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Decreased serum sodium level predicts symptomatic vasospasm in patients with subarachnoid hemorrhage

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Highlights:

- ◇We retrospectively investigated the predictors of symptomatic vasospasm in terms of water and sodium homeostasis after subarachnoid hemorrhage.
- ◇Symptomatic vasospasm occurs more often in older patients and affects outcome.
- ◇Serum sodium level decrease occurs one day before symptomatic vasospasm.
- ◇This observation may help predict symptomatic vasospasm.

Abstract

Background: Symptomatic vasospasm is one of the major causes of morbidity and mortality in patients with subarachnoid hemorrhage. Hyponatremia and dehydration due to natriuresis after subarachnoid hemorrhage is related to symptomatic vasospasm. Therefore, nowadays most institutions target to euvoolemia and eunatremia in subarachnoid hemorrhage patients to avoid complications. In this study, we retrospectively investigated the predictors of symptomatic vasospasm in terms of water and sodium homeostasis under maintaining euvoolemia and eunatremia after subarachnoid hemorrhage. **Methods:** We monitored changes in serum sodium levels, serum osmolality, daily sodium intake, daily urine volume, and daily water balance during 14 days after subarachnoid hemorrhage. Outcome was assessed using the modified Rankin scale one 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 and symptomatic vasospasm affected outcome. Serum sodium levels were sequentially significantly decreased within normal range from one day before occurrence of symptomatic vasospasm. Serum osmolality of the spasm group was lower than that of the non-spasm group. **Conclusions:** Symptomatic vasospasm occurs more often in older patients and affects outcome. Serum sodium level decrease occurs one day before symptomatic vasospasm. This observation may help predict symptomatic vasospasm.

(200 words)

Introduction

Symptomatic vasospasm (SVS) is one of the major causes of morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage (aSAH).[1-3] Preventing SVS is preferable to controlling symptoms of SVS or reversing existing spasms. Therefore, predicting SVS is important. Although many studies introduced predictors of SVS [4-8], predicting SVS correctly and in a timely manner is difficult because of its complex nature.

Hyponatremia and dehydration due to natriuresis after aSAH is related to SVS and predicts of SVS [9-15]. In addition, both hypernatremia and hypervolemia after SAH are associated with poor outcome [16,17]. Therefore, nowadays most institutions target to euvoolemia and eunatremia in a SAH patients to avoid complications. In this study, we retrospectively investigated the predictors of SVS in terms of water and sodium homeostasis under maintaining euvoolemia and eunatremia after aSAH.

Clinical material and methods

Patients

From April 2007 to June 2016, 86 patients with acute aSAH were treated with either surgical clipping or endovascular coiling in Steel Memorial Hirohata Hospital. From January 2014 to June 2016, 20 patients with acute aSAH were treated with endovascular coiling in Hyogo Brain and Heart Center. The institutional review boards in each hospital approved the study. Among these 106 patients, 97 were included in this study. Nine patients were excluded because they were treated for longer than 3 days after onset of aSAH (6 patients) or required dialysis (3 patients).

We did not include patients who suffered from dissecting aneurysms and those who died within 10 days after the onset of aSAH. The outcome was assessed using the modified Rankin scale (mRS) one month after onset of aSAH[18].

Management protocol

All patients with aSAH were managed in the intensive care unit. Patients underwent either surgical clipping or endovascular coiling for treatment of a ruptured aneurysm within 48 hours from the onset. The treatment modality was selected based on a consensus reached between the neurosurgical and endovascular team. 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 hours. Negative water balance was corrected with normal saline infusion. All of the patients were administered fasudil hydrochloride hydrate (Eril; Asahi Kasei Co., Tokyo, Japan) at a dose of 90 mg/d to prevent vasospasm from the day after surgery for aSAH to day 14 [19]. The Glasgow Coma Scale and pupil examinations were carried out every 2 hours.

