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Clinical Study

Plasma brain natriuretic peptide is elevated in the acute phase of intracerebral hemorrhage

Kensaku Shibazaki *, Kazumi Kimura, Kenichiro Sakai, Junya Aoki, Yuki Sakamoto

Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan

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ABSTRACT

Previous reports have shown that plasma brain natriuretic peptide (BNP) levels are increased in patients with subarachnoid hemorrhage and ischemic stroke. We examined BNP in patients with intracerebral hemorrhage (ICH). Between June 2006 and February 2010, we prospectively enrolled consecutive patients with acute ICH within 24 hours of onset. The plasma BNP level was measured twice, on admission and 4 weeks after onset or at discharge. We investigated whether plasma BNP was elevated in the acute phase of ICH and associated factors. The mean ± standard deviation (SD) plasma BNP level of all patients was 71.1 ± 104.1 pg/mL. The log BNP level positively correlated with the cardio–thoracic ratio ($r = 0.240$, $p = 0.0001$). Moreover, BNP was significantly associated with intraventricular extension ($p = 0.0039$) and hydrocephalus ($p = 0.0046$). The mean ± SD BNP level of patients with cerebellar hemorrhage was the highest (130.2 ± 152.0 pg/mL), followed by brainstem (84.5 ± 170.6 pg/mL), lobar (72.4 ± 148.1 pg/mL), thalamus (64.8 ± 72.1 pg/mL), and putamen (59.9 ± 62.6 pg/mL) hemorrhages. In 185 patients, BNP was measured in the subacute phase of ICH. The BNP level in the acute phase of ICH was significantly higher than that in the subacute phase of ICH (69.3 ± 108.1 *versus* 21.7 ± 23.5 pg/mL, $p < 0.0001$). In conclusion, plasma BNP appears to be elevated in the acute phase of ICH, particularly in those with cerebellar lesions.

1. Introduction

Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload.[1] Previous studies have shown that the BNP level is related to cardiac function[2,3] and it has been used as a biochemical marker for congestive heart failure.[4]

In addition, plasma BNP levels have also been shown to be elevated in the acute phase of subarachnoid hemorrhage[5–7] and in acute ischemic stroke patients.[8–17] However the relationship between plasma BNP and intracerebral hemorrhage (ICH) has not been fully examined.

Hypertension is the main risk factor for ICH[18] and induces an increased load on the cardiac ventricles. Thus, hypertension causes left ventricular hypertrophy[19] and systolic or diastolic dysfunction.[20,21] In addition, early elevation of blood pressure after ICH is well documented.[22] Therefore, we suspected that the plasma BNP level may be elevated in patients with ICH because of the increased load on the cardiac ventricles seen in the acute phase of ICH. We investigated this hypothesis and the presence of associated factors.

2. Patients and methods

We prospectively enrolled consecutive acute spontaneous ICH patients within 24 hours of onset who were admitted to our Stroke Center between June 2006 and February 2010. Patients with underlying aneurysm, vascular malformation, dissection, hemorrhagic transformation of ischemic stroke, traumatic ICH, or those who underwent emergency surgery were excluded. In addition, patients with atrial fibrillation, dialysis-dependent chronic renal failure, or a history of myocardial infarction or chronic pulmonary disease were excluded from the present study, because plasma BNP levels are increased in these patients.[23] The plasma BNP level was measured on admission. The study was conducted in compliance with the Declaration of Helsinki with regard to investigations in human subjects. The ethics committee of Kawasaki Medical School Hospital approved the study protocol.

A diagnosis of acute ICH was made by stroke neurologists, and confirmed by CT scans or MRI. The following factors were assessed: age, sex, prior ICH, vascular risk factors, left ventricular hypertrophy, creatinine, cardio–thoracic ratio (CTR) on chest radiograph, systolic and diastolic blood pressure on admission, National Institutes of Health Stroke Scale (NIHSS) score[24] on admission, ICH location, ICH volume on admission, ICH volume enlargement, subarachnoid extension, intraventricular extension, hydrocephalus, ICH score, and in-hospital death.

* Corresponding author. Tel.: +81 86 464 1111; fax: +81 86 464 1199.
E-mail address: shibaken@med.kawasaki-m.ac.jp (K. Shibazaki).

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We also evaluated the following vascular risk factors: 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, fasting blood glucose level ⩾126 mg/dL, or a glycosylated hemoglobin level ⩾6.4%), and hyperlipidemia (defined as the use of antihyperlipidemic agents or a serum cholesterol level ⩾220 mg/dL). Electrocardiographic left ventricular hypertrophy was defined as $S_{V1} + R_{V5}$ or $_{V6} \geqslant 3.5$ mV.[25]

Cranial CT scanning was carried out twice, at the baseline visit (<24 hours after onset) and on follow-up (24–48 hours after onset). All cranial CT scans were performed according to our radiology department protocol, with an image matrix of 340 × 340 and a slice width of 8–10 mm. The investigators who read the CT scans had no prior knowledge of the clinical data. ICH volume was measured using the A × B × C/2 method, as described previously.[26]

The site of the ICH was classified according to the location of the largest amount of hematoma, and categorized as the putamen, thalamus, lobar, brainstem, or cerebellum.[27] ICH enlargement was defined as a hematoma that grew by more than 33% of its initial volume.[28] The ICH score is a clinical grading scale that is composed of five components related to outcome after nontraumatic ICH: the Glasgow Coma Scale score, ICH volume, presence of intraventricular hemorrhage, infratentorial origin, and age.[29]

All patients had baseline blood samples drawn on admission. Serum creatinine and plasma BNP were assessed.

