HYPONATREMIA AND INAPPROPRIATE SECRETION OF VASOPRESSIN (ANTIDIURETIC HORMONE) IN PATIENTS WITH HYPOPITUITARISM

WOLFGANG OELKERS, M.D.

Abstract Severe hyponatremia occurs in some patients with untreated hypopituitarism, but it is not known whether such hyponatremia is caused by the hypersecretion of vasopressin (antidiuretic hormone). This report describes severe, symptomatic hyponatremia in five women 59 to 83 years old (serum sodium, 111 to 118 mmol per liter) who presented with hypopituitarism (which had been previously undiagnosed in four).

Plasma vasopressin was inappropriately high (1.3 to 25.8 pmol per liter [1.4 to 28 ng per liter]) in relation to plasma osmolality (236 to 260 mOsm per kilogram of body weight). All five patients had normal renal function and no signs of dehydration or volume depletion. The hyponatremia was resolved within a few days after the institution of hydrocortisone therapy, after infusion of normotonic or hypertonic saline had been found to be less effective. When four of the patients were later restudied while receiving maintenance hydrocortisone treatment, the relation between plasma vasopressin and osmolality was normal.

We conclude that ACTH deficiency may cause the syndrome of inappropriate secretion of antidiuretic hormone. The beneficial effect of hydrocortisone is probably exerted through the suppression of vasopressin secretion. (N Engl J Med 1989; 321:492-6.)

IN 1965, Bethune and Nelson[1] described eight patients with hypopituitarism and hyponatremia in whom the hyponatremia appeared to be due to water retention rather than to hypotonic dehydration. Ahmed et al.,[2] using a very sensitive bioassay, found increased plasma levels of vasopressin in untreated patients with Addison's disease and hypopituitarism; the levels decreased after the administration of supraphysiologic doses of cortisone or hydrocortisone. Cases of severe hyponatremia and hypopituitarism have also been reported[3-11] in which hydrocortisone replacement therapy usually corrected the hyponatremia after the infusion of isotonic or hypertonic saline had been less effective. The therapeutic responses suggest that hydrocortisone corrected hypersecretion of vasopressin, which was inappropriately elevated in relation to the low plasma osmolality.[2,12] Alternatively, a direct renal effect of hydrocortisone has been proposed.[13] These case reports of hyponatremia in hypopituitarism rarely included measurements of plasma vasopressin.[10] This report describes five patients with hypopituitarism and severe hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

METHODS

A retrospective study identified five women with symptomatic hyponatremia, four of whom had clinical signs of previously undiagnosed hypopituitarism. After the patients had recovered from the hyponatremia, their pituitary function was assessed, either by testing with the induction of hypoglycemia by insulin plus the injection of 200 μg of thyrotropin-releasing hormone and 100 μg of gonadotropin-releasing hormone, as described previously,[14] or testing with a combination of releasing hormones according to the method of Schopohl et al.[15] In the latter test, 100 μg of corticotropin-releasing hormone, 100 μg of growth hormone–releasing hormone (both from Bissendorf Peptide GmbH, Wedemark, West Germany), 200 μg of thyrotropin-releasing hormone, and 100 μg of gonadotropin-releasing hormone (both from Hoechst AG, Frankfurt, West Germany) were injected intravenously. In both tests, before injection and 15, 30, 45, 60, and 90 minutes after injection, blood samples for hormone measurement were drawn from an indwelling intravenous cannula in the forearm while the patient was recumbent and fasting. All tests were started in the morning, before 10 a.m. After insulin administration (0.1 IU per kilogram of body weight), glucose was measured in samples of venous blood every 15 minutes. Only the results of tests in which the glucose concentration was less than 2.2 mmol per liter (<40 mg per deciliter) were evaluated. All hormone measurements were performed with the use of sensitive radioimmunoassays. The normal values used for the comparison of basal and stimulated levels of pituitary hormone and cortisol were those of the endocrine laboratory of the Freie Universität Berlin and values derived from Schopohl et al.[15] In some patients, the short metyrapone test was performed according to the technique of Jubiz et al.[16] The normal values for the responses of plasma ACTH and serum 11-deoxycortisol were established[14,17] in 37 normal subjects. In one patient (No. 1), plasma vasopressin was measured by radioimmunoassay in the laboratory of Dr. K.A. Kirsch (Physiological Institute, Freie Universität Berlin), as described elsewhere.[18] All subsequent measurements of plasma vasopressin were performed by highly sensitive radioimmunoassay using extracted, platelet-free plasma, as described by Morton et al.[19] The vasopressin antibody was kindly given by Dr. J.J. Morton (Glasgow). The sensitivity of the assay was 0.11 pmol per liter. In our laboratory the range of plasma vasopressin in hydrated, normal subjects was 0.41 to 0.85 pmol per liter (0.45 to 0.92 ng per liter). An evaluation of this method has been reported previously.[20]

