR and comparison groups. The incidence of ICH was assessed as per 10,000 person-years, calculated from entry date to the first date of the occurrence of ICH, death, withdrawal from the insurance program, or the end of 2011. The Cox proportional hazards regression model was used to evaluate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) to

compare the risk of the development of ICH between the 2 cohorts. The risks of ICH were further analyzed by age ranges (≤ 49 , 50-64, and ≥ 65 y), sex, and prevalent comorbidities.

Data analysis also estimated the risk of ICH connected with the severity of AR, which was defined as the mean frequency of clinical visits per year because of AR. The severity of AR was further classified into mild (mean frequency of clinical visits: ≤ 3 times/y), moderate (mean frequency of clinical visits: 4-6 times/y), and severe (mean frequency of clinical visits: ≥ 7 times/y). Using the Kaplan–Meier model for both cohorts, the cumulative proportional risks of ICH were outlined and the log-rank test was applied to determine the difference between the 2 groups. A 2-tailed *P* value $< .05$ was defined as being significant. All statistical analyses were performed using SAS V9.1 (SAS Institute Inc., Carey, NC, USA).

Results

The AR and comparison cohorts showed no significant differences based on distributions of age, sex and comorbidities (Table 1). Females were slightly more predominant in the AR cohorts (53.3%), and more than 2 thirds of AR patients were younger than 64 years of age.

The overall incidence rates of ICH for AR and control groups were 7.04 and 11.6 per 1000 person-years, respectively (Table 2). After adjusting for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, coronary artery disease and chronic kidney disease, the aHR for developing ICH was 0.59-fold (95% CI=0.52-0.68) for the AR cohort as compared with patients without AR. Although the incidence of ICH was relatively higher for males than for females in both cohorts, the relative risk for ICH in the AR cohort was lower for both males and females (aHR = 0.57 [95% CI = 0.48-0.68] in males and aHR = 0.64 [95% CI = 0.51-0.80] in females) (Table 2). The incidence increased with age and the age-specific risks for ICH was lower for all age group. The ICH incidences in both AR and control groups increased with comorbidity, and, either with or without comorbidity, the comorbidity-specific risks for ICH in AR patients were lower than the controls (Table 2).

The aHR of ICH development was a 1.03-fold increase (95% CI = 1.02-1.03) with age (every one year) and a 1.73-fold increase for men as opposed to for women (95% CI = 1.53-1.96) (Table 3). Patients with comorbidities of diabetes, hypertension and CKD had higher risk of ICH, particularly among patients with hypertension. The Kaplan–Meier plot showed that the cumulative proportional incidence for ICH was lower for the AR cohort than for the comparison group (log-rank $P < .001$) (Figure 1).

Assessing the association between the severity of AR and risks of ICH revealed a

dose-response effect; the risk of ICH was increased with the increase in the severity of AR (Table 4). Compared with the control cohort, the aHRs for AR patients by severity ranged from 0.47 (95% CI = 0.40-0.56) for those in the mild group, to 0.88 (95% CI = 0.64-1.21) for those in the moderate group, to 2.55 (95% CI = 1.88-3.47) for those in the severe group.

Discussion

Previous research has shown that patients with HIV^{15,16} and VZV^{16,17} infections and autoimmune disorders, such as SLE^{18,19} and RA,^{19,20} are at an increased risk of ICH. In the present population-based investigation, AR patients were compared with patients without this disease during a follow-up period of 12 years. A 42% reduction in the risk of ICH was detected in the AR patients (Table 2). The risk of ICH decreased in patients with mild and moderate RA, although the risk increased in the more severe ones. A dose-response effect of ICH risk on by the severity of AR was ~~also~~ observed (Table 4). As shown in previous studies, chronic inflammatory processes, such as viral infections of HIV^{15,16} and VZV,^{16,17} and autoimmune disorders of SLE^{18,19} and RA,^{19,20} could cause arterial ectasia in cerebral arterioles, hence, increased the risk of ICH. In previous research, a Th2 associated anti-inflammatory

properties,²⁴⁻²⁶ which played a crucial role in the modulation of IgE-associated inflammation,²¹⁻²³ has been proved to play an important role in the disease process of RA. This Th2 associated anti-inflammatory properties might explain the decrease of ICH risk in the milder RA patients in this study.

