Brain Natriuretic Peptide in Acute Ischemic Stroke

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Elevated serum brain natriuretic peptide (BNP) levels are associated with cardioembolic stroke mainly because of atrial fibrillation (AF). However, the mechanisms of increased serum BNP levels are hitherto unclear. We aimed to identify the factors associated with increased BNP levels in patients with acute ischemic stroke. We measured serum BNP levels in consecutive patients aged 18 years or older. Stroke subtypes were classified using the Trial of ORG 10172 in Acute Stroke Treatment criteria. Categorical variables included age, sex, smoking status, alcohol consumption status, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease (CAD), AF, antiplatelet therapy, and anticoagulant therapy. Continuous variables included hemoglobin, creatinine (Cr), β-thromboglobulin, platelet factor 4, thrombin–antithrombin complex, and D-dimer levels. We further determined the relationship between serum BNP and intima–media thickness, left ventricular ejection fraction, size of infarction, National Institutes of Health Stroke Scale score on admission, and modified Rankin Scale (mRS) score at discharge. Of the 231 patients (mean age, 71 ± 12 years) with acute ischemic stroke (AIS), 36% were women. Serum BNP levels significantly correlated with CAD, AF, Cr, mRS, and cardioembolism (CE) (Dunnett method, $P = .004$). BNP levels were significantly higher in patients with larger infarcts, higher mRS scores, and higher $CHADS_2$ scores. The levels were higher in patients with larger infarcts, higher mRS scores at discharge, and higher $CHADS_2$ scores among AF patients. **Key Words:** Brain natriuretic peptide—acute ischemic stroke—atrial fibrillation—infarct size—$CHADS_2$ score—modified Rankin Scale.

Introduction

Brain natriuretic peptide (BNP), first isolated from porcine brains in 1988, is known to be of ventricular origin in humans and has been reported to be a useful marker of cardiac dysfunction.[1,2] Plasma BNP levels are also elevated in patients with acute ischemic stroke (AIS), particularly in those with atrial fibrillation (AF).[3-8] Recently, several studies have reported BNP levels to be predictive of AF after ischemic stroke or transient ischemic attack.[7-9] Elevated serum BNP levels, a powerful predictor of patient outcome in cardiovascular disease, have been associated with AF, cardioembolic stroke, and poststroke mortality. However, the mechanisms associated with

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increase in serum BNP levels are not well clarified. We aimed to identify the factors associated with increased BNP levels in patients with AIS.

Subjects and Methods

Subjects included 231 patients with AIS who had been consecutively admitted to our hospital between March 2010 and March 2012. Ischemic stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment classification guidelines.[10]

The categorical variables used for statistical analysis included age, sex, current smoking status, alcohol consumption status, hypertension, diabetes mellitus (DM), dyslipidemia, coronary artery disease (CAD), and AF. Hypertension was defined as a blood pressure of 140/90 mm Hg or more at admission or despite receiving an antihypertensive agent. DM was defined as fasting blood glucose of 126 mg/dL or more or random blood glucose of 200 mg/dL or more and hemoglobin (Hb) A1c of 6.4% or more (The National Glycohemoglobin Standardization Program) at admission or despite receiving an antidiabetic agent. Dyslipidemia was characterized by serum low-density lipoprotein cholesterol of 140 mg/dL or more, high-density lipoprotein cholesterol of 40 mg/dL or less, or serum triglycerides of 150 mg/dL or more at admission or despite receiving antihyperlipidemic agents, such as statins or fibrates. CAD was defined as the detection of an ischemic alteration on electrocardiography or a history of any medical treatment for ischemic heart disease. AF was diagnosed by 24-hour ambulatory electrocardiographic monitoring, performed on admission. Antiplatelet therapy included treatment with aspirin, clopidogrel, cilostazol, or ozagrel (a thromboxane A2 synthase inhibitor), and anticoagulant therapy included treatment with heparin, warfarin, or argatroban (thrombin inhibitor).

The continuous variables used for statistical analysis included Hb, creatinine (Cr), β-thromboglobulin (β-TG), platelet factor 4 (PF4), thrombin–antithrombin complex (TAT), D-dimer, maximum intima–media thickness (IMT) of the bilateral carotid arteries by high-resolution duplex ultrasonography, and left ventricular ejection fraction by the modified biplane Simpson method[11] for transthoracic echocardiography. We evaluated the National Institutes of Health Stroke Scale (NIHSS) score for each patient on admission.[12] Outcomes were evaluated using the modified Rankin Scale (mRS) score at discharge or 2 months after stroke onset.[13] We also examined the correlation between BNP levels and $CHADS_2$ score in patients with AF.[14]

Magnetic Resonance Imaging

All magnetic resonance images were performed with 1.5 T scanners. Sequences included diffusion-weighted images (DWIs) obtained by spin-echo echo planar imaging (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 160 × 160/144 × 144/128 × 115; repetition time [TR], 3014-4500 ms; echo time [TE], 78-95 ms; b = .100 s/mm^2 in 3 diffusion-gradient directions), fluid attenuated inversion recovery images (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 224 × 272/209 × 256/205 × 256; TR, 6000-1000 ms; TE, 95-102 ms; inversion time, 2000-2600 ms), and T2-weighted images (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 320 × 416/224 × 256/205 × 256; TR, 3294-4000 ms, TE, 90-105 ms). Isotropic DWIs and apparent diffusion coefficient maps were automatically calculated.

Magnetic Resonance Image Assessment

Areas of hyperintensity on DWIs were used to diagnose AIS and classify infarct sizes. Signal increases solely attributable to T2 shine through were ruled out by comparison with apparent diffusion coefficient maps. We classified the infarcts into 3 groups: S (≤.3-1.5 cm), L (one third the size of the cerebral hemispheres), and M (sizes between S and L). S infarcts were .3-1.5 cm and M infarcts were more than 1.5 cm in the brain stem and cerebellar hemisphere.

Hemostatic Markers

Venous blood samples were collected at the time of admission for measuring hemostatic marker levels, including β-TG, PF4, TAT, and D-dimer. β-TG was measured using the Asserachrom β-TG kit (Diagnostica Stago, Asnieres, France); PF4, using an Asserachrom PF4 kit (Diagnostica Stago); TAT, using a Stacia Cleia TAT kit (Mitsubishi Chemical Medicine, Tokyo, Japan); and D-dimer, using the Nampia D-dimer kit (Sekisui Medical Co., Tokyo, Japan).

Measurement of Brain Natriuretic Peptide

Whole blood samples were collected at the time of admission. Plasma BNP levels were measured using a chemiluminescence enzyme immunoassay (Fujirebio, Inc., Tokyo, Japan). This assay uses 2 monoclonal antibodies against human BNP, one recognizing the carboxyl-terminal sequence and the other the ring structure of BNP, and measures BNP by sandwiching the molecule between the 2 antibodies.[15]

Evaluation of Carotid Atherosclerosis

Vascular risk factors were assessed, and ultrasound measurements of the common carotid artery (CCA) were performed using high-resolution, duplex ultrasonography (ALPHA 7; Hitachi Aloka ProSound, Tokyo, Japan) with a 13-MHz linear probe. We measured IMT in the bilateral CCAs, carotid bulbs, and internal carotid