Plasma osmolality was measured in the same sample as was vasopressin, with an osmometer (Roebling, West Berlin). The relation between the plasma vasopressin concentration and plasma osmolality in the patients was compared with that in normal men[22] during water deprivation, water loading, and the infusion of hypertonic[21] or isotonic saline. The use of control values obtained in a younger male group seemed permissible since the osmotic threshold for vasopressin is similar in young and old subjects,[23] although the slope of the correlation between plasma osmolality and vasopressin in younger subjects may differ[23,24] from that in older subjects.

RESULTS

Between 1981 and May 1988, five women were admitted to hospital with severe symptomatic hyponatremia, pale skin, and complete or almost complete absence of axillary and pubic hair. A preliminary clinical diagnosis of pituitary insufficiency was later confirmed by appropriate testing in all five patients (Table 1). Since the possibility of hypersecretion of vasopressin as a cause of the hyponatremia was taken into consideration, plasma vasopressin and osmolality were measured in all patients within the first few days

From the Division of Endocrinology, Department of Internal Medicine, Klinikum Steglitz, Freie Universität Berlin, Hindenburgdamm 30, D 1000 Berlin 45, West Germany, where reprint requests should be addressed to Dr. Oelkers.

Table 1. Results of Testing and Clinical Diagnoses in Five Women with Hypopituitarism.*

Patient No. (Age)	Pituitary-Function Test†								Metyrapone Test‡		CT Scan§	Clinical Diagnoses
	Agent¶	Glucose	ACTH	Cortisol	GH	TSH	LH	FSH	Prolactin	ACTH	11-DOC		
		mmol/liter	*pmol/liter*	*nmol/liter*	*μg/liter*	*mU/liter*	*micrograms per liter*			*pmol/liter*	*nmol/liter*		
1 (72)	IT+RH	3.4	ND	132	2.7	1.2	5.2	7.7	13.5	ND	ND	Normal	Probable Sheehan's syndrome
		<1.4		147	4.5	5.9	9.6	8.0	14.2				
2 (59)	IT+RH	2.9	ND	102	0.2	2.3	1.0	2.1	2.4	ND	ND	Empty sella	Probable Sheehan's syndrome; empty sella; mild parkinsonism
		<1.4		110	0.5	2.5	4.6	2.3	3.0				
3 (73)	IT+RH	4.5	ND	61	0.6	<0.5	<1.0	<0.5	26.2	ND	ND	Normal	Hypopituitarism of undetermined cause; mild arterial hypertension
		1.8		70	1.3	3.4	<1.0	0.6	40.3				
4 (61)	RHT	ND	6.6	260	1.0	1.0	0.4	1.7	2.5	9.3	85	Empty sella	Hypopituitarism; empty sella; mild pneumonia
			8.2	308	2.8	2.9	0.8	1.6	5.3				
5 (83)	RHT	ND	2	158	0.5	5.1	0.6	2.5	5.0	7.3	93	Normal	Hypopituitarism of undetermined cause
			2.2	166	3.6	29.4	3.2	5.5	19.8				
Normal values‖	IT+RH			>200	1–10	0.5–5	>10	>10	3–17				
				Δ<200	>10	Δ>4	Δ>8	Δ>6	Δ>20				
										>38	>200		
	RHT		1–10	>200	1–10	0.5–5	>10	10	3–17				
			Δ>4.5	Δ>150	>8	Δ>4	Δ>8	Δ>6	Δ>15				

