Chronic Hypernatremia Derived from Hypothalamic Dysfunction: Impaired Secretion of Arginine Vasopressin and Enhanced Renal Water Handling

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Abstract. We analyzed the disorder of water metabolism in a 32 year-old female with chronic hypernatremia. She had meningitis at 4 years, and ventriculo-peritoneal shunt operation at 13 years because of normal pressure hydrocephalus. At 14 years hypernatremia of 166 mmol/l was initially found and thereafter hypernatremia ranging from 150 to 166 mmol/l has been persisted for the last 18 years. Physical and laboratory findings did not show dehydration. Urine volume was 750–1700 ml per day and urinary osmolality (Uosm) 446–984 mmol/kg, suggesting no urinary concentrating defect. Plasma arginine vasopressin (AVP) levels ranged from 0.4 to 1.2 pmol/l despite hyperosmolality of 298 through 343 mmol/kg under ad libitum water drinking. There was no correlation between plasma osmolality (Posm) and plasma AVP levels, but Uosm had a positive correlation with Posm (r=0.545, P<0.05). Hypertonic saline (5% NaCl) infusion after a water load increased Uosm from 377 to 679 mmol/kg, and plasma AVP from 0.2 to 1.3 pmol/l. There was a positive correlation between Posm and plasma AVP levels in the hypertonic saline test (r=0.612, P<0.05). In contrast, an acute water load (20 ml/kg BW) verified the presence of impaired water excretion, as the percent excretion of the water load was only 8.5% and the minimal Uosm was as high as 710 mmol/kg. Urinary excretion of aquaporin-2 remained low in concert with plasma AVP levels. No abnormality in pituitary-adrenocortical function was found. These results indicate that marked hypernatremia is derived from partial central diabetes insipidus and elevated threshold of thirst, and that enhanced renal water handling may contribute to maintenance of body water in the present subject.

Key words: Osmotic regulation, Hyperosmolality, Suprasellar arachnoid cyst, Urine concentrating ability

SODIUM (Na) distributes in extracellular fluid by approximately 90% in animals and human. A decrease in body fluid promptly elevates serum Na concentration in pathophysiological condition. Most of hypernatremia greater than 150 mmol/l is associated with such a deficit of body fluid [1]. Circu-
hemoconcentration, azotemia, hyperreninemia and changes in body weight associated with the development and/or correction of the hypernatremia. If Na content is extremely high, hypervolemia has to be accompanied secondarily. If dehydration seems to be absent, body fluid homeostasis could be altered to a new steady state. Such an alteration is hypothesized in the literature as a reset of the osmostat [4, 5, 7, 8], that controls release of arginine vasopressin (AVP). Also, this may come from central diabetes insipidus and the associated compensation of body fluid deficit.

We report here a marked hypernatremic subject whose hypernatremia has been persisted between 150 and 166 mmol/l for the last 18 years. The present study was undertaken to determine what alteration in AVP release and its action on kidney is linked with hypernatremia in this patient.

Case Report

A 32 year-old woman was examined to determine the pathogenesis of hypernatremia. She had meningitis at 4 years. At 9 years she became obese and thereafter obesity has been persisted. Epileptic attack occurred at 10 years, and she began to take antiepileptic agents. Brain ventricular dilatation was found on brain CT scan at 13 years. Because normal pressure hydrocephalus was diagnosed, she received a ventriculo-peritoneal shunt operation at 14 years in Department of Neurosurgery, Jichi Medical School Hospital. She was again admitted to our hospital because of pneumonia at 14 years. At that time, hypernatremia of 166 mmol/l was initially found, but she had no disturbance of consciousness. Endocrinological examination showed subclinical primary hypothyroidism and impaired secretion of growth hormone, but there was no other endocrine disorders, including central diabetes insipidus. After that hypernatremia has been persisted during the past 18 years period, and serum Na levels have ranged from 150 to 166 mmol/l. She has not complained of anything related to hypernatremia. During the 18 years period, she has taken 100 µg thyroxine, but any other specific treatment for hypernatremia had not been performed. She was hospitalized to our hospital to further examine the pathophysiology of hypernatremia on October 29, 1999.

Physical findings at hospitalization were height, 136 cm; weight, 63 kg; blood pressure, 118/62 mmHg without postural changes; and pulse rate, 84 beats /min with regular rhythm. She was conscious and alert. She had mental retardation and dysmenorrhea. She was not thirsty, and had no dry skin and tongue. Neurological examination showed no abnormal findings.

