

NOTE

## A Case of Initially Undiagnosed Hypoadrenalism Presenting Inappropriate Secretion of Anti-Diuretic Hormone

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**Abstract.** The case of a 55-year-old woman with inappropriate secretion of anti-diuretic hormone (ADH) is reported. Her pituitary-adrenocortical function test showed normal values on admission, but when she recovered from hyponatremia, severe panhypopituitarism became overt. Her adrenal insufficiency was considered to have been “masked” by endogenous stimulation of the hypothalamus-pituitary-adrenal axis under severe stress. One should be cautious in estimating the pituitary-adrenal function of severely ill patients.

**Key words:** SIADH, Hyponatremia, Hypoadrenalism, Hypopituitarism, Empty sella syndrome  
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**HYPONATREMIA** is one of the primary clinical features in patients with hypopituitarism, and it results in various complications including anorexia, lethargy, nausea and vomiting [1]. In more severe cases, swelling of brain cells causes serious neurological complications such as confusion, stupor, convulsion and coma, which could be life-threatening. This hyponatremia is due to water retention rather than hypotonic dehydration [2], and Oelkers demonstrated that secretion of ADH may be stimulated by adrenocorticotropin (ACTH) deficiency itself and that the beneficial effect of glucocorticoid therapy is based on the suppression of ADH [3].

We here report a case of hyponatremia with hypopituitarism. Her hypopituitarism was initially ruled out because of normal ACTH values and cortisol, which led to a delay in correct diagnosis. This

was probably due to extreme endogenous stimulation of the hypothalamus-pituitary-adrenal axis under stress. Caution should be exercised in estimating pituitary-adrenal function in patients with under stress.

### Case Report

A 55-year-old woman was referred to our hospital because of hyponatremia of unknown cause on October 22, 1985. According to her clinical record, she had high fever (up to 38.5 °C) in late September followed by vertigo and nausea, and was admitted to another hospital on October 1. Initial laboratory examination revealed abnormality in her serum electrolyte concentration (Na, 108 mEq/L; K, 3.6 mEq/L; Cl, 76 mEq/L), and fluid intake restriction was immediately started. Mild metabolic acidosis was observed, which had been compensated for by respiratory alkalosis (pH, 7.40; pO<sub>2</sub>, 87.0 mmHg; pCO<sub>2</sub>, 33.0 mmHg; HCO<sub>3</sub><sup>-</sup>, 20.0 mmol/L; BE, -3.0 mmol/L). Serum concentration of cortisol and aldosterone at 3:00 a.m. on October 12 were 7.2 µg/dL and 3.4 ng/dL, respectively, and

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adrenal insufficiency was therefore neglected as a cause of hyponatremia. Since admission, her temperature had been maintained below 37.0 °C by anti-inflammatory drugs, but a spiky fever reaching 38.4 °C was noted in the afternoon of this day. She had a history of high fever followed by incontinence and delirium in her forties. She recovered from this episode spontaneously. She also had a history of massive genital hemorrhage after delivery of her second child and received a blood transfusion. Her menstrual cycle became regular again, and three years later she delivered her third child with no complications. Her menopause occurred at 40 years of age.

### *Clinical course*

On admission to our hospital, various neurological complications were observed (drowsiness, hyperactive tendon reflexes, positive Babinski test and lead-pipe rigidity of extremities). Her consciousness level estimated by the Glasgow Coma Scale was E3-4V1M5-6. Her axillary and pubic hair was absent. Serum sodium concentration had been corrected to 132 mEq/L by fluid intake restriction and administration of sodium chloride (25–30 g/day), but it decreased progressively to 122 mEq/L by the eighth hospital day. Serum urea nitrogen (10 mg/dL), creatinine (1.1 mg/dL) and potassium (3.6 mEq/L) were normal. The blood glucose concentration was 108 mg/dL, and total cholesterol (201 mg/dL) and triglyceride (86 mg/dL) were not increased. The level of ADH was inappropriately high (15.3 pg/mL; normal range 1.3–9.5 pg/mL) in relation to the low serum osmolality of 270 mOsm/kg. Urine osmolality was 620–1015 mOsm/kg and the urine sodium concentration was 132–241 mEq/L during the initial five hospital days. Adrenal insufficiency was not observed (see below). A diagnosis of SIADH was therefore made.

