CASE REPORT

A patient with essential hypernatremia had good response to desmopressin acetate therapy

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Abstract

OBJECTIVES: Essential hypernatremia is very rare in clinical practice and the pathogenesis is unclear. We performed a set of clinical tests to a patient with chronic and sustained hypernatremia as well as absence of thirst in order to investigate the clinical characteristics and make the diagnosis, yet most importantly to analyze the possible pathogenesis and explore a possible therapy regime.

METHODS: Water deprivation test and acute water intravenous loading test were performed to observe the changes of urinary osmolality, plasma osmolality and plasma sodium. Free water clearance (C_{H2O}) was calculated. Osmolality was detected using the method of freezing point depression, and thirst grade using visual analogue scales. Desmopressin acetate (0.05–0.1 mg/d) was administered to the patient in order to observe the therapeutic effects to his disorder.

RESULTS: The patient had sustained hypernatremia over a long period of time, decreased thirst, normal renal function, as well as absence of clinical hypovoluemia. The plasma sodium was 160–190 mmol/L and plasma osmolality was 330–370 mOsm/L without any thirst perception which could not be corrected by water intake. An 18-hour period of water deprivation increased the urinary osmolality from 368 mOsm/L to 420 mOsm/L with plasma osmolality increasing from 362 mOsm/L to 369 mOsm/L and rising further to 857 mOsm/L after an injection of 5 u vasopresin. With the infusion of 1 250 ml 5%-glucose during 2 hours in an acute water loading test setting, plasma osmolality decreased from 350 mOsm/L to 334 mOsm/L associated with a plasma sodium decrease from 164.7 mmol/L to 155 mmol/L urinary osmolality dropped from a maximum of 632 mOsm/L to 135 mOsm/L urinary volume from 0.25 ml/min to 2.33 ml/min and C_{H2O} from –0.18 ml/min to 1.19 ml/min after acute water loading with 1 250 ml glucose dissolved in water. Our results reveal that treatment of the patient with Desmopressin acetate relieved the adypsia, hypernatremia and hyperosmolality effectively.

CONCLUSIONS: The patient was considered as suffering from essential hypernatremia which was associated with partial central diabetes insipidus and adypsia. Desmopressin acetate as a common therapeutic agent of central diabetes insipidus proved to be an effective treatment for essential hypernatremia.

INTRODUCTION

The level of plasma osmolality and sodium are controlled by a regulatory control system including the central thirst perception, osmoreceptor function, the synthesis and release of ADH in response to hemodynamic stimuli, normal function of adrenal cortical and the concentration function of the renal tubule. Dehydration under a normally functioning regulation system can lead to hypernatremia with noticeable thirst, which is commonly seen in a clinical setting; hypernatremia can be easily corrected by fluid supplementation. The dysfunction of the water and electrolytes regulatory system as mentioned above can also lead to hypernatremia (Verbalis 2003; Adler *et al.* 2006). Essential hypernatremia is a disease that results from the disorder of the water and electrolytes regulatory system. Only a limited number of cases have been reported up till now (Avioli *et al.* 1962; Holley *et al.* 2007; Assadi *et al.* 1977; Lascelles *et al.* 1972; Franco & Saenz *et al.* 1989; Dunger *et al.* 1987; Guo *et al.* 2007). The characteristics of this disorder include (Assadi *et al.* 1977; Halter *et al.* 1977; Oh *et al.* 1994) : 1) sustained hypernatremia over a long period of time, 2) decreased thirst perception, 4) absence of clinical hypovoluemia, 5) normal renal function, 3) the ability to secrete ADH under certain circumstances, and 6) renal tubule response is well to vasopressin. This type of disorder is seen rarely in clinical practice, and the management is difficult. The pathogenesis is unclear and the postulated pathogenesis is "upward resetting of the osmostat for ADH release (Assadi *et al.* 1977; Lascelles *et al.* 1972; Gossain *et al.* 1978; Gill *et al.* 1985). The purpose of this paper is to present a case with persistent hypernatremia and adypsia after the patient received γ radiation in the area of the hypothalamus and pituitary. A serial of clinical tests were performed to make the diagnosis clear, analyze the possible pathogenesis and observe the effect of therapy.

