

Risk relation between rhinitis and acute ischemic stroke

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ABSTRACT

Background and Purpose: Chronic inflammation that triggers endothelial dysfunction and atherosclerosis may promote the evolution of cardiovascular diseases, including acute ischemic stroke (AIS). In this study, we assessed the association between rhinitis (RN), an immunoglobulin E-related atopic disease, and the risk of AIS.

Methods: We used a Taiwan national insurance claims data set of 1 million enrollees to distinguish 61,899 patients with RN and 123,798 randomly selected age- and sex-matched controls from January 1, 2000, to December 31, 2010. Both cohorts were followed up until the occurrence of stroke or the end of follow-up. The risk of AIS was evaluated by using the Cox proportional hazards regression model.

Results: After adjustment of the relevant covariates, the RN group showed a lower risk of AIS (adjusted hazard ratio [aHR] 0.74 [95% confidence interval {CI}, 0.70–0.79]) compared with the control cohort at the end of follow-up. Among the participants without comorbidities, the RN cohort still had a lower risk of AIS compared with the control cohort (aHR 0.69 [95% CI, 0.59–0.81]). Moreover, in the three stratified age groups, RN was associated with a significantly decreased risk of AIS (ages ≤ 49 years: aHR 0.77 [95% CI, 0.63–0.95]; ages 50–64 years: aHR 0.72 [95% CI, 0.64–0.81]; ages ≥ 65 years: aHR 0.78 [95% CI, 0.71–0.85]).

Conclusions: RN was associated with a decreased risk of developing AIS. Although a reduction in risk of AIS was observed, it warrants further consideration to prevent AIS in patients with RN.

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Acute ischemic stroke (AIS) is one of the leading causes of death and adult disability worldwide.^{1–3} To decrease AIS-associated economic and health care burdens, early prevention of AIS by recognizing stroke risk factors is the main precedence. However, some patients with AIS exhibit no apparent risk factors, despite extensive searches of the prevalent stroke-related comorbidities.^{4,5} In addition to the established atherosclerosis-raising risk factors for AIS, including hypertension,^{1–7} diabetes,^{1–7} hyperlipidemia,^{1–3,5,7} cor-

onary artery disease (CAD),^{1,3,4,6,7} peripheral arterial disease (PAD),^{1,7,8} acute sinusitis (AS),^{9,10} and chronic sinusitis (CS),^{10,11} surveying uncommon risk factors for AIS more intensively is necessary.

Rhinitis (RN), a highly common atopic disease, is generally considered to be an immunoglobulin E (IgE) mediated chronic inflammatory disorder that involves nasal mucosa and causes pruritus, sneezing, rhinorrhea, and nasal congestion.^{12–15} Some studies have shown that T helper (Th) 2 cells play a crucial role in modulating IgE-related inflammation in RN.^{12–14} Through the possible mechanism that chronic inflammation causes endothelial dysfunction and accelerates atherosclerosis, a well-known cause of AIS,^{16,17} previous investigations linked stroke to chronic inflammations, such as infections caused by *Helicobacter pylori*^{18–20} and *Chlamydia pneumoniae*^{20,21} as well as autoimmune diseases, such as rheumatoid arthritis^{22,23} and systemic lupus erythematosus.^{24–27} However, in previous animal studies, the role of Th2 in the genesis of atherosclerosis has been controversial.^{27–30} Whether or not RN, a human Th2-modulated inflammatory disorder, can increase the risk of AIS remains unclear. In the present population-based study, with the advantage of a cohort of >1 million enrollees in a claims data base of the Taiwanese National Health Insurance (NHI) program, we investigated the correlation between RN and the risk of developing AIS in a study period of 11 years from January 1, 2000, to December 31, 2010.

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METHODS

Data Source

This retrospective cohort study used the Longitudinal Health Insurance Database, which consists of 1 million enrollees from 2000 to 2011, extracted from the beneficiary list of the National Health Insurance Research Database (NHIRD).^{31,32} The NHIRD was established based on the Taiwanese NHI program, which was implemented in 1995. The NHI program covers >98% of the total population in Taiwan. Before data collection, the identification numbers of the patients in the NHI data base were scrambled. Approval for this study from an institutional review board (or ethics committee), therefore, was unnecessary because the investigators were blinded to the identity of the patients. The diseases assessed in this study were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

C.-H. Tseng and C.-H. Kao designed the study. C.-L. Lin carried out the statistical analysis. All the authors drafted the manuscript. C.-H. Kao revised the manuscript. All the authors approved the final version submitted for publication.