SVS was defined as neurological deterioration in combination with radiographic studies (including perfusion computed tomography, magnetic resonance imaging, or angiography) and with 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. A blood cell count, serum biochemical data, and serum electrolytes were evaluated at least every 48 hours. Serum osmolarity was calculated from serum biological data and serum electrolytes as follows: serum osmolarity = $2(\text{Na}^+ + \text{K}^+) + \text{blood glucose value} / 18 + \text{blood urea nitrogen} / 2.8$ [20]. Daily sodium

intake and daily urine volume were recorded. Hyponatremia was defined as absolute values declining below 131 mEq/l [21], occurring at any time until day 14. Attempts were made to correct these values with normal saline infusion.

Statistical methods

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

Results

Patients' characteristics

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

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

Figure 1a shows the 14-day time course of serum sodium levels in the spasm and non-spasm groups. There were significant differences in serum sodium levels on days 2, 6, and 8 between the groups. On day 2, serum sodium levels in the spasm group were significantly higher than those in the non-spasm group. Serum sodium levels in the spasm group then became significantly lower than those in the non-spasm group on days 6 and 8. Figure 1b shows the 7-day time course of serum sodium levels in the spasm group from 3 days before onset of SVS to 3 days after onset. From 1 day before SVS, serum sodium levels sequentially significantly decreased. The mean values of serum sodium level were 138.1 ± 0.90 mEq/l on -2 day, 135.4 ± 1.04 mEq/l on -1 day and 132.9 ± 1.39 mEq/l on spasm day respectively. Figure 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. Figure 1d shows the 14-day time course of serum osmolality in the two groups. Serum osmolality in the spasm group was significantly lower than that in the non-spasm group on days 1 and 5 to 13.

Changes in daily urine volume and daily water balance

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

before SVS onset to 3 days after SVS onset. There is no significant change through the course. Patients in spasm group were also kept euvolesmia around SVS onset.

Discussion

We found that serum sodium levels significantly decreased sequentially from one day before SVS within normal range. This observation may help to predict SVS under maintaining euvolesmia and eunatremia after aSAH. Some studies have shown that the onset of SVS is related to hyponatremia, and hyponatremia predicts SVS [9-15]. However, no previous reports have shown that serum sodium levels decrease before occurrence of SVS within normal range. In many previous studies that focused on the existence of cerebral salt wasting syndrome (CSWS) and/or preventing SVS, serum sodium target levels were around 140 mEq/l and maintained with sodium administration [11-13], whereas in the 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 level were adjusted when become hyponatremia [22-24]. In these studies, hyponatremia due to SIADH was treated by restricted amount of 0.9% saline or 3% hypertonic saline [25]. In our study protocol, patients were treated to add 0.9% saline when their serum sodium level dropped to less than 131 mEq/l. In this management protocol, we could follow closely serum sodium levels on patients with aSAH to ready for early intervention.

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

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 affected hyponatremia and lower osmolality in the spasm group after day 5. Hypothalamopituitary dysfunction following aSAH is a common complication of aSAH [24,26,27], and may contribute to 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 increasing age is significantly associated with hyponatremia in patients with aSAH [29]. Therefore, hypopituitarisms after aSAH and renal dysfunction related to age are other possible causes of hyponatremia and lower osmolality in patients with aSAH.

There was no difference in daily urine volume between the spasm and non-spasm groups. Furthermore, patients in both groups were normovolemic during 14 days. These results are different from previous studies focused on the existence of CSWS [11-13]. Many reports have shown that polyuria caused by natriuresis occurs during 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. And then, patients received additional sodium boluses using 0.9% saline when their serum sodium levels dropped to less than 131 mEq/l [21]. We did not use hypertonic saline [30], which have some diuretic effects. These differences in management protocol may have resulted in less daily

urine volume in our study compared with that in previous studies [11,12,14]. Excess sodium intake for maintaining a high serum sodium level may lead to natriuresis and polyuria in patients with aSAH.

