Alterations in Plasma Concentrations of Natriuretic Peptides and Antidiuretic Hormone After Subarachnoid Hemorrhage

Eiji Isotani, MD; Ryuta Suzuki, MD; Kimio Tomita, MD; Mituhiro Hokari, MD; Seiji Monma, MD; Fumiaki Marumo, MD; Kimiyoshi Hirakawa, MD

Background and Purpose Hyponatremia is a common complication after subarachnoid hemorrhage. In this study we investigated the relations among hyponatremia, plasma natriuretic peptides, and antidiuretic hormone concentrations after subarachnoid hemorrhage.

Methods Blood samples for radioimmunoassay measurement of plasma brain natriuretic peptide–like immunoreactivity, atrial natriuretic peptide–like immunoreactivity, and antidiuretic hormone were obtained every 2 to 4 days until day 14 after subarachnoid hemorrhage.

Results Elevated plasma antidiuretic hormone (ADH) concentrations with free water retention and dilutional hyponatremia demonstrated mild hyponatremia (126 mEq/L < serum sodium < 135 mEq/L) during their clinical course. Atrial natriuretic peptide and antidiuretic hormone concentrations were significantly elevated on days 0 to 2 after onset of subarachnoid hemorrhage. Atrial natriuretic peptide concentrations remained high in patients who developed mild hyponatremia on days 6 to 14 after onset of subarachnoid hemorrhage. In contrast, antidiuretic hormone concentrations became significantly lower during the second week in these patients.

Conclusions Mild hyponatremia after subarachnoid hemorrhage may be attributable not to the syndrome of inappropriate secretion of antidiuretic hormone but to cerebral salt-wasting syndrome. Atrial natriuretic peptide may be a causal natriuretic factor in cerebral salt-wasting syndrome.

Subjects and Methods

Patient Population Twenty patients with verified SAH were investigated (13 women, 7 men; mean age, 56 years [range, 24 to 76 years]). On admission patients were graded according to the method of Hunt and Kornik, and the amount of blood on the computed tomographic scan was quantified according to the method of Fisher et al. When four-vessel cerebral angiography demonstrated an aneurysm, the patient received the following standard care: early operation with clipping of the aneurysm, intensive care, continuous intravenous infusion of the calcium channel blocker nicardine (0.10 to 0.15 mg/kg per hour for 2 weeks and then tapering over 1 week), and enteral administration of 200 mg/d of ticlopidine hydrochloride on and after day 4. All patients initially received approximately 170 mEq/d of sodium. Sodium administration was adjusted according to serum sodium concentration and urinary sodium loss when hyponatremia occurred. Induced hypertension and hypervolemic therapy were not performed routinely. Clinical outcome was assessed according to the Glasgow Outcome Scale. Early operations, within 2 days after SAH, were performed in 15 patients. Delayed operations were performed in 3 patients with poor clinical status on admission or with delayed admission. A woman without a clearly defined rupture site and a man with poor clinical status as a result of repeated rupture of the aneurysm did not undergo surgical intervention. The hyponatremia has been studied. In 1988 Sudoh et al. discovered brain natriuretic peptide (BNP). This peptide is composed of 32 amino acids in humans and is similar in terms of structure and pharmacology to ANP, which is composed of 28 amino acids. The purpose of this study was to examine the relations among natriuretic peptides, ADH plasma concentrations, and hyponatremia after SAH.

Key Words • antidiuretic hormones • atrial natriuretic peptide • inappropriate ADH syndrome • subarachnoid hemorrhage
patient’s status at admission, the ruptured aneurysm site, the number of patients who showed symptomatic vasospasm or mild hyponatremia, and Glasgow Outcome Scale classification are shown in Table 1.

Hyponatremia was defined as a serum sodium concentration below 135 mEq/L at least once in the clinical course. Eleven of 20 patients showed hyponatremia during this study period. There were no episodes of clinical deterioration (e.g., altered level of consciousness, convulsions) that could be attributed to hyponatremia alone. None of 11 hyponatremic patients showed hyponatremia less than 127 mEq/L during the entire study period. Consequently, we defined mild hyponatremia as a serum sodium concentration above 126 mEq/L.

Sample Collection

Blood samples were taken every 2 to 4 days until day 14. The samples were prepared according to the methods of Marumo et al and Togashi et al. Briefly, the blood was collected in tubes prepared with EDTA (1 mg/mL) and centrifuged at 3000 rpm for 10 minutes. Plasma was frozen (-20°C) and dis- patched to the laboratory on dry ice for peptide assays.

