

Intermittent Hyponatremia as a Clinical Presentation of Adrenal Insufficiency Caused by Pituitary Adenoma

Vikram Chandurkar, MD
Arshag D. Mooradian, MD

H yponatremia, an excess of water in relation to sodium, can occur as a result of impaired water excretion, which is often due to an inability to suppress antidiuretic hormone (ADH) release, or excessive water intake. Hyponatremia can develop in various disease states, including central nervous system disorders (eg, subarachnoid hemorrhage, severe head injury)¹ and pituitary adenoma,²⁻⁵ and as a postoperative complication of trans-sphenoidal surgery.^{3,6} In most of these instances, hyponatremia is observed at all times. In addition, hyponatremia rarely precedes all other common symptoms of pituitary tumors. This article discusses the case of a patient who was asymptomatic except for intermittent episodes of severe hyponatremia who was found to have adrenal insufficiency and hypogonadism secondary to a pituitary macroadenoma.

CASE PRESENTATION

History and Initial Presentation

A 52-year-old man presented to his primary care physician in a small rural town with a 2-week history of tiredness and fatigue and a 2-day history of muscle aches and a runny and congested nose. The patient assumed he had the flu but became concerned when the fatigue worsened to the point that he could not function well at work. Although details of this visit, including clinical findings, were not made available to the authors, apparently no specific clinical signs were discovered on examination and laboratory tests were ordered (including a complete blood count, electrolytes, serum glucose, serum creatinine, serum calcium, and liver function tests).

Presentation to the Emergency Department

The following day, the patient was at home and suddenly felt faint, experienced a brief syncopal episode, and fell to the floor. The patient's wife witnessed the fall and reported that no head trauma occurred.

He revived within minutes and was taken to the local emergency department.

The patient had no history of headache, nausea, blurry vision, or seizure. On physical examination, his blood pressure was 110/70 mm Hg, and his heart rate was 84 bpm. There were no neurologic deficits. Cardiovascular and respiratory examinations were unremarkable, and there was no pedal edema. An electrocardiogram and chest radiograph were normal. Cardiac monitoring did not reveal any arrhythmias.

Based on the physician's notes, the patient was considered euvoletic, with no mention of evidence of hypovolemia, dehydration, or hypervolemia. Initial laboratory results are shown in **Table 1**. Other laboratory results, including a complete blood count, were normal. A routine urinalysis showed a specific gravity of 1.013. Results of laboratory testing performed the previous day at the primary care physician's office included a sodium level of 116 mEq/L, chloride level of 81 mEq/L, and carbon dioxide level of 30 mmol/L; all other results were normal. The patient had not undergone testing of serum sodium levels or other blood work over the past year. The results of other tests that might have been performed at this time were not transmitted to the authors. (We tried to determine if serum or urine osmolality or urine sodium had been measured, and they apparently had not.)

The patient was admitted to the intensive care unit and a presumptive diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

At the time this patient was evaluated, Dr. Chandurkar was a subspecialty fellow-in-training, and Dr. Mooradian was a professor of internal medicine and director of the Division of Endocrinology; both were at the Division of Endocrinology, Diabetes and Metabolism, St. Louis University School of Medicine, St. Louis, MO. Dr. Chandurkar is now an assistant professor, Memorial University of Newfoundland, St. John's, NL, Canada. Dr. Mooradian is now professor and chairman, Department of Internal Medicine, University of Florida, Jacksonville, FL.

Table 1. Laboratory Results for the Case Patient Upon Presentation to the Emergency Department

Laboratory Test	Result	Normal Value
Sodium, mEq/L	104	135–146
Chloride, mEq/L	74	95–108
Potassium, mEq/L	3.5	3.5–5.3
Carbon dioxide, mmol/L	32	23–29
Blood urea nitrogen, mg/dL	8	7–20
Serum creatinine, mg/dL	1.0	0.7–1.4
Serum glucose, mg/dL	103	70–110

was considered. However, to the authors' knowledge, thyroid and adrenal testing were not performed. No attempt at fluid restriction was made, although this would be the expected treatment for SIADH. The patient was administered an infusion of normal saline, and the serum sodium level normalized over 2 days. He was discharged from the hospital and was instructed to follow-up with his primary care physician.

Follow-up with Primary Care Physician

Over the next 6 months, the patient had monthly visits with his primary care physician, during which time his blood pressure remained normal and his levels of serum electrolytes were within the normal range. No further work-up was pursued at this stage. Testing for renin and aldosterone levels was not performed.