Study Participants

By using patient registry data, either inpatient or outpatient, in the Longitudinal Health Insurance Database required approval from the insurance authority. In the Longitudinal Health Insurance Database, 61,899 patients who were newly diagnosed with RN (ICD-9-CM code 472.0 and 477) from January 1, 2000, to December 31, 2010, and had no medical history of stroke (ICD-9-CM codes 430–438) before RN diagnosis was distinguished. The entry date was defined as the date of RN diagnosis. For the control cohort, we randomly selected controls in a 2:1 ratio, frequency matched by age, sex, and index year to the RN cases by using the same exclusion criteria ($n = 123,798$).

Outcome and Relevant Variables

AIS (ICD-9-CM codes 433–437) that occurred during the study period (2000–2010) was the end point in this study. Relevant covariates comprised age, sex, and baseline comorbidities diagnosed before the index entry date, including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 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, and 414.9), PAD (ICD-9-CM codes 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 444.21, 444.22, and 444.81), AS (ICD-9-CM code 461), and CS (ICD-9-CM code 473).

Statistical Analysis

A χ^2 test and a t -test were performed to evaluate the differences in discrete and continuous variables between the RN and control cohorts. Person-years were calculated from the entry date to the first date of the AIS occurrence, withdrawal from the insurance program, death, or the end of 2010. The sex-, age-, and comorbidity-specific incidence rates (per 1000 person-years) of AIS were measured between the cohorts. Hazard ratios (HR) were assessed by using the Cox proportional hazards regression model to compare the risk of AIS development between the two cohorts. To evaluate the severity of RN, we assumed an RN severity index by using the mean frequency of RN-related clinic visits per year. RN severity was further categorized as mild (≤ 3 clinic visits per year), moderate (4–6 clinic visits per year), and severe (≥ 7 clinic visits per year). The cumulative incidences of AIS were graphed by using the Kaplan-Meier model, and the difference between the cohorts was estimated by using the log-rank test. A two-tailed p value of <0.05 was significant. All of the statistical analyses were executed by using SAS Version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Most of the patients with RN were ages <64 years, and diabetes, hypertension, hyperlipidemia, CAD, PAD, AS, and CS were more prevalent in the RN cohort than in the control cohort ($p < 0.001$) (Table 1). The overall incidence rates for AIS in the RN cohort and the control cohort were 3.25 and 3.94 per 1000 person-years, respectively (Table 2). In both groups, the incidence rates of AIS increased with age. After the variables of age, sex, hypertension, diabetes, hyperlipidemia, CAD, PAD, AS, and CS were adjusted with the Cox proportional hazards regression model, the risk of AIS was 0.74-fold (95% confidence interval [CI], 0.70–0.79) lower in the RN cohort compared with the control cohort (Table 2). The Kaplan-Meier analysis revealed that the incidence of AIS during the follow-up in both groups and that the cumulative incidence of AIS was significantly lower in the RN cohort compared with the control cohort (log-rank $p < 0.001$) (Fig. 1). With stratification with sex, the risks of AIS were significantly lower for both women with RN (adjusted HR [aHR] 0.81 [95% CI, 0.73–0.90]) and men with RN (aHR 0.71 [95% CI, 0.65–0.77]). The incident rate of AIS indicates that the absolute risks for AIS were low in both the younger RN and the control groups (age, ≤ 49 years: 0.80 and 0.93 per 1000 person-years, respectively). The age-specific aHR of AIS was similar in the three stratified age groups. In the non-comorbid subgroups, the risk of AIS was significantly lower in the patients with RN (aHR 0.69 [95% CI, 0.59–0.81]) than in the control cohort. For all prevalent comorbidities except AS and

