



Increased Risk of Stroke in Patients with Atopic Dermatitis: A Population-based, Longitudinal Study in Taiwan

Yueh-Feng Sung¹, Chun-Chieh Lin¹, Jiu-Haw Yin^{1,2}, Chung-Hsing Chou¹, Chi-Hsiang Chung^{3,4,5}, Fu-Chi Yang¹, Chia-Kuang Tsai¹, Chia-Lin Tsai¹, Guan-Yu Lin¹, Yu-Kai Lin¹, Wu-Chien Chien^{4,5}, Jiunn-Tay Lee¹

Departments of ¹Neurology and ⁵Medical Research, National Defense Medical Center, Tri-Service General Hospital, ²Department of Medicine, Division of Neurology, Cheng Hsin General Hospital, ³Taiwanese Injury Prevention and Safety Promotion Association, ⁴National Defense Medical Center, School of Public Health, Taipei, Taiwan, Republic of China

Background: Chronic inflammation has been linked to stroke, but it is not known whether atopic dermatitis (AD), a chronically inflammatory skin disease, is related to stroke. The aim of this study was to investigate the association of AD and stroke. **Materials and Methods:** In this population-based, cohort study, data were collected from a Longitudinal Health Insurance Database released from the National Health Research Institute in Taiwan in 2011. All patients with AD between 2000 and 2006 without prior stroke were included and an age- and gender-matched cohort without prior stroke, 4-fold of the AD sample size, was served as the control group. The two cohorts were followed until the end of 2010 for stroke incidence. Cox's proportional hazards regressions were used to assess the difference in stroke risk between groups. **Results:** During the follow-up period of 4–11 years, 471 (incidence: 4.46/1,000 person-years) and 1497 (incidence: 3.56/1,000 person-years) stroke incidents were noted in the study and control cohort, respectively. The patients with AD had an increased incidence of ischemic stroke (adjusted hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.08–1.36) but not hemorrhagic stroke (adjusted HR: 0.97; 95% CI: 0.74–1.29). The severity of AD was significantly correlated with the risk of ischemic stroke. **Conclusions:** These results suggest that AD is independently associated with ischemic stroke but not with hemorrhagic stroke. The risk of ischemic stroke is correlated significantly with the severity of AD. Further research is necessary to explore the underlying mechanism.

Key words: Atopic dermatitis; risk factors, ischemic stroke

INTRODUCTION

Stroke is one of the most frequent causes of death and permanent disability worldwide. In Taiwan, stroke is the leading cause of adult disability, the third leading cause of death and is the second highest in health-care expenditures for adults age 65 and older.¹ Although multiple risk factors

such as smoking, obesity, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, coronary artery disease (CAD), and atrial fibrillation (AF) have been identified, there are still some unknown risk factors which can predispose to stroke.

There is increasing evidence showing that chronic inflammation may be accounted for the trigger and progression of stroke.^{2–5} Previous studies have shown the association of stroke and chronic inflammatory diseases such as asthma,⁶ chronic obstructive pulmonary disease,⁷ hay fever,⁸ and rheumatoid arthritis.⁹ It is assumed that activation of microglia,¹⁰ blood coagulation pathways, and platelet play an important role in the inflammatory reactions.^{11,12}

Received: July 05, 2016; Revised: August 08, 2016;
Accepted: September 12, 2016

Corresponding Author: Dr. Jiunn-Tay Lee, Department of Neurology, National Defense Medical Center, Tri-Service General Hospital, No. 325, Section 2, Cheng-Kung Road, Neihs District, Taipei 11490, Taiwan, Republic of China. Tel: +886-2-87923311 ext. 12858; Fax: +886-2-87927174. E-mail: jiunntay@gmail.com

Prof. Wu-Chien Chien, Department of Medical Research, National Defense Medical Center, Tri-Service General Hospital, No. 325, Section 2, Cheng-Kung Road, Neihs District, Taipei 11490, Taiwan, Republic of China. Tel: +886-2-87923311 ext. 19189; Fax: +886-2-87927235. E-mail: chienwu@ndmctsgh.edu.tw

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Sung YF, Lin CC, Yin JH, Chou CH, Chung CH, Yang FC, *et al.* Increased risk of stroke in patients with atopic dermatitis: A population-based, longitudinal study in Taiwan. J Med Sci 2017;37:12-8.