Laboratory studies showed white blood cells were 4500/cmm; red blood cells, 385 x 104/cmm; hemoglobin, 12.6 g/dl; hematocrit, 37.8%; and platelets, 15.7 x 109/cmm. Serum Na level was 158 mmol/l; potassium (K), 3.7 mmol/l; chloride, 119 mmol/l. Blood urea nitrogen level was 5.0 mmol/l; serum creatinine level, 37.1 µmol/l; and serum uric acid level, 362.2 µmol/l. Fasting blood glucose was 5.3 mmol/l. Plasma osmolality (Posm) was 317 mmol/kg and urinary osmolality (Uosm), 611 mmol/kg. Urine volume ranged 750-1700 ml/day. Urinary excretion of Na and K were 87.2 and 9.6 mmol/day, respectively. A urinalysis showed no abnormalities. Creatinine clearance was 1.76 ml/s. Plasma AVP level was as low as 0.6 pmol/l despite hyperosmolality of 326 mmol/kg. Urinary excretion of aquaporin-2 (AQP-2) was 51.4 fmol/mg creatinine under ad libitum water drinking, which is 153.3 ±28.1 fmol/mg creatinine in the normal subjects [9]. Plasma ACTH level was 5.3 pmol/l and serum cortisol, 251.1 nmol/l in the early morning. Plasma renin activity was 0.56 ng/L/s and plasma aldosterone level, 270 pmol/l at supine position. The basal levels of anterior pituitary hormones were within the normal ranges, except for the reduced gonadotropin. Brain MRI shows cystic change in the suprasellar region with marked enlargement of lateral ventricles (Fig. 1), suggesting suprasellar arachnoid cyst. In addition, there was reduced high signal of the posterior pituitary on T1-weighted MRI.

Methods

Hypertonic saline test

After an overnight fast, the study was started at 0800 h as described previously [10]. The subjects were allowed to drink water freely before the start of the protocol. After urination, water (20 ml/kg BW)
were subjected to measurements of urine volume, Uosm, urinary excretions of creatinine and AQP-2, serum Na, Posm and plasma AVP levels [9, 11]. In addition, the hypertonic saline test was carried out in 5 normal subjects as a control, whose ages ranged 21–26 years. They were 3 males and 2 females. The present protocol was approved by the ethical committee of Jichi Medical School Hospital for the human study. We obtained informed consent from all the subjects who joined the present study.

Acute water load test

Acute water load test was performed, as described in our previous report [9]. After an overnight fast, the study was started at 0800 h. The subjects were allowed to drink water freely before the start of the protocol. After urination, blood was taken. Thereafter, water (20 ml/kg BW) was given orally for 30 min. Urine and blood collections were made at 30 min intervals during the 4 h observation period. The subjects were allowed to sit or stand to urinate. Urine samples were subjected to measurements of urine volume, Uosm and urinary excretions of creatinine and AQP-2, and blood samples were to measure of Posm and plasma AVP levels. Also, acute water load test was carried out in 7 normal subjects as a control. They were 4 males and 3 females, whose ages ranged 22–35 years.

Results

After founding hypernatremia at 14 years, she has been regularly examined by pediatricians, followed by our out-patient clinic. Since 1990 at her 22 years, blood and urine collections have been made under ad libitum water drinking at 0800 h–1000 h once every few months, and Posm, Uosm and plasma AVP levels were determined. Fig. 2 shows the relationships between Posm and plasma AVP levels and between Posm and Uosm. Plasma AVP levels were relatively low as compared to the elevated Posm, and there was no correlation between Posm and plasma AVP levels. In contrast, Uosm had a positive correlation with Posm ($r=0.545$, $P<0.05$). In addition, plasma renin activity and plasma aldosterone were examined at supine position at least once a year during the last one decade, but they had remained within the normal

![Fig. 1. Brain MRI at 32 year-old. (a) T1-weighted MRI, axial view, (b) T2 MRI, axial view, and (c) T2 MRI, coronal view.](image-url)
ranges (data not shown).