Attempts to identify the cause of SIADH were initiated. Positive C-reactive protein (5+), increased erythrocyte sedimentation rate (71 mm/h) and high-grade fever (up to 39.0 °C) indicated the presence of infection, but cultures of blood, urine and cerebrospinal fluid were all negative. The white cell count was 8200/cm<sup>3</sup> and the differential count was normal. The normal appearance of the cerebrospinal fluid ruled out disorders of the central nervous system. Chest X-ray showed old pleuritis at the right lung base but did not show other ab-

normal shadows which may indicate active pneumonia, tuberculosis or oat-cell carcinoma. Endocrine data are summarized in Table 1 (Oct., 1985). The serum concentrations of the adrenal steroids were within the normal range and she was therefore considered not to have adrenal insufficiency.

The inflammatory reaction was managed with intravenous administration of sulbenicillin by mid-November. Endocrine function tests were performed again in early December and severe adrenal insufficiency secondary to hypopituitarism was noted. Results of endocrine tests are summarized in Table 1 (Dec., 1985).

### *Cause of hypopituitarism*

On CT scanning performed in February, 1986, cisternal herniation to the pituitary fossa was found. Auto-antibodies to the pituitary, thyroid and adrenal gland were negative. The chest X-ray image in April, 1986 was essentially the same that in October, 1985.

### *Follow-up*

Supplement of thyroxine and hydrocortisone was started in early December, 1985. Normalization of the levels of thyroid and adrenal steroid hormones followed improvement of her neurological complications. The plasma ADH concentration was 5.4 pg/mL with normal serum osmolality (Table 1). Hyporesponsiveness of the pituitary gland to GHRH and LHRH was noted in April, 1986 (data not shown). TSH response to TRH was relatively well preserved (base; 3.8 mU/L, 30 min after TRH injection; 15.2 mU/L). During the follow-up period until 1994, she had not experienced any neurological complications or hyponatremia.

## **Discussion**

It is known that adrenal insufficiency causes water retention due to oversecretion of ADH, and glucocorticoid supplement therapy rapidly corrects dilutional hyponatremia within a few days. It has been experimentally demonstrated that adrenalectomy causes an increase in the plasma ADH level [4]. Although it has been noted that oversecretion of ADH in patients with adrenal insufficiency is a defensive reaction against hypovolemia and hy-

**Table 1.** Results of endocrine function tests

		Oct., 1985	Dec., 1985	Normal range
Cortisol ( $\mu\text{g}/\text{dL}$ )	(0700 h)	14.8	2.3	5.4–15.1
	(1400 h)	16.4	ND	
	(2300 h)	11.6	ND	
Aldosterone ( $\text{ng}/\text{dL}$ )	(0700 h)	65.9	ND	50–180
	(1400 h)	85.8	ND	
	(2300 h)	92.2	ND	
17-OHCS ( $\text{mg}/\text{day}$ )		8.6	1.3	4.8–10.6
ACTH ( $\text{pg}/\text{mL}$ )		23.9	<10	10–100
Total $\text{T}_3$ ( $\text{ng}/\text{dL}$ )		71.7	59.8	84–180
Total $\text{T}_4$ ( $\mu\text{g}/\text{dL}$ )		8.6	4.2	5.1–12.8
Free $\text{T}_4$ ( $\text{ng}/\text{dL}$ )		0.94	0.25	0.78–2.11
TSH ( $\text{mU}/\text{L}$ )		ND	12.7	2–10
ADH ( $\text{pg}/\text{mL}$ )		15.3	5.4	1.3–9.5
PRA ( $\text{ng}/\text{mL}/\text{h}$ )		1.08	ND	0.7–2.7
Serum-Na ( $\text{mEq}/\text{L}$ )		131	136	136–144
Serum-K ( $\text{mEq}/\text{L}$ )		3.9	3.9	3.3–4.8
Serum-Cl ( $\text{mEq}/\text{L}$ )		99	101	99–108
Serum-Osm ( $\text{mOsm}/\text{kg}$ )		270	296	285–295

ND: not done.

potension, the precise mechanism of the secretion is not fully understood. Several lines of experimental data suggest that persistent ADH secretion in glucocorticoid deficiency is a consequence of non-osmotic stimuli by impaired cardiac function [4, 5], and Kamoi *et al.* recently documented that the loss of hypotonic suppression of the osmostat for ADH release could be the underlying mechanism for ADH oversecretion in patients with adrenal insufficiency [6].