In this study population, the number of males and females used were nearly equal. This is consistent with previous reports that showed both sexes being equally affected by AR in adulthood.^{21,22} Although males had higher incidences of ICH in both the AR and control cohorts, only a minor risk difference in ICH was observed between males and females with AR.

The most critical risk factor for ICH is age.^{1-7,29-32} In this investigation, although the incidence of ICH gradually increased with age in the AR and comparison cohorts, and the age-specific risk of ICH was higher in the elderly age groups, the aHRs of ICH in all age ranges were lower in AR patients than in the controls (Table 2). The risk of ICH increased steadily with AR severity. These findings strengthen the relationship between AR and the development of ICH.

Comorbidities for Intracerebral Hemorrhage

Numerous studies have connected the risk of ICH with older age,^{1-7,29-32} male sex,^{1-3,5,29,32} and comorbidities of hypertension,^{1-7,29-34} diabetes,^{2-7,29,31-34}

hyperlipidemia,^{4-6,29-32,35} CAD,^{5,8,9,29,32} and CKD.^{7,10,xxx} The joint effect increased the risk of ICH for AR patients with the comorbidities of hypertension and CKD (Table 3).

Strengths and Limitations

With the advantages of using a large sample size and having low loss to follow-up in the longitudinal design, the present investigation allowed for the examination of the variations among groups, such as by sex, age, severity of AR, and comorbidities. The dose-response effect correlated with AR severity strengthened the validity of this examination. Comorbidities altered the relationship between AR and ICH. In Taiwan's NHI program, insurance claims for in- and outpatient reimbursements are strictly monitored to prohibit health care fraud. The NHI investigation system intensifies the diagnosis set on insurance claims.

However, several limitations are present in this study. First, other possible vascular risk factors, such as physical inactivity, and immunity alternation associated with AR, which might also affect patients by inhibiting the development of ICH could not be available in the NIH database. Second, since the major medicines prescribed for the treatment of AR, anti-histamines, were commonly available at the drugstores in Taiwan and the more severe AR patients might take more medications for their

disease, the influences of medication-disease interactions in ICH development in AR is very difficult to evaluate in Taiwan. Third, the laboratory results, such as serum levels of immunoglobulins (including the level of IgE), serum counts of T-helper cells (ie, T-helper 1 cells and Th2), erythrocyte sedimentation rate, and serum C-reactive protein levels, were not obtainable from the NHIRD. Therefore, it was impossible for the present study to evaluate the correlation between the various immune states in various AR patients and the risk of ICH. Forth, information regarding patients' personal behaviors, such as alcohol use and smoking habits, was not available in this study. However, the reduction of ICH risk was noted in both sexes in this investigation, and the extremely low cigarette-smoking rate among Taiwanese women (<4.5%)³¹ implies that smoking was not a confounding factor in the connection between AR and ICH. Fifth, although a higher prevalence of common comorbidities was noted in AR patients than in the comparison cohort, the results showed that even with these factors contributing to the incidence of ICH, AR still exhibited a lower risk for ICH. The anti-inflammatory effect of Th2 has been demonstrated in several studies.^{24-26,37,38} However, the exact mechanisms that protected the patients with AR from the development of ICH are unknown. Further investigation is required to determine the association between AR and the development of ICH.

Conclusions

The present investigation demonstrated that the overall risk of ICH was reduced in

AR patients; however, the risk of ICH may increase with an increase in the AR

severity which might be associated with medicine-disease interactions or other

unknown confounders, joints of prevalent comorbidities, and increased age.

Supplementary research is necessary to confirm the findings in this study. These

findings can be adopted for ICH prevention in AR patients, and particularly for those

at an advanced age.

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Figure Legend

Figure 1. The comparison of intracerebral-hemorrhage-free rates between allergic rhinitis and control cohorts using the Kaplan-Meier model.