Atopic dermatitis (AD) is a genetically determined, chronically relapsing, and inflammatory skin disease.¹³ The pathophysiology of AD includes impaired function of skin barrier, frequent allergic responses against allergens, defects in the antimicrobial immune defense, and a genetic predisposition.¹⁴ Previous studies showed controversial results about hemostatic alterations in AD. Patients with AD may have altered fibrin properties, which could cause thrombosis or delayed generation of thrombin, which can lead to bleeding.^{15,16}

The association between AD and the risk of stroke development is unclear. The purpose of this study was to investigate the associations between AD and the subsequent risk of stroke.

MATERIALS AND METHODS

Database

This study used the “Longitudinal Health Insurance Database (LHID)” released by the Taiwan National Health Research Institute (NHRI) in 2011 and covering the years between 1996 and 2010. The LHID contained all claimed data of 1,000,000 beneficiaries, who were randomly sampled from 23 million enrollees in National Health Insurance program. These enrollees covered around 98% of the population in Taiwan. There were no statistically significant differences in age, gender, or health-care costs between the sample group and all enrollees. These data have been used for epidemiological researches and more than one hundred of articles have been published. The LHID is de-identified secondary data released by NHRI for research purposes and this study is exempt from full review by the Institutional Review Board of Tri-Service General Hospital (TSGHIRB No.: 1-105-05-078).

Study sample

The study cohort and a comparison cohort were collected from the LHID. The study cohort comprised all patients who visited ambulatory care centers and inpatients for the treatment of AD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 691) for the first time between January 01, 2000, and December 31, 2006. For the validity of the diagnosis, we selected outpatients who received at least three consensus diagnoses. We excluded patients with previous diagnosis of all stroke (ICD-9-CM codes 430-438) and incomplete demographic information. The resulting study cohort enrolled 15103 patients with AD. The first medical visit that patients received AD diagnosis was set as an index ambulatory visit.

The comparison cohort was extracted from the remaining patients in the LHID. We assigned their first medical visits between January 01, 2000, and December 31, 2006, as index ambulatory visits. We excluded patients who had a diagnosis

of stroke before the index ambulatory visit. We randomly selected 60412 patients (4-fold of the study cohort) by SAS statistical package (Version 9.1.2, SAS Institute, Cary, NC, USA) and matched with the study cohort in terms of age and sex. Finally, we enrolled 75515 patients. Each patient was then individually followed till 31 December 2010 (i.e., for at least 4 years) from their index ambulatory visit to the outcome of all strokes (ICD-9-CM codes 430-438). The stroke types are divided by hemorrhagic stroke (ICD-9-CM codes 430-432) and ischemic stroke (ICD-9-CM codes 433-438). Similarly, for the validity of stroke diagnosis, we select patients who performed brain computed tomography or magnetic resonance imaging and at least three consensus diagnosis of stroke. For those who did not have stroke, the end day of follow-up is the last medical visit in the end of 2010.

Statistical analysis

In this study, SAS statistical package (version 9.1.2) was used to perform all statistical analysis. Pearson’s Chi-square test and *t*-test were performed to examine the differences in characteristics including age, gender, as well as the conventional risk factors of stroke including HTN (ICD-9-CM codes 401-405), DM (ICD-9-CM codes 250), CAD (ICD-9-CM codes 410-414), hyperlipidemia (ICD-9-CM codes 272), and AF (ICD-9-CM codes 4273). After adjustment for the variables mentioned, Cox’s proportional hazard regressions were performed to analyze the adjusted hazard ratio and 95% confidence interval [CI] using a significance level of 0.05.

