The Spectrum Of "Cerebral Hyponatremia" – Cerebral Salt Wasting Syndrome in a Patient with Pituitary Adenoma

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Hyponatremia associated with intracerebral disease is usually ascribed to SIADH, the syndrome of inappropriate secretion of antidiuretic hormone. A number of studies in recent years has shown, however, that hyponatremia in patients with intracranial disease may actually be caused by cerebral salt wasting syndrome, in which a renal loss of sodium leads to hyponatremia and a decrease in extracellular fluid volume. This syndrome, originally described by Peters et al. in 1950 [1], is often erroneously diagnosed as SIADH. However, the two syndromes differ from one another in many aspects, including the mechanism responsible for the hyponatremia, the volume status in each condition and the therapeutic strategy. Distinction between CSWS and SIADH is of paramount importance, since patients with the former disorder respond to salt and volume replacement rather than fluid restriction, which is the usual treatment for SIADH.

We report a patient with pituitary adenoma who manifested severe hyponatremia along with excessive natriuresis and overt signs of ECF volume deficit. Based on the clinical and laboratory data, we believe that the patient suffered from CSWS. Clinicians confronting a case of hyponatremia associated with central nervous system disease should include this disorder in their diagnostic workup.

* *Deceased*

SIADH = syndrome of inappropriate secretion of anti-diuretic hormone

CSWS = cerebral salt wasting syndrome

ECF = extracellular fluid

Case Description

A 73-year-old man was referred to the emergency room because of severe headache and vomiting for 1 day. Routine blood examination revealed hyponatremia of 127 mEq/L and he was admitted to our department for evaluation. The patient had a history of mild diabetes mellitus and peripheral vascular disease that was treated with pentoxifylline and aspirin. At routine examination 2 months prior to his admission serum sodium was 138 mEq/L.

Physical findings on admission were: height 169 cm, weight 68 kg (the patient had lost 5 kg over the month prior to admission), blood pressure 130/80 mmHg, with postural hypotension of 20 mmHg, heart rate 80/min, and body temperature 37.2°C. His skin was dry. The rest of the physical examination was normal. Routine laboratory blood tests revealed: sodium 127 mEq/L, potassium 4.0 mEq/L, blood urea nitrogen 14 mg/dL, and creatinine 1.2 mg/dl. Glucose, calcium, phosphorus, and liver function tests were normal. Plasma osmolality was 262 mOsm/L and urine osmolality 627 mOsm/L. Urinary excretion of sodium was 292 mEq/day. Chest X-ray and chest computed tomography scan were normal. Brain CT scan revealed enlarged hypophysis with a 1.5 x 1 cm space-occupying lesion caused by pituitary adenoma with apoplexy. Brain magnetic resonance imaging scan demonstrated similar findings. His endrocrine profile showed plasma renin activity in the supine position of 0.19 ng/ml/hour (normal range 0.51–2.64), and plasma aldosterone 80 pg/ml (normal range 12–150). Plasma renin activity did not increase after the patient had been in an upright position for 2 hours, but plasma aldosterone rose to 105 pg/ml (normal 70–350 pg/ml). The response of aldosterone to exogenous ACTH stimulation was normal.

As shown in Table 1, the patient manifested signs of hypopituitarism reflected by depressed levels of testosterone, luteinizing hormone, cortisol and thyroid-stimulating hormone. Plasma level of antidiuretic hormone was markedly low and prolactin was normal. TSH response to thyroid-releasing hormone stimulation was blunted. A similar phenomenon (i.e., flat curve) was noted when gonadotropins (follicle-stimulating hormone and LH) release was stimulated by LH releasing hormone. Although basal cortisol level was low, the glucocorticoid secretory response following stimulation with ACTH was normal as evidenced by an increase in cortisol

Table 1. Endocrine profile

Test	Patient	Normal range
Prolactin (mU/L)	140	Male <186
Antidiuretic hormone (pg/L)	<0.5	0.5–3.7
TSH (mU/L)	0.04	0.167– 2.87
Free thyroxine (pmol/L)	16.9	10.3–25.7
Cortisol (nmol/L)	30	193–690
FSH (U/L)	4.7	1–14
LH (U/L)	0.6	1.5–9.2
Testosterone (nmol/L)	1.0	10.4–45

TSH = thyroid-stimulating hormone

LH = luteinizing hormone

to 458 nmol/L following 1 hour of stimulation with 0.25 mg ACTH.

