Features of Acute Ischemic Stroke With Rheumatic Heart Disease in a Hospitalized Chinese Population

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Background and Purpose—Rheumatic heart disease (RHD) is an important risk factor for ischemic stroke in developing countries. Observational data on its characteristics and influence on outcome or recurrence of ischemic stroke are scarce. We aimed to investigate proportions, characteristics, functional outcome, and recurrence of acute ischemic stroke patients with RHD in a hospitalized Chinese population.

Methods—We prospectively enrolled consecutive patients with acute ischemic stroke who were admitted within 1 month of stroke onset from January 2003 to February 2007, into the analysis. Clinical characteristics such as age, gender, risk factors, and National Institutes of Health Stroke Scale on admission were investigated. Basic characteristics, functional outcomes, and recurrence were compared between RHD group and non-RHD group.

Results—Of the 1638 cases included, RHD was present in 130 patients (7.9%). RHD patients, compared with those without RHD, were younger, more frequently female, and more often had experienced atrial fibrillation and higher National Institutes of Health Stroke Scale score on admission (all \(P\leq0.006\)). After adjustment for age, sex, and National Institutes of Health Stroke Scale on admission, the death risk in patients with RHD was 2.0-fold higher at 3 months, 6 months, and 1 year compared with patients without RHD (all \(P\leq0.013\)). Compared with patients without RHD, those with RHD showed a significantly higher cumulative recurrence rate (13.6% vs 6.0%; \(P=0.001\), log rank test) by 1-year cumulative recurrent curves.

Conclusions—Stroke attributable to RHD is still common in the Chinese population. RHD was associated with 2-fold increased risk of death and 1-fold increased risk of recurrence in stroke patients. (Stroke. 2012;43:00-00.)

Key Words: death ■ disability ■ recurrence ■ rheumatic heart disease ■ stroke

Currently, China has a higher relative stroke burden overall with higher relative mortality. Stroke in China has increased to the first most common cause of death, whereas it is still the second most common cause of death and major cause of disability in the world. In Chinese population, stroke burden is also disproportionately higher compared with ischemic heart disease, and the mortality rate from stroke is 3-times than that from coronary heart disease. Therefore, China may require distinct strategies for stroke prevention and intervention.

Rheumatic heart disease (RHD) is an important risk factor for ischemic stroke in developing countries where 3% to 7.5% of all strokes have been estimated to be directly attributable to RHD, with 144 000 to 360 000 strokes and 108 000 to 269 000 stroke deaths caused by RHD each year. These data show RHD is of sufficiently important cause of stroke to warrant the attention. Worldwide, it is estimated that 15 to 20 million people have RHD and at least 282 000 people will have development of RHD each year. Although the incidence of rheumatic fever and RHD has significantly declined in most developed countries, clinical consequences of RHD still may be increasing and RHD is an ongoing problem. In China, the prevalence of RHD was 186 out of 100 000 adults and 10-times higher than the prevalence in industrialized countries such as Canada (0.22/1000) and Japan (0.14/1000). Hence, because the burden of RHD is so high in China, it is crucial to understand clinical profile of patients with RHD-related stroke for better-designing distinctive prevention and treatment strategies in China. Unfortunately, detailed information on this issue is scarce and there has been no recent attempt to collate such information. Therefore, it is of great value to provide large epidemiological data for patients who have experienced an ischemic stroke in the presence of RHD regarding long-term risk of stroke outcome.

We aimed to evaluate proportions, characteristics, and long-term outcomes and recurrence of ischemic stroke in patients with RHD in a hospitalized Chinese population.