RESULTS

The baseline characteristics between these two cohorts are shown in Table 1. After matching for age and gender, the AD patients are more likely to have HTN, DM, CAD, AF, and hyperlipidemia ($P < 0.0001$). Table 2 showed the incidence and hazard ratio of stroke by Cox’s proportional hazards regression analysis. During the follow-up period of 4–11 years, 471 (incidence: 4.46/1,000 person-years) and 1497 (incidence: 3.56/1,000 person-years) stroke incidents were noted in the study group and the control cohort, respectively. The hazard ratio [HR] for developing stroke of any type among patients with AD was 1.17 (95% CI = 1.06–1.30) as compared with cases in the control group. The incidence of stroke increased with elder age (HR: 106.46, 95% CI = 66.23–171.14, age 65 compared to age <20), male sex (HR: 1.41, 95% CI = 1.29–1.54), HTN (HR: 2.48, 95% CI = 2.21–2.79), DM (HR: 1.46, 95% CI = 1.31–1.63), CAD (HR: 1.44, 95% CI = 1.30–1.59), and AF (HR: 1.69, 95% CI = 1.32–2.15).

Table 3 showed stroke subgroup analysis between patients with AD and control group. After adjusting for age, sex, HTN, DM, CAD, AF, and hyperlipidemia, the adjusted-HR were

Risk of stroke in atopic dermatitis

1.21 (95% CI = 1.08–1.36) and 0.97 (95% CI = 0.74–1.29) for ischemic and hemorrhagic stroke, respectively.

To evaluate the roles of an interaction effect between AD and comorbidity in predisposition to stroke, we performed multivariate analyses with a forward selection model [Table 4]. The incidence of stroke risk increased when patients with AD have coincident conventional stroke risk factors such as HTN (HR: 3.25, 95% CI = 2.80–3.77), DM (HR: 2.15, 95% CI = 1.79–2.60), CAD (HR: 2.27, 95% CI = 1.96–2.64), AF (HR: 2.14, 95% CI = 1.29–3.56), and hyperlipidemia (HR: 1.81, 95% CI = 1.54–2.13). The *P* for trend is < 0.0001. Test for interactions between AD and comorbidities was not significant.

In Table 5, we employed multivariate Cox's proportional hazards regression analysis to explore the impact of AD severity in stroke incidence. The numbers of clinical visits for AD were representative as "surrogate markers" of disease severity of AD in our study. The increased clinical visits for AD was correlated significantly with higher rate of stroke incidence (<10 times, HR 1.14, 95% CI = 1.02–1.27; 10–19 times, HR 15.68, 95% CI = 10.79–22.78; and ≥20 times, HR 57.45, 95% CI = 35.62–92.66). After adjusting for age, sex, HTN, DM, CAD, AF, and hyperlipidemia, the correlation was still significant (<10 times, HR 1.08, 95% CI = 0.97–1.20; 10–19 times, HR 6.02, 95% CI = 4.13–8.76; and ≥20 times, HR 19.82, 95% CI = 12.23–32.13).

Table 1: Baseline characteristics of patients with atopic dermatitis and comparison cohort

Variable	Comparison cohort, <i>n</i> =60412 (%)	AD cohort, <i>n</i> =15103 (%)	<i>P</i>
Age, years (SD)*	34.0 (23.2)	33.9 (23.4)	
<20	21,004 (34.8)	5251 (34.8)	0.50
20–44	19,508 (32.3)	4877 (32.3)	
45–64	12,144 (20.1)	3036 (20.1)	
≥65	7756 (12.8)	1939 (12.8)	
Sex			
Female	32,768 (54.2)	8192 (54.2)	>0.99
Male	27,644 (45.8)	6911 (45.8)	
Comorbidity			
Hypertension	8820 (14.6)	2615 (17.3)	<0.0001
DM	3156 (5.2)	1031 (6.8)	<0.0001
CAD	4281 (7.1)	1387 (9.2)	<0.0001
AF	289 (0.5)	84 (0.6)	<0.0001
Hyperlipidemia	5208 (8.6)	1752 (11.6)	<0.0001