On admission, the patient's hyponatremia was attributed to SIADH and was treated with fluid restriction. On the third day the patient experienced a syncopal attack due to severe hypotension (70/50 mmHg). Blood withdrawn during that episode revealed sodium 117 mEq/L. A central venous line was inserted and showed central venous pressure of -2 cm H_2O. A massive i.v. infusion of normal saline was instituted and hemodynamic indices showed gradual improvement over the subsequent hours. On the following day a liberal dietary salt intake was prescribed and the patient was started on fludrocortisone acetale 0.3 mg/day. Within 4 days, plasma sodium increased to 137 mEq/L.

At the time of writing, the patient's serum electrolytes and kidney function are normal and he is awaiting a neurosurgical intervention for the pituitary tumor.

Comment

The patient described here manifested severe hyponatremia in association with large pituitary adenoma. It is likely that the two disorders are interlinked since the usual causes for hyponatremia could not be found – namely, use of diuretics, vomiting, sodium-losing nephropathy, congestive heart failure and liver disease. While hyponatremia in the presence of intracerebral disease has traditionally been attributed to SIADH, the constellation of findings in our patient argued against this diagnosis. Firstly, his ADH levels were markedly suppressed [Table 1] despite the deficit in ECF volume. Secondly, he developed overt signs of volume contraction (dry skin, poor skin turgor, very low CVP, severe orthostatic hypotension) in association with serum sodium of 117 mEq/L. Thirdly, he had a negative salt balance, as evidenced by the fact that on a normal salt diet and in the presence of severe hyponatremia he excreted 292 mEq/day sodium. Both the volume status of this patient and the negative salt balance are incompatible with the diagnosis of SIADH, which falls into the category of euvolemic hyponatremia and which usually shows moderate degrees of natriuresis, reflecting salt intake. The final proof that this patient did not have SIADH was his dramatic response to salt and water replacement – the exact converse of the usual treatment of SIADH where fluid restriction is the mainstay for correcting hyponatremia.

The combination of hyponatremia associated with excessive loss of sodium in the urine and volume contraction could have been caused by adrenal insufficiency, but this diagnosis is improbable in our patient. Although he probably had secondary adrenal hypofunction resulting from the pituitary adenoma [Table 1], the adrenal gland's glucocorticoid secretory capacity was intact (cortisol level rose from 30 to 458 nmol/L following ACTH stimulation). Moreover, pituitary adenomas causing decreased ACTH synthesis do not usually cause hypotension and natriuresis, since mineralocorticoids rather than glucocorticoids are important for maintaining salt balance (under basal conditions) and aldosterone release is only minimally regulated by the pituitary-adrenal axis. In fact, our patient manifested quite normal plasma aldosterone levels. Based on his clinical and laboratory findings we believe that the cerebral salt wasting syndrome was probably related to the intracranial tumor.

This syndrome was originally reported by Peters et al. in 1950 [1] who described three patients with intracranial disease (encephalitis, intracranial hemorrhage and bulbar poliomyelitis). Each patient had hyponatremia (serum sodium <120 mEq/L) and the inability to prevent loss of sodium in the urine. The patients demonstrated ECF depletion and responded well to salt replacement. It was originally thought that hyponatremia resulted from the disruption of the pituitary-adrenal axis, but subsequent studies demonstrated normal pituitary and adrenal functions in these patients, leading to the hypothesis that CSWS was caused by a defect in the direct neural regulation of renal tubular activity. After the identification of SIADH by Schwartz et al. in 1957 [2], hyponatremia in patients with CNS disease was almost exclusively ascribed to SIADH, and the concept of hyponatremia caused by renal salt wasting fell from favor so that authors often equated the term CSWS with SIADH. However, in recent years CSWS has gained increasing attention by the medical community and it is now recognized that many types of CNS disorders, such as metastatic carcinoma, primary brain tumors and head injury, are associated with hyponatremia due to a defective sodium conservation by the kidney that leads to severe extracellular volume depletion. Nowadays, most of the literature on CSWS concerns patients with aneurysmal subarachnoid hemorrhage [3]. Overall, in neurosurgical settings CSWS occurs as frequently as SIADH, if not more so [4].

