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Case Report

Transient Antidiuretic Hormone Insufficiency Caused by Severe Hyperosmolar Hyperglycemic Syndrome Based on Nephrogenic Diabetes Insipidus

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ABSTRACT

Background: The hyperosmolar hyperglycemic state (HHS), an acute complication of diabetes mellitus with plasma hyperosmolarity, promotes the secretion of anti-diuretic hormone (ADH) and reduces the storage of ADH. Magnetic resonance T1-weighted imaging reflects ADH storage in the posterior pituitary lobe, which disappears when the storage is depleted. Whether the HHS induces ADH depletion leading to clinical manifestations has been unclear.

Case Report: A 55-year-old Japanese woman was admitted to our center because of mental disturbance and hypotension. She had received lithium carbonate for bipolar disorder and presented with polydipsia and polyuria from 15 years of age. On admission, she had mental disturbance (Glasgow Coma Scale, E4V1M1), hypotension (systolic blood pressure, 50 mmHg), and tachycardia (pulse rate, 123/min). Plasma glucose was 697 mg/dL osmolality was 476 mOsm/kg•H_2O, and bicarbonate was 23.7 mmol/L. The diagnoses of HHS and hypovolemic shock were made. During treatment with fluid replacement and insulin therapy, the urine volume continued to be approximately 3 to 4 L/day, and an endocrine examination revealed ADH insufficiency and nephrogenic diabetes insipidus. Desmopressin 10 μg/day and trichlormethiazide 2 mg/day were necessary and administered, and the endogenous ADH secretion improved gradually. The signal intensity of the pituitary posterior lobe, initially decreased on magnetic resonance T1 images, was also improved.

Conclusion: This patient had ADH insufficiency associated with ADH depletion due to hyperosmolarity and nephrogenic diabetes insipidus. Clinicians should be aware of the risk of the development of critical HHS and relative ADH insufficiency in patients being treated with lithium carbonate.

Introduction

The hyperosmolar hyperglycemic state (HHS) is an acute complication of diabetes mellitus (DM) characterized by hyperglycemia (>600 mg/dL) and plasma hyperosmolarity (>320 mOsm/kg•H_2O). It is often observed in diabetic patients with diseases that increase counterregulatory hormones, but HHS can also be caused by dehydration alone in individuals who are unable to drink water freely.[1] Antidiuretic hormone (ADH), synthesized in the hypothalamus, is stored in the posterior pituitary lobe and secreted in response to plasma hyperosmolality and hypovolemic conditions, such as HHS. ADH concentrates urine by activating arginine vasopressin receptor 2 in the renal collecting ducts.[2] The high-intensity signal of the posterior lobe on magnetic resonance (MR) T1-weighted images (T1WIs) represents the storage of ADH secretory granules.[3] When ADH storage is depleted or exhausted, the MR T1WI signal in the posterior lobe decreases or disappears. This is

Abbreviations: ADH, antidiuretic hormone; CDI, central diabetes insipidus; DM, diabetes mellitus; HHS, hyperosmolar hyperglycemic state; MR, magnetic resonance; NDI, nephrogenic diabetes insipidus; T1WI, T1-weighted image.

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known as a "depleted posterior lobe."[4] ADH insufficiency complicated with HHS and "depleted posterior lobe" has not been reported in a way that links the status of ADH secretion and MR imaging findings at each time point.

We report a case of a patient with transient ADH insufficiency due to severe HHS and nephrogenic diabetes insipidus (NDI), including a detailed description of the patient's course of treatment along with MR imaging findings. Clinicians should be aware of ADH insufficiency as posing a risk of a critical condition in patients with DM who have been treated with lithium carbonate.

Case Report

A 55-year-old Japanese woman was transferred to our center from a psychiatric hospital for the treatment of mental disturbance and hypotension. She had been treated with lithium carbonate for bipolar disorder from the age of 15 years. She had had polydipsia and polyuria, drinking approximately 5 L of water per day since she was 15 years of age. She had no familial history of diabetes insipidus and had not been examined for glucose impairment. She had been admitted to a psychiatric hospital with a diagnosis of severe depression approximately 1 month before her admission to our center. Appetite loss and drinking volume insufficiency due to depression had led to her 5.0-kg weight loss before this admission. Lithium carbonate had been discontinued 5 days before the patient's present admission.