2.1. Measurement of plasma BNP levels

The plasma BNP level was measured twice, on admission and 4 weeks after ICH onset or at discharge. Samples were collected from a peripheral vein into tubes containing aprotinin and ethylene diamine tetra acetic acid (EDTA), and 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., 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. At our hospital the normal value of BNP is ⩽18.4 pg/mL. The minimum detectable quantity of BNP is 3.9 pg/mL. Investigators were blinded to the BNP results, and evaluated the clinical and radiographic findings.

3. Statistical analysis

The Mann–Whitney U test was used to examine factors associated with plasma BNP level on admission. Linear regression analysis was performed to assess factors related to log BNP. Because the plasma BNP level had skewed distributions, it was log-transformed to normalize its distributions for analysis. Furthermore, we compared the clinical characteristics, including BNP level, for each ICH location using a chi-squired test and Kruskal–Wallis test. We investigated the differences in plasma BNP level between admission and on day 28 or at discharge using the Wilcoxon signed rank test. Statistical analysis was performed using a commercially available software package (StatView, version 5; SAS Institute, Cary, NC, USA). Differences were considered statistically significant at the level of $p < 0.05$. Results are reported as mean ± standard deviation (SD) unless otherwise stated.

4. Results

A total of 306 consecutive acute spontaneous ICH patients were admitted to our Stroke Center within 24 hours of onset. Of these, 56 patients were excluded because the plasma BNP level was increased due to atrial fibrillation (n = 23), dialysis-dependent chronic renal failure (n = 23), a history of myocardial infarction (n = 9), or a history of chronic pulmonary disease (n = 1). Therefore, 250 patients (164 men; 68.5 ± 12.8 years) were enrolled in the present study. The NIHSS score on admission was 13.3 ± 8.5. The location of the hematoma was the putamen in 78 patients (31%), thalamus in 96 (38%), lobar in 29 (12%), in the brainstem in 29 (12%), and in the cerebellum in 18 (7%). The interval of time from ICH onset to initial CT scan examination was 5.0 ± 4.9 hours. The ICH volume was 19.9 ± 33.6 mL. A total of 29 patients (11.6%) died during hospitalization.

The interval from ICH onset to blood sample collection on admission was 4.1 ± 4.0 hours. The plasma BNP level of all patients was 71.1 ± 104.1 pg/mL. The log BNP level was positively correlated with age (r = 0.365, $p < 0.0001$), creatinine (r = 0.179, $p = 0.0046$), CTR (r = 0.240, $p = 0.0001$) and ICH volume (r = 0.132, $p = 0.0376$). The plasma BNP level was significantly higher in patients with intraventricular extension than in patients without intraventricular extension (77.9 ± 79.4 *versus* 66.6 ± 117.8 pg/mL, $p = 0.0039$) and was significantly higher in patients with hydrocephalus than in those without hydrocephalus (113.5 ± 159.7 *versus* 62.6 ± 86.9 pg/mL, $p = 0.0046$). The plasma BNP level of deceased patients was significantly higher than that of surviving patients (99.9 ± 101.6 *versus* 67.4 ± 104.1 pg/mL, $p = 0.0030$). There were no differences in other variables such as NIHSS score on admission (r = 0.081, $p = 0.2034$), or ICH enlargement ($p = 0.2114$). The BNP level of patients with cerebellar hemorrhage was the highest (130.2 ± 152.0 pg/mL), followed by brainstem (84.5 ± 170.6 pg/mL), lobar (72.4 ± 148.1 pg/mL), thalamus (64.8 ± 72.1 pg/mL), and putamen (59.9 ± 62.6 pg/mL) hemorrhage (Fig. 1). The plasma BNP level of patients with cerebellar hemorrhage was significantly higher than that of patients with putamen ($p = 0.0064$), thalamus ($p = 0.0098$), and lobar hemorrhage ($p = 0.0500$). The differences in BNP level between brainstem and cerebellum hemorrhage did not reach statistical significance ($p = 0.1204$). Table 1 shows the clinical characteristics in each ICH location. Older age, higher CTR, higher ICH score and intraventricular extension were more frequent in patients with cerebellar hemorrhage than in those with other ICH locations.

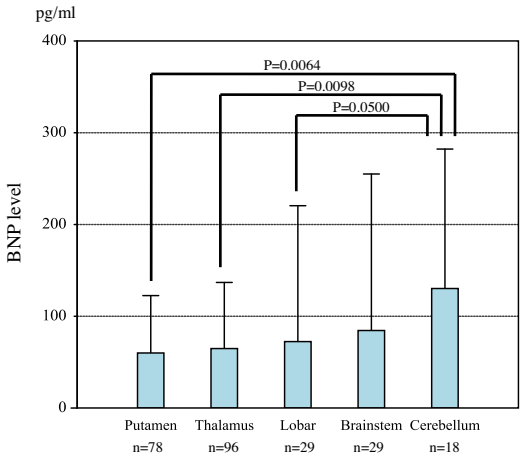

Fig. 1. Column graph showing mean plasma brain natriuretic peptide (BNP) levels and intracerebral hemorrhage (ICH) locations. The mean ± standard deviation BNP level of patients with cerebellar hemorrhage was the highest (130.2 ± 152.0 pg/mL), followed by brainstem (84.5 ± 170.6 pg/mL), lobar (72.4 ± 148.1 pg/mL), thalamus (64.8 ± 72.1 pg/mL), and putamen (59.9 ± 62.6 pg/mL) hemorrhage. The plasma BNP level of patients with cerebellar hemorrhage was significantly higher than that of patients with putamen ($p = 0.0064$), thalamus ($p = 0.0098$), and lobar hemorrhage ($p = 0.0500$) (adjusted for cardio–thoracic ratio and ICH score).