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Case study

Decreased serum sodium levels predict symptomatic vasospasm in patients with subarachnoid hemorrhage

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ABSTRACT

Background: Symptomatic vasospasm is a major cause of morbidity and mortality in subarachnoid hemorrhage patients. Hyponatremia and dehydration due to natriuresis after subarachnoid hemorrhage are related to symptomatic vasospasm. Therefore, most institutions are currently targeting euvolemia and eunatremia in subarachnoid hemorrhage patients to avoid complications. We retrospectively investigated the predictors of symptomatic vasospasm with respect to water and sodium homeostasis, while maintaining euvolemia and eunatremia after subarachnoid hemorrhage. *Methods:* We monitored changes in serum sodium levels, serum osmolarity, daily sodium intake, daily urine volume, and daily water balance for 14 days after subarachnoid hemorrhage. Outcomes were assessed using the modified Rankin scale at 1 month after subarachnoid hemorrhage. *Results:* Among 97 patients, 27 (27.8%) had symptomatic vasospasm. Patients with symptomatic vasospasm were older than those without symptomatic vasospasm; the occurrence of symptomatic vasospasm affected outcomes. Serum sodium levels were sequentially significantly decreased, but within the normal range from 1 day before the occurrence of symptomatic vasospasm. Serum osmolarity of the spasm group was lower than that of the non-spasm group. *Conclusions:* Symptomatic vasospasm occurs more often in older patients and affects outcomes. A decrease in serum sodium levels occurs a day before symptomatic vasospasm. This observation may help predict symptomatic vasospasm.

1. Introduction

Symptomatic vasospasm (SVS) is one of the major causes of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (aSAH) [1–3]. Prevention of SVS is preferable as compared to controlling the symptoms of SVS or reversing existing spasms. Although many studies have introduced predictors of SVS [4–8], prediction of SVS accurately and in a timely manner is difficult due to its complex nature.

Hyponatremia and dehydration due to natriuresis after aSAH are related to SVS and can predict SVS [9–15]. In addition, both hypernatremia and hypervolemia after SAH are associated with poor outcomes [16,17]. Therefore, most institutions are currently targeting euvolemia and eunatremia in aSAH patients to avoid complications. In this study, we retrospectively investigated the predictors of SVS in relation to water and sodium homeostasis while maintaining euvolemia and eunatremia after aSAH.

2. Clinical material and methods

2.1. Patients

From April 2007 to June 2016, 86 patients with acute aSAH were treated with either surgical clipping or endovascular coiling at Steel Memorial Hirohata Hospital. From January 2014 to June 2016, 20 patients with acute aSAH were treated with endovascular coiling at Hyogo Brain and Heart Center. The institutional review boards of both hospitals approved the study. Among these 106 patients, 97 were included in this study. Nine patients were excluded because they were treated for >3 days after the onset of aSAH (n = 6) or required dialysis (n = 3). We did not include patients who suffered from dissecting aneurysms and those who died within 10 days after the onset of aSAH. The outcomes were

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assessed using the modified Rankin scale (mRS) at 1 month after the onset of aSAH [18].

2.2. Management protocol

All patients with aSAH were managed in the intensive care unit. For the treatment of a ruptured aneurysm, patients underwent either surgical clipping or endovascular coiling within 48 h from the onset. The treatment modality was selected based on a consensus between the neurosurgical and endovascular teams. After surgery, the patients were maintained in a normotensive, normovolemic, normoglycemic, and normothermic state as much as possible. Their water balance was calculated every 8 h. A negative water balance was corrected with normal saline infusion. From postoperative days 1–14, all the patients were administered fasudil hydrochloride hydrate (Eril; Asahi Kasei Co., Tokyo, Japan) at a dose of 90 mg/day to prevent vasospasm [19]. Glasgow Coma Scale and pupil examinations were performed every 2 h.

SVS was defined as the neurological deterioration in combination with radiographic findings (including perfusion computed tomography, magnetic resonance imaging, or angiography findings), with the exclusion of other possible causes such as hydrocephalus, rebleeding, sepsis, and seizures. When SVS occurred, percutaneous transluminal angioplasty and/or intra-arterial injection of fasudil hydrochloride hydrate were performed. The blood cell counts, serum biochemical data, and serum electrolytes were evaluated at least every 48 h. The serum osmolarity was calculated from serum biological data and serum electrolytes as follows: serum osmolarity = $2(Na^{\pm} + K^{\pm})$ + blood glucose value/18 + blood urea nitrogen/2.8 [20]. The daily sodium intake and daily urine volume were recorded. Hyponatremia was defined as a decline in absolute values <131 mEq/L [21], occurring at any time until day 14. Attempts were made to correct these values with normal saline infusion.