**T*-test; Others: Chi-square test. AD = Atopic dermatitis; DM = Diabetes mellitus; CAD = Coronary artery disease; AF = Atrial fibrillation; SD = Standard deviation

DISCUSSION

This study demonstrated that AD is an independent risk factor for the development of ischemic stroke but not the hemorrhagic stroke. We obtained a crude HR of 1.30 (95% CI = 1.17–1.46) and adjusted HR of 1.21 (95% CI = 1.08–1.36) for developing ischemic stroke in the AD cohort compared with the non-AD cohort. Patients with AD are more likely to have HTN, DM, CAD, AF, and hyperlipidemia; however, AD and these comorbidities influence the ischemic stroke risk independently. Furthermore, the severity of AD was significantly correlated with the risk of subsequent ischemic stroke.

There is growing evidence to suggest that patients with chronic inflammation are at elevated stroke risk beyond common risk factors.^{2–5} Clinical and preclinical studies revealed that inflammation is implicated in ischemic stroke as a modifier, a possible immediate and exacerbating factors, and a marker of future risk.¹⁷ The systemic inflammatory status prior to and at the time of stroke can influence the acute outcome and long-term prognosis of stroke.² Diverse mechanisms have been proposed to account for inflammation-associated stroke, ranging from classic risk factors to disturbances of the immune and coagulation systems.¹⁸

AD is a chronically relapsing, noncontagious pruritic skin disease with two phases: acute and chronic. The lifetime prevalence of AD is 10%–20% in children and 1%–3% in adults.¹⁹ It is regarded as a chronic inflammatory disease characterized by cutaneous hypersensitivity to environmental triggers.^{13,20} Previous studies showed controversial results about hemostatic alterations in atopic cases. One study had found that atopic patients with hay fever and asthma have delayed generation of thrombin in clotting blood, which can lead to prolonged bleeding time.¹⁶ On the other hand, one study demonstrated an increased incidence of atopic diseases among patients with venous thromboembolism.²¹ Another study showed that plasma beta-thromboglobulin and platelet factor 4 as platelet activation markers are significantly higher in patients with AD.²² Recent studies have shown that AD is associated with reduced clot permeability, prolonged fibrinolysis time, faster fibrin polymerization, higher thrombotic mass, and thicker fibers,¹⁵ which are all known to be associated with prothrombotic tendency and seen in patients with coronary atherothrombosis.^{23,24} Our study demonstrated that patients with AD have increased risk of ischemic stroke but not hemorrhagic stroke [Table 3]; a finding was in concert with those of previous studies.

Many studies have shown that acute and chronic infections can act in combination with conventional risk factors to increase the risk of stroke. Our recent study also found that septicemia

Table 2: Incidence and hazard ratio of stroke by Cox's proportional hazards regression analysis

Variable	Event	PYs	Rate	HR (95% CI)	Adjusted HR (95% CI)
AD					
No	1497	420,962	35.56	1.00	1.00
Yes	471	105,658	44.58	1.25 (1.13-1.39)**	1.17 (1.06-1.30)**
Demographic					
Age group					
<20	18	199,974	0.90	1.00	1.00
20-44	115	169,850	6.77	7.58 (4.61-12.45)***	7.51 (4.57-12.34)***
45-64	531	102,215	51.95	58.23 (36.4-93.15)***	36.95 (23.01-59.34)***
≥65	1304	54,582	238.91	269.22 (169.05-428.75)***	106.46 (66.23-171.14)***
Sex					
Female	830	287,774	28.84	1.00	1.00
Male	1138	238,846	47.65	1.65 (1.51-1.81)***	1.41 (1.29-1.54)**
Comorbidity					
Hypertension					
No	592	458,277	12.92	1.00	1.00
Yes	1376	68,343	201.34	15.6 (14.17-17.19)***	2.48 (2.21-2.79)***
DM					
No	1462	502,181	29.11	1.00	1.00
Yes	506	24,440	207.04	7.05 (6.37-7.8)***	1.46 (1.31-1.63)**
CAD					
No	1176	493,624	23.82	1.00	1.00
Yes	792	32,996	240.03	10.03 (9.16-10.98)***	1.44 (1.30-1.59)**
AF					
No	1899	524,921	36.18	1.00	1.00
Yes	69	1699	406.16	10.98 (8.63-13.96)***	1.69 (1.32-2.15)***
Hyperlipidemia					
No	1331	483,215	27.54	1.00	1.00
Yes	637	43,406	146.76	5.29 (4.81-5.82)***	0.99 (0.90-1.10)