SUBJECTS AND METHODS

Case report

A 14-year-old boy was admitted to the Chinese PLA General Hospital in December 2003 because of intermittent headache, polyuria and polydipsia which started 2 years before the admittance, as well as fatigue and anorexia occurring for 2 months. Polyuria and polydipsia occurred initially in June 2001 accompanied by headache while visual acuity, visual field and mentality were normal. CT scanning in a local hospital suspected pituitary adenoma and consequently treatment with γ radiation was performed three times before January 2003. After that, the symptoms of polyuria and polydipsia disappeared, and the headache worsened accompanied by transient blurred vision. Two months later, the boy began to feel fatigue and anorexia. Blood chemistry examination revealed plasma potassium levels at 3.34–4.13 mmol/L, sodium at 163.7–199.5 mmol/L, chloride at 135.9–182.3 mmol/L, BUN at 14.2 mmol/L, and Cr at 93 μmol/L. So hypopituitarism was considered in the local hospital, while predinisolone 5 mg/d and levothyroxin were administered. The abnormalities mentioned above did not improve after these treatments, and as a consequence he was referred to our hospital. At admission the patient was in normal condition, and had no history of nausea, vomiting, diarrhea or abdominal distension. No history of similar diseases was seen in his family. On physical examination the child was alert, well nourished and noted to be mildly lethargic. Blood pressure was 90/60 mmHg pulse rate 80 /min temperature 36.5 °C, height 143 cm, and weight 30 kg. His skin was pale, cool, mildly rough, and in good elasticity with areas of desquamation. Visual field was found normal and reflex upon light was present. The beard, auxiliary hairs, pubic hairs, and laryngeal prominence had not developed. External genital organs were in a state of childhood.

Routine laboratory studies revealed no abnormalities in liver function, blood urea nitrogen and creatinine, and eGFR was 122 ml/min.m^2. Endocrinological evaluation showed LH<0.01 mIU/ml FSH<0.2 mIU/ml PRL 54.8 μg/L E_2 82.9 pmol/L T 0.1 nmol/L; FT_3 2.49 pmol/L (normal range 2.76–6.3) , FT_4 8.97 pmol/L (normal range 10.42–24.32) TT_3 1.02 nmol/L (normal range 1.01–2.95) TT_4 60 nmol/L (normal range 55.34–160.88) TSH 5.48 mU/L (normal range 0.35–5.50) ; 24h urinary aldosterone 0.6 umol/24h (normal range 2.77–22.2). Plasma ACTH level was <2.2pmol/L at 8 am, 0 am and 4 pm respectively plasma cortisol was 7.1 nmol/L at 8 am and 8.4 nmol/L at 0 am. After the hospitalization, the patient was forced to consume water at the amount of 2 000 ml each day and treated with predinisone (5 mg/d) and levethyroxine (50 μg/d) for one week. After that, the 24h urinary free cortisol was 233.6 μmol/24h (normal range 78.6–589.6) , FT_3 3.39 pmol/L FT_4 12.27 pmol/L TT_3 1.24 nmol/L TT_4 86.6 nmol/L and TSH 1.93 mU/L. However, the normal function of the adrenal cortical and thyroxine was still associated with persistent hypernatremia, plasma sodium 160.0–169.4 mmol/L plasma chloride 115.5–124.3 mmol/L BUN 8.09–9.25 mmol/l/L Cr 66.9–88.4 μmol/L, plasma osmolality 330–365 mOsm/L and urinary osmolality 280–634 mOsm/L.

Water deprivation test

Firstly, fluid intake was limited to 500–700 ml/d for 2 days, and plasma and urinary osmolality measured. Then the combination test of water deprivation and desmopressin acetate injection was performed. During the 12-hour period of overnight fast from 18:00 to 06:00, the urine and plasma were collected from 06:00 to 07:00, from 09:00 to 10:00 from 11:00 to 12:00, from 13:00 to 14:00, and from 14:00 to 15:00. At 12:00, 5u of desmopressin acetate were injected. During this study, the patient did not reveal apparent fluctuations in body weight and blood pressure. During this period of time,

the plasma and urinary osmolality, plasma sodium, urinary volume and blood pressure were detected every time the urine and plasma values were collected.

Water loading test

After an overnight fast starting from 18:00, an intravenous water load test was performed by giving an IV infusion of 5% glucose dissolved in water at 10ml/min for 2 hours between 08:00 and 10:00. Plasma and urine samples were collected at 07:00, 08:00, 09:00, 10:00, 11:00 and 12:00 to determine of electrolytes and osmolality. Plasma and urine values were collected before and after water loading with the intent of detecting plasma and urinary osmolality, plasma sodium, and urinary volume.