Table 1 Demographic factors and comorbidities in RN and control groups

Variable	RN		p Value
	No (N = 123,798)	Yes (N = 61,899)	
Age, no. (%) [*]			0.99
≤49 y	48,818 (39.4)	24,409 (39.4)	
50–64 y	46,478 (37.5)	23,239 (37.5)	
≥65 y	28,502 (23.0)	14,251 (23.0)	
Mean (SD) [#]	55.3 ± 12.0	55.7 ± 11.6	<0.001
Sex, no. (%) [*]			0.99
Women	66,234 (53.5)	33,117 (53.5)	
Men	57,564 (46.5)	28,782 (46.5)	
Comorbidity, no. (%) [*]			
Diabetes	10,582 (8.55)	5598 (9.04)	<0.001
Hypertension	36,995 (29.9)	23,469 (37.9)	<0.001
Hyperlipidemia	22,532 (18.2)	16,522 (26.7)	<0.001
CAD	10,523 (8.50)	7957 (12.9)	<0.001
PAD	156 (0.13)	103 (0.17)	0.03
AS	16,115 (13.0)	19,216 (31.0)	<0.001
CS	1045 (0.84)	2936 (4.74)	<0.001

* χ^2 test.[#]t-test.

Table 2 Incidence rate and HR for AIS between RN and control groups, stratified by demographic factors and comorbidities

Variables	Control			RN			Crude HR (95% CI) [#]	aHR (95% CI) [§]
	Event	PY	IR	Event	PY	IR		
Overall	3229	819,559	3.94	1384	426,321	3.25	0.82 (0.77–0.87)***	0.74 (0.70–0.79)***
Sex								
Women	1301	448,562	2.90	581	230,688	2.52	0.87 (0.79–0.95)**	0.81 (0.73–0.90)***
Men	1928	370,997	5.20	803	195,633	4.10	0.78 (0.72–0.85)***	0.71 (0.65–0.77)***
Stratified age								
≤49 y	323	347,414	0.93	143	178,410	0.80	0.85 (0.70–1.04)	0.77 (0.63–0.95)*
50–64 y	1089	306,618	3.55	435	158,317	2.75	0.77 (0.69–0.86)***	0.72 (0.64–0.81)***
≥65 y	1817	165,528	11.0	806	89,594	9.00	0.81 (0.75–0.88)***	0.78 (0.71–0.85)***
Comorbidity [¶]								
No	860	463,966	1.85	191	149,572	1.28	0.67 (0.58–0.79)***	0.69 (0.59–0.81)***
Yes	2369	355,593	6.06	1193	276,750	4.31	0.64 (0.60, 0.69)***	0.69 (0.65, 0.74)***

PY = Person-year; IR = incidence rate per 1000 PY.

[#]Relative HR.[§]Mutually adjusted with age, sex, diabetes, hypertension, hyperlipidemia, CAD, PAD, and AS by using Cox multivariable analysis.[¶]Patients with any one of the comorbidities were classified as the comorbidity group.* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

CS, the AIS risk was higher among the different ranks in the patients with RN (Table 3).

The aHRs of AIS development were with a 1.06-fold increase (95% CI, 1.06–1.07) with age (every 1 year) and with 1.52-fold increase for men in comparison with

women (95% CI, 1.43–1.62) (Table 3). Patients with the comorbidities of diabetes and hypertension had higher risks of AIS. Patients with AS had a lower risk of AIS (aHR 0.80 [95% CI, 0.73–0.88]). By further stratifying the severity of RN, we perceived an increasing trend in

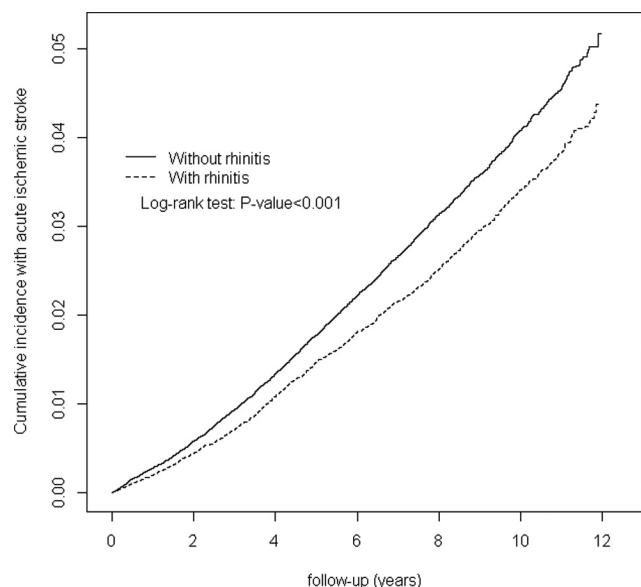


Figure 1. The comparison of AIS-free rates between RN and control cohorts by using the Kaplan-Meier model.

correlation with RN severity and the risk of AIS (mild: aHR 0.58 [95% CI, 0.54–0.63]; moderate: aHR 1.50 [95% CI, 1.31–1.73]; and severe: aHR 3.62 [95% CI, 3.14–4.18]) (Table 4).