Table 1. Demographic factors and comorbidities in allergic rhinitis and control groups

Variable	Allergic Rhinitis		<i>p</i> -value
	No	Yes	
	N=105680	N=52870	
	n (%)	n (%)	
Age [†] , year			0.99
≤49	40672(38.5)	20351(38.5)	
50-64	39718(37.6)	19862(37.6)	
≥65	25290(23.9)	12657(23.9)	
Mean [#] (SD)	55.7(12.0)	56.0(11.6)	0.05
Gender [†]			0.99
Female	56315(53.3)	28174(53.3)	
Male	49365(46.7)	24696(46.7)	
Comorbidity [†]			
Diabetes	9752(9.23)	4884(9.24)	0.95
Hypertension	41297(39.1)	20653(39.1)	0.96
Hyperlipidemia	28873(27.3)	14443(27.3)	0.99
Coronary artery disease	14177(13.4)	7105(13.4)	0.90
Chronic kidney disease	1368(1.29)	699(1.32)	0.65

SD, standard deviation.

[†]Chi-square test; [#]t-test.

Table 2. Incidence rate and hazard ratio for intracerebral hemorrhage between allergic rhinitis and control groups stratified by demographic factors and comorbidities

Variables	Control			Allergic Rhinitis			Crude HR [#] (95% CI)	Adjusted HR [†] (95% CI)
	Event	PY	IR	Event	PY	IR		
Overall	826	713115	11.6	260	369309	7.04	0.61 (0.53, 0.70)***	0.59 (0.52, 0.68)***
Gender								
Female	308	387912	7.94	102	198705	5.13	0.65 (0.52, 0.81)**	0.64 (0.51, 0.80)***
Male	518	325204	15.9	158	170604	9.26	0.58 (0.49, 0.70)***	0.57 (0.48, 0.68)***
Stratify age								
≤49	172	292728	5.88	47	149885	3.14	0.53 (0.39, 0.74)***	0.53 (0.39, 0.73)***
50-64	319	267216	11.9	82	137556	5.96	0.50 (0.39, 0.64)***	0.49 (0.39, 0.63)***
≥65	335	153172	21.9	131	81868	16.0	0.73 (0.60, 0.89)**	0.72 (0.59, 0.89)**
Comorbidity [‡]								
No	192	356199	5.39	48	183964	2.61	0.47 (0.34, 0.65)***	0.46 (0.34, 0.63)***
Yes	634	356916	17.8	212	185344	11.4	0.65 (0.55, 0.76)***	0.64 (0.55, 0.74)***

PY, person-years; IR, incidence rate per 10,000 person-years; HR, hazard ratio.

[#]Crude HR: relative hazard ratio.

[†]Adjusted HR: mutually adjusted with age, sex, diabetes, hypertension, hyperlipidemia, coronary artery disease and chronic kidney disease using Cox multivariable analysis.

[‡]Patients with any one of the comorbidities were classified as the comorbidity group.

p<0.01, *p<0.001

Table 3. Hazard ratios for intracerebral hemorrhage between allergic rhinitis and control groups stratified by demographic factors and comorbidities

Variable	Crude*	Adjusted [†]
	Crude HR [#] (95% CI)	Adjusted HR [†] (95% CI)
Age, years	1.05 (1.04, 1.05)***	1.03 (1.02, 1.03)***
Gender		
Female	1 (Reference)	1 (Reference)
Male	1.95 (1.73, 2.21)***	1.73 (1.53, 1.96)***
Comorbidities (yes vs. no)		
Diabetes	1.84 (1.54, 2.18)***	1.31 (1.09, 1.57)**
Hypertension	4.01 (3.52, 4.57)***	3.38 (2.91, 3.92)***
Hyperlipidemia	0.86 (0.75, 0.99)*	0.53 (0.45, 0.61)***
CAD	1.74 (1.49, 2.02)***	0.92 (0.78, 1.08)
CKD	4.10 (3.01, 5.58)***	2.31 (1.69, 3.16)***

HR, hazard ratio; CAD, coronary artery disease; CKD, chronic kidney disease.