Radioimmunoassay was performed in essentially the same manner as for α-hANP. In brief, the standard curve was constructed using B/Bo versus an hBNP or α-hANP standard. The amount of hBNP or α-hANP in the known samples was extrapolated from the standard curve linearized by a logit-log transformation. For chromatographic analysis of plasma hBNP-like immunoreactivity (hBNP-LI) or α-hANP-like immunoreactivity (α-hANP-LI), an aliquot of patient plasma was subjected to reverse-phase HPLC. Plasma ADH was measured by specific radioimmunoassay. hBNP-LI, α-hANP-LI, and ADH were determined from the same patient sample, and all samples from a patient were assayed at the same time. Serum sodium was measured using an ion-selective electrode.

Control Samples

A control plasma BNP-LI concentration (5.9±1.9 pg/mL; mean±SD) was obtained from 5 normal subjects (3 men, 2 women; age, 49.7±2.7 years) after overnight fasting. A control plasma ANP-LI concentration (38.0±13.6 pg/mL) was obtained from 21 normal subjects (11 men, 10 women; age, 26.6±4.6 years), and a control plasma ADH concentration (4.0±2.1 pg/mL) was obtained from 38 normal subjects (17 men, 21 women).

Statistical Analysis

Values are presented as mean±SD. Data were evaluated by two-sided, two-sample t test, and the level of significance was P<.05.
TABLE 2. Water Balance In 20 Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Patient group H</th>
<th>Entire study period</th>
<th>Study period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Intake</td>
<td>m·d^{-1}</td>
<td>mL·kg^{-1}·d^{-1}</td>
</tr>
<tr>
<td>mL · d^{-1}</td>
<td>3176±387</td>
<td>3359±709</td>
</tr>
<tr>
<td>mL · kg^{-1}·d^{-1}</td>
<td>60.1±11.9</td>
<td>61.8±15.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient group N</th>
<th>Entire study period</th>
<th>Study period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water Intake</td>
<td>mL · d^{-1}</td>
<td>mL · kg^{-1}·d^{-1}</td>
</tr>
<tr>
<td>mL · d^{-1}</td>
<td>3162±469</td>
<td>3427±366</td>
</tr>
<tr>
<td>mL · kg^{-1}·d^{-1}</td>
<td>63.8±10.3</td>
<td>74.3±9.6</td>
</tr>
</tbody>
</table>

Patient group H includes 11 hyponatremic patients; group N, 9 normonatremic patients; and study period 3, days 12 to 14 after subarachnoid hemorrhage. Values are mean±SD.

Results

Serum Sodium Concentrations and Water Balance

Serum sodium concentrations on days 0 to 2 (study period 1), 6 to 8 (study period 2), and 12 to 14 (study period 3) after SAH are shown in Fig 1. The normal range is shown as mean±SD. Eleven of 20 patients developed mild hyponatremia (126 mEq/L < sodium < 135 mEq/L) during the second week after SAH.

Table 2 shows mean water intake, mean urinary output, and mean water balance in both patients with hyponatremia (group H) or without (group N) during each study period. Although there were differences in these parameters between the groups, they were not statistically significant.

Plasma BNP-LI Concentrations

Mean plasma BNP-LI concentrations for all patients were 18.1±13.8 pg/mL (study period 1), 7.5±6.2 pg/mL (study period 2), and 6.7±5.5 pg/mL (study period 3) (Table 3). Plasma BNP-LI concentrations were highest in study period 1, but there were no significant differences when compared with normal subjects, and there were no differences between the values for each period. Mean plasma BNP-LI concentrations were 16.9±12.8, 11.5±10.9, and 7.4±6.0 pg/mL in group H, and the concentrations were 21.2±15.6, 6.5±5.3, and 4.5±2.9 pg/mL in group N during each study period, respectively. There were no significant differences between the values of these groups in each study period.

Plasma ANP-LI Concentrations

Mean plasma ANP-LI concentrations were 66.4±19.6, 61.7±18.1, and 55.9±16.3 pg/mL in each study period, respectively (Table 3). Plasma ANP-LI concentrations remained significantly higher than those of the healthy subjects during the entire study period. Mean plasma ANP-LI concentrations of group H were 62.0±19.7, 57.0±14.2, and 60.6±15.1 pg/mL, respectively. Those of group N were 76.2±15.7, 58.6±17.8, and 40.5±8.6 pg/mL, respectively. Groups H and N both had significantly higher ANP-LI concentrations than the normal subjects during study periods 1 and 2. There was also a significant difference between the values of groups H and N during study period 3 (Fig 3).

Plasma ADH Levels

Mean plasma ADH concentrations were 11.9±16.9, 2.1±1.5, and 2.3±1.4 pg/mL in each study period.