DISCUSSION

In addition to the traditional risk factors for stroke, such as hypertension, diabetes, hyperlipidemia, CAD, PAD, AS, and CS, previous studies disclosed that several diseases delineated by inflammatory processes, including infections of *H. pylori*^{18–20} and *C. pneumoniae*,^{20,21} and autoimmune disorders, such as rheumatoid arthritis^{22,23} and systemic lupus erythematosus,^{24–27} may increase the risk of AIS. By exploiting the large representative sample in the claims data set of the NHIRD, we further examined whether RN, an atopic disease with Th2-mediated and IgE-related chronic inflammation, was associated with the augmentation of stroke risk.

The RN group predominantly comprised of men and women aged <64 years (Table 1). In this study, analysis of the results indicated that RN was correlated with a reduced AIS risk (aHR 0.74 [95% CI, 0.70–0.79]), and this significant reduction in AIS development was observed in both men and women (Table 2).

Age is the major risk factor for AIS.^{1–7,33–35} In both cohorts, the absolute incidence rates for AIS increased constantly with age (Table 2). Nevertheless, the relative negative effect of RN on AIS risk was similar in the three age-stratified groups. The aHRs of 0.77, 0.72, and 0.78 were determined for the subgroups ages ≤49, 50–64, and ≥65 years, respectively. Although the comorbidities known to increase AIS risk were more prevalent in the RN group than in the control cohort

(Table 1) and the risk of AIS was observed to increase as RN severity gradually increased, from the lowest risk in the mild subgroup (aHR 0.58 [95% CI, 0.54–0.63]) to the highest risk in the most-severe subgroup (aHR 3.62 [95% CI, 3.14–4.18]) (Table 4), RN remained a relatively protective factor in the milder group in this study (Table 2).

Comorbidities for Ischemic Stroke

The number of risk factors for AIS, such as age,^{1–7,33–35} male sex,^{1,2,6,7,33–35} hypertension,^{1–7,33–36} diabetes,^{20,33–36} hyperlipidemia,^{1–3,5,7,33–36} CAD,^{1,3,4,6,7,33,36} PAD,^{1,7,8,33} AS,^{9,10} and CS,^{10,11} have been firmly established. Our research determined that, among the participants without comorbidities, the patients with RN had a lower risk of AIS (aHR 0.69 [95% CI, 0.59–0.81]) compared with the control cohort (Table 2). Even with relatively higher incidences of AIS in both cohorts with relevant comorbidities, the patients with RN still had a relatively lower risk of IS (aHR 0.74 [95% CI, 0.70–0.79]) compared with their counterparts (Table 2).

Strengths and Limitations

This population-based retrospective cohort study had numerous strengths. First, both the patients with RN and age- and sex-matched controls were identified from a large representative sample (which consisted of 1 million enrollees) extracted from the NHIRD. Another strength was the precision of our study data. In Taiwan, insurance claims for the reimbursement for patient management are controlled by strict monitoring and auditing of NHI payments. This NHI surveillance program fortifies the reliability of the diagnosis based on the insurance claims. The manifestation of well-known risk factors for AIS, including hypertension,^{1–7,33–36} diabetes,^{1–7,33–36} hyperlipidemia,^{1–3,5,7,33–36} CAD,^{1,3,4,6,7,33,36} PAD,^{1,7,8,33} AS,^{9,10} and CS,^{10,11} in correlation with increased stroke incidence rates in both the RN and control groups, indicates the validity of the data yielded in this study. In addition, the large sample size provided sufficient power for subgroup stratifications for further statistical analyses and enabled us to verify the negative effect of RN on stroke risk.