On admission, mental disturbance (Glasgow Coma Scale, E4V1M1) was observed, and her systolic blood pressure was 50 mmHg with a pulse rate of 123/min; the plasma glucose level was 697 mg/dL, plasma sodium level was 183.5 mEq/L, plasma osmolality was 476 mOsm/kg•H_2O, and bicarbonate level was 23.7 mmol/L (Table 1). An abdominal ultrasound examination revealed that the inferior vena cava was collapsed.

Under the diagnosis of hypovolemic shock followed by HHS, a large amount of fluid replacement with 0.9% saline and continuous intravenous insulin infusion was administered. On day 10 after admission, the patient's plasma sodium level was 150.9 mEq/L, and her ADH level was 2.0 pg/mL. ADH insufficiency was revealed (Fig. 1).[5] On day 15, the high-intensity signal in the pituitary posterior lobe was diminished on MR T1WI (Fig. 2). Desmopressin (sublingual tablet) was administered from hospital day 17 with a gradual dose increase to 720 μg/day. The patient's polyuria (approximately 3-4 L/day) was reduced to approximately 2 to 2.5 L/day, and her serum sodium level remained at 146.3 to 149.3 mEq/L (Fig. 3). Desmopressin was discontinued on day 31.

After the patient's HHS and hypovolemic shock had improved, a water restriction test and a vasopressin loading test were performed. In the water restriction test, the urine osmolality remained at 244 to 256 mOsm/kg•H_2O from 4 to 6 hours after the start of the test. The change in urine osmolality was within 30 mOsm/kg•H_2O in 2 hours, which meet the criteria of water restriction.[6] In response to a subcutaneous injection of 5 units of vasopressin, the change in urine osmolality was from 256 to 317 mOsm/kg•H_2O. The urine osmolality change of 23.8% (reference value, >50%) indicated NDI.

Desmopressin 10 μg/day (divided into 4 doses as nose drops) was initiated for ADH insufficiency. The patient's urine volume, urine osmolality, and plasma osmolality improved to 1500 to 2680 mL/day, 107 to 196 mOsm/kg•H_2O, and 293.8 to 297.8 mOsm/kg•H_2O, respectively. Trichlormethiazide 2 mg/day was administered for NDI. Her urine volume improved to 800 to 1500 mL/day, urine osmolality improved to 172 to 294 mOsm/kg•H_2O, and plasma osmolality improved to 281 to 291 mOsm/kg•H_2O. The ADH secretion in response to the serum sodium level also relatively improved,[5] and desmopressin was discontinued on hospital day 110. In addition, MR T1WI demonstrated the recovery of the high-intensity signal in the pituitary posterior lobe (Fig. 2). On hospital days 110 and 181, the serum sodium level and plasma osmolality were maintained in the normal range with preserved ADH secretion. The patient continued to be treated for her NDI using only trichlormethiazide 3 mg/day with stable laboratory findings including the ADH level.

Table 1
Laboratory Examination Results

Test	Value	Reference range
Blood chemistry		
AST, IU/L	562	13-30
ALT, IU/L	527	8-36
Total protein, g/dL	5.9	6.6-8.1
Albumin, g/dL	3.1	4.1-5.1
LDH, IU/L	2045	124-222
GGT, IU/L	47	9-47
BUN, mg/dL	169.6	8-20
Creatinine, mg/dL	4.77	0.49-1.08
Sodium, mEq/L	183.5	138-145
Potassium, mEq/L	4.87	3.6-4.8
Chloride, mEq/L	143.1	101-108
Creatine kinase, IU/L	1586	45-216
CRP, mg/dL	12.9	0.00-0.14
Glucose, mg/dL	697	73-109
HbA1c, NGSP; %	7.0	4.9-6.0
Anti-GAD antibody	<5.0	
ePosm[a], mOsm/Kg· H_2O	476.03	
Arterial blood gas analysis[b]		
pH	7.455	7.35-7.45
pCO_2, mmHg	34.2	
pO_2, mmHg	130	
HCO_3^-, mmol/L	23.7	
Urinalysis		
SG	1.019	
pH	5.0	
Urinary protein	1 +	
Occult blood	±	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; GAD = glutamic acid decarboxylase; GGT = γ-glutamyl transpeptidase; LDH = lactate dehydrogenase; SG = specific gravity.
[a] Estimated plasma osmolality as calculated as 2Na + glu/18 + BUN/2.8.
[b] O_2: 5 L/min.

