Increased risk of stroke in contact dermatitis patients
A nationwide population-based retrospective cohort study
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Abstract
Dermatologic diseases are not traditional risk factors of stroke, but recent studies show atop dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases. No previous studies have focused on the association between contact dermatitis and stroke.

We established a cohort comprised of 48,169 contact dermatitis patients newly diagnosed in 2000–2003 and 96,338 randomly selected subjects without the disorder, frequency matched by sex, age, and diagnosis year, as the comparison cohort. None of them had a history of stroke. Stroke incidence was assessed by the end of 2011 for both cohorts.

The incidence stroke was 1.1-fold higher in the contact dermatitis cohort than in the comparison cohort (5.93 vs 5.37 per 1000 person-years, P < 0.01). The multivariable Cox method analyzed adjusted hazard ratios (aHRs) were 1.12 (95% confidence interval [CI], 1.05–1.19) for all stroke types and 1.11 (95% CI, 0.94–1.30) for hemorrhagic stroke. The age-specific aHR of stroke for contact dermatitis cohort increased with age, from 1.14 (95% CI, 1.03–1.27) for 65 to 74 years; 1.27 (95% CI, 1.15–1.42) for 75 years and older. The aHR of stroke were 1.16 (95% CI, 1.07–1.27) and 1.09 (95% CI, 1.00–1.18) for men and women, respectively.

This study suggests that patients with contact dermatitis were at a modestly increased risk of stroke, significant for ischemic stroke but not for hemorrhagic stroke. Comorbidity, particularly hypertension, increased the hazard of stroke further.

Abbreviations: ACD = allergic contact dermatitis, aHRs = adjusted hazard ratios, CI = 95% confidence interval, HR = crude hazard ratio, ICD = irritant contact dermatitis, IL-2 = interleukin-2, LHID = Longitudinal Health Insurance Database, NHRI = National Health Research Institute, NHI = National Health Insurance, NHRI = National Health Research Institute, NTD = New Taiwan Dollar, RAS = renin–angiotensin system, Th2 = T helper type 2.

Keywords: contact dermatitis, insurance data, ischemic stroke, stroke

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C-HY and F-CS contributed equally to this study.

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The authors warrant that the article is original, and not under consideration by another journal, and has not been previously published.

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1. Introduction

Stroke is one of the leading causes of deaths in the world and the most frequent cause of permanent disability in Taiwan. Contact dermatitis is the main cause of occupational dermatitis because of exposing to irritants (irritant contact dermatitis, ICD) or allergens (allergic contact dermatitis, ACD). Both are induced by repeated skin contact with low-molecular-weight chemicals called xenobiotics or haptens. Although both disorders may have similar clinical and histological presentations, they are with different pathophysiological grounds. ICD is a nonspecific inflammatory dermatitis induced by chemicals with proinflammatory properties, which activate the innate immune system. ACD is a delayed hypersensitivity responding to skin inflammation mediated by hapten-specific T-cells. There is no specific test for the diagnosis of ICD. The patch test is the mainstay of ACD diagnosis with good sensitivity and specificity. Recent epidemiological studies have implied that atopic dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases. The contact dermatitis is an inflammation of the skin surface after exposure to an irritant or allergen. Allergens may bind to Langerhans cells and present them to activate T helper type 2 (Th2). Subsequently, pro-inflammatory cytokines and chemokines are produced and persisted during the inflammation process. During acute ischemic stroke, activated T lymphocyte (CD4+ and CD8+ T-cells) may induce brain injury through producing proinflammatory cytokines, including interleukin-2 (IL-2), IL-12, interferon-gamma, and tumor necrosis factor-alpha, which play a role in the pathogenesis of stroke. Another study have revealed that the elevations of proinflammatory cytokines in peripheral blood is associated with long-term functional outcome of stroke. Recent studies showed inflammation may increase the incidence of stroke and involved in the pathogenesis of acute stroke. However, the correlation between contact dermatitis and the risk of stroke has not been fully understood yet. This study estimated the risk of stroke among contact dermatitis patients during a 9-year follow-up period (2000–2008) after diagnosis of contact dermatitis, in comparison to a cohort of patients without contact dermatitis during the same period.