Six months after presenting to the emergency department, the patient again presented to his physician with flu-like symptoms, including weakness, tiredness, and a low energy level. The patient's serum sodium level was 117 mEq/L (normal, 135–146 mEq/L). He was started on sodium chloride tablets for several weeks, and the serum sodium concentration again normalized. Since his initial presentation, the patient's serum sodium level had been monitored regularly at least every month, and it had been normal except on these 2 occasions. On the second occasion, it gradually rose to normal over a period of 6 weeks after treatment with sodium chloride. The patient was referred by his physician to an endocrinologist.

Referral to Endocrinology

History and physical examination. In the endocrinology clinic, the patient had no specific complaints other than fatigue. He had a history of sinus infections, and he reported erectile dysfunction and questionable decreased libido. He was taking an expectorant/decongestant (guaifenesin/phenylephrine) as needed for intermittent symptoms of sinus congestion. There

was no family history of any endocrine disorder. On review of systems, he denied headaches or visual symptoms, muscle aches or cramps, dizziness, nausea, vomiting, or significant body weight change.

The physical examination was unremarkable. Pulse was 84 bpm, temperature was 97.1°F, and there were no significant orthostatic blood pressure changes (106/68 mm Hg supine and 100/70 mm Hg standing). Extraocular movements were intact, visual fields were full to confrontation, and pupils were reactive. Funduscopic examination was within normal limits. Oral mucosa was moist. The thyroid was not enlarged. Cardiac examination revealed regular rhythm without murmurs, and the lungs were clear to auscultation. The abdomen was soft and nontender and bowel sounds were normoactive. The lower extremities had normal pulses and no edema was appreciated. Muscle mass and strength were normal. Skin examination revealed no rashes or hyperpigmentation, and skin turgor was normal.

Laboratory and imaging studies. Results of plasma hormonal testing are shown in **Table 2**. Other laboratory tests, including complete blood count and basic chemistry panel (electrolytes, liver function tests, and a lipid profile), were unremarkable. Serum sodium was 137 mEq/L (normal, 135–146 mEq/L). A diagnosis of secondary hypogonadism was made based on the low testosterone level with relatively low gonadotropin levels. Further testing of serum and urine osmolality or urine sodium was not pursued, as the patient's serum sodium was normal.

Because the patient did not have hyperpigmentation, hyperkalemia, or other features suggestive of Addison's disease or primary adrenal insufficiency, secondary hypoadrenalism was considered. A corticotropin-releasing hormone (CRH) stimulation test was performed because it would yield a rapid diagnosis. An adrenocorticotropic hormone (ACTH) stimulation test was considered, but a near-normal result would not rule out pituitary pathology given the patient's intermittent symptoms and probable early stage of adrenal insufficiency. In the case of a near-normal or borderline cortisol response, follow-up testing with a CRH test or an insulin hypoglycemia test would be required. Following injection of 250 µg of CRH, the patient's ACTH level rose from a baseline of 12 pg/mL to 77 pg/mL at 30 minutes and decreased to 49 pg/mL at 60 minutes (normal morning basal values < 70 pg/mL). Serum cortisol increased from a baseline of 1 µg/dL to 6 µg/dL and 7 µg/dL at 30 and 60 minutes post-CRH, respectively (normal morning basal values, 4–22 µg/dL). A diagnosis of adrenal insufficiency was made based on the inadequate cortisol response to CRH stimulation.

Magnetic resonance imaging of the brain showed a 2 × 2 × 1.7-cm sellar and suprasellar mass suggestive of pituitary macroadenoma. The patient was started on glucocorticoid replacement with oral hydrocortisone (20 mg in the morning and 10 mg in the afternoon daily) and was referred to a neurosurgeon for surgical excision of the macroadenoma.

Hospital Course

On the day of hospital admission, the patient's serum sodium level was 136 mEq/L. The patient stated that his energy level had improved significantly since starting hydrocortisone. He was given stress-dose steroids preoperatively (intravenous hydrocortisone 100 mg every 6 hr). Transsphenoidal hypophysectomy was performed successfully without complications. There was no polyuria postoperatively. The dose of glucocorticoids was tapered, and the patient was given corticosteroid replacement with hydrocortisone 20 mg in the morning and 10 mg at noon on discharge, which was continued for at least 8 months (until the last follow-up visit to the endocrinology clinic). The patient's serum sodium level remained normal throughout the course of his hospital admission (7 days). On subsequent testing 4 weeks postoperatively, his free thyroxine level was normal without thyroxine replacement. He was also given testosterone replacement therapy transdermally at a dose of 5 mg/day for treatment of secondary hypogonadism, which was continued for 8 months.

