

Hyponatremia is predictable in patients with aneurysmal subarachnoid hemorrhage—clinical significance of serum atrial natriuretic peptide

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Abstract

Purpose Serum atrial natriuretic peptide (ANP) that is elevated after aneurysmal subarachnoid hemorrhage (SAH) causes diuresis and natriuresis (cerebral salt wasting) and might exacerbate delayed ischemic neurological deficit (DIND). We investigated relationships among hyponatremia, serum ANP elevation, and the onset of DIND after SAH.

Materials and methods Thirty-nine consecutive patients (15 women and 24 men) with SAH were assigned to a normonatremia group or a group that developed hyponatremia after SAH. Serum ANP and brain natriuretic peptide were assessed after SAH. All patients remained normovolemic and normotensive. We attributed DIND to vasospasm only in the absence of other causes and when supported by cerebral angiography.

Results Hyponatremia developed after SAH in 11 patients (28.2%), among whom serum ANP concentrations at 0 and 3 days thereafter were significantly increased. Furthermore, DIND developed in five (45.5%) and two (7.1%) hyponatremic and normonatremic patients, respectively ($P < 0.05$). The serum ANP levels on day 0 after SAH were higher in Hunt and Kosnik grades 3–4 than in 1–2 and in Fisher groups 3–4 than in 1–2 ($P < 0.05$).

Conclusions Increasing serum ANP concentrations were independently associated with hyponatremia resulting in DIND. Early treatment of hyponatremia might prevent DIND in patients after SAH.

Keywords Cerebral salt wasting syndrome · Delayed ischemic neurological deficit · Subarachnoid hemorrhage · Natriuretic peptide · Hyponatremia

Introduction

Hyponatremia with natriuresis is a common electrolyte disturbance after subarachnoid hemorrhage (SAH) that increases the risk of a delayed ischemic neurological deficit (DIND). Several studies have recently indicated that rapidly increasing levels of natriuretic peptides might be the cause of natriuresis and hyponatremia and cerebral salt wasting syndrome (CSWS) in patients with SAH [12, 15, 25]. Isotani et al. [12] demonstrated that elevated levels of serum atrial natriuretic peptide (ANP) were associated with hyponatremia and natriuresis after SAH. Berendes et al. [2] and Tomida et al. [26] confirmed that hyponatremia after SAH is associated with elevated levels of serum brain natriuretic peptide (BNP). Wijdicks et al. [30] suggested a correlation between the increase in both ANP and BNP levels and hyponatremia. However, findings from several studies contradict the notion that ANP is the primary factor behind CSWS [3, 16]. In this study, we investigated whether elevated levels of serum ANP precede the onset of hyponatremia or are predictive of DIND and whether they could potentially serve as a marker to guide diagnostic and therapeutic management.

Materials and methods

The patients included in this study were recruited from all those with aneurysmal SAH who were admitted to Ishinkai Yao General Hospital between July 2004 and July 2006.

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The clinical condition of the patients was graded upon admission according to the Hunt and Kosnik (H&K) classification [10], and the severity of SAH was classified based on the initial appearance on computed tomographic (CT) scans according to Fisher et al. [4]. Diagnostic cerebral angiography was performed during the first 12 h after admission. All patients underwent neck clipping or coil embolization of ruptured aneurysms within 24 h of SAH. Patients with any of the following conditions were excluded: H&K grade 5, head trauma, known endocrinological disturbances, renal disease, and congestive heart failure.

All patients remained normovolemic and normotensive after SAH. Their water balance was calculated every 12 h from the difference between the total amount of water intake and water loss, and water was replaced to maintain the balance. All patients were equipped with cisternal or spinal drainage to remove subarachnoid clots and to control intracranial pressure from the day after the onset of SAH to day 14. Hyponatremic patients were treated with fludrocortisone acetate (Florinef, Bristol-Myers Co.) at doses of 0.1–0.4 mg/day from the day after hyponatremia occurred until the serum sodium level normalized. When DIND developed, percutaneous angioplasty was applied and fasudil hydrochloride was transarterially injected. A ventriculo-peritoneal shunt was positioned when normal pressure hydrocephalus progressed.

Blood samples including serum sodium, potassium, protein, and glucose were measured at 24-h intervals. Serum ANP and BNP concentrations were assessed at days 0, 3, 7, 14, 21, and 28. Daily urine volume, sodium and potassium excretion, and osmotic pressure were also determined from stored urine samples every 24 h.

