Increased Risk of Ischemic Stroke in Patients with Systemic Lupus Erythematosus: A Nationwide Population-based Study

Chun-Chih Chiu, Chin-Chou Huang, Wan-Leong Chan, Chia-Min Chung, Po-Hsun Huang, Shing-Jong Lin, Jaw-Wen Chen and Hsin-Bang Leu

Abstract

Background  Systemic lupus erythematosus (SLE) has been reported to be associated with an increased risk of cardiovascular disease. However, most studies have been criticized for either a small sample size or the lack of a prospective control. Our study investigated the relationship of SLE and the subsequent development of ischemic stroke using a nationwide, population-based database in an Asian population.

Methods  From 2000 to 2007, we identified a study cohort consisting of a total of 11,637 newly diagnosed SLE patients using the National Health Insurance Research Database in Taiwan. A control cohort of 58,185 subjects without SLE, matched for age, gender, and comorbidities were selected for comparison to observe the occurrence of ischemic stroke in these two groups.

Results  During a follow-up period of up to 7 years, ischemic stroke developed in 258 (2.22%) of the patients with SLE and in 873 (1.5%) of patients in the comparison cohort. Kaplan-Meier analysis also revealed a tendency of SLE patients toward ischemic stroke development (log rank test, p = 0.001). After Cox model adjustment for patients’ demographic characteristics and selected comorbidities, patients with SLE were found to have a 1.67-fold (95% CI, 1.45 to 1.91) higher risk of developing ischemic stroke.

Conclusion  Patients with SLE have an increased risk of stroke.

Key words: stroke, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder characterized by the production of autoantibodies, generation of immune complexes, and activation of the complement system (1). The clinical presentation of SLE varies widely, with periodic flare-ups of symptoms impacting multiple organ systems and resulting in potentially life-threatening complications (1-3). Recently, an association has been noted between premature atherosclerosis and this chronic inflammatory disease (3-8). Accumulating evidence has shown that atherosclerosis is not just a cholesterol storage disorder in vasculature but a sustained, dynamic and chronic inflammatory process. However, estimates of cardiovascular risk among SLE patients vary widely, and the long-term morbidity and mortality related to atherosclerotic vascular disease in SLE remain substantial (7).

Although cardiovascular events are noted to be important causes of death in patients with SLE (9), the association be-
tween ischemic stroke and SLE has not yet been well established. Also, the incidence and prevalence of SLE in Asian populations are higher than in Caucasian populations (5, 10). To date, there have been few studies investigating the relationship between SLE and stroke in Chinese people (11, 12). Therefore, we conducted a nationwide population-based study to investigate the risk of future ischemic stroke among patients with SLE in Taiwan.

Materials and Methods

Database

The National Health Insurance program in Taiwan has operated since 1995; it enrolls nearly all of the inhabitants of Taiwan (21,869,478 beneficiaries out of 22,520,776 inhabitants at the end of 2002) (13). Currently, the National Health Insurance Research Database (NHIRD) at the National Health Research Institute (NHRI) in Miaoli (Taiwan) is responsible for the complete National Health Insurance claims database and has published several dozen extracted datasets for researchers (14-16).

In this study, we used two datasets from NHRI. First, we excerpted data from SLE patients in the registry of catastrophic illness, covering the period from January 1997 to December 2007. Second, we used a cohort dataset made up of 1,000,000 randomly sampled people who were alive during 2,000 and collected all of the records on these individuals. These random samples have been confirmed by the NHRI to be representative of the Taiwanese population. In these datasets, all claims including hospital admissions or outpatient clinics for medical treatment, diagnosis procedures can be identified separately. Each patient’s original identification number has been encrypted to protect privacy. But the encryption procedure is consistent, so that the linkage of claims belonging to the same patient is feasible within the NHIRD. This study was exempt from full review by the Institutional Review Board of Taipei Veterans General Hospital, since the dataset used consisted of deidentified secondary data released to the public for research purposes.