Subjects and Methods

Study Design
This study was conducted using prospective data from the Chengdu Stroke Registry. This registry project was approved by the Scientific
Research Department of West China hospital, which conformed to the local ethical criteria for research. Patients with either first-ever or recurrent stroke were registered consecutively after they were admitted to the ward of the Neurology Department, West China Hospital of Sichuan University, starting from March 1, 2002. All patients had a clinical diagnosis of stroke according to World Health Organization criteria, further confirmed by computed tomography or magnetic resonance imaging scan. Details of patient demographics, time of stroke onset, stroke severity on admission, risk factors, diagnostic tests, neurological imaging, treatments administered, and stroke-related complications during hospitalization were recorded at the time of assessment using a standardized structured form. Patients were followed-up at 3 months, 6 months, and 1 year after stroke onset by telephone interviews or letter inquiries. Details of the Chengdu Stroke Registry have been described previously. In the present study, we included patients admitted within 1 month after stroke onset from January 2003 to February 2007. Patients who refused to participate in the registry and refused to be followed up were excluded.

**Definition of Collected Data and Outcome**

RHD was diagnosed according to International Classification of Diseases, 10th edition, criteria and further confirmed by echocardiography. Atrial fibrillation (AF) was defined as a history of persistent AF or paroxysmal AF, supported by past ECG or diagnosed by the attending physicians based on ECG and/or 24-hour ECG monitoring during admission. Other vascular risk factors surveyed in this study included hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, previous transient ischemic attack, history of stroke, and current smoking and alcohol consumption, which have been described in previous reports. Stroke severity on admission was estimated by Kaplan–Meier product limit method and log rank tests were performed for comparison between groups for significant difference. Two-sided values of P<0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 16.

**Results**

**Baseline Characteristics**

A total of 1638 patients with ischemic stroke were enrolled in this study, with 40.5% being female and mean age of 64.9±13.0 years. One-hundred thirty patients (7.9%) had RHD, of which 14.6% cases were undiagnosed before stroke. In the RHD group, 41 (31.5%) were men and 89 (68.5%) were women and mean age at stroke onset was 57.9±12.9 years; 81.5% (106/130) of patients had AF diagnosed at discharge. Of them, only 61.3% (65/106) already had AF diagnosed before stroke onset; 7.7% (10/130) patients had received valve replacement surgery and oral anticoagulants before stroke.

Baseline characteristics of stroke patients with or without RHD are shown in Table 1. As compared with patients without RHD, patients with RHD were younger (57.9 vs 65.5 years; P<0.001), more often females (68.5% vs 38.1%; P<0.001), and had a higher median NIHSS score on admission (11 vs 4; P<0.001). Regarding vascular risk factors, patients with RHD had a significantly higher proportion of AF (81.5% vs 8.6%; P<0.001) and a significantly lower proportion of hypertension (16.2% vs 52.3%; P<0.001), diabetes (4.6% vs 16.1%; P<0.001), alcohol consumption (9.2% vs 19.0%; P=0.006), and current smoking (14.6% vs 29.4%; P<0.001) compared with patients without RHD.

**Table 1. Baseline Characteristics of Ischemic Stroke Patients With and Without Rheumatic Heart Disease**

<table>
<thead>
<tr>
<th></th>
<th>With RHD (n=130)</th>
<th>Without RHD (n=1508)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>57.9 (12.9)</td>
<td>65.5 (12.9)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>89 (68.5)</td>
<td>574 (38.1)</td>
<td>&lt;0.001*</td>
<td>3.532 (2.405–5.187)</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (16.2)</td>
<td>788 (52.3)</td>
<td>&lt;0.001*</td>
<td>0.176 (0.109–0.284)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (4.6)</td>
<td>243 (16.1)</td>
<td>&lt;0.001*</td>
<td>0.252 (0.110–0.578)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (3.1)</td>
<td>84 (5.6)</td>
<td>0.226†</td>
<td>0.538 (0.194–1.492)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5 (3.8)</td>
<td>94 (6.2)</td>
<td>0.273†</td>
<td>0.602 (0.240–1.507)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>106 (81.5)</td>
<td>129 (8.6)</td>
<td>&lt;0.001*</td>
<td>47.214 (29.262–76.179)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>19 (14.6)</td>
<td>443 (29.4)</td>
<td>&lt;0.001*</td>
<td>0.412 (0.250–0.670)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>12 (9.2)</td>
<td>287 (19.0)</td>
<td>0.006*</td>
<td>0.433 (0.236–0.794)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>1 (0.8)</td>
<td>36 (2.4)</td>
<td>0.358†</td>
<td>0.317 (0.043–2.331)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>15 (11.5)</td>
<td>132 (8.8)</td>
<td>0.286*</td>
<td>1.360 (0.771–2.397)</td>
</tr>
</tbody>
</table>

Stroke severity on admission

| NIHSS score, median | 11       | 4        | <0.001‡ |

*CI indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RHD, rheumatic heart disease; SD, standard deviation; TIA, transient ischemic attack.