The patients were assigned to either a normonatremic or a group that developed hyponatremia after SAH. Hyponatremia was defined as an absolute value of <135 mEq/L occurring at any time during the first 14 days of hospitalization. We attributed DIND to cerebral vasospasm only in the absence of other causes and when supported by cerebral angiography. Outcomes were evaluated using the modified Rankin Scale (MRS) at 30 days after onset.

All data are presented as means \pm standard deviation. Differences between groups were assessed using Fisher exact test. Other data were analyzed using the general mixed-model analysis of variance, and statistical significance was concluded at $P < 0.05$.

Results

Thirty-nine patients participated in the study (14 men, 25 women; mean age, 67.2 years old). Eleven (28.2%) of them who became hyponatremic at 9.0 ± 4.2 days after SAH were

assigned to the hyponatremia group. These patients were medicated with fludrocortisone acetate for 16.8 ± 2.2 days. None of age, gender, H&K grade, Fisher classification on initial CT, location of aneurysms, and therapeutic modality significantly differed between the two groups (Table 1).

Serum ANP levels at days 0 and 3 after SAH were significantly higher in the hyponatremic than in the normonatremic group (Fig. 1a). Serum BNP levels did not significantly differ between the two groups, although levels in both increased at 3 days after SAH (Fig. 1b). Serum sodium levels significantly decreased in the hyponatremic group at 7 days after SAH and gradually increased after supplementation with salt and attenuating natriuresis with mineralocorticoids (Fig. 1c). No major adverse effects of mineralocorticoids such as pulmonary edema or prolonged hypokalemia developed in any of the patients.

All of five (45.5%) and two (7.1%) patients in the hyponatremic and normonatremic groups, respectively, who developed DIND had an incomplete focal deficit or an impaired level of consciousness without coma. The incidence of DIND significantly differed between the two groups (Table 1).

Ruptured aneurysmal sites were not remarkably associated with serum ANP levels at day 0 or 3 after SAH (Table 2). However, the initial serum ANP levels were significantly higher in patients categorized as H&K grades 3–4 than 1–2 and Fisher groups 3–4 than 1–2 at the onset of SAH (Table 2).

Discussion

Prediction of hyponatremia and DIND

We show here that elevated serum ANP is associated with hyponatremia after aneurysmal SAH and that DIND is closely associated with hyponatremia. A previous report found that cerebral vasospasm clinically arises in about one third of patients with aneurysmal SAH, 3–7 days after the onset, and causes DIND [23]. For a diagnosis of asymptomatic cerebral vasospasm, several tools are reportedly useful, such as transcranial Doppler, perfusion CT, and perfusion magnetic resonance imaging [9, 24]. However, whether or not such spasms will subsequently progress to DIND cannot be predicted. Igarashi et al. [11] reported that symptomatic cerebral vasospasm (SVS) is closely related to severe natriuresis and osmotic diuresis induced by CSWS. However, they emphasized that strict observation is required because CSWS and subsequent SVS rapidly develop. Therefore, an additional earlier marker is required to predict the development of DIND and to initiate immediate treatment. Elevated serum ANP levels that precede the onset of hyponatremia do not comprise a

Table 1 Clinical summary of 39 patients

	Normonatremia (n=28)	Hyponatremia (n=11)
Age (years)	65.0±13.3	72.8±8.2
Gender		
Male	11	3
Female	17	8
H&K grade		
I–II	19	5
III–IV	9	6
Fisher group		
1–2	14	4
3–4	14	7
Aneurysm site		
ACA	8	5
MCA	9	3
ICA	7	3
Post.	4	0
Treatment		
Neck clipping	26	11
Coil embolization	2	0
VP shunt	4	3
DIND	2	5*
MRS		
0–1	12	3
2–3	8	3
4–5	8	5

Values are expressed as means ± standard deviation

ACA anterior cerebral artery, MCA middle cerebral artery, ICA internal cerebral artery, Post posterior circulation, VP shunt ventriculo-peritoneal shunt, DIND delayed ischemic neurological deficits, MRS modified Rankin Scale

* $P < 0.05$ (difference between groups)

perfect method for predicting which patients will develop DIND. However, it can be a clue to guide the diagnostic and therapeutic management of patients with a possibility of developing DIND.