Study population

In the SLE cohort, patients were identified from the registry of catastrophic illness. Patients with SLE were defined as those with catastrophic illness registration cards for SLE [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 710.0] after January 1, 2000. The diagnosis of SLE was established by specialists in rheumatology based on clinical manifestations and laboratory data which correlated with the American College of Rheumatology (ACR) 1997 revised criteria for SLE (1). In Taiwan, patients with SLE can apply for catastrophic illness registration cards from the Bureau of National Health Insurance. They then do not need to make co-payments when seeking health care for SLE. In order to observe the risk of developing stroke in SLE patients, subjects who have already been diagnosed to have any types of stroke (ICD-9-CM codes 430 to 438) before the diagnosed of SLE will be excluded from this study.

In the comparison cohort, subjects were selected from the cohort dataset made of 1,000,000 randomly sampled people using propensity score (17). Propensity matching was used in matching characteristics included the following: age, gender, preexisting comorbidities such as hypertension (ICD-9-CM codes 401.xx-405.xx), diabetes (250.xx), valvular heart disease (VHD) (398.9, 424.0-424.3), congestive heart failure (CHF) (428.xx), and hyperlipidemia (272.4), but SLE cases were selected.

Stroke event measurement

The stroke event was identified according to by any one of the following conditions: 1) hospitalization claims, or 2) more than 3 consecutive outpatient visits to hospitals; followed either by claims for various neurological imaging technology (computed tomography, MRI, transcranial or carotid Doppler sonography) and long-term prescriptions used for ischemic stroke, or 3) by claims for rehabilitation and long-term ischemic stroke prescriptions. The sensitivity and specificity for ischemic stroke identification were 100% and 95%, respectively (18), and similar definition of stroke and more details have been described in our previous studies (19). The identification of stroke using insurance claim was valid and used in a similar study.

Statistical analysis

The Microsoft SQL Server 2005 was used for data management and computing. Statistical analysis was performed utilizing SPSS software (Version 15.0, SPSS Inc., Chicago, Illinois, USA). All data were expressed as the frequency (percentage) for ordinal and categorical data or mean ± standard deviation (SD) for continuous data. The continuous data between the study group and comparison group were compared by Student’s t-test. The categorical data between them were compared with Chi-square test and Yates’ correction or Fisher’s exact test as appropriate. Ischemic stroke-free survival analysis was assessed using Kaplan-Meier analysis, with the significance based on the log-rank test. Multiple regression analysis was carried out using Cox proportional hazards regression analysis. Statistical significance was inferred at a two-sided p value of <0.05.

Results

The distributions of demographic characteristics and selected comorbid medical disorders for these 2 cohorts are presented in Table 1. The mean age of patients with SLE was 40.9 ± 15.3 years. Most (88.57%) of the sampled patients were female and the prevalence of comorbidities such as cardiovascular risk factors were similar between the SLE and control groups. The median follow-up period and interquartile range of the SLE group were 3.849 (1.836-5.978)
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SLE (n= 11,637)</th>
<th>Control (n= 58,185)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.9 ± 15.3</td>
<td>40.9 ± 15.3</td>
<td>0.825</td>
</tr>
<tr>
<td>Male</td>
<td>1,330 (11.43%)</td>
<td>6,650 (11.43%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>518 (4.45%)</td>
<td>2,606 (4.48%)</td>
<td>0.896</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>204 (1.75%)</td>
<td>1,007 (1.73%)</td>
<td>0.866</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>40 (0.34%)</td>
<td>217 (0.37%)</td>
<td>0.635</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>51 (0.44%)</td>
<td>221 (0.38%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>109 (0.94%)</td>
<td>556 (0.96%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Stroke</td>
<td>258 (2.22%)</td>
<td>873 (1.50%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus

Table 2. Independent Predictors of Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>(1.06 - 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.22</td>
<td>(1.05 - 1.42)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.88</td>
<td>(1.57 - 2.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.44</td>
<td>(1.10 - 1.89)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.47</td>
<td>(0.99 - 2.18)</td>
<td>0.053</td>
</tr>
<tr>
<td>SLE</td>
<td>1.67</td>
<td>(1.45 - 1.91)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus.

Discussion

Although premature atherosclerosis associated with SLE is well recognized (3-9), evidence of the association between SLE and ischemic stroke, especially in Asian populations, is still scarce (11, 12). The current study demonstrated that the risk of developing future ischemic stroke is significantly increased among patients with SLE after adjusting for possible confounding factors. To our knowledge, this is the largest prospective, population-based study to investigate the risk of ischemic stroke among SLE patients in an Asian population.