*Crude hazard ratio: relative hazard ratio.

[†] Adjusted hazard ratio: mutually adjusted age sex, diabetes, hypertension, hyperlipidemia, coronary artery disease and chronic kidney disease using Cox multivariable analysis.

*p<0.05, **p<0.01, ***p<0.001

Table 4. Hazard ratio for intracerebral hemorrhage stratified by visit frequency due to allergic rhinitis

Visit frequency ^{\$}	Event	IR	Hazard ratio (95% CI)	
			Crude [#]	Adjusted [†]
None	826	11.6	1 (Reference)	1 (Reference)
≤3	178	5.51	0.47 (0.40, 0.56)***	0.47 (0.40, 0.56)***
4-6	39	11.5	1.01 (0.73, 1.39)	0.88 (0.64, 1.21)
≥7	43	35.0	3.07 (2.26, 4.18)***	2.55 (1.88, 3.47)***
<i>p</i> for trend			<0.001	<0.001

IR, incidence rate per 10,000 person-years.

^{\$}Visit frequency: mean frequency per year of clinic visits due to allergic rhinitis.

[#]Crude hazard ratio: relative hazard ratio.

[†]Adjusted hazard ratio: mutually adjusted age sex, diabetes, hypertension, hyperlipidemia, coronary artery disease, and chronic kidney disease using Cox multivariable analysis.

****p*<0.001.

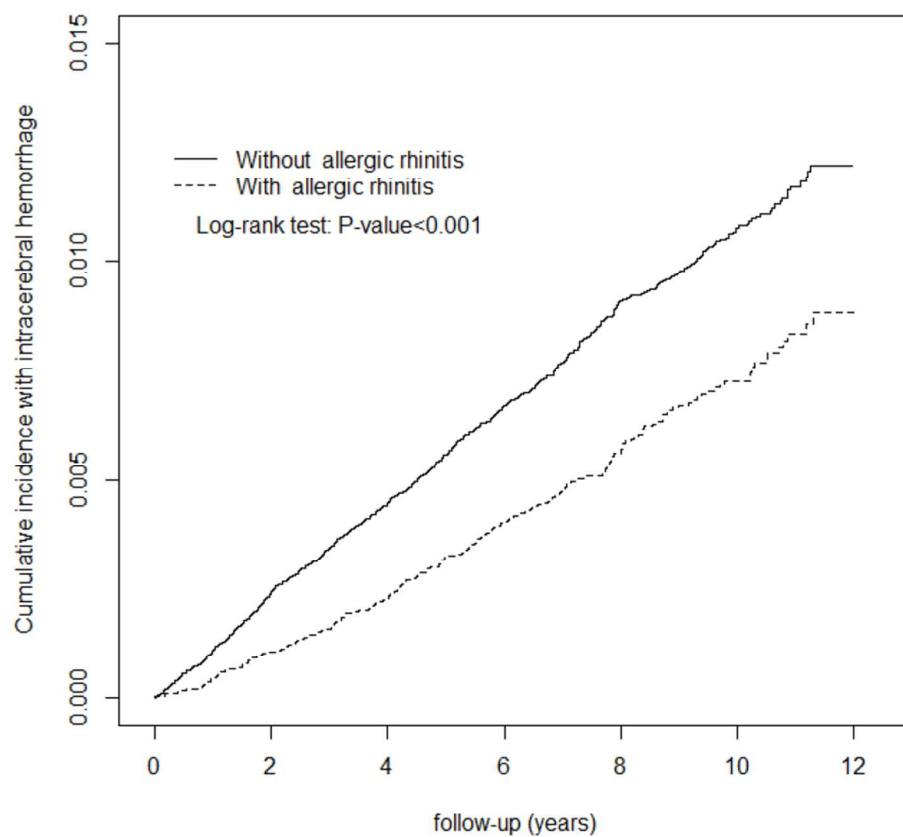


Figure 1. The comparison of intracerebral-hemorrhage-free rates between allergic rhinitis and control cohorts using the Kaplan-Meier model.
83x71mm (300 x 300 DPI)