Visual analogue scales

Thirst sensation was evaluated using a visual analogue scale. We used a 10 centimeter long graduated line, with the bottom of the line indicating no sense of thirst and the top of the line indicating a strong thirst feeling. The patient was encouraged to tell us where were his thirst sensation would measure on the line, with his statement equaling the thirst grade.

Trails of therapy

The patient was forced to consume water at the amount of at least 2 000 ml each day. However, the hypernatremia was still unrelieved. Then, Desmopressin acetate 0.05 mg QN was given to the patient in an attempt to observe the effect of correcting hypernatremia. After one week, the plasma osmolality and plasma sodium levels were reevaluated.

Methods

The studies were performed while the patient was an inpatient at the Endocrinology Ward in the Chinese PLA General Hospital. Informed consent was obtained prior to each study. Special studies were performed after an overnight fast with an IV line in antecubital vein. Blood samples for determination of plasma electrolytes and osmolality were collected in heparinized tubes. The plasma was separated by centrifugation and samples were stored at –20 °C until analyzed. Indwelling catheter was used to collect urine specimens for measurement of volume and osmolality. Urine and plasma osmolality were measured using freezing point depression with the Advanced Instruments Diginatic Osmometer. Free-water clearance rate (C_{H2O}) was calculated with the formula: C_{H2O} (ml/min) = V (1-Uosm/Posm). V (ml/min) indicating the urinary volume in one minute, and Uosm urinary osmolality, and Posm plasma osmolality.

RESULTS

Results of dehydration test

After water intake was limited to 500–700 ml/d for 2 days, the plasma sodium concentration changed from 169.4 mmol/L to 163.2 mmol/L, osmolality from 354 mOsm/L to 365 mOsm/L, urinary osmolality from 280 mOsm/L to 634 mOsm/L, and C_{H2O} from 0.23 ml/min to –0.31 ml/min. The combination test of water deprivation and desmopressin acetate injection (Table 1) showed that in line with on-going water deprivation, plasma osmolality fluctuated from 362 mOsm/L to 369 mOsm/L, while urinary osmolality increased from 368 mOsm/L to 420 mOsm/L which was higher than the plasma osmolality at that point of time, and it went up further to 799–857 mOsm/L after injection of desmopressin acetate. At the same time C_{H2O} changed accordingly from –0.02 ml/min to –0.08 ml/min, and further to –0.45 ml/min after injection of desmopressin acetate. During these studies, thirst perception was never apparent and no significant decrease or increase in bodyweight was observed.

Results of water loading before and after treatment with desmopressin acetate

With the infusion of 1 250 ml 5% glucose from 8:00 to 10:00 am in an acute water loading test setting, plasma osmolality decreased from 350 mOsm/L to 334 mOsm/L plasma sodium concentration from 164.7 mmol/L to 155 mmol/L and urinary osmolality from the maxi-

Tab. 1. Results of combination test of water deprivation and vasopressin injection.

Time	Weight (Kg)	Bp (mmHg)	Urinary volume (ml/min)	Plasma osmolality (mOsm/L)	Plasma sodium (mmol/L)	Urinary sodium (mmol/L) (μmol/min)	Urinary osmolality (mOsm/L)	C_{H2O} (ml/min)
06–07:00	33. 0	90/50	0. 75	362	177. 6	59. 7 (44. 78)	368	–0. 02
09–10:00	33. 0	80/50	0. 57	368	178. 4	71. 4 (40. 70)	394	–0. 04
11–12:00	33. 0	80/50	0. 60	369	175. 7	75. 8 (45. 48)	420	–0. 08
13–14:00	32. 5	90/50	0. 30	368	174. 8	156 (46. 80)	799	–0. 35
14–15:00	32. 5	90/50	0. 33	361	174. 3	126 (41. 58)	857	–0. 45

5u of vasopressin was injected subcutanouly at 12:00
Urinary sodium μmol/min = Urinary volume (ml/min) × Urinary sodium mmol/L

Tab. 2. Results of acute water loading before and after therapy with vasopressin.