TABLE 3. Changes In Plasma Natriuretic Peptides and Antidiuretic Hormone Concentrations In 20 Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Plasma BNP-LI</th>
<th>Plasma ANP-LI</th>
<th>Plasma ADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level, pg/mL</td>
<td>No. of Cases</td>
<td>Level, pg/mL</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>5.9±1.9</td>
<td>5</td>
</tr>
<tr>
<td>Patients with SAH</td>
<td>Study period 1</td>
<td>18.1±13.8</td>
</tr>
<tr>
<td>Study period 2</td>
<td>7.5±6.2</td>
<td>18</td>
</tr>
<tr>
<td>Study period 3</td>
<td>6.7±5.5</td>
<td>16</td>
</tr>
</tbody>
</table>

BNP-LI indicates brain natriuretic peptide-like immunoreactivity; ANP-LI, atrial natriuretic peptide-like immunoreactivity; ADH, antidiuretic hormone; and SAH, subarachnoid hemorrhage. Study periods 1, 2, and 3 include days 0 to 2, 6 to 8, and 12 to 14, respectively, after SAH. Values are mean±SD.

*Statistically significant compared with normal subjects (P<.05).
†Statistically significant compared with normal subjects (P<.01).
respectively (Table 3). Plasma ADH concentrations were significantly lower in study period 1 but thereafter became significantly lower compared with those of the normal subjects. The mean preoperative ADH value was 15.4±18.5 pg/mL and the mean postoperative ADH value was 3.06±2.23 pg/mL in study period 1. There was no significant difference between these two values.

Mean plasma ADH concentrations of group H were 11.6±19.4, 1.4±0.8, and 2.1±1.5 pg/mL and those of group N were 12.2±12.3, 3.0±1.7, and 2.6±1.2 pg/mL in each study period, respectively. Plasma ADH levels of both patient groups were significantly higher than those of the normal subjects in study period 1. In group H plasma ADH concentrations were significantly lower in study periods 2 and 3. There was also a significant difference between the values for groups H and N in study period 2 (Fig 4).

**Comparison of Plasma BNP-LI, ANP-LI, and ADH Concentrations by Other Modalities**

Plasma BNP-LI, ANP-LI, and ADH concentrations do not correlate significantly with serum sodium levels. Plasma BNP-LI, ANP-LI, and ADH concentrations were not significantly different among the patient groups by Hunt and Kosnik classification, by Fisher group, or by the site of the ruptured aneurysm. In addition, plasma BNP-LI, ANP-LI, and ADH concentrations did not correlate with symptomatic vasospasm, although all four patients with symptomatic vasospasm showed hyponatremia (Table 4).

**Discussion**

Various systemic changes have been described after SAH. These include elevated blood pressure, cardiomyopathy, electrocardiographic abnormalities, pulmonary edema, and hyponatremia. The phenomenon of hyponatremia after SAH was first reported by Joint al. Wijdicks et al. reported the development of hyponatremia in 44 (33%) of 134 SAH patients. They proposed hyponatremia as one of the factors predisposing to delayed neurological deficits. Hyponatremia after intracranial disorders was first thought to be due to SIADH in 1957. However, recent discoveries of the natriuretic peptides have opened the way to a reconsideration of the cause of hyponatremia after SAH. The concept of CSWS has taken on renewed significance in terms of the etiology of hyponatremia after SAH.

**Natriuretic Peptide Levels After SAH**

There have been conflicting reports regarding ANP concentrations after SAH. Dininger et al. reported that plasma ANP was increased in patients with SAH, but some authors have reported decreased concentrations. Doczi et al. reported that only the SAH patients with elevated intracranial pressure (>20 mmHg) had increased plasma ANP concentrations. Wijdicks et al. reported a markedly increased atrial natriuretic factor concentration and a relatively diminished vasopressin concentration in SAH patients with hyponatremia. Dininger et al. reported that atrial natriuretic factor concentrations were elevated but were not predictive of hyponatremia and that ADH concentrations were not suppressed. In the present study plasma ANP-LI and ADH concentrations were significantly elevated immediately after SAH. Only the ANP-LI concentrations remained high during the entire periods of study in patients with hyponatremia; ADH concentrations in these patients were significantly lower during the second week when hyponatremia occurred. These results suggest that ANP may participate in the occurrence of hyponatremia in SAH. The different methodologies and patient populations of the various studies may have resulted in their different conclusions. In contrast, plasma BNP-LI concentrations did not show any significant changes during the entire period of study. This is the first report that has examined the role of BNP in SAH. It appears that BNP may not have a role in the occurrence of hyponatremia after SAH.