** $P < 0.01$, *** $P < 0.001$. Model adjusted for AD, age (categorical), sex, and comorbidity. PYs = Person-years; Rate = Incidence rate, per 10,000 person-years; AD = Atopic dermatitis; DM = Diabetes mellitus; CAD = Coronary artery disease; AF = Atrial fibrillation; HR = Hazard ratio; CI = Confidence interval

Table 3: Incidence and hazard ratio of stroke and its subtypes in patients with atopic dermatitis and comparison cohort

Variable	Comparison cohort			AD cohort			HR (95% CI)	Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate		
All stroke	1497	420,962	35.56	471	105,658	44.58	1.25 (1.13-1.39)**	1.17 (1.06-1.30)**
Ischemic stroke	1250	420,962	29.69	409	105,658	38.71	1.30 (1.17-1.46)**	1.21 (1.08-1.36)**
Hemorrhagic stroke	247	420,962	5.87	62	105,658	5.87	1.00 (0.76-1.32)	0.97 (0.74-1.29)

** $P < 0.01$. Model adjusted for age, sex, and comorbidity. PYs = Person-years; Rate = Incidence rate, per 10,000 person-years; AD = Atopic dermatitis; HR = Hazard ratio; CI = Confidence interval

is associated with an increase in stroke risk.²⁵ Patients with AD have impaired epithelial barrier, which can predispose to colonization or infection by microbial organism, most notably *Staphylococcus aureus*²⁶ and widespread disseminated viral

infections.²⁷ It implies that chronic infection may be one of the possible contributors for stroke in patients with AD.

In Table 1, the average age of AD cohort in this study is 33.9 years old. The age distribution of onset (age < 20, 34.8%)

Risk of stroke in atopic dermatitis

Table 4: Interaction effect between atopic dermatitis and comorbidities contributing to stroke risk

Variable		Event	PYs	Rate	HR (95% CI)	P for interaction
AD	Hypertension					
No	No	458	368,200	12.44	1.00	0.4437
Yes	No	134	90,077	14.88	1.29 (1.06-1.56)	
No	Yes	1039	52,762	196.92	2.76 (2.45-3.12)	
Yes	Yes	337	15,581	216.29	3.25 (2.80-3.77)	
P for trend <0.0001						
Variable						
AD	DM					
No	No	1114	402,469	27.68	1.00	0.1702
Yes	No	348	99,711	34.90	1.29 (1.15-1.46)	
No	Yes	383	18,493	207.11	1.97 (1.75-2.21)	
Yes	Yes	123	5947	206.83	2.15 (1.79-2.60)	
P for trend <0.0001						
Variable						
AD	CAD					
No	No	929	395,993	23.46	1.00	0.5616
Yes	No	247	97,631	25.30	1.17 (1.02-1.35)	
No	Yes	568	24,969	227.49	1.83 (1.64-2.04)	
Yes	Yes	224	8027	279.05	2.27 (1.96-2.64)	
P for trend <0.0001						
Variable						
AD	AF					
No	No	1443	419,626	34.39	1.00	0.5995
Yes	No	456	105,295	43.31	1.27 (1.14-1.41)	
No	Yes	54	1336	404.30	1.97 (1.50-2.59)	
Yes	Yes	15	363	412.98	2.14 (1.29-3.56)	
P for trend <0.0001						
Variable						
AD	Hyperlipidemia					
No	No	1030	388,463	26.51	1.00	0.4878
Yes	No	301	94,751	31.77	1.26 (1.11-1.44)	
No	Yes	467	32,498	143.70	1.55 (1.39-1.73)	
Yes	Yes	170	10,907	155.86	1.81 (1.54-2.13)	
P for trend <0.0001						