Time	PO(mOsm/L)		PS(mmol/L)		PCL(mmol/L)		UO(mOsm/L)		UV(ml/min)		TG		C_{H2O}(ml/min)	
	before	after	before	after	before	after	before	after	before	after	before	after	before	after
7am	350	347	163. 7	158. 9	122. 4	112. 4	501	475	0. 57	0. 78	0	6	–0. 18	–0. 29
8am	350	339	164. 7	159. 1	123. 1	113. 6	632	489	0. 25	0. 33	1	2	–0. 20	–0. 15
9am	343	332	156. 8	153. 3	118. 5	109. 5	587	290	0. 70	1. 16	0	1	–0. 50	0. 15
10am	334	326	155. 1	151. 5	117. 2	107. 6	180	166	2. 33	3. 17	0	0	1. 07	1. 56
11am	335	319	155	156. 1	121	108. 7	135	188	2. 00	1. 16	0	0	1. 19	0. 48
12am	337	323	155	156. 9	120	109. 2	188	369	0. 75	0. 63	0	1	0. 33	–0. 09

PO stand for Plasma osmolality; PS stand for Plasma sodium; PCL stand for Plasma chloride; UO stand for Urinary osmolality; UV stand for Urinary volume; TG stand for Thirst grade

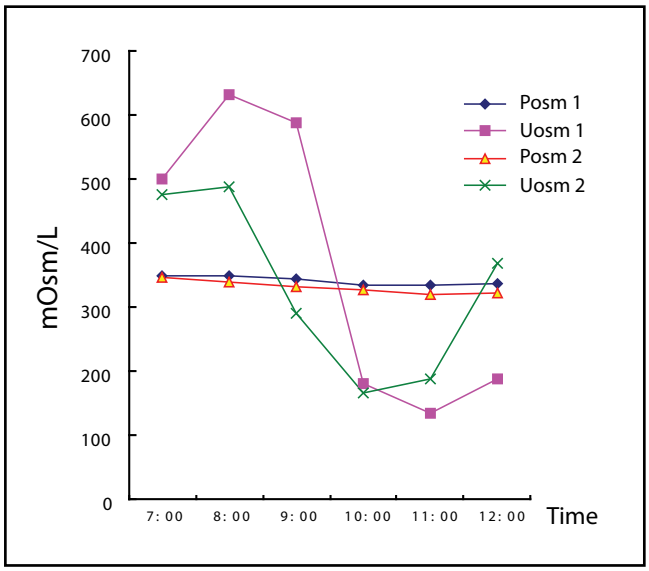

Fig. 1. The changes of plasma and urinary osmolality in acute water loading before and after therapy with vasopressin. Posm 1 stands for plasma osmolality before therapy, Uosm 1 stands for uriniary osmolality before therapy; Posm 2 stands for plasma osmolality after therapy, Uosm 2 stands for urinary osmolality after therapy.

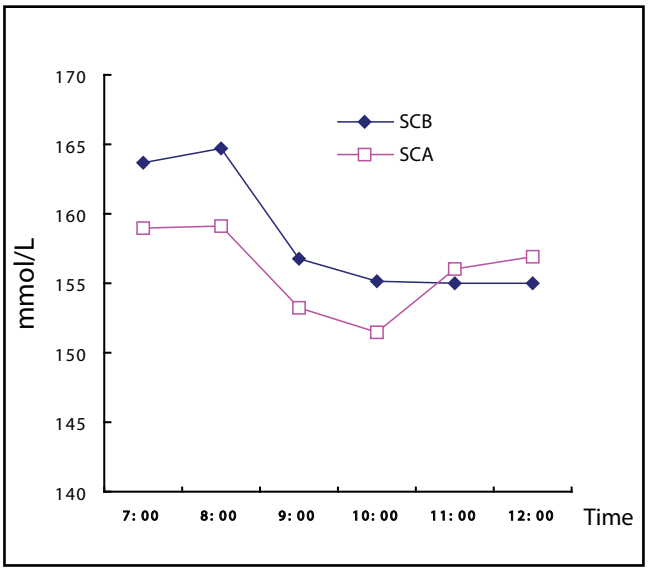

Fig. 2. The changes of plasma sodium in acute water loading before and after therapy with desmopressin acetate. SCB stands for sodium concentration before therapy, SCA stand for sodium after therapy.

mum of 632 mOsm/L to 135 mOsm/L which occurred one hour after the infusion (see Table 2). These findings were associated with the increase of 24 hour urinary volume from 600 ml at the beginning to 2 900 ml at the end and changes of C_{H2O} from –0.20 ml/min to –0.50 ml/min after one hour of loading, to 1.07 ml/min and to 1.19 ml/min after 2 and 3 hours of loading, and to 0.33 ml/min after 4 hours of loading.