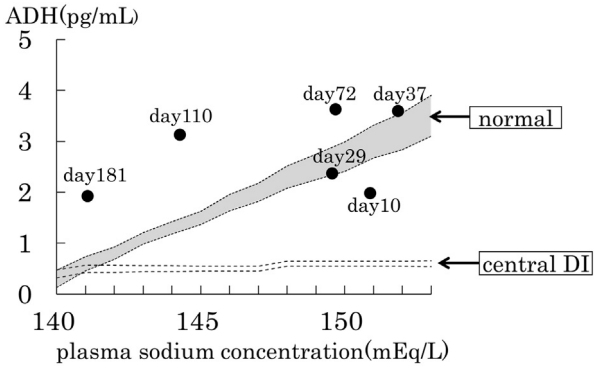

Fig. 1. The patient's ADH secretion against the plasma sodium level. The serum ADH level was relatively low on day 10 but had improved to normal secretion on hospital days 29 to 37 and then increased to hypersecretory levels. The two dashed areas represent the estimated values and standard error of the serum ADH level against the serum sodium level.[6] *ADH* = antidiuretic hormone.

Discussion

To our knowledge, this is the first case report of transient ADH insufficiency due to severe HHS based on lithium carbonate-

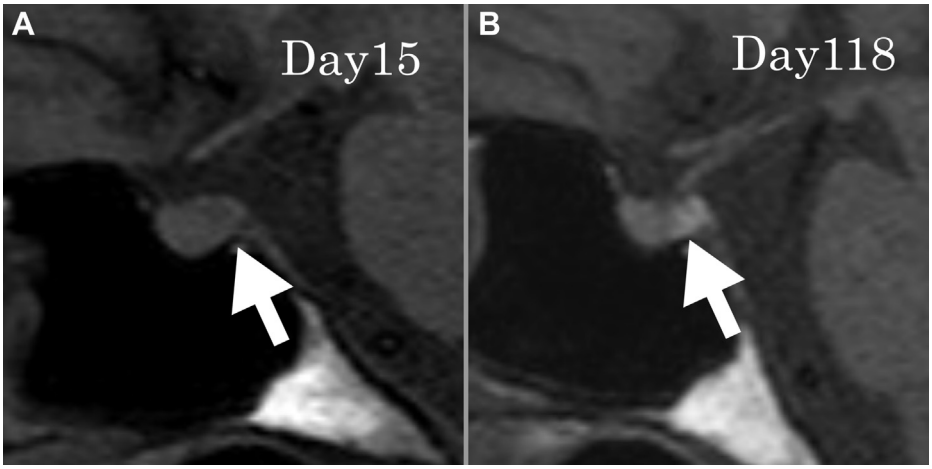

Fig. 2. Magnetic resonance imaging findings. T1-weighted images (sagittal sections) are shown. *A*, A depleted high-intensity signal in the pituitary posterior lobe (arrow) was observed on hospital day 15. *B*, On hospital day 118, the high-intensity signal had recovered in the pituitary posterior lobe (arrow). The signal intensity of MR T1WI increased from 481.1 (SD, 15.4; 452-692) to 757.2 (SD, 126.2; 565-930).

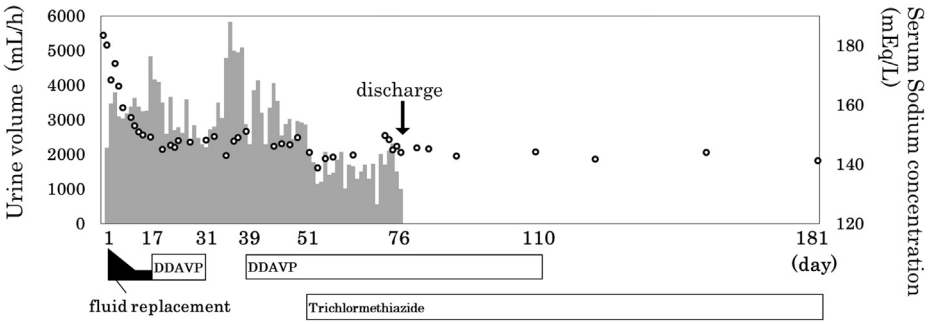

Fig. 3. The treatment course of treatment of the patient, a 55-year-old woman. *DDAVP* = 1-desamino-8-d-arginine vasopressin.