On follow-up over 8 months, there was no recurrence of hyponatremia or fatigue, and the patient's libido and sexual function had improved.

DISCUSSION

Signs and Symptoms of Hypopituitarism

Impaired vision and headaches are the most common symptoms of a nonfunctioning pituitary adenoma that prompt a patient to seek medical attention.⁷ Conversely, patients with pituitary hormone deficiencies often do not seek medical attention because their symptoms typically are insidious and slowly progressive. Hormone deficiencies may be revealed on comprehensive testing of pituitary function or when the clinical syndrome progresses to the point where the diagnosis becomes obvious. The diagnostic challenge is to make the diagnosis before significant morbidity occurs and when the risk/benefit ratio of surgery can be minimized by early intervention.

The most common pituitary hormone deficiency is impaired secretion of luteinizing hormone, which causes hypogonadism.⁸ Complete ACTH and cortisol deficiency may cause severe symptoms such as hypo-

Table 2. Laboratory Results of Serum Hormonal Levels for the Case Patient Upon Presentation to the Endocrinology Clinic

Laboratory Test	Result	Normal Value
Prolactin, ng/mL	19	2–18
Luteinizing hormone, mIU/mL	1.0	1.3–12.9
Thyroid-stimulating hormone, μ IU/mL	1.55	0.4–5.0
Free thyroxine, ng/dL	1.2	0.7–1.9
Free testosterone, ng/dL	9	34–194
Total testosterone, ng/dL	50	194–833

tensive shock, whereas partial ACTH deficiency may cause symptoms only during times of physical stress. Mild chronic partial adrenal insufficiency may cause postural hypotension, fatigue, anorexia, weight loss, decreased libido, and hypoglycemia.⁷ Low cortisol production and low plasma ACTH on laboratory testing and inadequate response to stimulatory testing (eg, an insulin hypoglycemia test or a CRH stimulation test) confirms a diagnosis of secondary adrenal insufficiency.⁷

Hyponatremia

Chronic hyponatremia as an initial symptom on presentation has been reported with primary adrenal insufficiency,⁶ secondary adrenal insufficiency due to pituitary causes,^{3–5} and hypothalamic pathology.⁹ ACTH deficiency may present clinically with hyponatremia, but the underlying mechanisms of hyponatremia in ACTH deficiency differ somewhat from those of primary adrenal insufficiency. In secondary adrenal insufficiency, hyponatremia results from impaired excretion of water loads, whereas in primary adrenal insufficiency, renal salt wasting is commonly seen, adrenal mineralocorticoid release is affected,⁷ and hyperkalemia may be seen.¹⁰ Clinically, patients with partial ACTH deficiency are euvolemic, which can cause clinicians to confuse ACTH deficiency with SIADH (as may have occurred in this case in the emergency department).

Patients with pituitary adenoma resulting in adrenal insufficiency may present with hyponatremia as one finding among a constellation of signs and symptoms (Table 3). However, it is rare for hyponatremia to precede all other common symptoms of pituitary tumors. It is also unusual for severe symptomatic hyponatremia to occur in the absence of other symptoms suggestive of adrenal insufficiency such as orthostatic hypotension, nausea, vomiting, dizziness, or presyncope or syncope. The case patient presented with only intermittent episodes of symptomatic hyponatremia.

Table 3. Presentation of Pituitary Tumors/Sellar Masses

Neurologic symptoms
Bitemporal hemianopsia
Diminished visual acuity
Headaches
Diplopia induced by oculomotor nerve compression
Pituitary apoplexy induced by sudden hemorrhage into the tumor, causing severe headache
Cerebrospinal fluid rhinorrhea (extremely rare)
Abnormalities related to undersecretion of pituitary hormones
Gonadal axis
In men: decreased libido and energy and erectile dysfunction
In premenopausal women: amenorrhea
Thyroid axis
Symptoms of hypothyroidism: cold intolerance, fatigue, muscle aches, somnolence
Adrenal axis
Symptoms of adrenal insufficiency: fatigue, weakness, nausea, vomiting, weight loss, dizzy spells, orthostatic hypotension, hyponatremia, hypoglycemia, syncope
Posterior pituitary
Diabetes insipidus
Abnormalities related to oversecretion of pituitary hormones
Gonadal axis: rare, clinical syndrome poorly delineated
Thyroid axis: rare
Adrenal axis: Cushing's disease (central obesity, weight gain, moon face, buffalo hump, stria, easy bruising of the skin, hypertension, hyperglycemia)
Growth hormone: acromegaly
Incidental finding on radiologic examination performed for another reason