2. Methods

2.1. Database

This study used the “Longitudinal Health Insurance Database (LHID)” released by the Taiwan National Health Research Institute (NHRI) in 2009, covering claims data from 1996 to 2008. The LHID contained life-time longitudinal claims data of both outpatient and inpatient cares for 1,000,000 beneficiaries who were randomly sampled from 23.74 million enrollees in the National Health Insurance (NHI) program (http://www.nhi.gov.tw/english/index.aspx). The NHI covers approximately 99% of the population of Taiwan. The sample cohort and all enrollees were similar in distributions of age, sex, and health care costs. The details of the LHID have been described in previous studies. The NHRI converted all personal identification numbers into surrogate numbers before releasing the data file to researchers as a scrambled secondary data file to secure the privacy of insured persons. This study was approved by the Research Ethics Committee at China Medical University and Hospital (CMU-REC-101-012).

2.2. Study samples

Faculty in biostatistics and epidemiology supervised data process, study cohorts establishment, and analysis. We established a contact dermatitis cohort and a comparison cohort from the population selected in LHID. The contact dermatitis cohort was identified from inpatients and patients ambulatory care clinics for the treatment of contact dermatitis (ICD-9-CM code 692) for the first time from 2000 to 2003, 20 years of age and older (Fig. 1). To ensure the validity of the diagnoses, we selected patients who had received at least 3 consensus diagnoses of the disease (n = 50,324). We excluded patients with a previous diagnosis of all types of stroke (ICD-9-CM codes 430 to 438, n = 1268) and those with incomplete demographic information (n = 887), resulting in 48,169 patients in the contact dermatitis cohort. The first medical visit, at which the patient received a diagnosis of contact dermatitis, was set as the index date of diagnosis. The comparison cohort consisting of 96,338 persons were randomly selected from the remaining patients in the LHID, frequency matched by sex, age, and index date. We assigned the first medical visit of the comparison subject between the years 2000 and 2003 as the index date of visit. Subjects with stroke at the baseline were excluded.

2.3. Outcome measures

We started to follow-up a study subject once was identified as an eligible person to be included in the specific study cohort. The person-years of followed-up was measured until the occurrence of stroke (ICD-9-CM codes 430–437) or December 31, 2008, or until censored because of loss to follow-up, death, or withdrawal from the insurance program. The stroke types were classified as hemorrhagic (ICD-9-CM codes 430–432) and ischemic (ICD-9-CM codes 433–437). Furthermore, we selected patients who had undergone brain computed tomography or magnetic resonance imaging and had at least 3 consensus diagnoses of stroke to ensure the validity of stroke diagnoses.

2.4. Data process and analysis

We used desk top computer equipped with SAS statistical package (version 9.1.2; SAS Institute, Inc., Cary, NC) to perform data process, study cohorts establishment and statistical analyses. The scrambled identification numbers were used to link data among claims data records for data analyses. We used Pearson’s χ² test and the t-test to examine the differences in sociodemographic characteristics, including age (<39, 40–59, 60–79, and >80 years), sex, monthly income (less than 15,840 New Taiwan Dollar [NTD], 15,841–25,000 NTD and more than 25,001 NTD), level of urbanization (from level 1 as the most urbanized to level 5 as the least urbanized), and the conventional risk factors for stroke, including hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), coronary heart disease (ICD-9-CM codes 410–414), dyslipidemia (ICD-9-CM code 272), and atrial fibrillation (ICD-9-CM code 4273). We then estimated the 9-year cumulative incidence of stroke using the Kaplan–Meier method, and the difference between 2 cohorts was examined using the Log-rank test. The incidence densities of stroke were calculated for both cohorts. Univariate and multivariate Cox proportional hazards regression models were used to estimate the crude hazard ratio (HR) and adjusted hazard ratio (aHR), respectively, and 95% confidence interval (CI) to assess the stroke hazards relating to contact dermatitis, compared...
with the noncontact dermatitis cohort. The multivariate model was simultaneously adjusted for age, sex, monthly income, level of urbanization, and comorbidities including hypertension, diabetes, coronary heart diseases, atrial fibrillation, and dyslipidemia. We further pooled both cohorts to measure whether there were joint effects on the hazards of stroke between contact dermatitis and comorbidities. A 2-tailed P value of <0.05 was considered statistically significant.

