ACID-BASE AND ELECTROLYTE TEACHING CASE

A Patient With Severe Hyponatremia and Hypokalemia: Osmotic Demyelination Following Potassium Repletion

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INDEX WORDS: Hyponatremia; hypokalemia; osmotic demyelination.

Note from Feature Editor Jeffrey A. Kraut, MD: This article is part of a series of invited case discussions highlighting either the diagnosis or treatment of acid-base and electrolyte disorders. Advisory Board member Horacio Adrogué, MD, served as the Consulting Editor for this case.

INTRODUCTION

Severe hyponatremia is a rare, but important, complication of thiazide diuretics. This often is associated with hypokalemia and other metabolic abnormalities, including hypophosphatemia and metabolic alkalosis. Treatment of hyponatremia requires in-depth understanding of the mechanisms leading to these metabolic disorders, especially the role of hypokalemia in the development of hyponatremia. We present a challenging patient with severe hyponatremia and hypokalemia who, despite careful management, developed osmotic demyelinating syndrome. We review the pathophysiologic characteristics of this disorder and lessons learned from this unfortunate incidence.

CASE REPORT

Clinical History and Initial Laboratory Data

A 59-year-old woman with a history of hypertension presented with 5 days of progressive weakness associated with cough and sinus congestion. On the day of admission, she was unable to arise from bed. She reported poor appetite with a significant decrease in oral intake. Other medical history included hyperlipidemia and long-term naproxen use (220 mg twice daily) for elbow pain.

Other medications included simvastatin, 5 mg/d, and losartan/hydrochlorothiazide, 50/12.5 mg/d. For 2 days, she had been using desloratadine and amoxicillin/clavulanate, 500/125 mg, twice daily. She denied use of laxatives, other cathartics, or herbal supplements.

Physical examination showed a tired-appearing woman with slurred speech. Weight was 73 kg, temperature was 97.8°F, blood pressure supine was 143/67 mm Hg with a heart rate of 59 beats/min, and blood pressure standing was 121/103 mm Hg with a heart rate of 129 beats/min. Oxygen saturation was 99% on room air. The rest of the examination findings were unremarkable, except for dry mucous membrane, diminished strength (3/5), and dysmetria, worst in the right upper extremity.

Initial laboratory studies are listed in Table 1.

Additional Investigations

Results of thyroid function and plasma cortisol tests and computed tomography of the head were normal. An electrocardiogram showed a heart rate of 56 beats/min with left-axis deviation and corrected QT interval of 584 ms. The patient had normal serum electrolyte levels 6 months earlier.

Diagnosis

Severe hyponatremia and hypokalemia.

Clinical Follow-up

The patient initially was treated with 300 mL of normal saline, then started on an 800-mL/d water restriction. She received 430 mEq (430 mmol) of potassium (as potassium chloride) in the first 24 hours. The course of sodium and potassium levels is shown in Fig 1.

During the next 2 days, the patient improved clinically with resolution of both weakness and metabolic abnormalities. During that time, she received another 200 mEq (200 mmol) of potassium and 50 mmol of phosphate orally.

Serum sodium level by day 7 increased to 130 mEq/L (130 mmol/L) and potassium level remained in the reference range. On day 8, she was noted to be shaky, unsteady, and incontinent. Serum sodium level was 132 mEq/L (132 mmol/L). On examination, she was unable to respond verbally or follow oral commands. She had normally reactive pupils and generalized weakness with muscle strength of 2/5, compatible with a diagnosis of "locked-in syndrome." Magnetic resonance imaging at this time had normal findings; however, 3 days later, it showed abnormal signals within the pons with diffuse signals in the basal ganglia sparing internal

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capsule. These findings were consistent with central pontine myelinolysis. Repeated magnetic resonance imaging 12 days later showed worsening of these findings (Fig 2).

The patient developed progressive weakness with total loss of motor function and severe spasticity. She became totally unresponsive by day 10. She was transferred to the intensive care unit, but did not require intubation. She had a prolonged hospitalization complicated by aspiration pneumonia and methicillin-resistant *Staphylococcus aureus* sepsis. During the next 5 weeks, she improved slowly, responding to simple commands, but continued to have generalized weakness and dysarthria. She was discharged to a rehabilitation hospital for further treatment.