2.3. Statistical methods

All data are presented as mean ± standard deviation. The distribution of baseline characteristics of the patients was evaluated between groups using descriptive statistics. The χ^2 and Fisher exact tests were used for paired data to test for differences in the distribution between groups. The Mann–Whitney *U* test was used to compare nonparametric data. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Table 1 shows the patients' characteristics. Among 97 patients with acute aSAH, 70 (72.2%) did not suffer from SVS throughout the postoperative course (non-spasm group), whereas 27 (27.8%) patients developed SVS within 14 days after the onset of aSAH (spasm group). The mean time of occurrence of SVS was at 8.81 ± 2.45 days after aSAH. The mean patient age was 56.6 ± 13.0 years in the non-spasm group and 65.0 ± 12.6 years in the spasm group. A total of 44 (62.9%) patients had good outcomes (mRS score, 0–2), 23 (32.9%) had poor outcomes (mRS score, 3–5), and three (4.2%) died (mRS score, 6) in the non-spasm group. Five (18.5%) patients had good outcomes, 18 (66.7%) had poor outcomes, and four (14.8%) died in the spasm group. Patients with SVS were older than those without SVS, and the occurrence of SVS affected outcomes.

Changes in serum sodium levels, daily sodium intake, and serum osmolarity

Fig. 1a shows the 14-day time course of serum sodium levels in the spasm and non-spasm groups. There were significant differences in the serum sodium levels between the groups on days 2, 6, and 8. On day 2, the serum sodium levels in the spasm group were significantly higher than those in the non-spasm group. Serum sodium levels in the spasm group subsequently became significantly lower than those in the non-spasm group on days 6 and 8. Fig. 1b shows the 7-day time course of serum sodium levels in the spasm group from 3 days before the onset of SVS to 3 days after the onset. From 1 day before SVS, serum sodium levels sequentially decreased significantly. The mean values for serum sodium were 138.1 ± 0.90 mEq/L at −2 days, 135.4 ± 1.04 mEq/L at −1 day and 132.9 ± 1.39 mEq/L on the spasm day. Fig. 1c shows the 14-day time course of daily sodium intake. Daily sodium intake was significantly higher in the non-spasm group than in the spasm group on day 3. Fig. 1d shows the 14-day time course of serum osmolarity in the two groups. Serum osmolarity in the spasm group was significantly lower than that in the non-spasm group on day 1 and on days 5–13.

3.2. Changes in daily urine volume and daily water balance

Fig.2a shows the 14-day time course of daily urine volume in the spasm and non-spasm groups. There was no significant difference in the daily urine volume between the groups. Fig.2b shows the 14-day time course of daily water balance in the two groups. Patients in both the groups were normovolemic throughout the study period, with no significant difference in the daily water balance between the groups. Fig.2c shows the 7-days course of daily urine volume in the spasm group from 3 days before the SVS onset to 3 days after the SVS onset. There was no significant change throughout the course. Fig.2d shows the 7-days course of daily water balance in the spasm group from 3 days before the SVS onset to 3 days after the SVS onset. There was no significant change throughout the course. Patients in the spasm group were also kept euvolemic around the time of the SVS onset.

4. Discussion

Serum sodium levels significantly decreased sequentially from 1 day before SVS but remained within the normal range. This observation may help to predict SVS under maintaining euvolemia and eunatremia after aSAH. Some studies have shown that the onset of SVS is related to hyponatremia, which predicts SVS [9–15]. However, no previous reports have shown that serum sodium levels decrease within the normal range before the occurrence of SVS. In many previous studies focused on the existence of cerebral salt wasting syndrome (CSWS) and/or preventing SVS, the target serum sodium levels were approximately 140 mEq/L and were maintained with sodium administration [11–13]. In other studies focused on elucidating the pathogenesis of hyponatremia [i.e., CSWS, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cortisol insufficiency], serum sodium levels were adjusted when hyponatremia was detected [22–24], and hyponatremia due to SIADH was treated with a restricted amount of 0.9% saline or 3% hypertonic saline [25]. In our study protocol, patients were treated with 0.9% saline when their serum sodium levels dropped to <131 mEq/L. Through this management protocol, we could closely follow serum sodium levels in patients with aSAH in order to provide early intervention.

We also demonstrated that serum osmolarity in the spasm group was significantly lower than that in the non-spasm group. Hyponatremia caused low serum osmolarity, which in turn led to brain edema. Brain edema might affect the microcirculation of the brain and aggravate SVS. Serum sodium levels in the spasm

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Table 1
Characteristics of patients who suffered from symptomatic vasospasm and those without symptomatic vasospasm.