SLE may involve multiple organs, and vascular events including ischemic stroke, however, acute myocardial infarction and peripheral arterial occlusive disease are not uncommon (3-8). Additionally, there are few studies which have compared the risk of developing future ischemic stroke in SLE with that of the general population among Caucasians (9, 20-23). In a large prospective cohort study over 28 years of follow-up in America, the relative risk of developing stroke in SLE patients was 2.29 times greater than for non-SLE patients (9). In a hospital discharge database study, Krishnan reported that patients with SLE had 2.04 times the risk of hospitalization because of stroke event than non-SLE patients (24). Mok et al reported that the mean standardized incidence ratio of all types of stroke in SLE patients was 2.02 in a longitudinal cohort study in an Asian population (11), suggesting that SLE is associated with an increased risk of developing ischemic stroke. However, most studies have been criticized for either a small sample size or the lack of a prospective control. In Taiwan, Yu et al reported that 9.6% of pediatric SLE patients may develop stroke event in 10 years (12). The current study using na-
tionwide population-based datasets linking the NHIRD with catastrophic illness card in our cohort study left little room for selection and non-response biases. The large sample size in this study provided adequate statistical power to detect differences in the risk of stroke comparing the patients with and without SLE. Our results demonstrate that SLE was associated with a higher stroke risk, further supporting the connection of SLE and ischemic stroke in the Chinese population.

The pathogenesis of stroke in SLE may be multifactorial and it still generates a lot of discussions and many research efforts. Elevated blood viscosity, autoantibodies, raised homocysteine concentrations and genetic polymorphism may play roles in the development of the disease. Selective elevated whole blood viscosity has been reported in patients with SLE with a history of arterial thrombotic events (25). Antiphospholipid antibodies, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β2-glycoprotein-1 (anti-β2-GP1) antibodies, are associated with an increased risk of arterial and venous thromboembolism, including stroke (26, 27). The antiphospholipid antibody syndrome (APS) is a prothrombotic condition characterized by the presence of these antibodies (28, 29). APS may exist in its primary form, but it may coexist with other conditions, especially with SLE (30). It may increase the incidence of stroke. Additionally, several genetic polymorphisms were also demonstrated in patients with SLE and vascular events. The CRP GT20 variant is more likely to occur in African-American and Hispanic SLE patients than in Caucasian patients, and patients with SLE carrying the GT20 allele are more likely to develop vascular arterial events (31). Another genetic study found that deficient mannose-binding lectin 1 polymorphisms were associated with stroke in patients with SLE but not with other vascular events (32). Raised homocysteine concentrations were observed in patients with SLE (33).

Potential limitations of this study merit discussion. First, the diagnosis of SLE and stroke were identified using the ICD-9 code from the database. Personal information such as body weight, smoking habit and biochemistry profiles were not available. This study was conducted with NHII database, in which the diagnosis was supposed to be confirmed clinically by the individual physicians in charge. In addition, the NHIRD lacks clinical information and therefore did not allow us to differentiate study participants according to the severity of their SLE and stroke. Second, stroke event could be established and identified only if there were also any one of the following conditions: 1) hospitalization claims, or 2) more than 3 consecutive outpatient visits to hospitals; followed either by claims for various neurological imaging technology (computed tomography, MRI, transcranial or carotid Doppler sonography) and long-term prescriptions used for ischemic stroke, or 3) by claims for rehabilitation and the long-term ischemic stroke prescriptions. We had previously defined the sensitivity (100%) and specificity (95%) for identifying the event of ischemic stroke with the above approach in another cohort study (18, 19). However, we could not completely exclude the possibility of misdiagnosis as institutions treating the patients later after stroke often just carry the initial diagnosis forward. It is one of the major imitations in this type of study with the NIH database. Third, the medication for SLE may also have effects on the outcomes. The SLE database was categorized as another separate registry of catastrophic illness. Although we can obtain the subsequent events for those patients from the database, we can not get the information of medications due to limitation of the database for this registry of catastrophic illness.

**Conclusion**

This nationwide cohort study found that SLE patients in Taiwan have an increased risk of developing ischemic stroke in the future. More aggressive primary and secondary prevention strategies are needed for this patient population. Further studies are needed to determine whether treating risk factors in these patients may substantially decrease the incidence of ischemic stroke.

**The authors state that they have no Conflict of Interest (COI).**

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**References**