*In pairs of values, the first is the base-line measurement and the second is the highest measurement of hormone obtained after stimulation with the test agent or (in measurements of ACTH) with corticotropin-releasing hormone, or the lowest measurement of blood glucose after stimulation with insulin. ND denotes not done, and Δ increment of change. To convert ACTH values to nanograms per liter, multiply by 4.54; to convert cortisol values to micrograms per deciliter, multiply by 0.036.

†GH denotes growth hormone, TSH thyrotropin, LH luteinizing hormone, and FSH follicle-stimulating hormone.

‡11-DOC denotes 11-deoxycortisol.

§Findings on tomography of the pituitary region.

¶IT+RH denotes administration of insulin plus injection of thyrotropin and gonadotropin-releasing hormone, and RHT administration of combined releasing hormones.

‖Values for LH and FSH were obtained in postmenopausal women.

of admission, but not always when the serum sodium concentration was lowest (Table 2). The clinical symptoms and signs that had led to hospital admission were somnolence, confusion, and weakness in Patients 1 and 2 (Table 1) and progressive weakness together with vertigo or chest pain in Patients 3 through 5, who later had at least one episode of disorientation and confusion, probably due to hyponatremia. No patient had focal neurologic abnormalities. Patient 2 had mild rigor without tremor of both arms, which was due to known mild parkinsonism (treated with amantadine). Patients 4 and 5 were febrile on admission. The fever of Patient 4 (37.9°C) was probably caused by an infiltrate of the right lower pulmonary lobe; the infiltration resolved soon after it was treated with cefaclor. Patient 5 (39.4°C) had some wheezing over both lungs; her fever was probably due to a viral infection (normal findings on the leukocyte count, chest film, urinalysis, and blood culture). Patient 3 had mild bilateral pretibial edema on admission. The initial blood-pressure level in all five patients ranged from 100/60 to 190/90 mm Hg, and the heart rate was between 80 and 90 beats per minute. No clinical signs of dehydration were present in any patient, and serum creatinine levels ranged from low to normal (Table 2). At presentation, serum potassium levels ranged from 3.3 to 4.0 mmol per liter, and blood glucose values from 3.5 to 7.1 mmol per liter. Except for Patient 3, who had taken furosemide and triamterene until three days before admission, the patients had taken no drugs known to cause hyponatremia, sodium loss, or water retention.

Hyponatremia and Plasma Vasopressin

All patients had severe hyponatremia on admission. In several, the lowest serum sodium level (range, 111 to 118 mmol per liter) was recorded on the second day of hospitalization. Between the first and fifth days of hospitalization, serum and plasma samples were obtained for simultaneous measurements of sodium, vasopressin, and osmolality. All five patients had slightly or markedly increased plasma vasopressin levels in relation to their plasma osmolality (Table 2 and Fig. 1). All patients had previously received an infusion of isotonic saline or of 1.6 percent saline solution in an attempt to reverse their hyponatremia. Therefore, serum sodium concentrations recorded at the time of vasopressin measurement were slightly higher than the minimum shown in Table 2. Urinary osmolality was 390 mOsm per kilogram in Patient 1 and 450 mOsm per kilogram in Patient 2 (respective values for plasma osmolality, 260 and 236 mOsm per kilogram). In the same two patients, the urinary excretion rate of aldosterone 18-glucuronide was measured and found to be in the low-normal range (8.9 and 8.8 nmol per day, respectively; normal, 8 to 40).

