Increased Risk of Stroke After Adhesive Capsulitis
A Population-Based Study

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Background and Purpose—No previous study has described the association between stroke and previous adhesive capsulitis (AC). This study aims to investigate the risk of stroke after AC with a population-based database.

Method—Records for 10 935 with a principal diagnosis of AC and 32 805 randomly selected controls were collected between 2000 and 2003. The log-rank test was performed to analyze the differences in accumulated stroke-free survival rates between the 2 groups. Cox proportional hazard regressions were performed to calculate the longitudinal hazard of stroke.

Results—During the follow-up period, 575 patients from the study group (5.3%) and 1201 from the comparison group (3.7%) had strokes. The crude hazard ratio for stroke for patients with AC was 1.46-times greater than for controls (95% CI, 1.32–1.62; \( P<0.001 \)), and the adjusted hazard ratio was 1.22 (95% CI, 1.06–1.40; \( P=0.002 \)).

Conclusions—Our study demonstrates increased prevalence and risk of stroke after AC. Further study is needed to confirm our findings and explore underlying mechanisms. (Stroke. 2010;41:1044-1047.)

Key Words: adhesive capsulitis • shoulder • stroke

Adhesive capsulitis (AC) is a relatively common musculoskeletal disease manifesting as chronic pain and progressive stiffness of the shoulder.\(^1,2\) The pathomechanism of AC is still unclear. Regional inflammatory and fibrotic change over the capsule of the glenohumeral joint can be recognized in pathological examination.\(^1\) Although AC is considered as a self-limiting condition, a disease course lasting for 1 to 2 years is not uncommon.\(^1,2\) Several systemic comorbid diseases, such as thyroid disease, hyperlipidemia, and diabetes mellitus, are noted to be associated with increasing risk for AC.\(^3,4\)

Clinical observation drew our attention to this issue. We noted several of the patients in our practice had strokes after AC. We did not know if these cases we observed were fortuitous or associated events. Development of shoulder stiffness over the affected side is not an uncommon condition among stroke patients. Nevertheless, to our knowledge, there is no previous literature describing the risk of stroke after AC. This population-based study aims to investigate the risk of stroke after AC.

Materials and Methods
We used the Longitudinal Health Insurance Database released by the Taiwan National Health Research Institute in 2006. The Longitudinal Health Insurance Database contains all medical claims data for 1 000 000 beneficiaries randomly sampled from all enrollees (\( n=25.68 \) million) in the National Health Insurance program. Because the Longitudinal Health Insurance Database consists of de-identified secondary data released to the public for research purposes, after consulting the chairman of the Institutional Review Board of Taipei Medical University, this study was exempt from full review by the Institutional Review Board.

In total, 12 760 patients with a principal diagnosis of AC of the shoulder (ICD-9-CM code 726.0) between 2000 and 2003 were selected. We excluded patients with AC diagnosed before 2000 (\( n=330 \)). Their first ambulatory care visits with a principal diagnosis of AC were assigned as the index visit. We also excluded patients who had any type of stroke (ICD-9-CM codes 430–438) before their index visit (\( n=20 \)) or had diagnoses of systemic rheumatologic disorder, fracture of upper extremities, shoulder dislocation, or operation over proximal upper extremities within 1 year before the index visit (\( n=230 \), and who were younger than 40 years old (\( n=1245 \)). In total, 10 935 patients with AC were included in the study group.

The comparison group was extracted from the remaining beneficiaries in the Longitudinal Health Insurance Database. We excluded patients who were younger than 40 years old and who had a history of stroke before 2000. We also excluded those patients who visited ambulatory care centers with a nonprincipal diagnosis of adhesive capsulitis of the shoulder between 2000 and 2006. A total of 32 805 (3 for every patient with adhesive capsulitis of the shoulder) out of 298 120 enrollees were randomly selected from the remaining beneficiaries using the SAS program. We assigned their first ambulatory care visits occurring in 2000 as their index visit. Each patient was individually traced for 3 years to identify those who subsequently received diagnosis of stroke (ICD-9-CM codes 430–437).

We used the SAS statistical package (version 8.2, SAS System for Windows; SAS Institute Inc) to perform statistical analyses. Pearson \( \chi^2 \) tests and \( t \) tests were conducted to examine the differences in sociodemographic characteristics, including age, gender, monthly income, level of urbanization, and the geographical location (North-
ern, Central, Eastern, and Southern Taiwan; please see Supplemental Figure II, available online at https://stroke.ahajournals.org) of the community where the patient resided for the study and comparison groups. Monthly income was categorized into 4 groups: 0; New Taiwan (NT) $1–NT $15 840; NT $15, 841–NT $25 000; and ≥NTS 25 001 (US $1.00=NT $33.00 in 2003).