3. Results

Eligible study subjects consisted of 48,169 patients in the contact dermatitis cohort and 96,338 people in the noncontact dermatitis comparison cohort, with similar sex and age distributions (Table 1). The mean age was slightly higher for the contact dermatitis cohort (45.3 vs 45.1 years old). Contact dermatitis patients were more likely to have hypertension (12.8% vs 9.31%), diabetes (8.75% vs 6.03%), coronary heart disease (8.64% vs 5.99%), atrial fibrillation (0.45% vs 0.29%), and dyslipidemia (8.74% vs 6.19%). The mean duration of follow-up was shorter in the contact dermatitis cohort than in the control cohort (5.95 vs 6.15 years, P < 0.001) (data not show).

During the 9-year follow-up period, the cumulative incidence of stroke was significantly greater in the contact dermatitis cohort than in the comparisons (Log-rank test P < 0.001) (Fig. 2). The overall incidence of stroke were 5.93 and 5.37 per 1000 person-years (P < 0.01), respectively, with the crude HR of 1.10 (95% CI, 1.04–1.17) (Table 2). After adjusting for age, sex, monthly income, level of urbanization, and comorbidities including hypertension, diabetes, coronary heart diseases, atrial fibrillation and dyslipidemia, the aHR of stroke for the contact dermatitis cohort compared with the comparison cohort was 1.12 (95% CI, 1.05–1.19). The incidence rates of ischemic stroke were 5.11 and 4.60 per 1000 person-years for the contact dermatitis and comparison cohorts, respectively, with the adjusted HR of 1.12 (95% CI, 1.05–1.20) for the contact dermatitis cohort. The aHR of contact dermatitis for hemorrhagic stroke was 1.11, but was not statistically significant (95% CI, 0.94–1.30). The stroke incidence increased with age in both cohorts, and the contact dermatitis cohort to comparison cohort HR of stroke also increased with age. Men had greater incidence rates of stroke than women in both the contact dermatitis cohort (7.32 vs 4.86 per 1000 person-years) and the comparison cohort (6.86 vs 4.09 per 1000 person-years). Table 3 shows that the aHR of stroke was greater for subjects with hypertension than for subjects with contact dermatitis, with the joint effects increased slightly, to an aHR of 1.33 (95% CI, 1.26–1.41; P = 0.02). The joint effects between contact dermatitis and other comorbidities changed minorly, such as with diabetes (adjusted HR = 1.33, 95% CI, 1.25–1.40), coronary heart disease (adjusted HR = 1.32, 95% CI, 1.24–1.39), atrial fibrillation (adjusted HR = 1.31, 95% CI, 1.24–1.39), and dyslipidemia (adjusted HR = 1.32, 95% CI, 1.25–1.40).
4. Discussion

To the best of our knowledge, this study represents the first attempt to investigate the risk of stroke among patients with contact dermatitis, adjusting for patient demographic characteristics, and comorbid medical disorders.