During these studies, the thirst sensation was not apparent but recovered partially after the therapy with desmopressin acetate for one week. Furthermore, the drop in plasma osmolality from 347 mOsm/L to 319 mOsm/L and plasma sodium concentration from 159.1 mmol/L to 151.5 mmol/L (Figure 2) during repeated acute water loading (Table 2) was associated with urinary osmolality falling sharply from 489 mOsm/L to 166 mOsm/L (Figure 1) which occurred immediately after the water loading. Plasma osmolality and sodium concentration were still higher than normal but lower than before. The decline of urinary osmolality happened one hour earlier than before, which was associated with a C_{H2O} change from negative to positive immediately after water loading which took place only one hour after loading before the treatment was initiated.

The effect of therapy with desmopressin acetate

The therapy with desmopressin acetate resulted in a decrease of plasma sodium concentration from 158.9 mmol/L to 148.4 mmol/L and of plasma osmolality from 347 mOsm/L to 321 mOsm/L as well as an increase of urinary from 475 mOsm/L to 580 mOsm/L. Thirst perception partially increased from grade 0 to grade 6.

DISCUSSION

The initial symptoms of polyuria and polydipsia in this case were indicative of the existence of diabetes insipidus, but the symptoms disappeared after three times γ radiation therapy of the hypothelumus and pituitary, which were followed by persistent hypernatremia. Clinical observation of thirst was not apparent despite existing hypernatremia (plasma sodium 163.7–199.5 mmol/L) and hyperosmolality (plasma osmolality 330–365 mOsm/L) , not even during the period of water limitation and deprivation. The clinical features of the patient indicate the existence of hypodipsic hypernatremia; being defined as the absence of thirst in the light of plasma osmolality levels over 305 mOsm/L and plasma sodium concentration above 150 mmol/L (Vokes *et al.* 1988). Hypodipsic hypernatremia can only be caused by hypodipsia (Arem *et al.* 1986; Golonka *et al.* 1970; Robertson *et al.* 1984; Assadi *et al.* 1989; Zund *et al.* 1998) or essential hypernatremia (Assadi *et al.* 1977; Hammond *et al.* 1986; Garcia & Luna *et al.* 1987). Since the hypernatremia could not be corrected by intentional water intake, we assumed that the hypernatremia was not induced by hyodipsia only.

The term essential hypernatremia was first proposed by Louis Welt in 1962 in an editorial related to a 12 year old girl with destruction lesions in the hypothelemic hypophysial area who suffered from chronic persistent hypernatremia, diabetes insipidus, and absence of thirst as reported by Avioli *et al.* (1962) Welt reasoned that the only actual abnormality in this condition was regulation of ADH release at higher than usual extra cellular osmolality, and defined the term as upward resetting of the osmostat for ADH release (Welt 1962) , maintenance of the ability to dilute the urine at higher than normal plasma sodium concentration. Afterwards, only a limited number of cases were reported. Characteristics of these patients included (Assadi *et al.* 1977; Halter *et al.* 1977; Oh *et al.* 1994) sustained hypernatremia over a long period of time, decreased thirst perception, normal renal function, absence of clinical hypovolumia, and the ability to form concentrated urine with dehydration. The patient in our department had no apparent thirst perception, was alert, and showed absence of clinical dehydration even under the condition of plasma sodium 160–190 mmol/L and plasma osmolality 369 mOsm/L. During an acute water loading test, with the plasma osmolality and sodium concentration falling gradually, the increase of urinary volume, the decrease of urinary osmolality from 587 mOsm/L to 180 mOsm/L, and the changes of C_{H2O} from negative to positive seemed to occur right at the point of plasma osmolality levels reaching 343 mOsm/L and plasma sodium concentration reaching 156.8 mmol/L which was higher than normal after loading. This loading test indicated that the inhibition of the ADH release took place when plasma osmolality was at 343 mOsm/L, which might be the new threshold value of ADH release in this patient while the value in a normal, healthy subject is about 280–284 mOsm/L. However, during the water limitation test, the rises in plasma osmolality from 354 mOsm/L to 365 mOsm/L, urinary osmolality from 280 mOsm/L to 634 mOsm/L and C_{H2O} from 0.23 ml/min to –0.31 ml/min, suggest that the stimulation of ADH release occurred when plasma osmolality was at about 354–365 mOsm/L. Further evidence for a regulatory control of ADH release at higher plasma osmolality was obtained from the results of the acute water deprivation test. An 18-hour period of dehydration resulted in an urinary osmolality increase from 323 mOsm/L to 420 mOsm/L which was higher than the plasma osmolality of 362–369 mOsm/L. In other words, the process of stimulating ADH release happened when plasma osmolality was at 362–369 mOsm/L. These studies suggest that the regulatory control of ADH release by increasing plasma osmolality and inhibiting ADH release by decreasing the plasma osmolality was still active but occurred at a higher level of osmolality. This upward resetting of osmostat resulted then in hypernatremia. So, the clinical features and the good response to the ADH support the diagnosis of essential hypernatremia for this patient; the pathogenisis could thus be the upward resetting of osmostat.

