Impact of Sex Difference on Severity and Functional Outcome in Patients with Cardioembolic Stroke

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Introduction: Female sex is a risk factor for thromboembolic events in Caucasian, but not in Japanese, patients with nonvalvular atrial fibrillation. However, it remains unclear whether the female sex is also a risk factor for severe stroke and unfavorable functional outcome in patients with cardioembolic (CE) stroke. *Methods:* Three hundred fifty-five consecutive patients with CE stroke within 48 hours after onset and with a modified Rankin Scale (mRS) score of 1 or lower before onset were studied. We compared basic characteristics, stroke severity, and functional outcome between female (n = 157) and male (n = 198) patients. *Results:* The mean age was higher in female than in male patients (80 ± 8 versus 75 ± 9 years, $P < .00001$). The congestive heart failure, hypertension, age [≥ 75 years], diabetes, stroke/transient ischemic attack [TIA] ($CHADS_2$) score before onset was similar between the two groups (median, 3 [2-4] in both groups). Stroke severity on admission, assessed by the National Institutes of Health Stroke Scale (NIHSS), was higher in female than in male patients (13 [5-20] versus 8 [3-16], $P = .0009$). Functional outcome at discharge, assessed by mRS, was unfavorable in female than in male patients (3 [1-5] versus 2 [1-4], $P = .005$). An mRS score of 3 or higher at discharge was found more in female than in male patients (59% versus 39%, $P = .0001$). Multivariate analyses confirmed that female sex was a significant determinant of severe stroke (NIHSS ≥ 8) on admission (odds ratio [OR] to male = 1.97; 95%

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confidence interval [CI]; 1.24-3.15, $P = .004$) and for the mRS score of 3 or higher at discharge (OR = 1.83; 95% CI, 1.16-2.89; $P = .01$). Similar results were obtained by propensity-score matching analysis. *Conclusions:* Female sex is a risk factor for severe stroke on admission and unfavorable functional outcome at discharge in Japanese patients with CE stroke. **Key Words:** Female sex—cardioembolic stroke—stroke severity—functional outcome.

Introduction

Female sex is a risk factor for thromboembolic events in patients of the Caucasian population with nonvalvular atrial fibrillation (NVAF).[1] Accordingly, recent European and American guidelines recommend the congestive heart failure, hypertension, age [>75 years], diabetes, stroke/TIA, vascular disease, age [65-74 years], sex category [female] (CHA_2DS_2-VASc) score for thromboembolic risk stratification in patients with NVAF, which includes female sex (Sc) as a risk factor.[2,3] In contrast, female sex is not a risk factor for thromboembolic events in Japanese patients with NVAF.[4] More importantly, when cardioembolic (CE) stroke occurs in patients with NVAF, it is still uncertain whether female sex is also a significant risk factor for severe stroke and unfavorable functional outcome. In the present study, we assessed this critical issue in Japanese patients with CE stroke.

Materials and Methods

Study Patients

Hirosaki Stroke and Rehabilitation Center (HSRC) has both a stroke care unit for acute therapy and a stroke rehabilitation unit for further rehabilitation therapy. Accordingly, all patients with acute ischemic stroke admitted to HSRC receive consistent therapies in the acute phase and subsequently in the chronic phase during hospitalization.

During a 3-year period from April 2011 to March 2014, a total of 516 consecutive patients with CE stroke were admitted to the HSRC for acute therapy within 7 days after the onset. Of them, 355 patients with CE stroke admitted to the HSRC within 48 hours after onset and with a modified Rankin Scale (mRS) score of 0 or 1 before onset were included in the present study. Clinical characteristics, stroke severity on admission, and functional outcome at discharge were compared between female (n = 157) and male (n = 198) patients. This study was approved by the ethics committees of the HSRC and the Hirosaki University Graduate School of Medicine.

Diagnosis, Stroke Severity, and Outcome

All patients underwent brain computed tomography on admission. When intracerebral hemorrhage was not detected, we further performed brain magnetic resonance imaging including transversal diffusion weighted image, T2-weighted image, fluid-attenuated inversion recovery, and magnetic resonance angiography (Signa Excite HD 1.5T; GE Medical Systems, Waukesha, WI). Carotid ultrasonography, chest X-ray, 12-lead electrocardiogram, and standard blood test were performed on all patients. For required cases, 24-hour Holter electrocardiogram and transesophageal echocardiography were also performed. CE stroke was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment classification.[5]

Thrombolysis therapy with intravenous recombinant tissue plasminogen activator (rt-PA) was performed according to the Japanese Guideline.[6] Treatment with oral anticoagulants (OACs) before onset was also assessed. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score on admission. Severe stroke was defined by an NIHSS score of 8 or higher.[7] The mRS score at discharge was evaluated for functional outcome. The $CHADS_2$ and CHA_2DS_2-VASc scores for risk stratification of thromboembolism before onset were determined in each patient, as previously described.[2,8] Risk factors were determined as follows: congestive heart failure (left ventricular ejection fraction <40%, New York Heart Association class II or higher heart failure symptoms within 6 months before stroke onset), hypertension (treatment with antihypertensive medication or documented systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), diabetes mellitus (treatment with insulin or antidiabetic medication, or at least 2 determinations of diabetic type on separate days evaluated by oral glucose tolerance test, fasting blood glucose ≥ 126 mg/dL, casual blood glucose ≥ 200 mg/dL, or HbA1c ≥ 6.5%), vascular disease (coronary artery diseases, ankle brachial index ≤ .9, or aortic plaque), and dyslipidemia (treatment with lipid-lowering medication, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL, or triglyceride ≥ 150 mg/dL). The period of hospitalization including both acute therapy and rehabilitation therapy was calculated after excluding patients with an mRS score of 6 (death).

Statistical Analysis

Data were expressed as mean ± standard deviation, median (25th-75th percentiles), or n (%). Unpaired *t* test, Mann–Whitney *U* test, or chi-square test was used to