†Mann–Whitney test.

‡Fisher exact test.

**Statistical Analysis**

The χ² or Fisher exact tests were used to compare categorical variables. Analysis of variance or Mann–Whitney U tests were used to compare continuous variables when appropriate. Binary logistic regression model was used to evaluate the association between RHD and outcomes. One-year cumulative survival and recurrence rates were estimated by Kaplan–Meier product limit method and log rank tests were performed for comparison between groups for significant difference. Two-sided values of P<0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 16.
Outcomes at the End of 3-Month, 6-Month, and 1-Year Follow-Up

As shown in Table 2, in patients with RHD the 3-month death rate was 23.1%, the 6-month death rate was 27.1%, and the 1-year death rate was 31.4%. The death rates in patients with RHD were significantly higher than that in patients without RHD at the end of 3-month, 6-month, and 1-year follow-up (P<0.001). After adjustment for age, sex, and NIHSS score on admission, the death risk in patients with RHD was 2.0-fold (95% confidence interval [CI], 1.155–3.487; P=0.013) higher at 3 months, 2.1-fold (95% CI, 1.242–3.601; P=0.006) higher at 6 months, and 2.0-fold higher (95% CI, 1.184–3.388; P=0.010) at 1 year compared with patients without RHD. One-year survival curves demonstrated a significantly lower cumulative survival rate for patients with RHD compared with patients without RHD (68.6% vs 85.2%; P<0.001, log rank test; Figure 1).

Patients with RHD had a significantly higher proportion of disability (modified Rankin Scale score, 3–5) at the end of 3-month and 6-month follow-up than patients without RHD (47.0% vs 33.4%, P=0.006 and 37.2% vs 27.6%, P=0.045; Table 2). However, there was no significant difference at the end of 1-year follow-up. After adjusting for age, sex, and NIHSS score on admission, there was no significant difference at 3 months (95% CI, 0.554–1.685; P=0.904) and 6 months (95% CI 0.482–1.534; P=0.609).

Regarding the composite outcomes (death and disability rate), patients with RHD had a higher proportion of poor outcomes compared with patients without RHD at the end of 3-month, 6-month, and 1-year follow-up, and there were significantly statistical differences (P<0.001; Table 2). However, after adjusting for age, sex, and NIHSS score on admission, there was no significant difference at 3 months (95% CI, 0.612–1.725;
Recurrence During Follow-Up

During the entire follow-up period after stroke onset, 11.4% of patients (187/1638) were lost to follow-up at the end of 1 year but they had at least a 3-month follow-up assessment. At the end of 1 year, 96 patients (6.6%) had development of recurrent stroke. Of them, 4 patients had intracerebral hemorrhagic stroke, 1 case was unclear, and the remaining 91 patients had ischemic stroke. Figure 2 shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for patients with RHD and without RHD. The 1-year curves demonstrated a significantly higher cumulative recurrence rate for patients with RHD compared with patients without RHD (13.6% vs 6.0%; \( P=0.001 \), log rank test).

Discussion

Although RHD is still a significant health problem in developing countries, little information on epidemiology of stroke in patients with RHD is currently available. In the present study, we investigated the features of acute ischemic stroke patients with RHD in a hospitalized Chinese population and observed that stroke attributable to RHD was common and it affected a younger population and caused more severity on admission. Moreover, RHD was associated with a 2.0-fold increased risk of death in stroke patients even after adjustment for age, sex, and NIHSS score on admission and was associated with \( \approx 1.0 \)-fold increased risk of recurrence. These findings emphasized the necessity of better management strategies to reduce the RHD-related stroke risk and mortality in China.