Pituitary-Function Tests and Hydrocortisone Therapy

At the time of plasma vasopressin measurement, plasma cortisol levels were below normal in three patients and in the low-normal range in two. The results

Table 2. Concentrations of Sodium, Vasopressin, and Creatinine and Plasma Osmolality during Hyponatremia and at Follow-up (November 1988).

PATIENT NO.	DURING HYPONATREMIA						AT FOLLOW-UP		
	LOWEST SERUM SODIUM	FIRST VASOPRESSIN MEASUREMENT			SERUM CREATININE*		SECOND VASOPRESSIN MEASUREMENT		
		serum sodium	plasma osmolality	plasma vasopressin	serum creatinine		serum sodium	plasma osmolality	plasma vasopressin
	mmol/liter		*mOsm/kg*	*pmol/liter*†	*μmol/liter*		*mmol/liter*	*mOsm/kg*	*pmol/liter*†
1	118	124	260	5.9 9.5	60	82	‡	‡	‡
2	115	119	236	1.3	80	94	140	275	0.45
3	111	132	250	25.8	44	83	142	272	0.46
4	117	119	252	1.6	78	92	138	275	0.20
5	112	120	244	10.7	59	76	143	280	0.47
Normal values	135–148		275–295	0.41–0.85	50–98		135–148	275–295	0.41–0.85

*Value after hydrocortisone therapy for five to seven days.

†To convert to nanograms per liter, multiply by 1.085.

‡Patient died before follow-up measurement.

of the pituitary-function tests are shown in Table 1. At the time of these tests, basal plasma cortisol levels were below normal in all but one patient (No. 4). They increased little or not at all in all patients during the induction of hypoglycemia or after the administration of corticotropin-releasing hormone. In Patients 4 and 5, plasma ACTH increased very little after the injection of the hormone, and the response to metyrapone was abnormally low. In all five patients the levels of follicle-stimulating hormone and luteinizing hormone were lower than in normal postmenopausal women, and the response of plasma growth hormone to insulin or growth hormone–releasing hormone was diminished. Basal and stimulated levels of plasma prolactin and thyrotropin were normal or low. Patients 2 and 3 had slightly decreased plasma levels of thyroxine, triiodothyronine, or both.

Hydrocortisone replacement therapy was initiated in Patient 1 six days after admission, when her serum sodium was 124 mmol per liter. After two and four days of hydrocortisone therapy (30 mg per day, in two doses), the serum sodium concentration rose to 133 mmol per liter and then to 138 mmol per liter. In Patient 2, the same dose of hydrocortisone (together with 50 μg of thyroxine) led to an increase in the serum sodium level from 120 to 135 mmol per liter within two days. In Patient 3, the serum sodium level rose from 111 to 132 mmol per liter within two days, while she was receiving an infusion of hydrocortisone hemisuccinate (100 mg per day); it became normal after the oral administration of hydrocortisone (30 mg per day). In Patient 4, the serum sodium level rose from 121 to 138 mmol per liter within two days, while she was receiving oral hydrocortisone (40 mg per day). In Patient 5, the serum sodium rose from 120 to 133 mmol per liter within two days and to 141 mmol per liter within a week during hydrocortisone therapy (70 mg per day). When hydrocortisone therapy was later interrupted, her serum sodium fell to 120 mmol per liter within two weeks; when it was resumed (40 mg per day), the sodium level became normal within four days. In all patients, serum creatinine levels increased within five to seven days after hydrocortisone therapy was begun (Table 2).

Causes of Hypopituitarism

CT scanning of the hypothalamic–pituitary region revealed an empty sella turcica in Patients 2 and 4 and normal findings in the other patients (Table 1). In Patients 1 and 2, the diagnosis of partial postpartum pituitary necrosis (Sheehan's syndrome) was likely, since both had become oligomenorrheic or amenorrheic after pregnancy. Patient 4 (empty sella) was nulliparous. No obvious cause of hypopituitarism was found in her or in Patients 3 and 5.

