Plasma Concentrations of Brain Natriuretic Peptide in Patients With Subarachnoid Hemorrhage

Mamoru Tomida, MD; Masaaki Muraki, MD; Kenichi Uemura, MD; Kenji Yamasaki, MD

Background and Purpose—Hyponatremia after subarachnoid hemorrhage (SAH) is commonly associated with diuresis and natriuresis, but the causes are still controversial. We investigated whether brain natriuretic peptide (BNP) was related to such hyponatremia.

Methods—Plasma BNP concentrations were measured by immunoradiometric assay in 18 patients at 0 to 2 days (period 1), 7 to 9 days (period 2), and >14 days (period 3) after SAH. Plasma concentrations of antidiuretic hormone (ADH), atrial natriuretic peptide (ANP), and noradrenaline were also measured during period 2.

Results—The 11 patients with hyponatremia (serum sodium concentration of <135 mEq/L) had much higher plasma BNP concentrations during each period than did healthy controls (P<.05), whereas the 7 patients with normonatremia did not show statistically higher values. In the patients with hyponatremia, the plasma BNP concentration during period 2 was statistically higher than that during periods 1 and 3 (P<.05). The plasma noradrenaline concentration during period 2 was higher in patients with hyponatremia than in those with normonatremia (P<.05), whereas the plasma concentrations of ADH and ANP during period 2 were not statistically different between the hyponatremic and normonatremic patients.

Conclusions—we conclude that BNP may be related to hyponatremia associated with natriuresis following SAH. The increase of noradrenaline may promote the secretion of BNP. (Stroke. 1998;29:1584-1587.)

Key Words: hyponatremia ■ natriuretic peptide, brain ■ subarachnoid hemorrhage

Hyponatremia after SAH has been reported to have an incidence of 30% to 40%. Recent studies have demonstrated that this phenomenon is frequently associated with hypovolemia, which is caused not by the syndrome of inappropriate secretion of ADH but by CSW. However, the cause of CSW is still controversial. Some authors have reported that ANP and digoxinlike peptides may cause the hyponatremia, while others have suggested that these agents are not involved. BNP, which was isolated from porcine brain in 1988, causes natriuresis and diuresis. It has recently become possible to measure BNP accurately by immunoradiometric assay. We investigated whether BNP was related to hyponatremia after SAH by measuring plasma BNP concentrations with use of an immunoradiometric assay in patients with acute SAH.

Subjects and Methods

Patients and Management

Eighteen patients (4 men and 14 women without cardiac, renal, or endocrine diseases; mean±SD age, 62.3±10.8 years) with SAH verified by CT scan were investigated from January 1995 through December 1996. All patients underwent cerebral angiography and aneurysm clipping within 48 hours of the onset, except for 1 patient in whom angiography failed to identify the source of hemorrhage. Each patient received intravenous fluid at approximately 2500 to 3000 mL/d to maintain a central venous pressure of 4 to 12 cm H₂O. Sodium administration ranged from 280 to 320 mEq/d in patients without hyponatremia, while sodium loss was replaced according to urinary excretion when hyponatremia occurred. When symptomatic vasospasm occurred, ozagrel sodium (Xanbon, Kissei Pharmaceutical Co Ltd) was intravenously administered at 80 mg/d in patients treated from January 1995 through July 1995, and fasudil hydrochloride (Eril, Asahi Chemical Industries) was intravenously administered at 60 to 90 mg/d in patients treated from August 1995 through December 1996. Daily fluid and sodium balances were recorded until day 14 from the onset.

Methods

Blood samples were collected into tubes containing 1 mg/mL EDTA and 1000 KIU/mL aprotinin and were then centrifuged at 2500 rpm at 4°C. Plasma was stored at −40°C. Plasma BNP concentrations were measured 3 times during the study at 0 to 2 days (period 1), 7 to 9 days (period 2), and >14 days (period 3) after SAH. Plasma ANP, ADH, and noradrenaline were measured once during period 2, and the serum sodium concentration was measured at least every 3 days.

Plasma BNP concentrations were determined by a recently developed highly sensitive 2-site immunoradiometric assay (SHIONORIA BNP, Shionogi & Co, Ltd). Two monoclonal antibodies, BC-203 (which recognizes the C-terminal region of BNP) and KY-BNP-2 (which recognizes the disulfide bond ring structure of BNP), were used. A mixture of standard BNP (100 µL) or sample (100 µL), 125I-labeled KY-BNP-2 (200 µL), and a bead coated with immobilized BC-203 were incubated at 2°C to

Received March 25, 1998; final revision received May 7, 1998; accepted May 7, 1998.

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8°C for 18 to 22 hours. The buffer for the calibrators was 0.1 mol/L sodium phosphate containing 0.3 mol/L NaCl, 10^6 KIU/L aprotinin, 1 mmol/L EDTA-2Na, 1 g/L NaN3, 0.2 mmol/L cystine, 2 g/L bovine serum albumin, and 0.05 g/L mouse γ-globulin. After removing the supernatant by aspiration, we washed the antibody bead twice with 2 mL washing buffer (0.01 mol/L sodium phosphate containing 0.15 mol/L NaCl, 0.2 mL/L Tween 20, and 1 g/L NaN3). Then the radioactivity bound to the bead was counted with a gamma counter (ARC950, Aloka Inc). A plot of radioactivity counts versus the concentrations of BNP calibrator was used to estimate plasma BNP concentration. The detection limit was 0.2 pg/mL. The interassay and intra-assay coefficients of variation were 2.30% to 10.6% and 6.98% to 10.9%, respectively. Cross-reactivity between natriuretic peptides was less than 0.1%. The plasma BNP concentration determined in 106 healthy volunteers (56 men and 50 women) was 6.68±4.89 pg/mL (data provided by SRL Inc). Plasma ANP concentrations were also measured by immunoradiometric assay (SHIONORIA ANP, Shionogi & Co, Ltd), ADH levels were measured by radioimmunoassay (AVP RIA “Mitsubishi,” Mitsubishi Chemical Corporation, Inc), and noradrenaline levels were measured by high-performance liquid chromatography.