We found the proportion of RHD in ischemic stroke patients to be 7.9%, which is similar to that reported in a systematic review we have recently published. According to data mostly derived before 2000, the proportion of RHD in patients with ischemic stroke ranged from 3.4% to 23.2% in Asia. Therefore, we speculated that stroke burden attributable to RHD still may have not declined. This also could be supported by a community population-based study on prevalence of RHD in China, which showed that the approximate prevalence of RHD was 186 out of 100,000 adults and no down trend was shown. Therefore, our data support that stroke associated with RHD continues to be a common health problem in China.

Interestingly, similarly to what is often observed with AF, delayed diagnosis of RHD and underuse of anticoagulants were found in RHD patients before the index stroke onset. The previous population-based investigation for prevalence of RHD in China supported our results, which found 6 of 15 cases were underdiagnosed. One possible explanation is that improvement in health care resulted in these subjects having their rheumatic fever treated earlier, which could have resulted in silent and/or less severe symptoms during the chronic phase and, moreover, these patients were reluctant to receive echocardiography because of poverty. In addition, there were 2 possible reasons for not receiving oral anticoagulants. First, less severe symptoms and the difficulty and high economic burden in monitoring and adjusting international normalized ratio were the main barriers. Second, doctors might not give enough attention to the importance of prescribing oral anticoagulants in patients with RHD. These data point out that many potentially preventable strokes occur every year in China because of the delayed diagnosis and underuse of anticoagulants therapy. Hence, better diagnosis and management of RHD may greatly reduce the impact on the individual health and decrease the stroke burden to society in terms of medical and social care resources.

Another finding arising from our study is the high 1-year death rate of stroke patients with RHD (31.4%). It was much higher than that reported by 1 previous study in Thailand, which showed the death rate for RHD-related stroke at 18 months after diagnosis was 16.7%. This might be partly

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Figure 2. Kaplan–Meier estimates of cumulative recurrence rates of stroke for all patients divided by rheumatic heart disease (RHD; with RHD vs without RHD, \( P=0.001 \), log rank test).
explained by chance because of hospital-based studies and different participants’ enrolled criteria. Whether there are real differences between Asian countries is unclear and warrants further investigation. According to our previous systematic review, in Asia in the past 3 decades, overall, the death rate for RHD-related stroke ranged from 8.5% to 47.4%. Our study confirmed poor prognosis in stroke patients with RHD. Despite the fact that there are few studies specifically focused on stroke recurrence in RHD patients, there are many studies that have investigated recurrence rates in the general stroke population. According to a systematic review conducted by Mohan et al., the pooled cumulative risk of stroke recurrence after first-ever stroke was 11.1% at 1-year follow-up. Compared with that study, our cumulative recurrence was a little lower. This may be explained by methodological differences such as differing definitions of recurrence and variations in inclusion criteria. In addition, unfortunately, we cannot clarify the relationship between secondary prevention therapy and stroke recurrence because of less detailed data on the ongoing treatments during follow-up periods, which are now observed in another ongoing cohort study. However, no matter whether the specific number is high or low, we confirmed that RHD was associated with 1.0-fold increased risk of recurrence.

The limitation of our study was that it was a hospital-based study, which might not reflect the information from community in the local area. Some stroke patients might not be hospitalized, especially those whose symptoms were mild or who died before being admitted to hospital. We cannot exclude inclusion bias in this study. Another limitation was that follow-up was not in person, only by telephone interview or letter, which might cause some bias. However, in large studies in which face-to-face assessment of modified Rankin Scale score is impractical, follow-up by telephone interview or letter can achieve higher levels of follow-up and good reliability with least risk of bias. Despite these limitations, this probably is one of the first prospective studies with a large sample size to investigate the features of acute ischemic stroke patients with RHD.

In conclusion, our study provides important new information regarding features of stroke with RHD in China. We found that stroke associated with RHD is common in a hospitalized Chinese population and has a poor prognosis in terms of death and recurrence. Prevention and care of stroke with RHD are still major challenges for Chinese health systems, which need implementation of distinct treatment and management strategies.

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Disclosures
None.

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