Model adjusted for age and sex. PYs = Person-years; Rate = Incidence rate, per 10,000 person-years; AD = Atopic dermatitis; DM = Diabetes mellitus; CAD = Coronary artery disease; AF = Atrial fibrillation; HR = Hazard ratio; CI = Confidence interval

is compatible with the fact that atopic diseases are less frequent with increasing age. Although AD usually presents during early age, it can persist into or start in adulthood.²⁸ In this study, the AD group was associated with higher rate of comorbidity

including HTN, DM, CAD, AF, and hyperlipidemia compared to the control group. In one study, disruption of lipid and sugar metabolism in the liver was found in AD animal.²⁹ Besides, studies have shown that significant stress³⁰ caused by AD can not only influence mental defects but can also influence other pathological conditions such as metabolic syndrome³¹ and cardiovascular diseases.³² These results can support the findings in our study that the patients with AD have higher incidence of comorbidities for stroke. Table 4 showed the interaction effect between AD and comorbidity contributing to stroke risk. The nonsignificant interaction between AD and comorbidities means that AD and other comorbidities influence the ischemic stroke risk independently. However, AD in a combination of traditional risk factors of stroke may further potentiate the stroke risk. AD and these traditional risk factors for stroke may possibly involve inflammatory mechanisms both in the periphery and in the central nervous system which finally result in thrombotic events.

We hypothesized that AD may initiate a systemic inflammatory reaction, which causes disordered coagulation and platelet activation and lead to subsequent ischemic stroke. Moreover, the inflammatory process caused by AD may be important both before, in predisposing to a stroke, and afterward, where it is related to the outcome and prognosis.

Notably, a recent nationwide, population-based study demonstrated that patients with AD had an increased risk of ischemic stroke.³³ The adjusted HR was 1.33 (95% CI, 1.12–1.59; $P = 0.001$). However, the study excluded patients who aged <20. Actually, AD has been well known to have a higher prevalence in younger age groups, and the percentage of patients with AD who aged <20 were 34.8% in our study. Enrollment of AD patients with all age groups can reflect the real AD population group. In addition, the follow-up period was longer in our study (4–11 years vs. 1–5 years). Longer follow-up period is needed to detect stroke development.

An important strength of this study was the use of a population-based data set that allows inclusion of all cases of AD and stroke during the designated study period. We were able to obtain a well-matched control group without AD from the same population for the long follow-up period of 4–11 years. However, this study has several limitations. First, LHID does not contain detailed information regarding clinical, laboratory, and image examinations. The potential risk factors for stroke, such as obesity, alcohol use, smoking habit, genetic background, family history of stroke, and sedentary lifestyle, were not available. The association risk between AD and stroke may be mediated by the above risk factors or even confounded by them. Second, data used in the present study do not include medications that may impact on stroke risk. Medications such

Table 5: Incidence and adjusted hazard ratio of stroke stratified by numbers of clinical visits for atopic dermatitis

Numbers of clinical visits for AD	Event	PYs	Rate	HR (95% CI)	Adjusted HR (95% CI)
Comparison cohort	43	1,363,377	0.32	Reference	Reference
AD cohort (times)					
<10	16	301,852	0.53	1.14 (1.02-1.27)**	1.08 (0.97-1.20)**
10-19	8	28,749	2.78	15.68 (10.79-22.78)***	6.02 (4.13-8.76)***
≥20	13	15,658	8.30	57.45 (35.62-92.66)***	19.82 (12.23-32.13)***

