Severe Hyponatremia with High Urine Sodium and Osmolality

Joost van der Hoek,1* Ewout J. Hoorn,1 Gijs M.T. de Jong,2 Emile N.W. Janssens,2 and Wouter W. de Herder1

CASE

A 49-year-old woman (previous history of childhood asthma, no medication) presented to the emergency department with nausea and vomiting that had occurred for 5 days and slurred speech for 1 day prior to presentation. The patient denied use of alcohol and illicit drugs. Physical examination revealed her blood pressure to be 125/70 mmHg; she had no postural drop and had a regular pulse of 72 beats/min. She had no fever and no signs of contracted extracellular fluid volume. Results of further physical and neurological examination were unremarkable and revealed no goiter, pigmentation, or vitiligo. Her laboratory results are shown in Table 1. Additional diagnostic tests included chest x-ray, abdominal ultrasound, and brain computed tomography, none of which revealed abnormalities. The syndrome of inappropriate antidiuretic hormone secretion (SIADH)3 was suspected. However, fluid restriction (500 mL/day) did not lead to increased serum sodium.

DISCUSSION

Because of the lack of response to therapy for SIADH, the diagnosis was reconsidered and hypothyroidism and/or adrenal insufficiency were suspected, especially because serum glucose was also low. Serum thyroid-stimulating hormone was 63 mU/L (reference interval 0.4–4.0 mU/L) with free thyroxine of 5 pmol/L (reference interval 9–24 pmol/L; to convert pmol/L of free thyroxine to ng/dL, divide by 13). Random cortisol was 151 nmol/L (reference interval 150–700 nmol/L; to convert nmol/L of cortisol to μg/L, divide by 0.0157), and a stimulation test with the 1–24 fragment of adrenocorticotropic hormone (ACTH) showed a baseline cortisol of 56 nmol/L, which increased only to 57 nmol/L (normal response >500 nmol/L). Plasma ACTH was 1124 ng/L (reference interval 7–50 ng/L; to convert ng/L of ACTH to pmol/L, multiply by 0.220). These results confirmed the presence of both primary adrenal insufficiency and primary hypothyroidism. Antibodies against the adrenal cortex, thyroid peroxidase, parietal cells, and intrinsic factor were present, establishing the diagnosis of autoimmune polyglandular syndrome type 2. Intravenous hydrocortisone was administered (bolus 100 mg followed by 200 mg/24 h), which corrected serum sodium (Fig. 1). After a sodium concentration within the reference interval was achieved, the patient was switched to oral hydrocortisone (10–5–5 mg daily) and L-thyroxine (50 μg).

This case has 2 salient features. First, it illustrates the diagnostic challenges of severe hyponatremia with high urine sodium and osmolality. Second, it illustrates quite strikingly how atypical the presentation of adrenal insufficiency can be.

APPROACH TO A PATIENT WITH SEVERE HYPONATREMIA

When a clinician is confronted with a case of hyponatremia, the first question should be whether it is acute or chronic (1).

In acute hyponatremia the most important risk to address is cerebral edema, because brain cells have too little time to adapt to cell swelling. Conversely, when chronic hyponatremia is treated too fast, the risk is osmotic demyelination (brain cells have adapted and are exposed to sudden changes in tonicity). The presenting symptoms in this case patient already posed a chal-
Challenges, because nausea and vomiting can be symptoms of both adrenal insufficiency and early cerebral edema. Because symptoms had been present for more than 2 days, the patient was judged to have chronic hyponatremia, and serum sodium was not corrected aggressively. Anecdotal evidence supports this approach, because both primary adrenal insufficiency and malnutrition can be risk factors for osmotic demyelination (2).