**Mechanisms of the Release of ANP and ADH After SAH**

Wijdicks et al. speculated that ANP might be released from hypothalamic areas. However, the brain contains 1000-fold less ANP than does the heart. Recent reports have indicated several pathological conditions, including pulmonary hypertension and heart failure, that are associated with enhanced release of ANP from the heart. SAH may also stimulate the heart to enhance the release of ANP. Therefore, the possible mechanisms of the release of ANP and ADH immediately after the onset of SAH are considered. The first possibility is that SAH stimulates the hypothalamus to release ADH, and this excess release of ADH results in the redistribution of the circulating plasma volume into the central venous compartment, followed by atrial
whether the cardiac atrium is stretched. In the present study atrial stretching could not be caused by the excess preload to the right cardiac atrium because there were no significant differences between the groups in either water intake or water balance. Since SAH frequently causes neurogenic pulmonary edema, increased afterload to the right cardiac atrium may occur in SAH. The excess afterload caused by the increased resistance of pulmonary vessels results in atrial stretching and a secondary excess release of ANP. A condition with elevated plasma ADH and ANP is not physiological but rather is compatible with SIADH. However, no patients showed hyponatremia during this period. The second possibility is that SAH contributes to the release of ANP from the heart independent of the excess release of ADH. However, the mechanisms that may mediate a relation between the brain and cardio-pulmonary system are as yet unknown, although SAH is known to have serious effects on the cardiopulmonary system. Possible candidates for these mediators include catecholamines and endothelin.

### ANP and ADH Concentrations in the Late SAH Period

In the second week after SAH, two patient groups can be defined: a patient group that showed asymptomatic hyponatremia (group H) and a group that demonstrated normonatremia during the entire study period (group N). Plasma concentrations of ANP were elevated during the entire study period in group H, while they remained normal in group N. The plasma concentrations of ADH were suppressed in group H and normal in group N. It is known that ANP has inhibitory effects on ADH release.

The interactions between ANP and ADH may have been of a physiological nature in this late period. Hyponatremia in this period did not correlate with the presence of vasospasm, ADH concentration, or BNP concentration, but it did correlate with the plasma ANP concentration. CSWS is thought to be caused by the release of some unknown natriuretic factors after intracranial disease. Our results indicated that the mild hyponatremia seen in the second week after SAH was due to CSWS and that the natriuretic factor causing CSWS after SAH may be ANP.

If the primary factor defining the patient groups in the second week after SAH is the plasma ANP concentration, the onset of hyponatremia may be regulated by whether the cardiac atrium is stretched. In the present study atrial stretching could not be caused by the excess preload to the right cardiac atrium because there were no significant differences between the groups in either water intake or water balance. Since SAH frequently causes neurogenic pulmonary edema, increased afterload to the right cardiac atrium may occur in SAH. The excess afterload caused by the increased resistance of pulmonary vessels results in atrial stretching and a secondary excess release of ANP. A condition with elevated plasma ADH and ANP is not physiological but rather is compatible with SIADH. However, no patients showed hyponatremia during this period. The second possibility is that SAH contributes to the release of ANP from the heart independent of the excess release of ADH. However, the mechanisms that may mediate a relation between the brain and cardio-pulmonary system are as yet unknown, although SAH is known to have serious effects on the cardiopulmonary system. Possible candidates for these mediators include catecholamines and endothelin.

### References


**Table 4. Comparison of Plasma Natriuretic Peptides and Antidiuretic Hormone Concentrations Between Patients With and Without Symptomatic Vasospasm**

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Plasma BNP-LI Level, pg/mL</th>
<th>Plasma ANP-LI Level, pg/mL</th>
<th>Plasma ADH Level, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Samples</td>
<td>No. of Samples</td>
<td>No. of Samples</td>
</tr>
<tr>
<td>With symptomatic vasospasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17.8±14.1</td>
<td>62.3±17.6</td>
<td>17.7±23.9</td>
</tr>
<tr>
<td>2</td>
<td>10.5±6.8</td>
<td>75.0±18.8</td>
<td>5.5±1.9</td>
</tr>
<tr>
<td>3</td>
<td>2.2±0.8</td>
<td>59.2±8.4</td>
<td>2.1±0.9</td>
</tr>
<tr>
<td>Without symptomatic vasospasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17.5±12.6</td>
<td>67.5±21.0</td>
<td>9.0±9.8</td>
</tr>
<tr>
<td>2</td>
<td>8.3±6.7</td>
<td>54.2±16.0</td>
<td>3.9±2.8</td>
</tr>
<tr>
<td>3</td>
<td>8.2±5.5</td>
<td>52.5±16.5</td>
<td>3.2±2.0</td>
</tr>
</tbody>
</table>

BNP-LI indicates brain natriuretic peptide-like immunoreactivity; ANP-LI, atrial natriuretic peptide-like immunoreactivity; and ADH, antidiuretic hormone. Study periods 1, 2, and 3 include days 0 to 2, 6 to 8, and 12 to 14, respectively, after subarachnoid hemorrhage. Values are mean±SD.
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