Among the age- and sex-matched subjects, the likelihood of all strokes was 1.12-fold higher for patients with contact dermatitis during the 9-year follow-up period, after adjusting for other stroke risk factors (Table 2). The risk was significant for both male and female patients, but male patients had a higher risk of developing a subsequent stroke. In addition, the risk of stroke associated with contact dermatitis increased with age and significant in the oldest age group. This may be due to the incidence of stroke increasing with age and the influence of contact dermatitis on stroke may have been modest. However, the effect of contact dermatitis on stroke seemed to be more obvious in the elderly. The likelihood of ischemic stroke was also 1.12-fold higher among patients with contact dermatitis. There was no significant increase in the risk of hemorrhagic stroke.

Accordingly, our study found a link between contact dermatitis and subsequently all stroke and ischemic stroke, but not hemorrhagic stroke. The actual mechanisms contributing to the association between contact dermatitis and stroke are not known. We hypothesize chronic inflammation may play a role in the pathogenesis to increase the risk of ischemic stroke.[11,20]

Several studies support the associations between chronic inflammation and cardiovascular disease and type 2 diabetes. Most attentions focused on the role of inflammatory cytokines such as interleukins and tumor necrosis factor-α to increase oxidative stress, increase insulin resistance, and oxidize low density lipoproteins.[21,22] These actions, which lead to endothelial dysfunction, are all proatherogenic and may contribute to atherosclerotic plaque vulnerable to rupture and initiate a clinical cardiovascular disease event.[20,23] A recent study showed that

| Table 1 | Demographic characteristics and conventional risk factors for stroke in patients with contact dermatitis and the comparison cohort, 2000–2003 (n = 144,507). |
|---------|-----------------------------------------------------------------------------------|
| Variables | Contact dermatitis (Yes (N = 48,169)) | Contact dermatitis (No (N = 96,338)) | P |
| Age, mean, SD | 45.3 (18.2) | 45.1 (18.0) | 0.99 |
| ≤39 | 21,573 44.8 | 31,416 44.8 |
| 40–59 | 15,707 32.6 | 17,746 18.4 |
| 60–79 | 8871 18.4 | 4037 4.19 |
| >80 | 2018 4.19 |  |  |
| Gender | 26,524 55.1 | 53,048 55.1 | 0.99 |
| Male | 21,645 44.9 | 43,290 44.9 |
| Female |  |  |  |
| Hypertension | 6162 12.8 | 8968 9.3 | <0.0001 |
| Diabetes | 4215 8.7 | 5806 6.0 | <0.0001 |
| Coronary heart disease | 4163 8.5 | 5770 5.9 | <0.0001 |
| Atrial fibrillation | 215 0.45 | 279 0.29 | <0.0001 |
| Dyslipidemia | 4210 8.7 | 5966 6.1 | <0.0001 |
| Monthly income, NTD |  |  |  |
| <15,840 | 16,171 34 | 33,727 35 | <0.0001 |
| 15,841–25,000 | 21,614 44.9 | 43,809 45.5 |  |
| ≥25,001 | 10,384 21.6 | 18,802 19.5 |  |
| Urbanization level |  |  |  |
| 1 highest | 14,010 29.1 | 29,297 30.4 | <0.0001 |
| 2 | 14,288 29.7 | 27,807 28.9 |  |
| 3 | 4163 8.5 | 5770 5.9 |  |
| 4 | 215 0.45 | 279 0.29 |  |
| 5 lowest | 4210 8.7 | 5966 6.1 |  |

NTD = New Taiwan Dollar, SD = standard deviation.
P = Chi-square test, a t-test.
*The urbanization level was categorized into 5 levels based on population density, with level 1 as the most urbanized and level 5 the least urbanized.
Thus cause local and systemic inflammation. Polymorphic inflammation in both ICD and ACD are cytokines and chemokines involved, leading to misclassification such as ICD and ACD.