When analyzing the water deprivation test and the water-loading test, we found the existence of partial diabetes insipidus in this patient. The urinary osmolality was at 280 mOsm/L when his plasma osmolality reached 354 mOsm/L. After two days of water limitation, the urinary osmolality increased to 634 mOsm/L which was obviously higher than the plasma osmolality (365 mOsm/L) at that time but not sufficiently high compared with the latter value, as ADH begins to release in a normal person when his plasma osmolality increases to 280–284 mOsm/L, and the person will feel thirsty when plasma osmolality increases to 290–294 mOsm/L, where his urinary osmolality will be 1 000–1 200 mOsm/L. The urinary osmolality of 634 mOsm/L in this patient was associated with plasma osmolality of 365 mOsm/L, which indicated that this patient still had some degree of ADH secretion with the secretion not being sufficient. An 18-hour period of water deprivation afterwards resulted in a maximum urinary osmolality of 420 mOsm/L which was higher than the plasma osmolality of 369 mOsm/L. The administration of 5u vasopressin at the end of the 18-hour period resulted in a further rise in urinary osmolality to 857 mOsm/L within the next two hours. These changes of urinary osmolality were also suggestive of partial ADH secretion. Furthermore, the changes of free-water clearance rate from positive to negative in the two above-mentioned studies support a partial ADH secretion. The presence of partial rather than complete central diabetes insipidus was suggested further by the results of an acute water-loading test. An infusion of 1 250 ml of 5% glucose in water resulted in a decrease in urine osmolality from 632 mOsm/L to 180 mOsm/L, an

increase in urinary flow from 0.25 ml/min to 2.33 ml/min, and a change of C_{H2O} from –0.18 ml/min to 1.19 ml/min. These changes suggested that the release of residual endogenous antidiuretic hormone was suppressed during water loading. Vasopressin (ADH) plays an important role in the regulation of osmolality by reabsorbing water from renal proximal tubules and collecting tubules. The absence of ADH could cause complete central diabetes insipidus while the decreasing of ADH would lead to partial diabetes insipidus (Garcia & Luna *et al.* 1987). We can thus conclude that the patient suffered from partial diabetes insipidus.

The patient suffered from polyuria and polydipsia until thirst perception disappeared after γ radiation, and several tests at hand support the existence of partial central diabetes insipidus. We thus deduce that the hypernatremia in this patient was caused by a combination of partial diabetes insipidus and hypodipsia. The so-called pathogenesis of essential hypernatremia, meaning that the threshold value of regulating ADH release increased, might be the result of a combination of partial diabetes insipidus and hypodipsia.

In terms of treatment, there was no ready-made solution for essential hypernatremia. It was said that dihydrochlorothiazide and chlorpropamide might have some effect (AvRuskin *et al.* 1981). The mechanism by which dihydrochlorothiazide improves essential hypernatremia is unclear but this agent might have some side effect in the long run and chlorpropamide is rarely used due to its severe side effects. In this practice, we propose that the pathogenesis of essential hypernatremia can be the combination of partial central diabetes insipidus and hypodipsia, and thus the administration of ADH, which is a routinely used agent for treatment of central diabetes insipidus, might be effective. In fact, we tried this drug and the subsequent therapy of Desmopressin acetate 0.05–0.1 mg every day on the patient. After one week of therapy, the hypernatremia, adypsia and hyperosmolality improved dramatically. During repeated acute water loading, urinary osmolality decreased immediately after the loading, occurred one hour earlier than before, and rose quickly after the end of the loading, which suggests that the increased threshold value of ADH regulatory system was decreased to some extent. The good response of Desmopressin acetate therapy indirectly supports our deduction of a pathogenesis of essential hypernatremia.

In summary, this patient was considered to be suffering from essential hypernatremia which was associated with partial central diabetes insipidus and hypodypsia. Desmopressin acetate has proved to be an effective treatment to essential hypernatremia.

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