Table 1. Laboratory Studies on Admission

Parameter	Value
Blood chemistries	
Sodium (mEq/L)	96
Potassium (mEq/L)	1.6
Chloride (mEq/L)	<60
Bicarbonate (mEq/L)	38
Serum urea nitrogen (mg/dL)	10.9
Creatinine (mg/dL)	0.5
Glucose (mg/dL)	156
Serum osmolality (mOsm/L)	201
Calcium (mg/dL)	8.4
Magnesium (mg/dL)	1.9
Phosphorus (mg/dL)	1.8
Arterial blood gases	
pH	7.66
P_{CO_2} (mm Hg)	34
Bicarbonate (mEq/L)	38
P_{O_2} (mm Hg)	87
Complete blood count	
Hematocrit (%)	41
WBC count ($\times 10^3/\mu L$)	14.2 (86% PMN, 4% lymphocytes, 9% monocytes)
Platelets ($\times 10^3/\mu L$)	191
Urinary chemistries	
Sodium (mEq/L)	22
Potassium (mEq/L)	48
Osmolality (mOsm/L)	546
FE_{Na} (%)	0.06
TTKG	11

Note: Conversion factors for units: serum urea nitrogen in mg/dL to mmol/L, ×0.357; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. No conversion necessary for sodium, potassium, chloride, and bicarbonate in mEq/L and mmol/L or white blood cells and platelets in $10^3/\mu L$ and $10^9/L$.

Abbreviations: FE_{Na}, fractional excretion of sodium; PMN, polymorphonuclear; TTKG, transtubular potassium gradient; WBC, white blood cell.

DISCUSSION

This patient was admitted with multiple electrolyte disorders, which included severe potassium depletion that put her at risk of life-threatening arrhythmias. Pseudohyponatremia and translocational hyponatremia were ruled out easily by low serum osmolality.[1] The focus of the present discussion therefore is on the pathogenesis and treatment of severe hyponatremia complicated by severe hypokalemia caused by hydrochlorothiazide and nonsteroidal anti-inflammatory drug (NSAID) use.

The association of thiazide-type diuretics with the development of severe hyponatremia has been known for several decades.[2] Most affected patients are older women with low body mass who were using hydrochlorothiazide to treat hypertension, rather than edema-forming states.[3] In patients with severe hyponatremia (sodium < 115 mEq/L [<115 mmol/L]), mortality attributable to hyponatremia is high, reaching 9% in 1 study.[4] Although hyponatremia can occur very quickly in susceptible individuals,[2,5-7] the duration of hydrochlorothiazide use varied widely from 1 day to 12 years in 1 series.[8] In another series, 37% of participants were on hydrochlorothiazide therapy for more than 1 year.[9]

The mechanisms of thiazide-induced hyponatremia are complex. In 1962, Fuisz et al[2] studied a single patient and concluded that hyponatremia was caused by both urinary sodium loss and transcellular shift of sodium; however, the contribution of potassium loss to hyponatremia was not appreciated. Both the infusion of sodium chloride and ethanol resulted in partial correction of urinary hyperosmolality, supporting a role for antidiuretic hormone (ADH) in the development of hyponatremia.[2] Sodium and potassium loss has been documented in many studies,[2,5-7] resulting in hypovolemia, which triggers an increase in both ADH levels and thirst. Ashraf et al[6] rechallenged a patient with 2 days of metolazone treatment and noted a subsequent sodium deficit of 218 mEq (218 mmol) and potassium loss of 166 mEq (166 mmol) in a 36-hour period concurrent with serum sodium levels decreasing from 142 to 124 mEq/L (142 to 124 mmol/L). This cation loss resulted in an increase in urinary