** $P < 0.01$, *** $P < 0.001$. Model adjusted for age, sex, and comorbidity. PYs = Person-years; Rate = Incidence rate, per 10,000 person-years; AD = Atopic dermatitis; HR = Hazard ratio; CI = Confidence interval

as antihistamine and corticosteroids are commonly prescribed in AD. These kinds of medications are reported to influence the fibrin clots formation.^{34,35} Third, we used numbers of clinical visits for AD as “surrogate markers” of disease severity of AD. The disease severity evaluated by the scoring tools such as Scoring AD,³⁶ three-Item Severity³⁷ could not be acquired based on the LHID. Furthermore, we did not include asthma or other allergic disorders as comorbidities in our analysis. Previous studies had found that patients with AD often have concomitant asthma and other allergic disorders,³⁸ which had been supposed as possible independent risk factors or possible confounder for stroke.⁶

CONCLUSIONS

AD was associated with an increased risk for developing ischemic stroke but not hemorrhagic stroke. The severity of AD was significantly correlated with the risk of subsequent stroke. Patients with AD were associated with higher rate of HTN, DM, CAD, AF, and hyperlipidemia, but AD and these comorbidities influence the ischemic stroke risk independently. Future prospective study of patients with AD is warranted to expand and confirm results of the present study regarding the impact of AD on ischemic stroke risk.

Financial support and sponsorship

This study was supported in part by grants from the Tri-Service General Hospital (TSGH-C104-084; TSGH-C105-084; TSGH-C100-101; TSGH-C101-080; TSGH-C103-085; TSGH-C104-083; TSGH-C105-083; and TSGH-C105-085), Ministry of National Defense-Medical Affairs Bureau (MAB-105-090), Teh-Tzer Study Group for Human Medical Research Foundation (A1031031). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Jeng JS, Su TC. Epidemiological studies of cerebrovascular diseases and carotid atherosclerosis in Taiwan. *Acta Neurol Taiwan* 2007;16:190-202.
- McColl BW, Allan SM, Rothwell NJ. Systemic infection, inflammation and acute ischemic stroke. *Neuroscience* 2009;158:1049-61.
- Beamer NB, Coull BM, Clark WM, Briley DP, Wynn M, Sexton G. Persistent inflammatory response in stroke survivors. *Neurology* 1998;50:1722-8.
- Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: Recent and emerging concepts. *Lancet Neurol* 2008;7:341-53.
- Goldstein LB. Novel risk factors for stroke: Homocysteine, inflammation, and infection. *Curr Atheroscler Rep* 2000;2:110-4.
- Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, *et al.* Asthma and incident cardiovascular disease: The Atherosclerosis Risk in Communities Study. *Thorax* 2005;60:633-8.
- Arboix A, Morcillo C, García-Eroles L, Oliveres M, Massons J, Targa C. Different vascular risk factor profiles in ischemic stroke subtypes: A Study from the Sagrat Cor Hospital of Barcelona Stroke Registry. *Acta Neurol Scand* 2000;102:264-70.
- Matheson EM, Player MS, Mainous AG 3rd, King DE, Everett CJ. The association between hay fever and stroke in a cohort of middle aged and elderly adults. *J Am Board Fam Med* 2008;21:179-83.
- Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, *et al.* Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- Drake C, Boutin H, Jones MS, Denes A, McColl BW, Selvarajah JR, *et al.* Brain inflammation is induced by co-morbidities and risk factors for stroke. *Brain Behav Immun* 2011;25:1113-22.
- Shimizu S, Shimizu T, Morser J, Kobayashi T, Yamaguchi A, Qin L, *et al.* Role of the coagulation