Patients with subclinical hypopituitarism may develop hyponatremia in the presence of a stressor. Stressors found to be associated with hyponatremia include infection,¹¹ operative procedures,¹² certain drugs,¹³ and fever of unknown cause.² In borderline adrenal insufficiency, increased sensitivity to water-retaining drugs such as chlorpropamide resulting in hyponatremia has been reported.¹⁴ The case patient apparently had minimal symptoms of hypopituitarism (decreased libido, low energy level), and the hypothalamic-pituitary-adrenal axis insufficiency resulted in symptoms only during ill-defined minor stressful events. He recalled that during his first presentation he may have had a mild upper respiratory tract infection associated with increased thirst and consequent increased intake of fluids. The patient's inability to handle water loading became apparent and

resulted in severe hyponatremia (sodium, 104 mEq/L) and a syncopal episode. Severe hyponatremia is an uncommon presentation for pituitary adenoma and has only rarely been described in the literature.^{2,7,9} Information about the serum and urine osmolality, urine sodium, or ADH/vasopressin levels at the time the patient was severely hyponatremic would have been useful to confirm or rule out SIADH, but this testing was not done. No clear diagnosis explaining the hyponatremia was made at the time of initial presentation. In addition, when the patient presented to the emergency department, SIADH may have been considered but this diagnosis cannot be made without ensuring normal thyroid and adrenal function, which were not tested until later.

Adrenal insufficiency from any cause may result in water retention and hyponatremia that is correctable by glucocorticoid replacement.⁶ The impaired ability to excrete a water load has been shown to involve both vasopressin-dependent and -independent processes.^{9,15-22} Increased secretion of ADH may be a defense mechanism protecting against possible hypotension. Experimental evidence has shown that bilateral adrenalectomy causes an increase in plasma ADH levels in dogs, which is correctable by corticosteroid administration but not by mineralocorticoid replacement alone.⁶ It has been shown that loss of suppression of the osmostat for ADH release could be the underlying mechanism for ADH hypersecretion in adrenal insufficiency.⁹ In a patient with hypothalamic dysfunction, the osmotic threshold for ADH secretion was raised by glucocorticoid replacement.¹⁶ Thus, the benefit of corticosteroid replacement is thought to be mainly due to suppression of ADH.²³⁻²⁷

One of the interesting features of this patient's history is the correction of his hyponatremia with normal saline in the first instance and with salt tablets in the second. Correction of hyponatremia by these treatments suggests that the patient had a component of dehydration or sodium deficiency due to salt wasting in addition to water loading and dilutional hyponatremia. The absence of a thorough examination of volume status, especially orthostatic blood pressure at the time of hyponatremia, raises the possibility that both mechanisms may have been operative at that time and underscores the necessity of a thorough examination of fluid status in the evaluation of hyponatremia.

This case serves to highlight several issues with regard to the assessment, work-up, and management of hyponatremia. It is important to obtain adequate laboratory studies at the time of presentation so that a diagnosis can be reached expeditiously. Treatment with normal saline as a knee-jerk response may delay the

diagnosis. A detailed study of volume status, sodium and water balance, and endocrine control mechanisms in the setting of ACTH deficiency is lacking and may be the subject of future studies to elucidate the exact mechanism.

CONCLUSION

Severe hyponatremia may be precipitated in otherwise asymptomatic patients (or patients with minimal symptoms) with subclinical hypopituitarism or adrenal insufficiency in the setting of even trivial stress such as a minor viral infection. The etiology in most cases is inappropriate hypersecretion of ADH in the setting of glucocorticoid deficiency. This report serves as a reminder that thyroid, adrenal, and pituitary function should be assessed as part of the evaluation of hyponatremia. **HP**