Natriuretic peptide levels after SAH

Both ANP and BNP produce several effects that could lead to CSWS. The heart releases ANP in response to atrial stretch [28], and ANP was released from the hypothalamic area with intracranial disease [2], which induces vasodilation as well as natriuresis and diuresis. Nevertheless, several studies have indicated that ANP is not the primary mechanism underlying CSWS [13, 16, 29]. Although levels of ANP are elevated after SAH according to recent studies, the peptide cannot be directly linked to hyponatremia after SAH [1, 21]. Our results also showed that ANP concentrations do not correlate with hyponatremia (Fig. 1a, c). All of these findings together suggest that ANP participates in the initiation of hyponatremia and that another factor is responsible for CSWS.

However, findings from several studies support the notion that BNP underlies the occurrence of CSWS [2, 25]. McGirt et al. [15] described the timing of BNP elevation relative to the onset of DIND; they found that

serum BNP levels significantly increase during the first 24 h after onset of DIND and predict 2-week Glasgow Coma Scale scores. Increasing BNP levels might directly exacerbate cerebral vasospasm due to natriuresis and diuresis induced by CSWS, although hypertensive hypervolemic therapy could have caused increasing plasma BNP levels due to an increased load on the heart. However, increased BNP is not an apparent early marker warning of impending DIND.

Natriuretic peptide secretion in SAH patients is thought to be closely associated with bleeding intensity and clinical severity [25, 27], a notion that is supported by the present study. We also showed that ANP tends to be high in patients with anterior cerebral artery aneurysm, but the difference was not statistically significant. These findings suggest that an initial hypothalamic insult of massive SAH around the anterior circle of Willis causes ANP hypersecretion from the hypothalamus where natriuretic peptides are widely distributed and synthesized [26, 30]. Nakamura et al. [19] reported that the primary cause of natriuretic peptide secretion lies in the central nervous system, but they supported the notion that the site of secretion is not the central nervous system but the heart, according to their observation of cardiopulmonary parameters. Further investigations are required to resolve this issue.