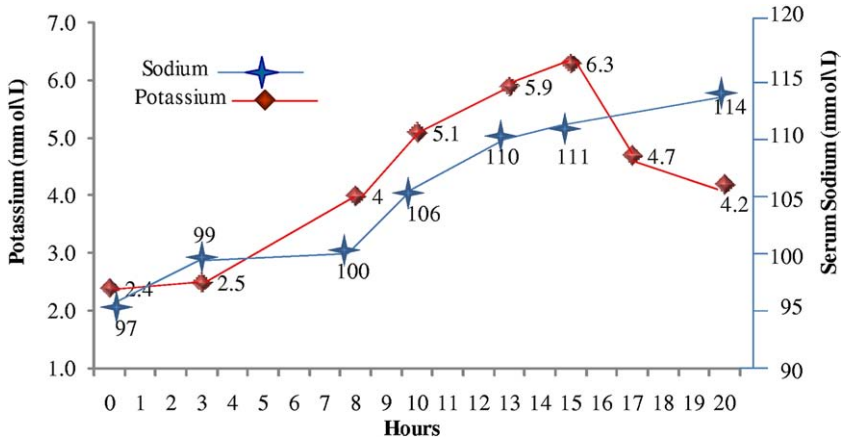

Figure 1. Serum sodium (stars) and serum potassium (diamonds) levels in the first 20 hours. No units conversion necessary for serum sodium and serum potassium in mEq/L and mmol/L.

osmolality and decrease in electrolyte-free water excretion. ADH first was measured using a bioassay method,[5] then confirmed with a detectable ADH level in 6 patients with severe hypo-osmolality.[10] These findings strongly suggest volume-dependent ADH release resulting in water retention and hyponatremia.

In an animal model of lithium-induced nephrogenic diabetes insipidus, hydrochlorothiazide also has upregulated aquaporin 2 levels, increasing water reabsorption in the inner medulla.[11,12] In contrast, chronic hypokalemia downregulates aquaporin 2 expression in rat collecting duct, resulting in polyuria.[13] Patients with hydrochlorothiazide-induced hyponatremia often appear clinically euvolemic. This may be caused by continued ingestion of water despite severe hypo-osmolality. Friedman et al,[7] studying the effect of a single dose of hydrochlorothiazide-amiloride tablet in patients with a history of hydrochlorothiazide-induced hyponatremia, noted a decrease in sodium level of 5.5 mEq/L (5.5 mmol/L) in 6 hours associated with mild weight gain. The weight gain could be explained only by water ingestion and retention, compounding the cation loss.

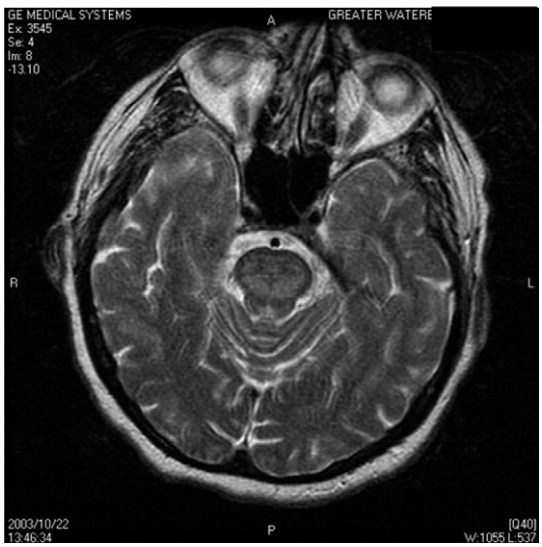

Figure 2. Magnetic resonance image of the brain on day 12 shows pontine myelolysis.

Hypokalemia is an independent predictive factor for the development of hyponatremia.[14] Because intracellular and extracellular osmolality are always equal, loss of either sodium or potassium, unless accompanied by loss of water, would result in hypotonicity. Although it is intuitively evident why changes in body sodium and water levels should determine serum sodium concentration, the role of potassium is less obvious, but as illustrated in this case, nevertheless is very important. Edelman et al[15] showed that serum sodium concentration is a function not only of total exchangeable sodium and total-body water, but also of total exchangeable potassium. The primary mechanism is that potassium depletion results in a shift of sodium into the cell with a commensurate exit of potassium from the cell into extracellular fluid.[16,17] The reverse occurs during potassium repletion and explains Laragh's[18] observation that oral potassium chloride administration resulted in an increase in serum sodium levels in

hyponatremic patients in the absence of administered sodium. A similar observation was reported by Fichman et al[5] in patients with diuretic-induced hyponatremia and hypokalemia. This effect of potassium repletion to increase serum sodium concentration may be enhanced by the entry of chloride into cell along with the potassium, which renders the cell hypertonic and draws water from the extracellular fluid. Potassium entry also may be accompanied by the movement of hydrogen ions from the intracellular to extracellular space, where they are buffered and thereby made osmotically inactive. This would decrease effective extracellular tonicity, again causing water to move into the cells, increasing the extracellular concentration of sodium. Whichever mechanism is dominant, the important observation is that potassium depletion could be associated with hyponatremia, and potassium repletion results in an increase in serum sodium concentration.[19]

