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A simple score for predicting paroxysmal atrial fibrillation in acute ischemic stroke

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ABSTRACT

Background and purpose: Our aim in this study was to investigate factors associated with paroxysmal atrial fibrillation (PAF) in acute stroke patients and to develop a risk score to predict the presence of PAF.
Methods: We retrospectively enrolled patients with acute ischemic stroke within 24 h of onset between June 2006 and April 2008. Patients with sustained AF were excluded. Patients were divided into two groups according to the presence of PAF: the PAF group or the non-PAF group. The clinical factors associated with PAF were investigated. Furthermore, we devised a new risk score to predict the presence of PAF.
Results: There were 215 patients enrolled. The PAF group had 32 (14.9%) patients. Multivariate logistic regression analysis demonstrated that NIHSS score ≥ 8 (OR, 4.2; 1.38–12.88), left atrial size ≥ 3.8 cm (OR, 4.8; 1.65–13.66), mitral valvular disease (OR, 7.5; 2.17–25.90), and plasma BNP level ≥ 144 pg/ml (OR, 12.8; 4.12–40.00) were independent factors associated with PAF. We developed a risk score from these variables (total score 0 to 5): NIHSS score ≥ 8 (1 point); left atrial size ≥ 3.8 cm (1 point); mitral valvular disease (1 point); and BNP level ≥ 144 pg/ml (2 points). The frequency of PAF was 0% with a score of 0, 4% with a score of 1, 14% with a score of 2, 26% with a score of 3, 50% with a score of 4 and 100% with a score of 5
Conclusion: Our simple score can predict the presence of PAF during hospitalization in acute ischemic stroke.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, and a major risk factor for ischemic stroke [1]. Furthermore, ischemic stroke patients with AF are at high risk of recurrent stroke [2], and have increased short-term, as well as long-term mortality. Therefore, identification of AF in acute ischemic stroke patients is important, and adequate anticoagulant therapy can prevent further ischemia.

Patients with paroxysmal AF (PAF) had stroke rates similar to patients with sustained AF [3]. However, PAF often goes undetected during hospitalization for acute stroke or transient ischemic attack (TIA). Different approaches to detect PAF in patients with acute ischemic stroke have been investigated, and the detection rate of PAF is approximately 5% [4]. Recent reports suggest that prolonged monitoring is likely to result in higher detection rates [5–7]. However, the limitations of these methods include the amount of time and effort involved to detect PAF. In addition, monitoring methods may need to be applied more broadly, including patients with and without AF. Therefore, identifying the patients with the highest risk of PAF is critically important. More intensive diagnostic tests for such patients may improve PAF detection rates.

Several risk factors have been reported for AF such as aging, diabetes, hypertension, obesity, congestive heart failure [8], valvular heart disease [9], and left atrial (LA) dilatation [10]. Recently, we demonstrated that plasma brain natriuretic peptide (BNP) is a strong predictor of PAF after ischemic stroke and TIA [11]. The aim of the present study is to clarify the factors most closely associated with PAF from various parameters such as clinical, blood test including BNP, transthoracic echocardiography (TTE), and neuroimaging, and to develop a risk score for the prediction of PAF.

2. Methods

We retrospectively enrolled consecutive patients with acute ischemic stroke within 24 h of onset between June 2006 and April 2008. Patients with AF on admission electrocardiography (ECG) or a history of sustained AF were excluded. Patients with dialysis-dependent chronic renal failure were also excluded from the present study because the plasma BNP level is elevated in such patients [12]. All patients underwent routine 12-lead ECG on admission, 24 h Holter ECG, or bedside continuous ECG monitoring during hospitalization to detect PAF. This study was approved by the Ethics Committee of Kawasaki Medical School Hospital and was conducted in a manner consistent with the Declaration of Helsinki.