To some extent, these physiological changes in our study (euvolemia with decreased serum sodium level and low osmolality) met the criteria of 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]. Treatment of CSWS requires volume replacement and maintenance of a positive sodium balance. On the other hand, 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 by restricted amount of 0.9% saline or 3% hypertonic saline [25].

Several studies reported that SIADH is more likely to occur than CSWS [22-24]. Some researchers 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]. The early phase hyponatremia is consistent with SIADH and the latter with CSWS [15]. Actually antidiuretic hormone surge occur on the day of aneurysm rupture, and then immediately dropped to normal level [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, nowadays most institutions target to euvoemia and eunatremia in a SAH patients to avoid complications. Precise water and sodium management are usually carried out. Considering such a particular clinical setting, it is difficult to distinguish SIADH from CSWS clearly. Actually, there is no published data on the appropriate treatment of hyponatremia in aSAH patients. We need a large prospective study to resolve the appropriate management protocol to maintain sodium and water homeostasis in patients with aSAH.

There are some limitations of 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.

Conclusion

SVS occurs more frequently in older patients and affects outcome. Serum sodium level decrease occurs on the day before SVS. This observation may help predict SVS when patients with aSAH are treated under euvolemic state. A further large prospective study is required to resolve the detailed pathophysiology among the sodium and water homeostasis and SVS in patients with aSAH.

Disclosure Statement

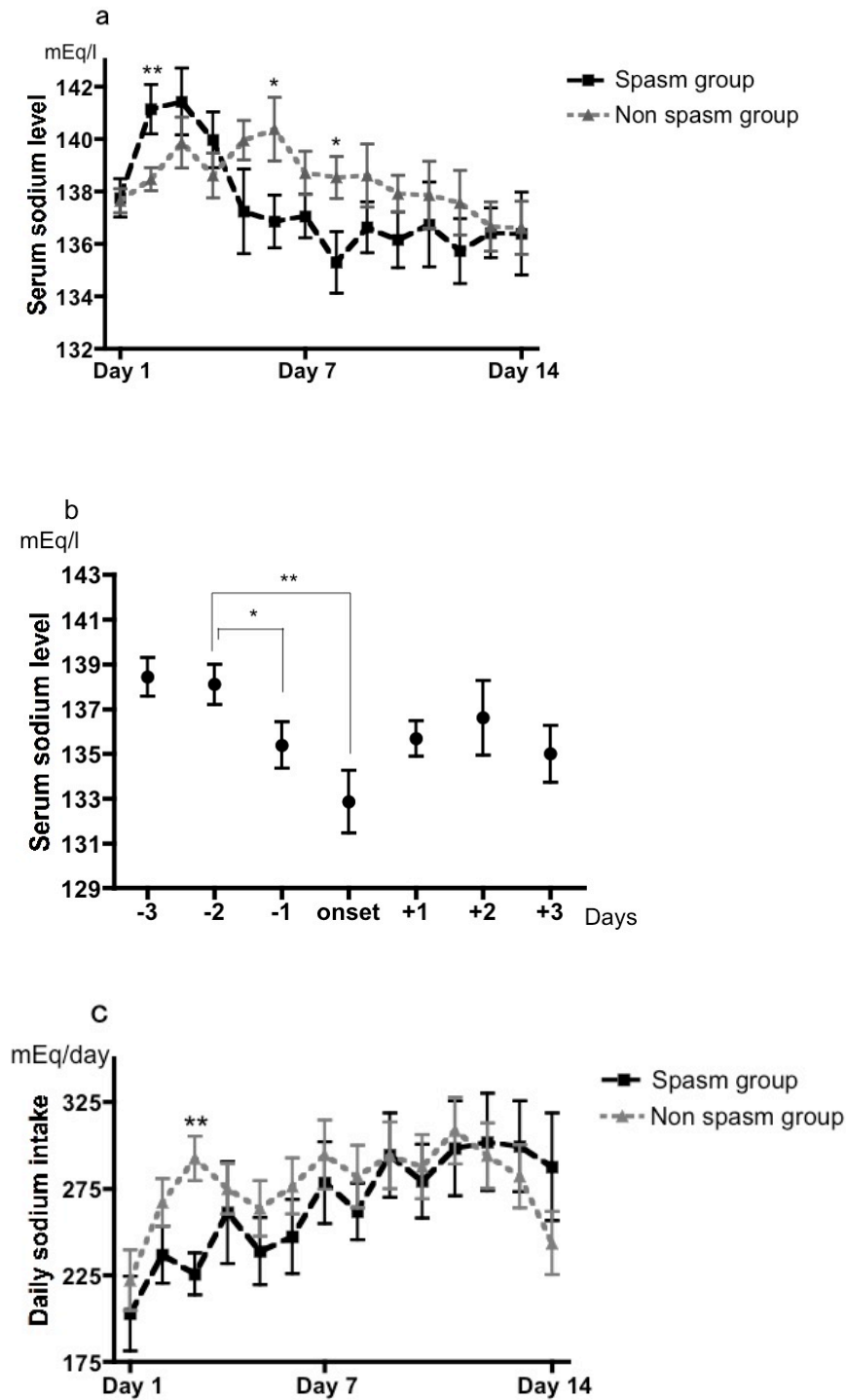
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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.