The Kaplan–Meier method was used for univariate analyses to examine survival times of baseline variables at time 0.6 The log-rank test was performed to test the differences in cumulative stroke-free survival rates between 2 groups.6 Cox proportional hazard regression was performed to calculate the longitudinal hazard ratio (HR) of stroke.7,8 after adjusting for patient’s basic variables, comorbidities, and the interaction terms of AC by gender and AC by age. The alpha level was set as P<0.05.

Results

Table 1 presents the differences in variables between the 2 groups. Compared to controls, patients with AC were significantly more likely to be female, have low income, reside in less urbanized areas and in the northern part of Taiwan, and to have comorbid hypertension, coronary heart disease, diabetes, and hyperlipidemia.

The survival times for these 2 groups by Kaplan–Meier survival analysis are displayed in supplemental Figure I, available online at http://stroke.ahajournals.org. The distribution and the crude and adjusted HR of stroke during the follow-up period are presented in Table 2. During the follow-up period, 575 patients in the study group (5.3%) and 1201 in the comparison group (3.7%) had strokes. There was a significant difference in stroke-free survival rates between the 2 groups (P<0.001). The crude HR for stroke for patients with AC is 1.46 (95% CI, 1.32–1.62; P<0.001) and the adjusted HR was 1.22 (95% CI, 1.06–1.40; P=0.002).

We further analyzed the hazard of stroke between these 2 groups by stroke type. Of the total sample of 1776 strokes, 341 (19.2%), 1053 (59.3%), and 382 (21.5%) were classified as hemorrhagic stroke, ischemic stroke, and other types of stroke, respectively. We found that the adjusted HR for ischemic stroke for patients with AC of the shoulder is 1.34 (95% CI, 1.11–1.62; P=0.002) as compared to patients in the comparison group, but we found no significant difference between patients with AC and patients in the comparison group in the hazard of hemorrhagic stroke and other types of stroke (not shown in Table).

Table 3 presents the crude and adjusted HR for stroke stratified by patient gender and age. The adjusted HR for stroke for female AC patients was 1.30 (95% CI, 1.11–1.51; P=0.005). However, there was no significant difference between the 2 groups regarding the hazard of stroke among male patients. Compared to controls, the adjusted HR of stroke was 1.39 (95% CI, 1.19–1.61; P=0.031) for AC patients younger than 65 years old and 1.17 (95% CI, 1.01–1.36; P=0.043) for AC patients age 65 years or older.

Discussion

Interestingly, we find the increased risk for stroke after AC compared to the controls was significant, even after adjusting for common cerebrovascular risk factors. The prevalence of AC is estimated at ≈2% in the general population.1 The population affected by AC is massive and thus the association between stroke and previous AC should not be overlooked. We suggest that this association be investigated through a long-term prospective study.

That AC would directly cause the development of stroke is not likely. We hypothesize some mechanisms to explain our findings. First, shared common factors, such as genetic background or underlying conditions, could contribute to development of both diseases. Furthermore, the pain in AC patients is usually severe, particularly in the initial inflammatory stage, which can last for several weeks or a few...
The symptoms of AC induce considerable emotional distress, sleep deprivation, and physical inactivity, all potentially detrimental to cardiovascular systems. Finally, nonsteroidal antiinflammatory drugs and steroids are usually prescribed to control the symptoms. These medications can theoretically contribute to increased cardiovascular risk.

**Conclusion**

There are several limitations to our study. First, the validity of AC diagnoses is difficult to determine from a nationwide registry. Although arthrogram and arthroscopy are considered the gold standard diagnostic tools for AC, in a general practice the majority of patients do not receive the diagnosis of AC via these invasive procedures. Most AC cases can still be diagnosed with good agreement through detailed history taking and physical examination. The prevalence of AC in our study is consistent with previous observations. Therefore, we believe that the data quality is acceptable for analyzing the issue. Second, the onset of AC is usually insidious. The starting points in our cohort are heterogeneous and the risk for stroke during follow-up could be misestimated. Third, our study was unable to link with the Taiwan death certificate database to ascertain mortality, because of the nature of the de-identified secondary data. Almost all stroke cases, regardless of whether the patient survived or died, would be recorded in our database. However, it is worth noting the left-censored bias attributable to the possibility that death could be disproportional between the 2 groups. Finally, data on some variables, such as smoking, dietary habits, body mass index, alcohol intake, and physical activity, which might contribute to stroke, are not available in this database, which may compromise our findings.

**Disclosures**

This study is based in part on data from the National Health Research Institute provided by the Bureau of National Health Insurance, Department of Health, Taiwan, and managed by the National Health Research Institutes. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance.
Insurance, Department of Health, or the National Health Research Institutes.

References

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