Variable		Number of patients		P value
		Non spasm N = 70	Spasm N = 27	
Mean age (range)		56.6 (25–85)	65.0 (46–87)	<0.01
Men		20 (28.6%)	12 (44.4%)	0.13
Women		50 (71.4%)	15 (55.6%)	
WFNS grade	I–II	32 (45.7%)	9 (33.3%)	0.27
	III–V	38 (54.3%)	18 (66.7%)	
Fisher group	3	56 (80.0%)	20 (74.1%)	0.52
	4	14 (20.0%)	7 (25.9%)	
Aneurysm site	Anterior	59 (84.3%)	23 (85.2%)	0.91
	Posterior	11 (15.7%)	4 (14.8%)	
Treatment	Clipping	47 (67.1%)	14 (51.9%)	0.16
	Coiling	23 (32.9%)	13 (48.1%)	
Outcome (mRS)	0–2	44 (62.9%)	5 (18.5%)	<0.01
	3–5	23 (32.9%)	18 (66.7%)	
	6	3 (4.2%)	4 (14.8%)	

Non-spasm group: patients without symptomatic vasospasm, spasm group: patients with symptomatic vasospasm, mRS; modified Rankin scale, WFNS; World Federation of Neurosurgical Societies.

group were significantly higher than those in the non-spasm group on day 2. This result may have led to the finding that sodium intake in the spasm group was significantly lower than that in the non-spasm group on day 3. Insufficient sodium intake might have contributed to the hyponatremia and lower osmolarity in the spasm group after day 5. Hypothalamopituitary dysfunction is a common complication of aSAH [24,26,27] and may contribute to the malfunction of sodium homeostasis in patients with aSAH. In the current study, SVS was more frequent in older patients. Age significantly affects the kidney's capacity to conserve sodium [28], and an increase in age is significantly associated with hyponatremia in patients with aSAH [29]. Therefore, hypopituitarism after aSAH and renal dysfunction related to age are other possible causes of hyponatremia and lower osmolarity in patients with aSAH.

There was no difference in the daily urine volume between the spasm and non-spasm groups. Furthermore, patients in both groups were normovolemic during the 14–day observation period. These results are different from those of previous studies focused on the existence of CSWS [11–13]. Many reports have shown that polyuria caused by natriuresis occurs during the 14 days from the onset of aSAH [10,11–14] and that natriuresis and an increased urine volume are predictors of SVS [10,12,14]. Daily urine volume and daily water balance did not significantly change in our study, and these two factors were not predictors of SVS. In our management protocol, patients were not treated with prophylactic fluid therapy to prevent SVS. Furthermore, patients received additional sodium boluses using 0.9% saline when their serum sodium levels dropped to <131 mEq/L [21]. We did not use hypertonic saline [30], which has some diuretic effects. These differences in the management protocol may have resulted in a lower daily urine volume in our study compared with that in previous studies [11,12,14]. Excess sodium intake to maintain a high serum sodium level may lead to natriuresis and polyuria in patients with aSAH.

To some extent, the physiological changes observed in our study (euvolemia with decreased serum sodium levels and low osmolarity) met the criteria for SIADH [31]. We did not measure other essential markers for diagnosing SIADH, such as urinary osmolality, urinary sodium levels, and thyroid and adrenal function. Therefore, we could not clearly distinguish SIADH from CSWS in our study.

CSWS is defined as a renal loss of sodium during intracranial disease, leading to hyponatremia and a decrease in extracellular fluid volume [32]. The pathogenesis of this disorder is still not completely understood [23,33]. The treatment of CSWS requires volume replacement and the maintenance of a positive sodium balance. Conversely, the treatment of SIADH requires fluid restriction [33,34]. However, fluid restriction is potentially dangerous in patients with aSAH and SVS [1,2,33]. Therefore, hyponatremia due to SIADH is treated with a restricted amount of 0.9% saline or 3% hypertonic saline [25].