A study of records from different hospitals and from family doctors revealed that Patients 3 and 5 had been hospitalized several times before because of "unexplained hyponatremia." In Patient 3, hypopituitarism had been diagnosed during a hospital stay in 1981, but she had failed to take the prescribed hydrocortisone continuously.

Follow-up

Patient 1 died of uterine cancer complicated by pneumonia in 1986, five years after the diagnosis of hyponatremia. Patients 2 through 5 have continued to visit the endocrine clinic. They are in good health and regularly take between 15 and 25 mg of hydrocortisone per day. In November 1988, serum sodium levels and plasma vasopressin levels and osmolality were remeasured in these patients (Table 2 and Fig. 1); the plasma vasopressin concentration was normal in relation to the plasma osmolality. Plasma renin activity and the plasma aldosterone level were also measured then to exclude the presence of hypoaldosteronism. All values were normal (data not shown).

Discussion

The suggestion of Dingman and Despointes[12] and of Ahmed et al.[2] that vasopressin secretion is tonically inhibited by glucocorticoids is supported by studies in animals and clinical observations. Boykin et al.[25] found that in dogs subjected to adrenalectomy, plasma vasopressin levels were increased and the excretion of a water load was impaired when the animals were given hormone replacement with deoxycorticosterone acetate alone; after additional dexamethasone substitution, plasma vasopressin levels and water excretion returned to normal. In rats that had un-

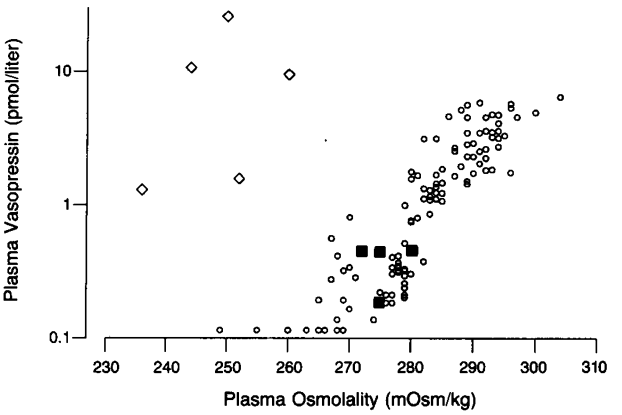

Figure 1. Plasma Osmolality in Relation to Plasma Vasopressin Concentration in Patients with Hyponatremia and Hypopituitarism and in Normal Subjects.

The scale for vasopressin values is logarithmic; undetectable levels were assigned a value of 0.11 pmol per liter, the limit of sensitivity of the assay.

The diamonds represent the initial values in all five patients, and the squares the values recorded after hydrocortisone therapy for several months. The circles represent normal subjects studied during water deprivation, infusion of 5 percent saline, 0.9 percent saline, and water loading.[22]

dergone hypophysectomy and were receiving thyroxine replacement, increased plasma vasopressin levels and impaired water excretion could be fully corrected by corticosterone treatment.[26] In patients with untreated Addison's disease, plasma vasopressin is usually elevated.[27,28] In eight such patients, the interruption of the administration of fludrocortisone (mineralocorticoid) for two weeks while hydrocortisone substitution was continued did not lead to an increase in plasma vasopressin, although hyperreninemia and hyperkalemia developed in most patients.[29] Thus, glucocorticoid deficiency seems to be an important nonosmotic stimulus of vasopressin secretion, in addition to the known stimuli of severe hypotension, hypovolemia, and nausea.[30]