Risk of stroke in atopic dermatitis

- system in allergic inflammation in the upper airways. *Clin Immunol* 2008;129:365-71.
12. Tamagawa-Mineoka R, Katoh N, Kishimoto S. Platelets play important roles in the late phase of the immediate hypersensitivity reaction. *J Allergy Clin Immunol* 2009;123:581-7.e1-9.
13. Boguniewicz M, Leung DY. Atopic dermatitis: A disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242:233-46.
14. Homey B, Steinhoff M, Ruzicka T, Leung DY. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 2006;118:178-89.
15. Nastalek M, Wojas-Pelc A, Undas A. Plasma fibrin clot properties in atopic dermatitis: Links between thrombosis and atopy. *J Thromb Thrombolysis* 2010;30:121-6.
16. Szczeklik A, Schmitz-Schumann M, Krzanowski M, Virchow C Sr. Delayed generation of thrombin in clotting blood of atopic patients with hayfever and asthma. *Clin Exp Allergy* 1991;21:411-5.
17. Muir KW, Tyrrell P, Sattar N, Warburton E. Inflammation and ischaemic stroke. *Curr Opin Neurol* 2007;20:334-42.
18. Emsley HC, Tyrrell PJ. Inflammation and infection in clinical stroke. *J Cereb Blood Flow Metab* 2002;22:1399-419.
19. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest* 2004;113:651-7.
20. Leung DY. New insights into atopic dermatitis: Role of skin barrier and immune dysregulation. *Allergol Int* 2013;62:151-61.
21. Undas A, Ciesla-Dul M, Drazkiewicz T, Potaczek DP, Sadowski J. Association between atopic diseases and venous thromboembolism: A case-control study in patients aged 45 years or less. *J Thromb Haemost* 2011;9:870-3.
22. Tamagawa-Mineoka R, Katoh N, Ueda E, Masuda K, Kishimoto S. Elevated platelet activation in patients with atopic dermatitis and psoriasis: Increased plasma levels of beta-thromboglobulin and platelet factor 4. *Allergol Int* 2008;57:391-6.
23. Undas A, Szuldrzynski K, Stepień E, Zalewski J, Godlewski J, Tracz W, *et al.* Reduced clot permeability and susceptibility to lysis in patients with acute coronary syndrome: Effects of inflammation and oxidative stress. *Atherosclerosis* 2008;196:551-7.
24. Collet JP, Allali Y, Lesty C, Tanguy ML, Silvain J, Ankri A, *et al.* Altered fibrin architecture is associated with hypofibrinolysis and premature coronary atherothrombosis. *Arterioscler Thromb Vasc Biol* 2006;26:2567-73.
25. Lee JT, Chung WT, Lin JD, Peng GS, Muo CH, Lin CC, *et al.* Increased risk of stroke after septicaemia: A population-based longitudinal study in Taiwan. *PLoS One* 2014;9:e89386.
26. Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol* 1974;90:525-30.
27. Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: Pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003;112:667-74.
28. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112 6 Suppl: S118-27.
29. Seino S, Tanaka Y, Honma T, Yanaka M, Sato K, Shinohara N, *et al.* Atopic dermatitis causes lipid accumulation in the liver of NC/Nga mouse. *J Clin Biochem Nutr* 2012;50:152-7.
30. Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. *Curr Allergy Asthma Rep* 2008;8:312-7.
31. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, *et al.* Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004;114:1752-61.
32. Schwartz AR, Gerin W, Davidson KW, Pickering TG, Brosschot JF, Thayer JF, *et al.* Toward a causal model of cardiovascular responses to stress and the development of cardiovascular disease. *Psychosom Med* 2003;65:22-35.
33. Su VY, Chen TJ, Yeh CM, Chou KT, Hung MH, Chu SY, *et al.* Atopic dermatitis and risk of ischemic stroke: A nationwide population-based study. *Ann Med* 2014;46:84-9.
34. Stanbury RM, Graham EM. Systemic corticosteroid therapy – side effects and their management. *Br J Ophthalmol* 1998;82:704-8.
35. Pandit HB, Spillert CR. Effect of methylprednisolone on coagulation. *J Natl Med Assoc* 1999;91:453-6.
36. Severity scoring of atopic dermatitis: The SCORAD index. Consensus report of the European task force on atopic dermatitis. *Dermatology* 1993;186:23-31.
37. Wolkerstorfer A, de Waard van der Spek FB, Glazenburg EJ, Mulder PG, Oranje AP. Scoring the severity of atopic dermatitis: Three item severity score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Derm Venereol* 1999;79:356-9.
38. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC, *et al.* Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: A national study 2000 to 2007. *Acta Derm Venereol* 2010;90:589-94.