After the acuity of hyponatremia has been assessed, the next questions should be whether vasopressin (antidiuretic hormone) is acting, and if so, what is the reason for its release (1). Vasopressin is not measured routinely clinically, although the recent introduction of its stable precursor copeptin may change this protocol (3). Urine osmolality is a good surrogate marker for the renal actions of vasopressin, and a urine osmolality exceeding serum osmolality nearly always indicates high circulating vasopressin. If the renin-angiotensin system is also activated, the urine sodium concentration will be low, because aldosterone stimulates sodium reabsorption in the distal nephron. High urine osmolality with low urine sodium occurs with nonrenal sodium loss (as occurs with hypovolemia, diarrhea, and burns), heart failure, and liver cirrhosis. The differential diagnosis of hyponatremia with a high urine sodium and osmolality (as determined in this case) consists of diuretic use, primary or secondary adrenal insufficiency, cerebral salt wasting, salt-wasting nephropathy, and SIADH (1). Many physicians tend to diagnose SIADH before excluding the other causes. However, according to the criteria, SIADH is a diagnosis of exclusion (1).

Some diagnostic tests are better than others to assist in the differential diagnosis. For example, the clinical assessment of the extracellular fluid volume in patients with hyponatremia has a low diagnostic sensitivity and specificity (1). Instead, uric acid appears to be a more valuable index to assess the extracellular fluid volume during hyponatremia. During extracellular fluid volume expansion (SIADH, hypocortisolism), uric acid reabsorption in the renal proximal tubule is inhibited, producing a low serum concentration and a high fractional excretion. The opposite is usually true for a contracted extracellular fluid volume (such as occurs with diuretics, primary adrenal insufficiency, and salt-wasting nephropathy), although a caveat is that cerebral and some forms of renal salt wasting can also cause renal uric acid loss. In these instances, it may be useful to also analyze urea (serum concentration close to the upper limit of the reference interval, low fractional excretion) as a measure of extracellular fluid volume contraction. A tendency toward metabolic alkalosis suggests SIADH or diuretic use, whereas metabolic acidosis suggests primary adrenal insufficiency (4). Hypokalemia may accompany hyponatremia in diuretic use, whereas hyperkalemia is more typical for primary adrenal insufficiency. In this patient, urea was at the low end of the reference interval, whereas creatinine and uric acid were below the lower limit of the reference interval, supporting the presence of volume expansion and a diagnosis of either SIADH or hypocortisolism. Another test to differentiate dilutional

### Table 1. Laboratory results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mmol/L</td>
<td>101</td>
<td>135–145</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.0</td>
<td>3.5–5.0</td>
</tr>
<tr>
<td>Osmolality, mOsm/kg</td>
<td>209</td>
<td>280–300</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>3.5</td>
<td>4.0–7.6</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.19</td>
<td>2.20–2.65</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>69</td>
<td>75–110</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>2.9</td>
<td>2.5–6.4</td>
</tr>
<tr>
<td>Uric acid, mmol/L</td>
<td>0.19</td>
<td>0.20–0.42</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>8.8</td>
<td>7.5–9.5</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>42</td>
<td>35–50</td>
</tr>
<tr>
<td>Urine Sodium, mmol/L</td>
<td>95</td>
<td>—b</td>
</tr>
<tr>
<td>Osmolality, mOsm/kg</td>
<td>812</td>
<td>50–1200</td>
</tr>
</tbody>
</table>

*To convert nanomoles per liter of glucose to milligrams per deciliter, multiply by 18.

*There are no reference interval values for urine sodium, because measured values depend on the diet and the clinical circumstances. During hyponatremia, high or low urine sodium concentrations (typically with 20 mmol/L as cutoff) can be used for differential diagnosis.

---

**Fig. 1.** Serum sodium concentrations on admission, following subsequent treatment with fluid restriction, and hydrocortisone.
from depletional hyponatremia assessment of the response to isotonic saline.

Although SIADH is more common than adrenal insufficiency, the consequences can be grave when adrenal insufficiency is missed (5, 6). Random cortisol can be used to diagnose adrenal insufficiency, but concentrations between 100 and 700 nmol/L still do not exclude it (5). The better test is therefore an ACTH stimulation test. We have not performed the high-dose ACTH stimulation test (250 μg of synthetic ACTH 1–24 per 1.73 m²). Also important, however, is the low-dose ACTH stimulation test (1 μg synthetic ACTH 1–24 per 1.73 m²). The low-dose test may be a more sensitive index of adrenocortical responsiveness, and it was recently validated for primary adrenal insufficiency (7). In both tests, the administration of synthetic ACTH should lead to cortisol concentrations of 500 nmol/L or higher with normally functioning adrenal glands (7).

