Hyponatremia: A Diagnostic Problem
R. N. Walmsley and G. H. White

Hyponatremia, a common clinical problem, may result from a wide variety of causes. Treatment can vary from fluid restriction to rehydration, depending on the pathogenesis of the disorder. Essential to evaluation of hyponatremic patients is correct estimation of the status of the extracellular fluid volume, because this determines the type of therapy: a patient who is hypovolemic will not benefit from fluid restriction; a euvolemic patient should not be "rehydrated." To distinguish between these two conditions requires a searching history and clinical examination, including measurement of the blood pressure both while the subject is standing and lying. Not all patients with the classical biochemical features of the syndrome of inappropriate secretion of vasopressin (low plasma [Na+] and osmolality, high urinary [Na+] and osmolality) will have the disorder, because these same features may also be present in other hyponatremic disorders, including hypovolemic hyponatremia.

Hyponatremia is a common disorder, occurring in up to 22% of hospitalized patients (1, 2). It may be associated with a normal (euvolemic), decreased (hypovolemic, dehydration), or increased (hypervolemic, edema) extracellular fluid volume.

The evaluation and proper management of this fluid-electrolyte imbalance depend on correct assessment of the patient's extracellular fluid volume (3). If the patient is hypovolemic, rehydration is necessary. On the other hand, if the patient is euvolemic or edematous, fluid restriction or active measures to ensure a negative fluid balance, or both, will be required.

Usually there is little difficulty in the clinical recognition of patients who are either severely dehydrated or edematous. However, it is often difficult to distinguish between those patients who are euvolemic and those who have a slight to mild hypovolemia (dehydration). Failure to differentiate between these two groups of patients can result in inappropriate therapy and a worsening of the condition.

The following case presentation illustrates this diagnostic dilemma, and highlights the following:
(a) the necessity of a thorough clinical examination in the evaluation of fluid and electrolyte disorders,
(b) difficulties in the interpretation of urinary electrolyte values, and
(c) the possible consequences of diagnosing the syndrome of inappropriate secretion of vasopressin without adhering to rigid criteria in making this diagnosis.

Case Presentation

An 86-year-old woman presented at hospital with a five-day history of anorexia, nausea, vomiting, and diarrhea. On examination she was confused and disoriented. She had a myxedematous-like facies but no evidence of peripheral edema. Her pulse rate was 90 beats per minute, her blood pressure was 140/90 mmHg while supine. Her mucus membranes were moist. Her skin turgor was decreased, but this was thought to be compatible with her age.

The patient had a history of hypertensive cardiac disease for which she had been prescribed one tablet of a diuretic, Moduretic (amiloride hydrochloride 5 mg, hydrochlorothiazide 50 mg), night and morning. She had been on this therapy for four months and had continued to take the tablets up to, and during, her present illness.

The patient was not thought to be dehydrated and was admitted to the ward for investigation of her confusional state and possible hypothyroidism. Laboratory tests requested on admission included plasma electrolytes, urinary electrolytes, and thyroid-function tests.

Values for plasma electrolyte concentrations (mmol/L except as noted) on admission were as follows (normal reference intervals in parentheses):

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Value</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>104</td>
<td>(132–144)</td>
</tr>
<tr>
<td>K</td>
<td>3.7</td>
<td>(3.2–4.8)</td>
</tr>
<tr>
<td>Cl</td>
<td>&lt;70</td>
<td>(98–108)</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>25</td>
<td>(23–33)</td>
</tr>
<tr>
<td>Urea</td>
<td>6.1</td>
<td>(3.0–8.0)</td>
</tr>
<tr>
<td>Creat.</td>
<td>0.99</td>
<td>(0.06–0.12)</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.0</td>
<td>(3.5–5.5)</td>
</tr>
<tr>
<td>Osmol.</td>
<td>232 mmoL/kg</td>
<td>(281–297)</td>
</tr>
</tbody>
</table>

Analysis of an unmeasured urine specimen collected 45 min after the venesection revealed:

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Value</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Na</td>
<td>72 mmoL/L</td>
<td></td>
</tr>
<tr>
<td>Urine K</td>
<td>57 mmoL/L</td>
<td></td>
</tr>
<tr>
<td>Osmol.</td>
<td>524 mmoL/kg</td>
<td></td>
</tr>
</tbody>
</table>

On the basis of the clinical picture, and the plasma and urinary electrolyte values, the provisional diagnosis was inappropriate secretion of vasopressin secondary to hypothyroidism. The immediate treatment included fluid restriction to 500 mL per 24 h.

Comment

For the purpose of evaluation and management, patients with hyponatremia can be conveniently divided into three groups, on the basis of their hydration state (3):
(1) edematous (hypervolemia).
(2) dehydrated (hypovolemia).
(3) euhydrated (euvolemia).