Figure 1. Comparison of serum sodium levels between the spasm and non-spasm groups.



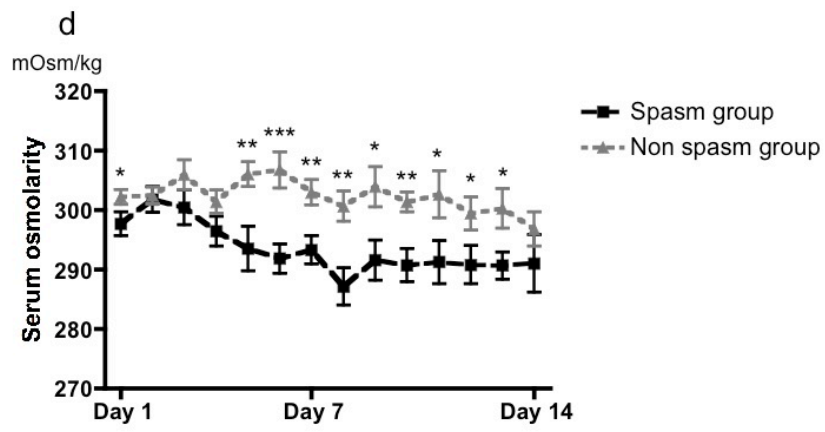
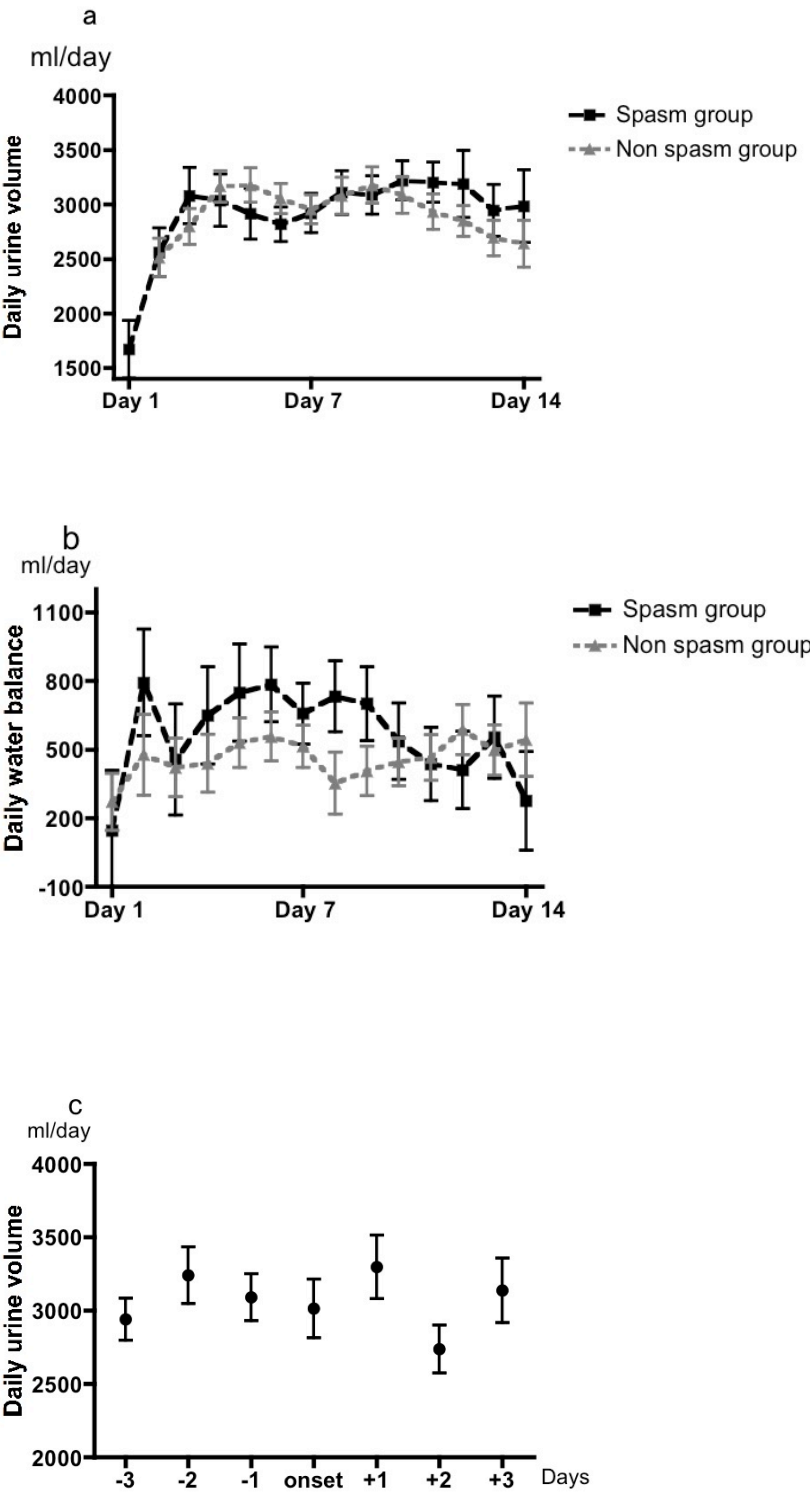
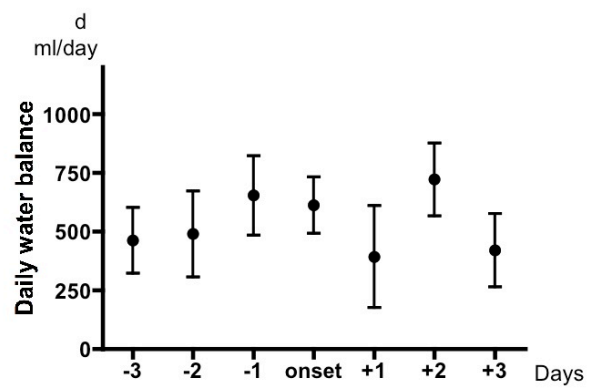


Figure 2. Changes in daily urine volume and daily water balance.





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Figure legends

Figure 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 onset of SVS to 3 days after onset (b). The 14-day time course of daily sodium intake (c). The 14-day time course of serum osmolality (d). *P < 0.05, **P < 0.01, ***P < 0.001. SVS; symptomatic vasospasm.

Figure 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-days course of daily urine volume in spasm group from 3 days before SVS onset to 3 days after SVS onset (c). The 7-days course of daily water balance in spasm group from 3 days before SVS onset to 3 days after SVS onset (d). SVS; symptomatic vasospasm