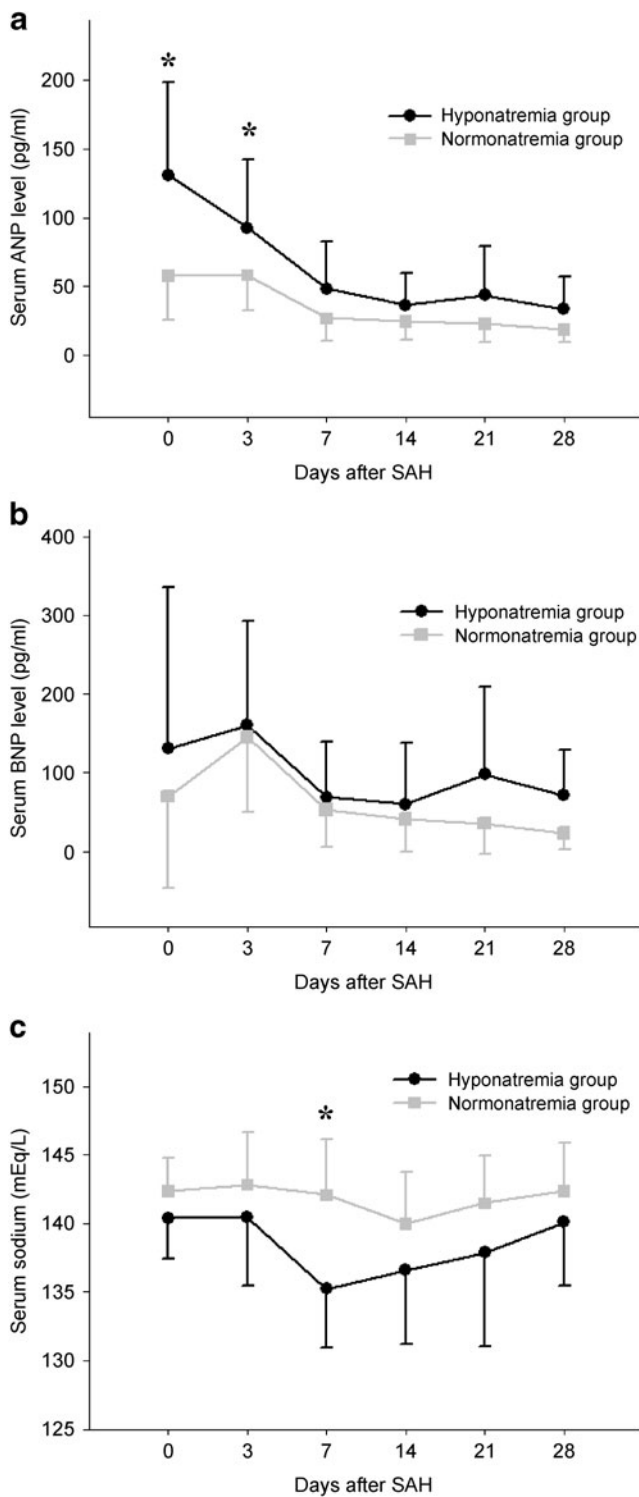


Fig. 1 Plasma concentrations of ANP, BNP, and sodium after subarachnoid hemorrhage in hyponatremic and normonatremic patients. **a** Serum ANP levels at days 0 and 3 after SAH were significantly higher in the hyponatremic than in the normonatremic group. **b** No significant differences between groups. **c** Serum sodium level significantly decreased 7 days after SAH and gradually increased with salt supplementation and mineralocorticoids in hyponatremic patients

Table 2 Relationship between ANP value at days 0 and 3 and parameters in 39 patients

Serum ANP (pg/ml)	Day0	Day3
Aneurysm site		
ACA	76.6±52.0	76.8±41.1
MCA	62.0±18.9	69.3±48.6
ICA	69.4±49.3	72.7±46.5
Post.	60.7±17.2	49.3±34.6
H&K grade		
I–II	54.0±26.9*	62.9±32.0
III–IV	112.6±70.7	91.1±66.8
Fisher group		
1–2	52.1±24.6*	63.1±36.6
3–4	97.0±65.8	83.5±57.0

Values are expressed as means ± standard deviation

ACA anterior cerebral artery, MCA middle cerebral artery, ICA internal cerebral artery, Post posterior circulation

* $P < 0.05$ (difference between classifications)

Relationship between hyponatremia and DIND

Hyponatremia occurs in up to 30% of patients after aneurysmal SAH, and it is associated with CSWS [8, 22] which involves renal salt loss, leading to a negative sodium balance, hyponatremia, and intravascular volume depletion [6]. Patients with asymptomatic cerebral vasospasm reportedly become symptomatic when CSWS occurs [20, 31]. Igarashi et al. [11] demonstrated that DIND is closely related to CSWS, which is supported by our present results. Morinaga et al. [17] showed in a large cohort of patients with ruptured aneurysms that clinical manifestations of vasospasm developed in 16 of 19 patients with hyponatremia. However, Qureshi et al. [22] concluded that the presence of hyponatremia was not associated with increased risk of DIND. More analyses are required to assess whether or not CSWS can predict DIND.

Optimal treatment for DIND underlying hyponatremia

In the previous report, patients with SAH and SVS who do not show an early clinical improvement in response to volume or pressor therapy are at high risk for death or disability [5]. Hypervolemic therapy and increasing the sodium intake cannot be safely applied under such conditions because urinary sodium excretion might be enhanced, which would eventually accelerate water loss. Consequently, hyponatremia would not be readily corrected by intravenous infusion alone.

Fludrocortisone acetate, a mineral corticoid that enhances sodium reabsorption in the renal distal tubules and supports efficient hypervolemic therapy under appropriate serum sodium levels and plasma osmolality, can help prevent post-SAH hyponatremia. Morinaga et al. [17]

treated hyponatremia with fludrocortisone and reported a decrease in natriuresis and recovery from hyponatremia within 5 days. Here, we also administered fludrocortisone to patients with hyponatremia and reconfirmed its effect [16]. Hypokalemia and pulmonary edema are side effects of fludrocortisone [7, 32] that can be easily controlled as long as patients with impaired cardiopulmonary function are excluded.

Hydrocortisone, which is being used widely because of its glucocorticoid effects, also efficiently inhibits hyponatremia and hypovolemia, and its effects are easily controllable because of its shorter elimination half-life [14]. However, hydrocortisone also has the potential risk of side effects, such as hyperglycemia, an immunocompromised state, and gastrointestinal hemorrhage [33].

We consider that sodium and fluid supplementation must be started and natriuresis must be inhibited using mineralocorticoids before hyponatremia develops to prevent DIND in patients with SAH [18].

Conclusions

We demonstrated a conspicuously increased initial serum ANP level in patients who became hyponatremic after SAH and eventually developed DIND. Significantly high serum ANP levels at the onset of SAH could be a factor that predicts hyponatremia and subsequent DIND. We suggest that the early inhibition of natriuresis using mineralocorticoid for patients who are likely to become hyponatremic is an option that could prevent DIND.

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