The immune mechanisms of both ICD and ACD are cytokines and chemokines involved, associating with apoptosis and cellular necrosis, and denoting a polymorphic inflammatory reaction. Contact dermatitis may thus cause local and systemic inflammation as well as modification of endothelial function.\cite{11} The immune mechanisms of contact dermatitis might also cause the activation of local renin-angiotensin system (RAS) in the skin. And activation of the RAS system was associated with the development of stroke and other cardiovascular disease.\cite{13–15} It is well known that risk factors for stroke include hypertension, diabetes mellitus, high cholesterol, coronary heart disease, atrial fibrillation, and so on. Patients with hypertension are particularly at an elevated risk for stroke. These factors may confound or interact with contact dermatitis for the stroke risk. However, results in Table 3 show that the stroke risk associated with contact dermatitis may be independent of these traditionally recognized risk factors. Hypertension remains the major risk for stroke. The risk of stroke increased slightly for subjects with both hypertension and contact dermatitis. As we know, data regarding cardiovascular risk among patients with contact dermatitis are still lacking. Nevertheless, stroke incidence remained higher in patients with contact dermatitis than those without contact dermatitis after adjusting for these cardiovascular risk factors.

A particular strength of the present study is the use of a population-based dataset, which enables us to trace all cases of contact dermatitis and stroke during the study period. Moreover, the large sample size affords considerable statistical power for detecting real differences between the 2 cohorts. However, this study does have some limitations.

First, patients with contact dermatitis were identified using ICD-9 codes in the claims database; coding errors might be introduced, leading to misclassification such as ICD and ACD. The proportion of ICD and ACD cases were not defined in our study. ICD is a response to irritants inducing localized inflammatory in skin because of direct cytotoxic effect of irritants. Skin lesions in ICD are limited to the contact site. In contrast, ACD is a T-cell-mediated delayed-type hypersensitivity response to repeated skin exposure to contact allergens. Skin lesions in ACD are not limited to the contact site.\cite{14} Therefore, the “inflammation burden” in ACD is more “systemic” than that in ICD. Hence, we suspect the association between ACD and stroke may be relatively stronger than that with ICD, but further studies are needed to verify this hypothesis.

Second, under the NHI program, out-of-pocket co-payments for outpatient care are very low. Nearly all acute stroke patients in Taiwan are admitted to the hospital for several days. Therefore, it was highly unlikely for patients with acute stroke not to seek medical care during this period. However, there are still patients with contact dermatitis who prefer undergoing topical steroid treatment at the local pharmacy due to the convenience, and who have not sought medical help, or have only made 1 or 2 visits to ambulatory care centers. These patients may have been enrolled in the control cohort. If contact dermatitis is a risk factor for stroke, this bias may have mildly

### Table 2

Incidence densities of stroke and the contact dermatitis cohort to comparisons cohort hazard ratios of stroke by demographic characteristics.

| Variables | Contact dermatitis | Contact dermatitis cohort to comparisons |
|-----------|--------------------|-----------------------------------------|
|           | Yes event | Stroke rate | No event | Stroke rate | cHR (95% CI) | aHR (95% CI) |
| All       | 1698 | 286,515 | 5.93 | 3183 | 592,628 | 5.37 | 1.10 (1.04, 1.17)*** | 1.12 (1.05, 1.19)*** |
| Subtype   | Ischemic | 1464 | 286,515 | 5.11 | 2729 | 592,628 | 4.6 | 1.11 (1.04, 1.18)*** | 1.12 (1.05, 1.20)*** |
| Age, y    | ≤64 | 604 | 251,643 | 2.4 | 1190 | 567,961 | 2.34 | 1.02 (0.93, 1.13) | 0.93 (0.84, 1.02) |
|           | 65–74 | 559 | 21,941 | 24.6 | 1029 | 53,050 | 19.4 | 1.26 (1.14, 1.40)*** | 1.14 (1.03, 1.27)*** |
|           | >74 | 555 | 12,931 | 42.0 | 964 | 31,617 | 30.5 | 1.39 (1.25, 1.54)*** | 1.27 (1.15, 1.42)*** |
| Gender    | Male | 908 | 124,069 | 7.32 | 1795 | 261,666 | 6.86 | 1.16 (1.06, 1.27)*** | 1.16 (1.07, 1.27)*** |
|           | Female | 790 | 162,446 | 4.86 | 1388 | 330,962 | 4.09 | 1.07 (0.98, 1.15) | 1.09 (1.00, 1.18)† |

aHR = adjusted hazard ratio; cHR = crude hazard ratio (HR); CI = confidence interval; PY = person-years.