Regarding therapeutic administration of hydrocortisone, it important to emphasize that hyponatremia may correct quickly once hydrocortisone is instituted. To avoid osmotic demyelination, the correction of hyponatremia should be limited to 8 mmol/L per day (1). If the increase in serum sodium exceeds this limit, the administration of hypotonic fluids and/or exogenous vasopressin should be considered (1, 2).

ATYPICAL PRESENTATION OF PRIMARY ADRENAL INSUFFICIENCY
Soule previously demonstrated that hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, and eosinophilia were present in only 78%, 52%, 21%, 18%, and 23% of 50 patients with primary adrenal insufficiency (6). He described primary adrenal insufficiency as another "great mimicker in medicine" (6).

We suggest 2 possible explanations why the patient we describe presented without hypotension and hyperkalemia. The first is that the patient had isolated hypocortisolism with sufficient aldosterone remaining to prevent renal sodium loss and allow potassium secretion. The second is that there was aldosterone deficiency, but defense mechanisms prevented hypotension and hyperkalemia.

If isolated hypocortisolism were present, the next question would be why the secretion of cortisol but not aldosterone was affected. One possible explanation is that angiotensin II is a more potent or longer-lasting secretagogue for aldosterone than ACTH is for cortisol. Another possibility is that the cortisol-producing zona fasciculata was selectively perturbed. For example, one could hypothesize that autoantibodies somehow have a higher affinity for the zona fasciculata than for the zona glomerulosa. Pathophysiologically, cortisol deficiency causes hyponatremia through a different mechanism than aldosterone deficiency. When cortisol concentrations are low, its feedback to the hypothalamus is lost. As a consequence, corticotrophin-releasing hormone (CRH) is no longer inhibited. High CRH concentrations stimulate the secretion of vasopressin. CRH and to a lesser extent vasopressin are ACTH secretagogues, which may explain the high ACTH concentrations. The fact that serum uric acid was low and urea was close to the lower limit of the reference interval may also favor the possibility of isolated hypocortisolism (Table 1, see also above). The second possibility is that there was a deficiency of aldosterone, but that hypotension and hyperkalemia were prevented by other mechanisms. Cherney et al. postulated 3 reasons why a large sodium deficit does not necessarily result in hemodynamic instability (8). First, hyponatremia will cause red blood cell swelling, which will increase plasma volume and thus the effective circulating volume. Second, imminent hypovolemia will induce a high adrenergic state, which will cause venous vasoconstriction, diminishing the size of the vascular compartment and allowing better filling pressures. Third, hyponatremia implies cell swelling, which will increase interstitial pressure and may shift volume from the interstitial space to the intravascular space.

In addition to hypotension, hyperkalemia is estimated to be absent in approximately 30% to 50% of patients with primary adrenal insufficiency (6, 9). Pos-

### POINTS TO REMEMBER

1. Primary adrenal insufficiency can present without pigmentation, orthostatic hypotension, hyperkalemia, hypoglycaemia, and hypercalcemia.

2. The syndrome of inappropriate antidiuresis is a diagnosis of exclusion that can be established only if diuretic use and adrenal, thyroid, and pituitary insufficiency are excluded.

3. Primary adrenal insufficiency can be confirmed by low random cortisol concentrations, but normal concentrations still require an ACTH stimulation test for exclusion.

4. The presentation of adrenal insufficiency without orthostatic hypotension and hyperkalemia may be due to isolated hypocortisolism or the prevention of these symptoms by defense mechanisms.

