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<0.05), 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<0.05). The plasma noradrenaline concentration during period 2 was higher in patients with hyponatremia than in those with normonatremia (P<0.05), 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
Selected Abbreviations and Acronyms

ADH = antidiuretic hormone
ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CSW = cerebral salt-wasting syndrome
KIU = kallikrein inhibitor units
SAH = subarachnoid hemorrhage

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 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, 124±2.4 mEq/L; duration, 5.9±2.7 days; nadir time, 9.8±2.7 days). Table 1 shows the age, Hunt and Kosnik grade, and Fisher’s classification on admission, location of aneurysm, and location of aneurysm in the hyponatremic and normonatremic groups. The cumulative water balance until day 7 (insensible loss of water was defined as 500 mL/d) was 

\[-2600±1600 \text{ mL}\] in the hyponatremic group and 

\[-950±1500 \text{ mL}\] in the normonatremic group (P<0.05); the cumulative sodium balance until day 7 was 

\[-173±285 \text{ mEq}\] in the hyponatremic group and 

\[90.8±195 \text{ mEq}\] in the normonatremic group. Symptomatic vasospasm, including mild deterioration of consciousness, occurred in 11 patients; 10 of these belonged to the hyponatremic group and only 1 to the normonatremic group (P<0.01).

Table 2 shows plasma BNP concentrations in the hyponatremic and normonatremic groups. In the hyponatremic group, the BNP level at 7 to 9 days was statistically higher than at 0 to 2 days and after 14 days (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).

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 in the hyponatremic group.

Table 2. Plasma Concentrations of BNP in Each Period

<table>
<thead>
<tr>
<th>Group</th>
<th>Days 0–2</th>
<th>Days 7–9</th>
<th>After Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremic group</td>
<td>38.2±33.3</td>
<td>95.3±74.9*</td>
<td>34.5±36.5</td>
</tr>
<tr>
<td>Normonatremic group</td>
<td>109.0±146.5</td>
<td>58.6±80.3</td>
<td>23.2±30.6</td>
</tr>
</tbody>
</table>

*P<0.05.
TABLE 3. Plasma Concentrations of ANP, ADH, and NA on Days 7 to 9

<table>
<thead>
<tr>
<th>Group</th>
<th>ANP (pg/mL)</th>
<th>ADH (pg/mL)</th>
<th>Noradrenaline (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremic</td>
<td>27.3±0.8</td>
<td>2.4±2.6</td>
<td>517.6±189.1*</td>
</tr>
<tr>
<td>Normonatremic</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.

Some authors²,³,¹² have reported that hyponatremia results from CSW in most patients with SAH, while others have reported hyponatremia may result from the syndrome of inappropriate secretion of ADH.¹³ In our study, hyponatremia was associated with natriuresis and diuresis in all patients, and the plasma concentration of ADH was normal in the patients with hyponatremia. Therefore, we believe that all the hyponatremia in our present series resulted from CSW. The etiology of CSW is controversial, with several substances having been proposed as the cause. ANP has been investigated as a promising factor.³,⁴ However, some authors have pointed out that ANP alone is not sufficient to cause hyponatremia.²,¹⁴ In the present study, the mean plasma ANP concentration on days 7 to 9 was within the normal range in both the hyponatremic and normonatremic groups.

BNP is another natriuretic peptide consisting of 32 amino acids that was found in 1988.⁵ It has as much effect on diuresis and natriuresis as ANP; however, there are some differences.⁵,¹⁶ The primary stimulus is the load on the cardiac ventricles for BNP, whereas it is the atrial load for ANP; the plasma half-time of BNP is approximately 20 minutes, which is about twice as long as that of ANP; and the response of BNP to cardiac failure is faster than that of ANP. Berendes et al¹⁷ suggested that BNP may induce hyponatremia due to salt wasting in patients with SAH by subsequent suppression of aldosterone synthesis. Wijdicks et al¹⁸ also concluded that both BNP and ANP increase after SAH, which results in a negative fluid balance. In the present study, the plasma BNP concentration was statistically higher in the hyponatremic group than in the healthy volunteers, and the plasma BNP concentration on days 7 to 9 was approximately twofold that on days 0 to 2 and after day 14 in the hyponatremic group. Therefore, we speculate that the increase of plasma BNP may induce hyponatremia. Two patients in our normonatremic group showed very high plasma BNP concentrations on days 0 to 2 (>100 pg/mL), which decreased gradually. However, a surge of BNP within 2 days of SAH should not in itself induce hyponatremia around day 9, because the plasma half-life of BNP is about 20 minutes.¹⁵ Therefore, a second increase of BNP around days 4 to 9 or a persistent high concentration of BNP may be necessary to induce hyponatremia.

In the present study, the plasma noradrenaline level and the incidence of symptomatic vasospasm were higher in the hyponatremic group than in the normonatremic group. Some authors have reported that an increase of plasma noradrenaline is related to symptomatic vasospasm¹¹ and that patients with symptomatic vasospasm frequently have hyponatremia.⁵ Although the mechanism of the release of BNP after SAH still remains unknown, Berendes et al¹⁷ 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 al⁴ 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 al¹⁷ and Wijdicks et al,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

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References

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