Statistical Analysis

Values were expressed as mean±SD. Statistical analysis was performed using Welch’s t test to compare differences among plasma concentrations of BNP during each period and for comparison with the normal control values. The unpaired Student t test was used to assess differences between the hyponatremic and normonatremic groups with respect to the plasma concentrations of ANP, BNP, ADH, and noradrenaline on days 7 to 9 as well as differences in the water and sodium balances. The χ² test was used for assessing differences of symptomatic vasospasm between the 2 groups. Results were interpreted as significant at the level of 5% probability.

Results

We defined hyponatremia as a serum sodium concentration of <135 mEq/L. Hyponatremia occurred in 11 patients (serum sodium, 127±2.2 mEq/L; duration, 5.9±2.7 days; nadir time, 9.8±2.7 days). Table 1 shows the age, Hunt and Kosnik grade on admission, Fisher’s classification on initial CT scan, and location of aneurysms in the hyponatremic and normonatremic groups. The cumulative water balance until day 7 (insensible loss of water was defined as 500 mL/d) was 1500 mL in the hyponatremic group (P<0.05), whereas BNP levels tended to decrease in the normonatremic group. Plasma BNP concentrations in the hyponatremic group were always statistically higher than in the healthy controls (P<0.05), while levels in the normonatremic group were not. However, the plasma BNP concentration on days 7 to 9 was not statistically higher in the hyponatremic group than in the normonatremic group.

Table 2 shows plasma concentrations of ANP, ADH, and noradrenaline on days 7 to 9. There were no statistical differences between the 2 groups for ANP and ADH levels. However, plasma noradrenaline levels were higher in the hyponatremic group than in the normonatremic group (P<0.05).

Discussion

Our results suggested that BNP may cause diuresis and natriuresis after SAH. Both diuresis and natriuresis were more severe in the hyponatremic group than in the normonatremic group. Plasma BNP concentrations during the study period were higher in the hyponatremic group than in healthy volunteers. Moreover, plasma BNP concentration on days 7 to 9 was statistically higher than on days 0 to 2 and after day 14 (P<0.05), whereas BNP levels tended to decrease in the normonatremic group. Plasma BNP concentrations in the hyponatremic group were always statistically higher than in the healthy controls (P<0.05), while levels in the normonatremic group were not. However, the plasma BNP concentration on days 7 to 9 was not statistically higher in the hyponatremic group than in the normonatremic group.

Table 3 shows plasma concentrations of ANP, ADH, and noradrenaline on days 7 to 9. There were no statistical differences between the 2 groups for ANP and ADH levels. However, plasma noradrenaline levels were higher in the hyponatremic group than in the normonatremic group (P<0.05).

**TABLE 1. Clinical and CT Grading and Location of Aneurysms in Hyponatremic and Normonatremic Groups**

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Hyponatremic Group</th>
<th>Normonatremic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±12</td>
<td>58±8</td>
</tr>
<tr>
<td>Hunt and Kosnik grade</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>3</td>
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<tr>
<td>IV</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>V</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fisher’s class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MCA</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>ICA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; MCA, middle cerebral artery; and ICA, internal carotid artery.
BNP after SAH still remains unknown, Berendes et al.\textsuperscript{17} speculated that BNP release may result from the stress response to surgery or intensive care as well as damage to the hypothalamic region. Our results raise the possibility that noradrenaline may cause an increase in the load on the cardiac ventricles, which may stimulate BNP secretion, and that the increase of BNP then induces hyponatremia associated with volume depletion that may lead to symptomatic vasospasm.

In contrast, Isotani et al.\textsuperscript{4} reported that plasma BNP was not significantly higher in patients with SAH than in the normal control group, although BNP levels on days 0 to 2 were above normal. We speculate that this difference may result from variations in the sodium load and clinical condition. We loaded our patients with approximately twice as much sodium as did Isotani et al. Such an amount of sodium, which was also administered to the patients of Berendes et al.\textsuperscript{17} and Wijdicks et al.,\textsuperscript{18} may increase the plasma BNP concentration. Moreover, the precise cardiac status of the patients was not estimated in our study or in their studies. Therefore, the response of the left cardiac ventricle to a mild volume load may have been different between the 2 studies.

We conclude that BNP may play an important role in hyponatremia in patients with SAH. However, the studies on BNP in SAH performed to date (including ours) have involved small populations; further investigations focusing on cardiac ventricular function are needed.

**Acknowledgments**

We thank SRL Inc for measuring plasma BNP concentrations in our patients and providing the data on BNP in healthy volunteers. We also thank Noriyuki Makishi for a precise explanation of the immunoradiometric assay for BNP.

**References**


**TABLE 3.** Plasma Concentrations of ANP, ADH, and NA on Days 7 to 9

<table>
<thead>
<tr>
<th>Group</th>
<th>ANP</th>
<th>ADH</th>
<th>Noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremic group</td>
<td>27.3±0.8</td>
<td>2.4±2.6</td>
<td>517.6±189.1*</td>
</tr>
<tr>
<td>Normonatremic group</td>
<td>24.1±30.3</td>
<td>3.1±2.7</td>
<td>274.1±164.3</td>
</tr>
</tbody>
</table>

Values are mean±SD picograms per milliliter.

*P<0.05.


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Stroke. 1998;29:1584-1587
doi: 10.1161/01.STR.29.8.1584

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