5. Cortisol deficiency causes hyponatremia because it increases CRH, which stimulates vasopressin release, whereas aldosterone deficiency causes hyponatremia because of renal sodium loss, hypovolemia, and baroreceptor-mediated vasopressin release.
sible confounding factors are a low dietary intake of potassium (loss of appetite is common in adrenal insufficiency) and loss of potassium through vomiting. Another interesting possibility is the presence of circulating cationic proteins in the context of autoimmunity or cancer (9). These proteins can activate the calcium-sensing receptor in the thick ascending limb (9,10). This receptor activation can inhibit the sodium-potassium chloride cotransporter and produce a loop-diuretic effect with natriuresis and kaliuresis.

For this patient isolated severe hyponatremia was the only characteristic feature of primary adrenal insufficiency. Adrenal insufficiency should always be excluded in individuals with unexplained hyponatremia who have high urine sodium and osmolality.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References


Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Commentary

Glen L. Hortin,* Neil S. Harris, and William E. Winter

This case illustrates that initial laboratory results suggestive of SIADH do not rule out other potential causes of hyponatremia, such as hypothyroidism and hypoglycemia. To date, SIADH has been a diagnosis of exclusion, but advances in mass spectrometry offer prospects for accurately measuring ADH in the future.

When analyzers yield low sodium values, an initial priority is to exclude factitious hyponatremia. When sodium is measured by indirect methods, pseudohyponatremia due to a high serum protein or lipid content does not usually lower the sodium concentration to the degree observed in this case; however, the multiple potential sources of large errors in sodium measurements should be considered (e.g., sample dilution by intravenous fluids, storage of blood samples at reduced temperature, instrument failure, plugging of sample probes with clots, separator gel or cryoglobulins, sampling errors from inadequate samples or from bubbles in samples, or interfering substances) (1–3). Electrode methods can be affected by surfactants such as alcohols or other compounds used as skin disinfectants or by surfactants from other sources, such as catheter surfaces (3). Fortunately, well-trained laboratory staff can detect many of these errors before the reporting of results by repeating the analyses, by comparing the present value with previous results, and by evaluating other test results for the same sample. Sample re-collection may be required. In this case, the very low osmolality independently supports a severe electrolyte deficiency. The albumin and hemoglobin values suggest that no substantial sample dilution occurred. Fig. 1 indicates the analysis of additional samples that further rules out factitious hyponatremia.

Affecting women more often than men, autoimmune polyglandular syndrome type 2 is a polygenic disorder with onset in childhood or early adulthood; it is characterized by primary adrenal insufficiency or adrenal autoantibodies plus either autoimmune thyroid disease or type 1 diabetes (4). Because primary adrenal insuffi-
ciency typically involves destruction of the adrenocortical glomerulosa and fasciculata, measurement of renin and aldosterone would have been of interest in this case.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Commentary
Robert Richardson

Patients with chronic hyponatremia have vasopressin acting on the kidney, causing water retention and dilution of the sodium in the extracellular fluid. In surveys of hospitalized patients with hyponatremia, the stimulus for vasopressin secretion is low effective circulating volume via the baroreceptor in about two-thirds of patients. The remaining one-third have a variety of stimuli for vasopressin secretion, including surgery, nausea, hypothyroidism, adrenal insufficiency, and SIADH. Although physical examination is often extremely helpful in detecting signs of altered effective circulating volume (such as edema, ascites, hypotension, and abnormal jugular venous pressure), physical exam is unreliable in a significant proportion of patients.

The urine sodium concentration is a critical diagnostic aid in differential diagnosis. It should be low (<30 mmol/L) with reduced effective circulating volume, because sodium-retaining factors, including angiotensin II, catecholamines, the sympathetic nervous system, and aldosterone, are activated and stimulate renal tubular sodium reabsorption. When the urine sodium concentration is high, as in this case, SIADH should be strongly considered. This rule has 2 important exceptions, however. The first is diuretic use, which can cause baroreceptor-mediated vasopressin release through reduced effective circulating volume with a high urine sodium concentration. The second is adrenal insufficiency, in which cortisol or aldosterone deficiency can lead to vasopressin secretion. Urine sodium is high because of aldosterone deficiency. Adrenal insufficiency must always be ruled out in cases of severe hyponatremia, because the classic clinical and biochemical features may not be present.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References