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI). The following factors were assessed: age, gender, vascular risk factors, body mass index (BMI), prior myocardial infarction and cerebral infarction, National Institutes of Health Stroke

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Scale (NIHSS) [13] score on admission, blood samples, TTE findings, and nonlacunar infarction on CT or MRI. The following vascular risk factors were evaluated: hypertension (defined as the use of antihypertensive agents, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg before stroke onset or 2 weeks after stroke onset); diabetes mellitus (defined as the use of oral hypoglycemic agents or insulin, or fasting blood glucose level ≥ 126 mg/dl, or glycosylated hemoglobin level ≥ 6.4%); hyperlipidemia (defined as the use of antihyperlipidemic agents or serum cholesterol level ≥ 220 mg/dl); and smoking habit (defined as smoking during the preceding 3 months). All patients had baseline blood samples drawn on admission, and C-reactive protein (CRP), D-dimer, and BNP were assessed.

2.1. Measurement of plasma BNP levels

We measured plasma BNP for all patients on admission. Samples were collected from a peripheral vein into tubes containing aprotinin and ethylene diamine tetra acetic acid. The plasma was isolated and then stored at −80 °C until analysis. The plasma BNP concentration was measured using a chemiluminescence enzyme immunoassay for human BNP (Shionogi & Co., Ltd., Osaka, Japan). Briefly, this assay uses two monoclonal antibodies against human BNP, one recognizing a carboxyl-terminal sequence and the other the ring structure of BNP, and measures BNP by sandwiching it between the two antibodies. BNP can be accurately quantified within 11 min. The normal value of BNP is 18.4 pg/ml or less in our hospital. The minimal detectable quantity of BNP is 3.9 pg/ml.

2.2. Transthoracic echocardiography data

It was performed using a SONOS 7500 (Philips Ultrasound, Bothell, Washington) by the ultrasonographers and cardiologists in Kawasaki Medical School. The following transthoracic 2-dimensional and Doppler echocardiography data was evaluated during hospitalization: LA size, ejection fraction (EF), and mitral valvular disease. All measurements and calculations were made following the recommendations of the American Society of Echocardiography (ASE) [14–16]. Mitral valvular disease included mitral valve stenosis, mitral regurgitation and mechanical prosthetic mitral valve. Color Doppler echocardiography was used to detect mitral regurgitant jet and were rated none, trivial, mild, moderate, or severe; the latter 3 were combined into a single entity of mitral regurgitation. Mitral stenosis was based on the appearance of the mitral valve orifice on the 2-dimensional echocardiography and on the pulsed Doppler recording of the mitral flow velocity. LV ejection fraction (EF) was also measured and calculated by a modified Simpson's rule from apical two- and four-chamber views. LA size was measured with the use of leading-edge-to-leading-edge measurement of the maximal distance between the anterior and the posterior LA wall at end-systole.

2.3. Statistical analysis

We divided the patients into two groups according to the presence of PAF: the PAF group, who documented PAF during hospitalization or a history of PAF, and the non-PAF group, and compared the clinical characteristics between the two groups. The significance of intergroup differences was assessed using the chi-squared test and the Mann–Whitney *U* test. The optimal cut-off points of each continuous variable to discriminate the PAF group from the non-PAF group were obtained by receiver operating characteristics (ROC) curves. Then, the factors with a probability of $P < 0.1$ in univariate analysis were entered into a multivariate logistic regression to determine adjusted odds ratios. A continuous predictive score was produced from variables significantly associated with PAF by logistic regression analysis. A score was attributed to these variables from their β coefficient. The predictive ability of this score was performed by the ROC curve. Data were statistically analyzed using SPSS (version 11, Chicago, Illinois). Differences were considered statistically significant at the level of $P < 0.05$.