induced NDI, including the total course of treatment along with MR imaging findings. Patients with NDI may be at risk of developing HHS and subsequent ADH insufficiency due to excessive ADH secretion. Clinicians should be aware of the possibility of ADH insufficiency complicated with NDI when they encounter patients with HHS who have been treated with an NDI-inducing drug (eg, lithium carbonate).

Central diabetes insipidus (CDI) is classically diagnosed by changes in urine osmolality in a water restriction test and a vasopressin loading test.[6] A simple nomogram to diagnose the cause of disorders of plasma osmolality based on the relationship between plasma osmolality and urine osmolarity has also been reported.[7] These diagnostic methods assume a normal urine-concentrating capacity. It was, thus, difficult to diagnose the present case as CDI. An estimated serum ADH level for the serum sodium level was proposed in healthy subjects and patients with CDI.[6] In our patient's case, the secretion of ADH in response to her plasma sodium level was initially decreased but improved during the treatment (Fig. 1).

Impairment of the hypothalamic-pituitary system caused by pituitary stroke, traumatic brain injury, Sheehan syndrome, carbon monoxide poisoning, hypoxemia due to cardiopulmonary arrest, and brain edema caused by a rapid correction of hypernatremia can decrease the production of ADH. In our patient's case, these factors were ruled out based on the interviewed history, MR imaging findings, and course of treatment. In patients with poorly controlled diabetes, ADH can be depleted by excessive secretion of ADH in response to dehydration.[4] We ruled out all of the possible causes of ADH insufficiency and diagnosed the cause as decreased ADH storage. During the period of the patient's treatment with desmopressin supplementation, her endogenous ADH secretion improved over time, and desmopressin supplementation was no longer necessary by day 110. The depleted posterior lobe on MR T1WI also improved to a normal appearance. This course of treatment and the changes in the MR imaging findings are consistent with a course of increased ADH storage and improved endogenous ADH secretion.

We confirmed that our present patient had NDI with a deficient response to vasopressin loading.[6] Long-term lithium use with a prolonged history of polyuria may indicate occult persistent NDI. ADH secretion is increased in patients with NDI due to ADH resistance, but this generally does not lead to ADH depletion.[8] However, it has been confirmed that under the influence of NDI, ADH secretion in response to increased plasma osmolality is also excessive.[9] In this case, ADH was secreted in excess due to her NDI, and ADH storage resulted in a shortage due to the excessive secretion of ADH in response to the HHS.

NDI was suggested to contribute to the development and exacerbation of the HHS due to free-water depletion.[10,11] ADH insufficiency also reciprocally induces further high plasma osmolality. Patients with NDI may be at high risk of developing both the HHS and a subsequent ADH insufficiency due to excessive ADH secretion. It was reported that lithium carbonate caused NDI in approximately 10% to 20% of chronic lithium users.[12] Lithium carbonate is frequently administered to patients with bipolar disorder, and this population has a significantly higher prevalence of DM than the general population.[13] Clinicians should, therefore, be aware that occult NDI is a high-risk factor for the development of the HHS. ADH insufficiency should also be considered as an exacerbating factor for the HHS.

This case report has some limitations. We speculate that our patient's ADH secretion was initially increased and then decreased as the storage decreased. However, we failed to measure the temporal changes in plasma ADH levels and plasma osmolality before and immediately after admission.

Conclusion

We presented the details of a case of transient ADH insufficiency due to a severe HHS based on lithium-induced NDI, and we included the patient's course of treatment along with MR imaging findings. Patients with NDI are at high risk of the development of both the HHS and subsequent ADH insufficiency due to excessive ADH secretion. Clinicians should be aware of the relationships among NDI, HHS, and ADH insufficiency as critical factors in this type of patient.

Disclosure

The authors have no multiplicity of interest to disclose.

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