Several studies have reported that SIADH is more likely to occur, than is CSWS [22–24]. Some researchers have pointed out that the underlying etiology of hyponatremia that is observed in patients with aSAH is multifactorial, with different mechanisms occurring at different time points [15,29]. Early-phase hyponatremia is consistent with SIADH and later-phase hyponatremia with CSWS [15]. Actually, an antidiuretic hormone surge occurs on the day of aneurysm rupture and then immediately drops to normal levels [35]. The important difference between CSWS and SIASH is that CSWS involves hypovolemia caused by natriuresis, whereas SIADH is a euvolemic or hypervolemic condition. However, most institutions are currently targeting euvolemia and eunatremia in aSAH patients to avoid complications. Precise water and sodium management is usually performed. Considering such a particular clinical setting, it is clearly difficult to distinguish SIADH from CSWS. Furthermore, there are no published data on the appropriate treatment of hyponatremia in aSAH patients. Large prospective studies are needed to establish an appropriate management protocol for the maintenance of sodium and water homeostasis in patients with aSAH.

There are some limitations in this study. First, this was a retrospective study. Second, the patient population was small, with less than 100 patients. Third, we did not measure urinary osmolality, urinary sodium levels, and endocrinological factors, which are required to accurately understand the clinical condition of patients with aSAH.

5. Conclusion

SVS occurs more frequently in older patients and affects outcomes. The decrease in serum sodium levels occurs on the day before SVS. This observation may help predict SVS when patients with aSAH are treated under euvolemic conditions. Additional large prospective studies are required to resolve the detailed pathophysiology in relation to sodium and water homeostasis and SVS in patients with aSAH.

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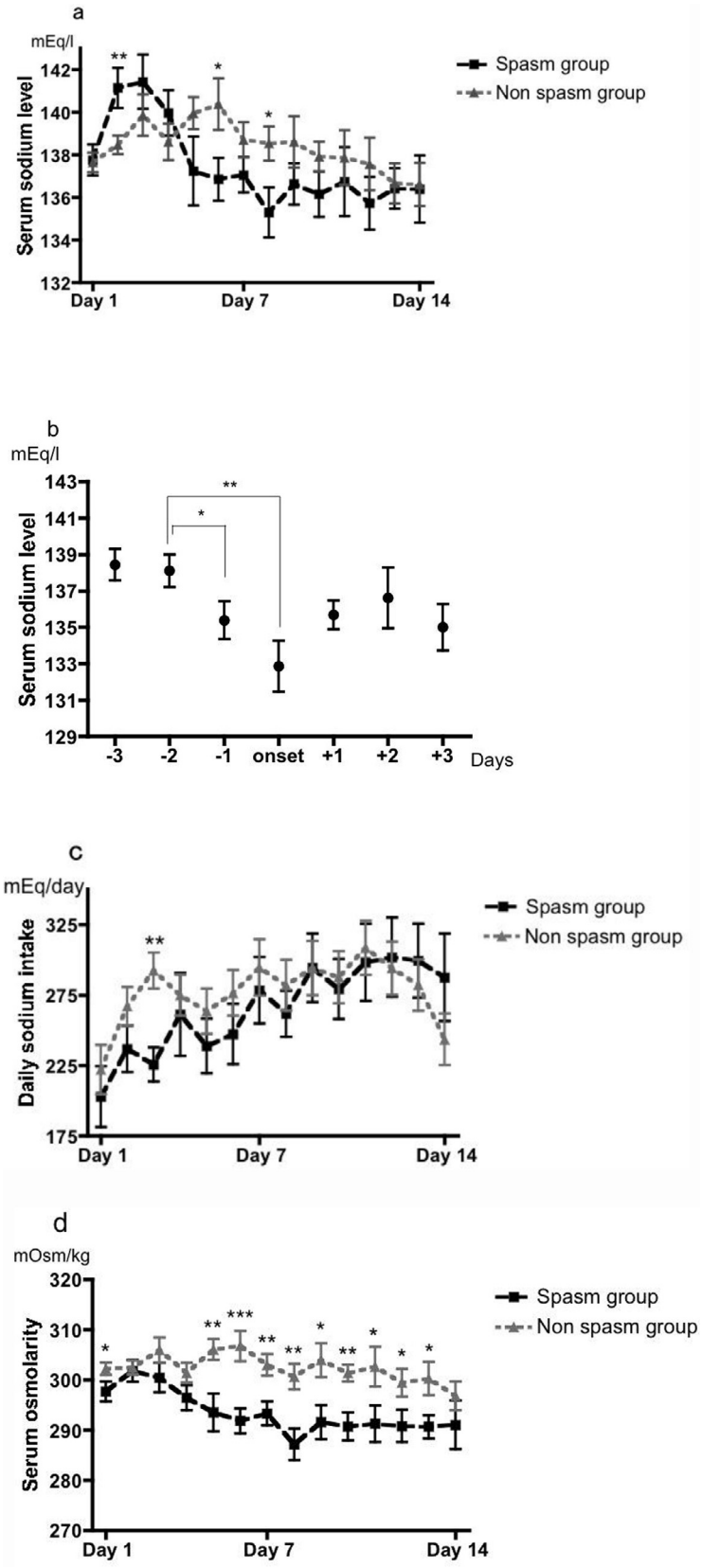

Fig. 1. Comparison of serum sodium levels between the spasm and non-spasm groups. The 14-day time course of serum sodium levels (a). The 7-day time course of serum sodium levels in the spasm group from 3 days before the onset of SVS to 3 days after the onset (b). The 14-day time course of daily sodium intake (c). The 14-day time course of serum osmolarity (d). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. SVS, symptomatic vasospasm.