(1) Hyponatremia and edema: Most patients who present with this combination are usually hyponatremic secondary to diuretic therapy (thiazides, furosemide). However, a small proportion of untreated, edematous patients (congestive cardiac failure, nephritic syndrome, cirrhosis of the liver), usually with an advanced state of the disease, present with hyponatremia. These patients have a severe defect in renal excretion of sodium and water, with the renal retention of water being proportionately greater than that of sodium. The urinary electrolyte and osmolality values in these patients reflect the renal retention of sodium and water, i.e., low urinary [Na+] (<10 mmoL/L) and high urinary osmolality (>200 mmoL/kg) (4, 5).

(2) Hyponatremia and dehydration: In this condition there is water and salt depletion, the depletion of sodium...
being relatively greater than that of water. The hyponatremia reflects the body's attempt to maintain the extracellular volume at the expense of the extracellular tonicity, by decreasing renal water excretion. This response is due mainly to a hypovolemia-induced secretion of vasopressin, which results in a urine osmolality that exceeds the plasma (extracellular) osmolality. The urinary [Na⁺] in these patients will be <10 mmol/L if there is an extrarenal cause for the fluid-electrolyte imbalance, such as vomiting, and (or) diarrhea. On the other hand, if there is a renal cause for the disturbance (mineralocorticoid deficiency, salt-losing nephritis, diuretic therapy) the urinary [Na⁺] will be greater than 20 mmol/L (4, 5).

(3) Hyponatremia and euvolemia: This condition is associated with a normal, or slightly decreased, extracellular sodium content, and a normal, or slightly increased, extracellular volume. It occurs in patients whose kidneys cannot excrete electrolyte-free water. This inability is usually ascribable to an increased concentration of circulating vasopressin, e.g., syndrome of inappropriate secretion of vasopressin, or of a substance with vasopressin-like activity such as antidiuretic drugs. In these cases the urine osmolality usually exceeds the plasma osmolality, or at least is inappropriately high relative to that of plasma—for example, >200 mmol/kg. The urinary [Na⁺] is usually high (>20 mmol/L), because of concentration of the urine, and Na⁺ excretion possibly is also increased as a consequence of an increased extracellular volume (4, 5).

Thus a crucial feature in evaluating patients with hyponatremia is to assess the hydration status, because the three groups will require different therapy:

- edema: diuretic therapy
- dehydration: rehydration
- euvhydration: fluid restriction

The above patient was considered to be euhydrated on the basis of the moist mucus membranes, normal supine blood pressure, skin turgor normal for age, and lack of evidence of peripheral edema.

The diagnosis of the syndrome of inappropriate secretion of vasopressin was entertained because:

1. plasma [Na⁺] was low, plasma osmolality was low, urine [Na⁺] was high, and urine osmolality exceeded plasma osmolality (6, 7).

2. hyponatremia has been described as a cause of the syndrome of inappropriate secretion of vasopressin (8).

Response to Therapy

During the next two days, as fluid was restricted to 500 mL/24 h, the plasma electrolyte concentrations (mmol/L) were:

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>109</td>
<td>114</td>
</tr>
<tr>
<td>K</td>
<td>3.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Cl</td>
<td>&lt;70</td>
<td>83</td>
</tr>
<tr>
<td>HCO₃</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Urea</td>
<td>7.2</td>
<td>11.5</td>
</tr>
<tr>
<td>Creat.</td>
<td>0.10</td>
<td>0.13</td>
</tr>
<tr>
<td>Osmol.</td>
<td>241</td>
<td>253</td>
</tr>
</tbody>
</table>

During this period the patient's condition deteriorated and her electrolyte-fluid status was re-evaluated. The positive clinical findings were:

- still disoriented.
- skin turgor: decreased.
- mucus membranes: dry.
- blood pressure: lying—135/65 mmHg.
- sitting—110/70 mmHg.
- pulse rate: 95 beats/min.

These findings, coupled with the increasing urea and creatinine concentrations in the plasma, indicated that the patient was hypovolemic. The fluid therapy was then changed to intravenous isotonic saline, about 3 L/24 h. After three days of this therapy (five days after admission) the patient had a positive fluid balance of some 4 L, and she was showing marked clinical improvement.

The results of the thyroid-function tests indicated the thyrometabolic status to be normal, thus ruling out the possibility of a syndrome of inappropriate secretion of vasopressin secondary to hypothyroidism.

The plasma electrolyte values on the fifth day after admission were: Na 131, K 4.6, Cl 97, HCO₃ 27, urea 6.5, and creatinine 0.07 mmol/L.

Discussion

This case clearly demonstrates the importance of the history and the clinical examination in the evaluation of patients with hyponatremia. It also indicates the importance of correct interpretation of the urinary electrolyte and osmolality values in such patients.