In the case we reported here, a diagnosis of adrenal insufficiency due to panhypopituitarism as a cause of hyponatremia was considered but initially rejected because of laboratory test results which showed both ACTH and cortisol within the normal range. If adrenal insufficiency is relatively mild, the endogenous stimulation of the hypothalamus-pituitary-adrenal axis under stress could lead to misleadingly "normal" hormone levels. When patients with subclinical hypopituitarism were severely stressed, especially by infection, hyponatremia could be precipitated [7]. In our case, common-cold like symptoms preceded the episode. Recent studies demonstrated that inter-

leukin- $1\beta$  and interleukin-6 stimulate ADH secreting neurons [8, 9]. It is therefore likely that inflammation-induced release of these cytokines from monocytes significantly contributed the oversecretion of ADH in this case. We also note that this patient complained of severe nausea, which is known to be a strong inducer of ADH secretion [10, 11].

There are no practical standards to evaluate the pituitary-adrenal function of patients under severe stress. Clayton noted in his review article that a peak cortisol value of over 400 nmol/L (14.4  $\mu\text{g}/\text{dL}$ ) after exogenous ACTH stimulation would be acceptable to rule out adrenal insufficiency [12]. However, this value could be applied only to outpatients and not to critically ill patients, whose basal concentration is usually much higher [7]. In fact, the basal cortisol level of our patient was near or above this value. Therefore ACTH stimulation test would not have been useful as a diagnostic method in this case. There are numbers of case reports with hyponatremia due to hypopituitarism [13–16], but as far as we searched, we found no cases with cortisol levels as high as this patient.

It is to be noted that our patient did not have resistance to glucocorticoid [17, 18]. She has been taking 25 mg hydrocortisone per day and maintains normal metabolism. Her serum cortisol level at outpatient clinic is also within the normal range.

The cause of hypopituitarism in this patient is unknown. Despite the history of massive hemorrhage after delivery, subsequent normal delivery denies the possibility of Sheehan's syndrome. One may speculate that brain edema due to hyponatremia caused cisternal herniation and her hypopituitarism is thus rather the consequence of hyponatremia than the cause of that. We reason, however, that this patient already had subclinical hypopituitarism and subsequent adrenal insufficiency which could have been well compensated for under normal circumstances. Once she was under severe stress, which requires augmented secretion of adrenal glucocorticoid, incomplete compensation may have led to clinical manifestation of adrenal insufficiency. Early menopause,

loss of pubic hair, and a history of consciousness disturbance after the common cold all point to pituitary hypofunction.

This patient had mild hypothyroidism. Hypothyroidism is known to cause water retention and subsequent hyponatremia. Several reports suggest that this metabolic disorder is due to reversible derangement of renal tubular function [19, 20], and not due to over-expression of ADH [21, 22]. Therefore in this case, the supplementation of thyroxine may have contributed in part to normalizing the serum sodium concentration, but it may not be related to the suppression of ADH secretion.

In conclusion, although it is generally accepted that adrenal insufficiency should be considered for patients with hyponatremia, caution has to be exercised in evaluating the results of pituitary-adrenocortical function tests. In general, early initiation of glucocorticoid supplement is to be recommended.