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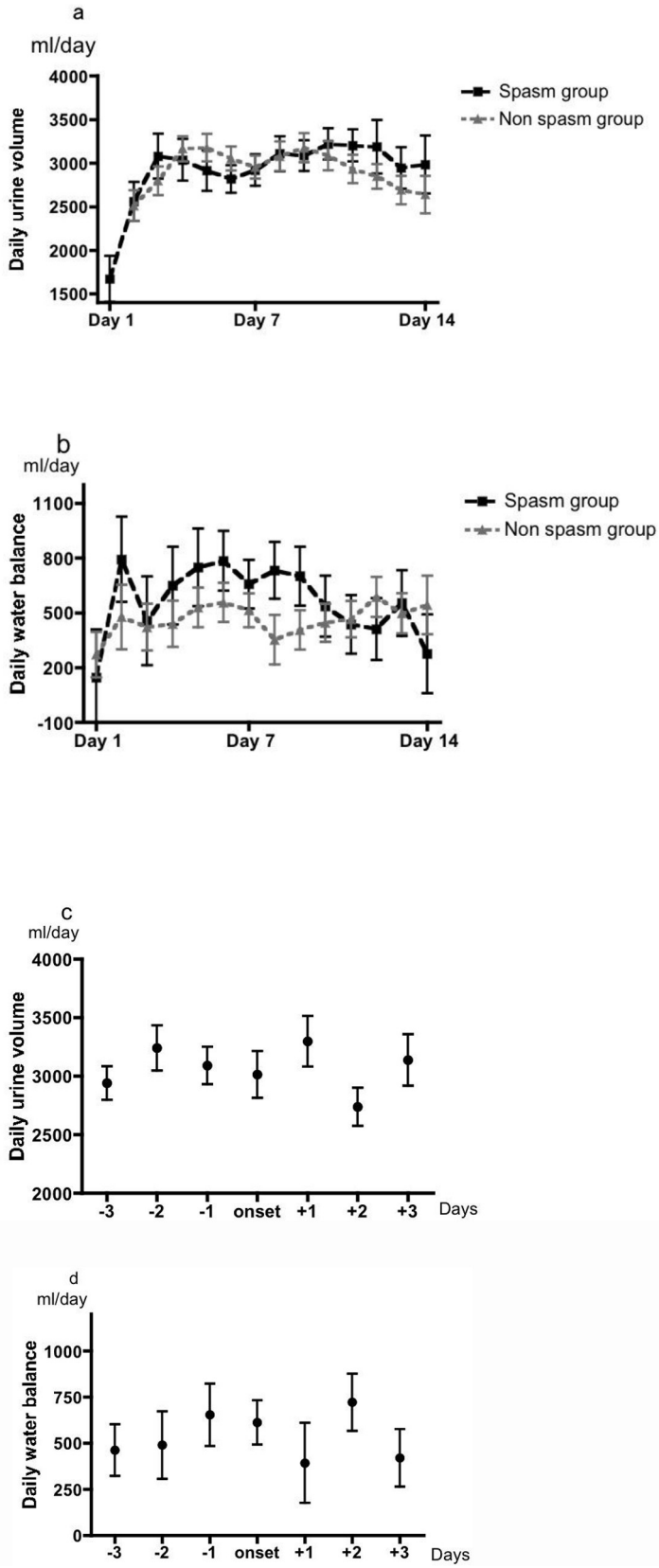

Fig. 2. Changes in daily urine volume and daily water balance. The 14-day time course of daily urine volume in the spasm and non-spasm groups (a). The 14-day time course of daily water balance in the spasm and non-spasm groups (b). Patients in both groups were kept normovolemic throughout this period. The 7-day course of daily urine volume in the spasm group from 3 days before SVS onset to 3 days after SVS onset (c). The 7-day course of daily water balance in the spasm group from 3 days before SVS onset to 3 days after SVS onset (d). SVS, symptomatic vasospasm.

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Disclosure statement

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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