Nevertheless, this study had several limitations. First, we could not exclude other possible vascular protective factors, physical activity, immunity alternations, and the medications frequently provided for RN (e.g., antihistamines and intranasal sodium cromoglycate [Lomudal, Sanofi-Aventis, Paris, France]) that might have reduced the risk of stroke in patients with RN. Sodium cromoglycate is a mast cell blocker that could reduce the immediate IgE-mediated response as well as a late-phase response of mast cells characterized by recruitment of eosinophils, basophils, and Th cells, which might express Th2 cytokines, including

Table 3 HRs of AIS in association with age, sex, and comorbidities in univariable and multivariable Cox regression models

Variable	Crude HR (95% CI)#	Adjusted HR (95% CI)§
Age, y	1.08 (1.07–1.08)***	1.06 (1.06–1.07)***
Sex		
Women	1 (reference)	1 (reference)
Men	1.75 (1.65–1.86)***	1.52 (1.43–1.62)***
Comorbidities (yes vs no)		
Diabetes	3.66 (3.42–3.93)***	1.91 (1.77–2.06)***
Hypertension	4.62 (4.35–4.92)***	2.20 (2.05–2.36)***
Hyperlipidemia	1.94 (1.83–2.07)***	1.06 (0.99–1.13)
CAD	2.80 (2.61–3.01)***	1.06 (0.98–1.14)
PAD	4.43 (2.75–7.14)***	1.47 (0.91–2.36)
AS	0.59 (0.53–0.64)***	0.80 (0.73–0.88)***
CS	0.94 (0.76–1.15)	—

#Relative HR.

§Mutually adjusted with age, sex, diabetes, hypertension, hyperlipidemia, CAD, PAD, and AS by using Cox multivariable analysis.

*** $p < 0.001$.

Table 4 HRs for AIS, stratified by RN severity with frequency of clinic visits due to RN

Frequency of Clinic Visit#	Event	IR	HR (95% CI)	
			Crude§	Adjusted¶
None	3229	3.94	1 (reference)	1 (reference)
≤3	966	2.50	0.63 (0.58–0.67)***	0.58 (0.54–0.63)***
4–6	218	7.51	2.01 (1.75–2.30)***	1.50 (1.31–1.73)***
≥7	200	19.4	5.30 (4.59–6.11)***	3.62 (3.14–4.18)***
<i>p</i> for trend			<0.001	<0.001

IR = Incidence rate per 1000 person-years.

#Frequency of clinic visit: mean frequency per year of clinic visits due to allergic RN.

§Relative HR.

¶Mutually adjusted with age, sex, diabetes, hypertension, CAD, PAD, and AS by using Cox multivariable analysis.

*** $p < 0.001$.

interleukin 4, a switch factor for IgE synthesis, and interleukin 5, an eosinophil growth factor.³⁷ Therefore, we could not exclude that, through the significance of mast cell stabilization, sodium cromoglycate might play an important role in AIS protection in the current study. Second, the results of laboratory studies, such as serum Th cell counts (both Th1 and Th2), serum IgE levels, serum levels of C-reactive protein, and erythrocyte sedimentation rate, are unavailable in the NHIRD. Hence, the association between patients with RN with different immune states and the risk of AIS could not be assessed in this investigation. Third, because the most common medicines used for treating RN, antihistamines, can easily be bought at the Taiwan drugstores and the patients with more-severe RN might take more medications, the impact of medication-disease interac-

tions in AIS development in RN is very difficult to estimate in Taiwan. Fourth, information on patients' personal behaviors (*e.g.*, cigarette smoking and alcohol consumption) was not available in our study. Nevertheless, RN reduced the risk of AIS in both the male and female patients, and the markedly low cigarette-smoking rate (<4.5%) among women in Taiwan³⁸ indicates that cigarette smoking is unlikely to be a confounding factor for the association between RN and AIS. Finally, although we noticed a higher prevalence of comorbidities in patients with RN than in the control cohort, the outcomes showed that, even among those with risk factors for AIS, RN was still associated with a decreased risk of developing AIS. Because, according to previous animal studies, the role of Th2 in the genesis of atherosclerosis is controversial,^{27–30,39–42} how

RN, a human Th2-modulated atopic disorder, reduces the risk of AIS remains unclear. Additional studies are required to continue to investigate the relationship between RN and AIS.

CONCLUSIONS

The patients with RN exhibited a significantly lower relative risk of AIS comparative with those without RN; however, the risk of AIS extended with an augmentation of the RN severity, which might be associated with medicine-disease interactions, joint effects of comorbidities of AIS, expansion of age, or other unknown confounding factors. Although the relative risk of AIS was low among the three stratified age groups in the patients with RN, the absolute incidence rate for AIS increased with age in both the RN and control groups. Therefore, AIS warrants further attention in patients with RN for administering interventions in AIS prevention, even though they have a lower stroke risk compared with the general population.

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