## References

1. Levinsky NG (1994) Fluids and electrolytes. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds) *Principles of Internal Medicine*. McGraw Hill, New York: 242–253.
2. Bethune JE, Nelson DH (1965) Hyponatremia in hypopituitarism. *N Engl J Med* 272: 771–776.
3. Olkers W (1989) Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 321: 492–496.
4. Boykin J, de Torrenté A, Erickson A, Robertson G, Schrier RW (1978) Role of plasma vasopressin in impaired water excretion of glucocorticoid deficiency. *J Clin Invest* 62: 738–744.
5. Mandell IN, DeFronzo RA, Robertson GL, Forrest Jr JN (1980) Role of plasma arginine vasopressin in the impaired water diuresis of isolated glucocorticoid deficiency in the rat. *Kidney Int* 17: 186–195.
6. Kamoi K, Tamura T, Tanaka K, Ishibashi M, Yamaji T (1993) Hyponatremia and osmoregulation of thirst and vasopressin secretion in patients with adrenal insufficiency. *J Clin Endocrinol Metab* 77: 1584–1588.
7. Park GR, Raggatt P (1989) Diagnosis of adrenal insufficiency (letter). *Brit Med J* 298: 669–670.
8. Raber J, Pick EM, Koob GF, Bloom FE (1994) IL-1 beta potentiates the acetylcholine-induced release of vasopressin from the hypothalamus *in vitro*, but not from the amygdala. *Neuroendocrinology* 59: 208–217.
9. Mastorakos G, Weber JS, Magiakou M-A, Gunn H, Chrousos GP (1994) Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: Potential implications for the syndrome of inappropriate vasopressin secretion. *J Clin Endocrinol Metab* 79: 934–939.
10. Koch KL (1991) Nausea and vasopressin. *Lancet* 337: 1133–1134.
11. Coslovsky R, Bruck R, Estrov Z (1984) Hypo-osmolar syndrome due to prolonged nausea. *Arch Int Med* 144: 191–192.
12. Clayton RN (1989) Diagnosis of adrenal insufficiency. *Brit Med J* 298: 271–272.
13. Luboshitzky R, Sobel JD, Kurtzbaum A, Better OS, Spitz IM (1979) Hypopituitarism with water intoxication and coma: Favorable outcome following early treatment. *J Endocrinol Invest* 2: 423–426.
14. Aasen G, Frey HM (1980) Excessive sensitivity to the hyponatremic effect of chlorpropamide in a patient with diabetes mellitus and anterior pituitary insufficiency. *Acta Med Scand* 208: 233–236.
15. Sordillo P, Matarese RA, Novich RK, Zabetakis PM, Michelis MF (1981) Specific modalities of therapy for inappropriate antidiuretic hormone secretion. *Clin Nephrol* 15: 107–110.
16. Okuno S, Inaba M, Nishizawa Y, Miki T, Inoue Y,

- Morii H (1987) A case of hyponatremia in panhypopituitarism caused by the primary empty sella syndrome. *Endocrinol Japon* 34: 299–307.
17. Lamberts SWJ, Polderman D, Zweens M, de Jong FH (1986) Familial cortisol resistance: Differential diagnostic and therapeutic aspects. *J Clin Endocrinol Metab* 63: 1328–1333.
18. Hurley DM, Accili D, Stratakis C, Karl M, Vamvakopoulos N, Rorer E, Constantine K, Taylor SI, Chrousos GP (1991) Mutation of the human glucocorticoid receptor gene in familial glucocorticoid resistance. *J Clin Invest* 87: 680–686.
19. Koide Y, Oda K, Shimizu K, Shimizu A, Nabeshima I, Kimura S, Maruyama M, Yamashita K (1982) Hyponatremia without inappropriate secretion of vasopressin in a case of myxedema coma. *Endocrinol Japon* 29: 363–368.
20. Ali M, Guillon G, Balestre MN, Clos J (1987) Effects of thyroid deficiency on the vasopressin receptors in the kidney of developing and adult rats. *Horm Metab Res* 19: 115–121.
21. Ceccatelli S, Giardino L, Calza L (1992) Response of hypothalamic peptide mRNAs to thyroidectomy. *Neuroendocrinology* 56: 694–703.
22. Iwasaki Y, Oiso Y, Yamauchi K, Takatsuki K, Kondo K, Hasegawa H, Tomita A (1990) Osmoregulation of plasma vasopressin in myxedema. *J Clin Endocrinol Metab* 70: 534–539.