Table 1 and Fig. 3 show the results of hypertonic saline test. After the water intake, plasma AVP levels were decreased in response to the decrease in Posm in the control subjects. The plasma AVP level was relatively low compared with the Posm in the patient. Accordingly, Uosm was reduced to 76.2 ± 7.9 mmol/kg, in accordance with the minimal urinary excretion of AQP-2 of 27.4 ± 10.9 fmol/mg creatinine in the control subjects. In the patient, the water load did not reduce Uosm, and the urinary excretion of AQP-2 remained low. After the infusion of hypertonic saline, plasma AVP levels were increased in response to an elevation of Posm in the control subjects. In the patient plasma AVP increased from 0.2 to 1.3 pmol/l in accordance with an increase in Posm from 321 to 341 mmol/kg. Uosm and urinary excretion of AQP-2 promptly increased in the control subjects. In contrast, Uosm increased from 377 to 679 mmol/kg and free water clearance decreased from -0.09 to -0.61 ml/min, but urinary excretion of AQP-2 did not increase in the patient. As shown in Fig. 3, plasma AVP levels have a positive correlation with Posm in both the control subjects and the patient [the control subjects: plasma AVP (pmol/l) = 0.077 × Posm (mmol/kg) - 21.449, r = 0.874, P < 0.0001, and the patient: plasma AVP = 0.032 × Posm - 9.930, r = 0.612, P < 0.05]. In the patient plasma AVP levels were shifted to the right, suggesting the reduced secretion of AVP.

Acute water load test was carried out in the patient and the control subjects. Percent excretion of the water load was 77.3 ± 7.8% in the control subjects, but it was only 8.5% in the patient. As shown in Fig. 4, the minimal Uosm was as high as 710 mmol/kg in the patient, whereas it was decreased to 112.9 ± 16.4 mmol/kg in the control subjects. In the patient Posm was extremely as high as 316 mmol/kg and the water load only reduced Posm to 305 mmol/kg. Plasma AVP level and urinary excretion of AQP-2 remained low and did not alter after the acute water load. In the control subjects the acute water load significantly decreased Posm from 288.6 ± 3.2 to 282.9 ± 3.3 mmol/kg, followed by significant reduction in plasma AVP levels and urinary excretion of AQP-2.

Discussion

The patient has a peculiar clinical course as hypernatremia ranging from 150 to 166 mmol/l has been persisted for the last 18 years. Physical finding had not shown dehydration. Plasma renin activity and plasma aldosterone concentration at supine position, and renal function had remained within the normal ranges during the last one decade. Also, there was no noticeable changes in hematocrit and hemoglobin levels during the same period. These findings did not support hemoconcentration in the present patient. However, the alteration in serum Na levels was changeable in a wide range among the successive samples, and this could suggest that hypernatremia is dependent on variations in total body water, but not on body Na content itself. Whenever she had body fluid deficit less than 10%,
we have to note that physical and laboratory findings could not accurately detect her body fluid state.

The maneuvers of the hypertonic saline test and the acute water load test characterized her urinary concentrating ability. Though the plasma AVP levels were extremely low as compared to the high Posm, urinary concentrating ability may have been kept normal. The urine volume was in the normal range, and the Uosm ranged from 446 to 984 mmol/kg under ad libitum water drinking. Such hypertonic urine was also found in chronic hypernatremic patients in the literature [6-8]. Also, the Uosm and plasma AVP increased after the hypertonic saline loading, but their increments were not sufficient as compared to those in the control subjects, suggesting partial central diabetes insipidus. On the contrary, urinary diluting defect was also evident, as the percent excretion of the water load was markedly reduced and the minimal Uosm remained high in the acute water load test. This is the first report to verify the impairment in urinary diluting ability, as the previous studies had not evaluated at all [6-8]. The urinary excretion of AQP-2 was less in the patient than that in the control subjects, which is in concert with the reduced levels of plasma AVP. The impairment in water excretion was evident, and two possible mechanisms for water retention could be involved. First, physical and laboratory findings of normal glomerular filtration rate, normal plasma renin activity and aldosterone concentration seem unlikely to support the presence of severe dehydration.