* = Rate = incidence rate, per 1000 person-years; PY = person-years.

† Adjusted HR: multivariable analysis including age, sex, monthly income, level of urbanization and comorbidities of hypertension, diabetes, coronary heart diseases, atrial fibrillation, dyslipidemia.

P<0.05.

** P<0.01.

*** P<0.001.

The risks of cardiovascular diseases and type 2 diabetes mellitus increased across a range of organ-specific (include psoriasis and bullous skin disease) and multisystem chronic inflammatory disorders with evidence that risk is associated with severity of inflammation.\cite{11} It strongly supports the hypothesis that any source of chronic inflammation is associated with cardiovascular disease and type 2 diabetes.

Recent studies have shown that atopic dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases. The exact underlying mechanism is unknown, although the chronic inflammation has been linked to these cardiovascular events.\cite{6–11} The immune mechanisms of both ICD and ACD are cytokines and chemokines involved, associating with apoptosis and cellular necrosis, and denoting a polymorphic inflammatory reaction. Contact dermatitis may thus cause local and systemic inflammation as well as modification of endothelial function.\cite{14–27} We suspect the chronic “inflammation burden” of contact dermatitis can play a role to increase the risk of ischemic stroke, in the same manner as other dermatologic diseases mentioned above. But the exact mechanism needs further investigation. We also found that patients with contact dermatitis were more prevalent with cardiovascular risk factors. This finding has been reported is also seen in previous studies in patients with psoriasis and atopic dermatitis.\cite{28–32} We hypothesize the immune-response raised from these dermatological diseases including contact dermatitis might also cause the activation of local renin-angiotensin system (RAS) in the skin. And activation of the RAS system was associated with the development of stroke and other cardiovascular disease.\cite{13–15} It is well known that risk factors for stroke include hypertension, diabetes mellitus, high cholesterol, coronary heart disease, atrial fibrillation, and so on. Patients with hypertension are particularly at an elevated risk for stroke. These factors may confound or interact with contact dermatitis for the stroke risk. However, results in Table 3 show that the stroke risk associated with contact dermatitis may be independent of these traditionally recognized risk factors. Hypertension remains the major risk for
increased the incidence rate of stroke in the comparison cohort. Besides, the diagnosis of “contact dermatitis” may be underreported in the inpatient databases and this may underestimate the incidence of stroke in the contact dermatitis cohort. So the HR of contact dermatitis for stroke in this study may be relatively underestimated.

Third, residual confounding variables, including obesity, physical activity, smoking, and alcohol use, dietary habits, and family history, are associated with stroke, but were not included in our database. The association between contact dermatitis and these factors is unknown. Further study is suggested to clarify this issue.

Finally, as a further potential limitation, the study population mainly consisted of Taiwanese Chinese; therefore, the results may not be applicable to other ethnic groups.

5. Conclusion

We found that, over a 9-year follow-up period, the risk of both all stroke or ischemic stroke was 1.12-fold higher among patients with contact dermatitis than in the comparison cohort, and that this association was independent of any initial comorbid hypertension, diabetes, coronary heart disease, dyslipidemia, or atrial fibrillation, as well as the monthly income or level of urbanization. Hypertension acts as a significant effect modifier in the synergistic role in our study. Our study is among the first to provide evidence that contact dermatitis, the main cause of occupational dermatitis, may be a modest but significant risk factor for all stroke and ischemic stroke. Further studies should be conducted to determine whether our findings can be replicated and to explore the exact underlying pathomechanisms.

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