The synthesis of vasopressin by the hypothalamus and its secretion by the posterior pituitary lobe seem to be under inhibitory control by glucocorticoids, although the feedback sensitivity is lower than that of the ACTH–cortisol system.[31] Severe hyponatremia has often been observed in patients with hypopituitarism.[3-11] The published case reports and the five cases described in this paper are similar in that glucocorticoid therapy usually corrected hyponatremia within a few days, whereas the infusion of isotonic or hypertonic saline was less effective. The symptoms of volume depletion (hypotension and impaired renal function) and hyperkalemia are absent in these patients in contrast to those with decompensated Addison's disease. It is surprising that plasma vasopressin levels have not been reported in most of the recent clinical studies on this syndrome. Only Okuno et al.[10] have described a woman with unexplained hyponatremia and a slightly increased plasma vasopressin level (3.2 pmol per liter; plasma osmolality, 254 mOsm per kilogram), in whom hypopituitarism due to the empty sella syndrome was diagnosed subsequently. Although the patient had hypothyroidism, and hypothyroidism itself may be associated with hyponatremia,[32] she had a prompt response to glucocorticoid therapy, with normalization of her plasma sodium concentration. An empty sella also was found in two of our five patients (Patients 2 and 4). In Patient 1, who had a negative CT scan, postpartum pituitary necrosis was the most likely cause of hypopituitarism; in Patients 3 and 4 the cause was obscure.

The question arises whether the empty sella syndrome with hypopituitarism or Sheehan's syndrome predisposes in a special way to the hyponatremic syndrome. Purnell et al.[3] found mild to severe hyponatremia in 9 of 13 patients with Sheehan's syndrome. However, among the patients with hypopituitarism and hyponatremia studied by Bethune and Nelson,[1] the majority had pituitary tumors. Many patients with hyponatremia and pituitary failure have previously undiagnosed hypopituitarism,[1,6] as in four of the five patients described above. Thus, hypopituitarism should always be considered as a possible cause unexplained hyponatremia. According to Bethune and Nelson,[1] hyponatremia in patients with hypopituitarism is often precipitated by the stress of an operation, a severe infection, or the administration of an excessive amount of fluid without the administration of an adequate dose of hydrocortisone. In the five patients described here, possible precipitating events were hypoglycemia (Patient 2), mild pulmonary infection (Patient 4), and a febrile state of undetermined cause (Patient 5). In Patient 3, antihypertensive treatment with diuretics may have been a precipitating factor, but signs of dehydration were absent. Two patients had had several episodes of hyponatremia in the past, probably also due to chronic hypopituitarism.

Since this was not a prospective study, the patients were not evaluated in a standardized manner. However, plasma vasopressin levels were measured during an early stage of the hyponatremic syndrome in all five patients. Figure 1 shows that even the slightly elevated plasma vasopressin levels in Patients 2 and 4 were unequivocally abnormal in relation to their low plasma osmolality values. In all patients, serum creatinine levels were low initially and tended to rise after the beginning of hydrocortisone therapy, thus indicating a state of volume expansion that was corrected by water excretion rather than sodium retention. However, it is recognized that sodium loss also contributes to hyponatremia in patients with SIADH and in subjects given overdoses of vasopressin experimentally.[33] Hydrocortisone probably restored sodium excretion to normal by inhibiting vasopressin directly.[2,12] The arterial hypotension and consequent baroreceptor-mediated vasopressin secretion that may occur in severe glucocorticoid deficiency[25] could also

have been corrected by hydrocortisone administration, but this is less likely in the patients in the present study, who were normotensive while hyponatremic.

In four of the five patients, basal plasma cortisol levels were decreased and responded very little to insulin-induced hypoglycemia or corticotropin-releasing hormone. In Patient 4, basal plasma levels of cortisol were low to normal, but the responses to corticotropin-releasing hormone and the metyrapone test were clearly abnormal. Therefore, when hypopituitarism is being considered as a possible cause of hyponatremia, one should not rely on the measurement of basal plasma cortisol levels alone. Dynamic function should be tested once the patient has recovered from the acute illness.

The cases presented here show that the hyponatremic syndrome is due to hypersecretion of vasopressin. Hypopituitarism should therefore be considered as a cause of SIADH.

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