### Table 1. Changes in Uosm, urinary excretion of AQP-2 (UAQP-2), Posm and plasma AVP levels in the hypertonic saline (5% NaCl) test

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>30</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uosm, mmol/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>641</td>
<td>736</td>
<td>532</td>
<td>377</td>
<td>679</td>
</tr>
<tr>
<td>Controls</td>
<td>987.4±99.1</td>
<td>172.2±35.9</td>
<td>76.2±7.9</td>
<td>505.2±106.7</td>
<td>728.2±55.2</td>
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<tr>
<td>UAQP-2, fmol/mg creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>34.1</td>
<td>26.4</td>
<td>25.6</td>
<td>47.8</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>288.0±27.8</td>
<td>186.2±67.9</td>
<td>27.4±10.9</td>
<td>211.3±27.6</td>
<td>249.6±30.5</td>
</tr>
<tr>
<td>Posm, mmol/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>326</td>
<td>321</td>
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<tr>
<td>Controls</td>
<td>288.5±1.5</td>
<td>284.5±0.9</td>
<td>297.0±0.8</td>
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<td>Plasma AVP, pmol/l</td>
<td></td>
<td></td>
<td></td>
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<td>Patient</td>
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<td>0.2</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
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<td>0.4±0.1</td>
<td>1.7±0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control group has 5 normal subjects. Values are means±SEM.

![Fig. 3. Relationship between plasma osmolality (Posm) and plasma AVP levels in the hypertonic saline test.](image)

Closed circles (●) show the control subjects, which have: plasma AVP levels (pmol/l)=0.077×Posm (mmol/kg)−21.449, r=0.874, P<0.0001. Open circles (○) show the patient, which has: plasma AVP=0.032×Posm−9.930, r=0.612, P<0.05.
but it is not ruled out that the impairment in water excretion may be linked to body fluid deficit by reducing renal blood flow. Second, alteration in free water clearance suggested the involvement of hydro-osmotic effect of AVP, though the plasma AVP levels and urinary excretion of AQP-2 were low. In addition, the collection of plasma and urine during the last one decade showed no correlation between Posm and plasma AVP levels. However, there was weak positive correlation between Posm and Uosm. The small variation in plasma AVP levels might affect the statistical analysis, but these findings also support that urinary concentrating ability could closely linked to plasma AVP levels. Renal water handling seems likely to be kept normal, and it should participate in the maintenance of body water in compensation for the reduction in osmotically-regulated AVP secretion in the present patient. The findings regarding the hydroosmotic action of AVP were not always consistent, and further study will be necessary to elucidate the exact mechanisms for AVP-dependent water retaining.

Is AVP release still regulated by an osmotic stimulation? [12, 13]. Plasma AVP levels and urinary excretion of AQP-2 remained low in the patient, but Uosm had a positive correlation with Posm under ad libitum water drinking (Fig. 2), and the free water clearance became further negative in the hypertonic saline test. These findings may suggest that the urinary concentrating mechanism is controlled by an osmotic release of AVP in the present patient. Osmotic regulation of AVP release in the hypertonic saline test is shown in Fig. 3, and there was clearly the positive correlation between Posm and plasma AVP levels in the control subjects. In the patient the plasma AVP levels were shifted to the right, and the values of plasma AVP were markedly low as compared to the respective Posm. However, there was a weak positive correlation between Posm and plasma AVP levels. The osmotic control of AVP release is deranged in the patient, indicating partial central diabetes insipidus. The abnormality should be associated with an organic disorder in the brain. Hydrocephalus and suprasellar arachnoid cyst may be the major determinant for the present abnormality. Besides hypernatremia, she had short stature, obesity and dysmenorrhea. Basal levels of anterior pituitary hormones were normal except for the reduced gonadotropin release. Since the impaired secretion of growth hormone was detected at 14 years, the diminished response of growth hormone secretion may be found if tolerance tests were carried out. Hydrocephalus may deteriorate her hypothalamic function, particularly the osmoreceptor function, hypothalamic hormone secretion, and eating and drinking behaviours. Dysfunction of pituitary-adrenocortical axis causes increases in hypothalamic AVP mRNA expression and AVP release, which profoundly produce impaired water excretion [14-16]. However, as plasma ACTH and serum cortisol levels were both in the normal ranges in the patient, the role of secondary adrenal dysfunction in

![Graph showing alterations in urinary osmolality (Uosm), plasma AVP levels and urinary excretion of aquaporin-2 (UAQP-2) in the acute water load test (20 ml/kg BW). Closed circles (●) show the control subjects (n=7), and open circles (○) show the patient. Values are means ± SEM.](image-url)
the impairment in water excretion is ruled out. The elevation of thirst threshold may be an additional factor to permit hypernatremia in the present patient.

In conclusion, we demonstrated the hypernatremic subject in association with derangement of body fluid volume control. She had normal urinary concentrating ability despite low levels of plasma AVP. The marked hypernatremia is derived from partial central diabetes insipidus and elevated threshold of thirst, and enhanced renal water handling may contribute to maintaining body fluid.

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References