Although the mechanism for salt wasting was not fully determined in our patient, most investigators believe that CSWS associated with an intracerebral insult is due to the release of natriuretic peptides from the brain into the systemic circulation [5]. The best known of these peptides is the atrial natriuretic peptide, a 28 amino acid polypeptide found in atrial muscle as well as in the brain. The biological effects of ANP have been extensively studied and include natriuresis and diuresis, vasodilation and suppression of renin and aldosterone secretion [6]. In fact, the suppressed plasma renin activity levels in our patient (which was remarkable considering the state of volume deficit) could be the result of ANP effect on renin secretion. Aldosterone levels were in the low to normal range. Nonetheless, the "normal" aldosterone response was inappropriately weak considering the state of excessive natriuresis and ECF reduction in this patient. Again, this diminished response was probably related to the suppressive effect of natriuretic

CVP = central venous pressure

ANP = atrial natriuretic peptide

peptides on aldosterone secretion [6]. Aldosterone was partly stimulated by the effect of two other secretagogues affecting aldosterone secretion, namely ACTH and hyponatremia.

Interestingly, despite the ECF volume deficit, the BUN to creatinine ratio was kept at a normal value (approximately 12). In fact, this phenomenon is quite a common occurrence in CSWS, and again this is ascribed to the unique effect of natriuretic peptides, which play a pathogenetic role in CSWS. The commonly observed increment in BUN levels as compared to creatinine levels during the "usual" setting of ECF reduction is due to a significant decrease in urine flow that allows for enhanced reabsorption of urea from the tubular lumen into the circulation (given increased urine concentration and the fact that urea is freely diffusible across cell membranes). The decreased urine flow under these conditions is mainly due to intense renal vasoconstriction consequent to the effect of elevated circulating vasoconstrictors during ECF reduction (e.g., angiotensin II, catecholamines). In contrast, CSWS presents a unique combination of ECF reduction on the one hand and normal urine volume on the other. The latter is due to excessive natriuresis that maintains good urine flow. In addition, owing to the special role of natriuretic peptides in CSWS the sympathetic nervous system is inhibited, leading to diminished renal vasoconstriction when compared to other cases of ECF reduction. We therefore believe that these events could account for the normal BUN/creatinine ratio observed in our patient. Due to the complexity and cost of the assay for ANP and the fact that there are multiple forms of brain-derived natriuretic peptides, we did not perform direct measurements of these peptides in the serum of our patient. Nonetheless, the clinical and laboratory findings as described above support the role of one of the natriuretic peptides in the salt losing disorder in our patient.

In order to fully normalize serum sodium levels we administered fludrocortisone acetate in addition to fluid and salt replacement. This protocol was based on recommendations in other reports that increasing salt intake during CSWS may further enhance sodium excretion, and that prevention of volume depletion by reducing renal sodium excretion may be more appropriate. This could be achieved by the mineralocorticoid fludrocortisone acetate that acts directly on the renal tubule to enhance sodium reabsorption. The fact that endogenous secretion of aldosterone was not sufficient to prevent excessive natriuresis, thereby necessitating exogenous administration of fludrocortisone, may suggest that in addition to circulating natriuretic peptide there was also a distal tubular dysfunction (manifested as resistance to aldosterone) that contributed to salt wasting in this patient.

In summary, we have described a patient who developed CSWS in association with pituitary adenoma. CSWS broadens the clinical spectrum of hyponatremia in neurological and neurosurgical settings. Since this syndrome bears certain similarities to SIADH, also common in these settings, the two syndromes must be clearly distinguished from one another. Clearly, a decrease in ECF volume and a negative salt balance are the most salient features of CSWS that set it apart from SIADH. Therefore, evaluation of hyponatremia associated with intracranial disease mandates the consideration of volume status in these patients before the initiation of treatment. Fluid restriction in patients who suffer from CSWS and who are erroneously diagnosed as having SIADH can lead to hemoconcentration and increased blood viscosity and thus jeopardize cerebral perfusion.

BUN = blood urea nitrogen

This article is dedicated to the memory of Dr. Dagash who died tragically three years ago at the age of 27. Dr. Dagash was born in the village of Magar in the Lower Galilee. He graduated at the Hebrew University-Hadassah Medical School with honors and undertook his internship at the Rambam Medical Center in Haifa. On completion of this training Dr. Dagash began his service in the Israel Defense Force where he distinguished himself once again, receiving military honors and decorations from the Chief of Staff. Dr. Dagash was part of a Navy Commando Unit that was ambushed by the Hizballah and many soldiers were killed. This unfortunate event took place in September 1997, just five weeks after his marriage. We, his colleagues and friends, remember Dr. Dagash as a talented physician, a modest human being and a gentleman. We will cherish his memory forever.

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If I'd known I was gonna live this long, I'd have taken better care of myself.

Eubie Blake, American jazz musician (1883–1983)