3. Results

A total of 354 patients were admitted to our hospital within 24 h of the onset of acute ischemic stroke. We excluded 139 of them for the following reasons: 77 with AF on admission ECG or a history of sustained AF, 16 with dialysis-dependent chronic renal failure, and 46 with incomplete or poor quality TTE data. Finally, 215 patents were enrolled in the present study (mean age, 70.2 years, 138 males). There were 19 patients with a history of PAF and 13 newly diagnosed cases of PAF during hospitalization. Therefore, there were 32 patients (14.9%) in the PAF group. Newly diagnosed PAF was observed in 13 (11.5%) of 113 patients who were diagnosed with cryptogenic stroke on admission. PAF was detected in 8 patients by continuous ECG monitoring and in 5 patients by 24 h Holter ECG. The mean ± SD interval of time from admission to detection of PAF was 6.0 ± 7.1 days. The non-PAF group consisted of 183 (85.1%) patients.

Table 1 shows the baseline clinical, laboratory and radiographic findings of the non-PAF and the PAF groups. The median and interquartile range (IQR) of age (non-PAF versus PAF group: 72.0 (61.0–78.0) vs. 74.5 (66.5–85.0) years, $P = 0.022$), NIHSS score on admission (3.0 (1.0–9.0) vs. 12.5 (5.5–19.5), $P < 0.001$), LA size (3.5 (3.1–3.8) vs. 4.1 (3.6–4.5), $P < 0.001$), mitral valvular disease (38.8% vs. 65.6%, $P = 0.005$), D-dimer (0.6 (0.5–1.5) vs. 2.1 (0.8–3.2), $P < 0.001$), BNP (40.5 (16.7–92.6) vs. 250.5 (124.0–462.5) pg/ml, $P < 0.001$), and nonlacunar infarction (58.5% vs. 87.5%, $P = 0.002$) were significantly higher in the PAF than in the non-PAF group. Of 92 patients with mitral valvular disease, 91 had mitral regurgitation and 1 had mitral stenosis. No patients had a mechanical prosthetic mitral valve. On the other hand, the frequency of diabetes mellitus (30.0% vs. 12.5%, $P = 0.040$) was significantly higher in the non-PAF than in the PAF group.

Age, non-diabetes mellitus, NIHSS score on admission, LA size, mitral valvular disease, D-dimer, BNP and nonlacunar infarction were chosen as possible admission factors that could be closely associated with PAF. ROC curves analysis demonstrated that the cut-off levels of continuous variables that identified PAF with high sensitivity and

Table 1
Baseline characteristics of patients in the non-PAF and PAF groups.

	Non-PAF	PAF	p value
	n = 183	n = 32	
Age, years	72.0 (61.0–78.0)	74.5 (66.5–85.0)	0.022
Male	121 (66.1)	17 (53.1)	0.157
Vascular risk factors			
Hypertension	121 (66.1)	18 (56.3)	0.281
Diabetes mellitus	55 (30.0)	4 (12.5)	0.040
Hypercholesterolemia	55 (30.0)	7 (21.9)	0.346
Smoking	98 (53.6)	13 (40.6)	0.177
Past history			
Myocardial infarction	10 (5.5)	3 (9.4)	0.392
Cerebral infarction	41 (22.4)	6 (18.8)	0.644
NIHSS score	3.0 (1.0–9.0)	12.5 (5.5–19.5)	<0.001
Left atrial size, cm	3.5 (3.1–3.8)	4.1 (3.6–4.5)	<0.001
EF < 55%	20 (10.9)	4 (14.3)	0.663
Mitral valvular disease	71 (38.8)	21 (65.6)	0.005
BMI	23.0 (20.5–25.3)	21.8 (19.9–23.9)	0.317
CRP, mg/dl	0.10 (0.05–0.23)	0.13 (0.05–0.36)	0.547
D-dimer, μg/ml	0.6 (0.5–1.5)	2.1 (0.8–3.2)	<0.001
BNP, pg/ml	40.5 (16.7–92.6)	250.5 (124.0–462.5)	<0.001
Absence of lacunar imaging	107 (58.5)	28 (87.5)	0.002

Data were median (interquartile range) or number (%).
NIHSS; National Institutes of Health Stroke Scale, EF; ejection fraction, BMI; body mass index, CRP; C-reactive protein, BNP; brain natriuretic peptide.