REFERENCES

- Harrigan MR. Cerebral salt wasting syndrome: a review. *Neurosurgery* 1996;38:152-60.
- Sakurai A, Yamada T, Hashizume K. A case of initially undiagnosed hypoadrenalism presenting as inappropriate secretion of anti-diuretic hormone. *Endocr J* 1995;42:811-5.
- Yamashiro S, Fuwa I, Seto H, Ushio Y. Initial and postoperative hyponatremia associated with pituitary adenoma: a case report. *Acta Neurochir (Wien)* 1997;139:987-91.
- Greiss KC, Moses AM, Krieger DT. Pituitary adenoma associated with inappropriate antidiuretic hormone secretion. *Acta Endocrinol (Copenh)* 1974;76:59-66.
- Van't Hoff W, Zilva JF. Chromophobe adenoma and hyponatremia. *Clin Sci* 1961;21:345-54.
- Boykin J, DeTorrente A, Erickson A, et al. Role of plasma vasopressin in impaired water excretion of glucocorticoid deficiency. *J Clin Invest* 1978;62:738-44.
- Melmed S, Kleinberg D. Anterior pituitary. In: Larsen R, editor. *Williams textbook of endocrinology*. 10th ed. Philadelphia: Saunders; 2003.
- Snyder PJ. Gonadotroph cell adenomas. In: Melmed S, editor. *The pituitary*. 2nd ed. Malden (MA): Blackwell Publications; 2002:575.
- Shibata T, Oeda T, Saito Y. Severe hyponatremia caused by hypothalamic adrenal insufficiency. *Intern Med* 1999;38:426-32.
- Szwed JJ, White C. Normokalemic nonazotemic adrenal insufficiency. *South Med J* 1983;76:919-20.
- Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 1989;321:492-6.
- Salik JM, Kurtin P. Severe hyponatremia after colonoscopy preparation in a patient with the acquired immune deficiency syndrome. *Am J Gastroenterol* 1985;80:177-9.
- Aasen G, Frey HM. Excessive sensitivity to the hyponatremic effect of chlorpropamide in a patient with diabetes mellitus and anterior pituitary insufficiency. *Acta Med Scand* 1980;208:233-6.
- Hung SC, Wen YK, Ng YY, Yang WC. Inappropriate antidiuresis associated with pituitary adenoma—mechanisms not involving inappropriate secretion of vasopressin. *Clin Nephrol* 2000;54:157-60.
- Kamoi K, Tamura T, Tanaka K, et al. Hyponatremia and osmoregulation of thirst and vasopressin secretion in patients with adrenal insufficiency. *J Clin Endocrinol Metab* 1993;77:1584-8.
- Mandell IN, DeFronzo RA, Robertson GL, Forrest JN Jr. Role of plasma arginine vasopressin in the impaired water diuresis of isolated glucocorticoid deficiency in the rat. *Kidney Int* 1980;17:186-95.
- De Leacy EA, Bowler S, Brown JM, Cowley DM. Corticotropin deficiency: a rare cause of hyponatremia mimicking SIADH. *Pathology* 1991;23:8-10.
- Raff H. Glucocorticoid inhibition of neurohypophysial vasopressin secretion. *Am J Physiol* 1987;252(4 Pt 2):R635-44.
- Kern PA, Robbins RJ, Bichet D, et al. Syndrome of inappropriate antidiuresis in the absence of arginine vasopressin. *J Clin Endocrinol Metab* 1986;62:148-52.
- Kamoi K. Syndrome of inappropriate antidiuresis without involving inappropriate secretion of vasopressin in an elderly woman: effect of intravenous administration of the nonpeptide vasopressin V2 receptor antagonist OPC-31260. *Nephron* 1997;76:111-5.
- Bethune JE, Nelson DH. Hyponatremia in hypopituitarism. *N Engl J Med* 1965;272:771-6.
- Luboshitzky R, Sobel JD, Kurtzbaum A, et al. Hypopituitarism with water intoxication and coma: favorable outcome following early treatment. *J Endocrinol Invest* 1979;2:423-6.
- Oleesky S. A specific water diuresis test for adrenocortical insufficiency. *Lancet* 1953;1:769-70.
- Dingman JF, Despointes RH. Adrenal steroid inhibition of inhibition of vasopressin release from the neurohypophysis of normal subjects and patients with Addison's disease. *J Clin Invest* 1960;39:1851-63.
- Ahmed AB, George BC, Gonzalez-Auvert C, Dingman JF. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucosteroids. *J Clin Invest* 1967;46:111-23.
- Ishikawa S, Fujisawa G, Tsuboi Y, et al. Role of antidiuretic hormone in hyponatremia in patients with isolated adrenocorticotrophic hormone deficiency. *Endocrinol Jpn* 1991;38:325-30.
- Davis BB, Bloom ME, Field JB, Mintz DM. Hyponatremia in pituitary insufficiency. *Metabolism* 1969;18:821-32.

Copyright 2007 by Turner White Communications Inc., Wayne, PA. All rights reserved.