In the clinical evaluation of a patient's hydration state the first clues will be found in the history, if it is available. In the above case the story of diarrhea, vomiting, and diuretic therapy suggests the probability of hypovolemia is greater than that of euvolemia (edema was absent).

The results of this patient's physical examination (moist mucus membranes and normotension) misled the clinician into believing that the patient was not hypovolemic. Moist mucus membranes are not incompatible with mild dehydration, especially in patients with severe hyponatremia, where they may reflect intracellular overhydration. Patients with a mild hypovolemia often present with a normal supine blood pressure but will generally exhibit a drop in pressure on standing (postural hypotension). Thus in these patients it is necessary to check the blood pressure with the patient both lying and standing (or sitting). This feature is well demonstrated in the above patient during the second clinical examination.

Information on concentrations of urea and creatinine in plasma can be helpful in assessing hydration status: both usually are increased in hypovolemia, both often decreased in hypervolemia. However, these data may be misleading because:

- Both may be increased, in the absence of hypovolemia, owing to pre-existing renal insufficiency.
- Hypovolemia is usually associated with a high plasma urea concentration, but not necessarily so if the patient is vomiting—decreased dietary protein intake leads to decreased synthesis of urea.
- The plasma creatinine concentration is a function of the muscle mass and so patients of small stature—e.g., infants and elderly women—ordinarily will have a low-normal plasma creatinine concentration which may be some two- to threefold below the upper limits of the normal reference interval for adults of average size.

The estimation of the urinary electrolytes and osmolality is an important procedure in the evaluation of a patient with hyponatremia, but again there are traps for the unwary. A urine osmolality that is inappropriately high (>100–200 mmol/kg) in the face of a subnormal plasma osmolality often suggests the syndrome of inappropriate secretion of vasopressin, i.e., inappropriate concentration of the urine (vasopressin activity) in the presence of extracellular hypo-osmolality (stimulus for suppression of vasopressin secretion). However, most if not all patients with hypotonic hyponatremia will have an inappropriately high urine osmolality, because the primary defect in these patients is an
inability of the kidney to excrete electrolyte-free water (if 
they were able to excrete free water, the extracellular water 
would decrease and eventually result in normotonicity and 
normonatremia). All cases of the syndrome of inappropriate 
secretion of vasopressin have an inappropriately high urine 
osmolality, but not all patients who have a low plasma 
osmolality associated with a high urine osmolality will have 
the syndrome of inappropriate secretion of vasopressin.

The high urinary sodium concentration (>20 mmol/L) in 
the above patient also misled the clinician into believing 
that she had the syndrome of inappropriate secretion of 
vasopressin. A urine [Na+] exceeding 20 mmol/L is consist-
ent with the syndrome of inappropriate secretion of vaso-
pressin, but it also occurs in other situations associated with 
hyponatremia such as Addison's disease, salt-losing nephri-
tis, and diuretic therapy. This patient's urinary sodium 
concentration reflects her diuretic therapy.

Before the diagnosis of the syndrome of inappropriate 
secretion of vasopressin can be substantiated, at least the 
following six criteria should be satisfied (6, 7).

(1) plasma: hyponatremia and hypo-osmolality 
(2) urine: [Na+] >20 mmol/L and an inappropriately high 
osmolality (>200 mmol/kg) 
(3) no evidence of hypovolemia 
(4) no evidence of renal, adrenal, pituitary, or cardiac 
disease 
(5) patient must not be on any drug therapy (especially 
diuretics) 
(6) clinical and biochemical improvement in response to 
fluid restriction

In the above patient, conditions 3, 5, and 6 were not 
satisfied and therefore the diagnosis of the syndrome of 
inappropriate secretion of vasopressin was untenable.

The correct diagnosis for the above patient was hypovole-
mic hyponatremia (hypotonic dehydration) secondary to the 
effects of diarrhea, vomiting, and diuretic therapy. The 
subsequent response to therapy (deterioration on fluid re-
striction and dramatic clinical and biochemical improve-
ment with rehydration) confirms this diagnosis. This pa-
tient was misdiagnosed because an inadequate clinical 
examination categorized the patient as euvolemic rather 
than hypovolemic.

Although the early misdiagnosis in this patient was the 
result of an inadequate clinical workup, this case illustrates 
a situation where the clinical chemist can, and should, 
provide the clinician with valuable assistance. If the earlier 
samples sent to the laboratory had been accompanied by 
adequate clinical information—for example, diuretic ther-
apy and a provisional diagnosis of the syndrome of inap-
propriate secretion of vasopressin—then the clinical chemist 
would have noted that the diagnosis was tenuous and that 
the urinary electrolyte values were possibly the result of the 
diuretic therapy. Consultation between the clinical chemist 
and the clinician would then perhaps have resulted in early 
appropriate therapy.

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