NSAIDs, including cyclooxygenase 2 inhibitors, inhibit free water excretion by 2 independent mechanisms. In the loop of Henle, NSAIDS block prostaglandin E_2 synthesis locally and activate the sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) cotransporter, resulting in an increase in medullary and papillary tonicity and urinary concentration.[20] Indomethacin and meclofenamate have been shown to inhibit water diuresis in Brattleboro rats that lack endogenous vasopressin.[20] The second mechanism is through inhibition of vasopressin-induced synthesis of prostaglandin E_2 in the collecting duct that normally inhibits the effect of vasopressin. The disinhibition of the negative feedback loop results in this hormonal effect on the collecting duct, increasing water reabsorption.[21] Clinically, although NSAID-induced hyponatremia has been reported, it often is in patients with high endogenous vasopressin and/or excess fluid intake.[22]

In summary, the hyponatremia in this patient is multifactorial, including volume depletion, severe total-body potassium deficit, and NSAIDs potentiating the effect of vasopressin.

Because the hyponatremia in this patient developed during several days and therefore can be classified as chronic (arbitrarily defined as duration >48 hours), more attention is needed to the rate of correction to ensure that this does not result in an increase in serum sodium level >10-12 mEq/L (>10-12 mmol/L) during the first 24 hours and 18 mEq/L (18 mmol/L) in 48 hours (Box 1). Although no rate of correction is 100% safe, exceeding these parameters clearly places the patient at risk of osmotic demyelination and its associated neurologic consequences.[23] The treating physicians, well aware of these facts, instituted only moderate water restriction (800 mL/d) and specifically avoided the administration of sodium-containing solutions while focusing their attention on treatment of severe hypokalemia.

Table 2. Solute and Water Balance on Day 1

Component	Intake	Output
Solute Balance (net = +277 mmol/d)		
Sodium (mmol/d)	45	66
Potassium (mmol/d)	430	132
Total (mmol/d)	475	198
Water Balance (net = −2.46 L/d)		
Oral water (mL)	800	3,060
Water with sodium chloride[a] (mL)	300	500
Total (mL)	1,100	3,560

[a]Patient was insensible.

Let us analyze why this patient sustained a 17-mEq/L (17-mmol/L) increase in serum sodium levels in less than 24 hours by examining changes in solute (sodium and potassium) and water balance. We assume that given her age, 50% of body weight (73 kg) is water.

$$\text{Serum } [Na^+] \propto \frac{Na_E^+ + K_E^+}{Total\ Body\ Water}$$

$$= \frac{3{,}504}{73 \times 0.5} = 96 \text{ mEq/L}$$

where $[Na^+]$ is sodium concentration, Na_E^+ is exchangeable sodium, and K_E^+ is exchangeable potassium. Table 2 lists the first day's solute and water balance, resulting in the following:

$$\left[Na^+\right] = \frac{3{,}504 + 277}{36.5 - 2.5} = \frac{3{,}781}{34.0} = 111 \text{ mEq/L}$$

Thus, the predicted change in sodium levels in 24 hours is 15 mEq/L (ie, 111 − 96), a calculation that agrees with the observed change in serum sodium levels of 17 mEq/L (17 mmol/L). It must be noted that this patient's serum sodium level would have increased in the absence of the administration

of large amounts of solutes because she is excreting free water. This can be garnered from the fact that the urinary sodium plus urinary potassium concentration (70 mEq/L [70 mmol/L]) is lower than serum sodium level (at 96 mEq/L [96 mmol/L]). Thus, ~30% of urine output is electrolyte-free water, determined by using the following equation:

$$C_{H_2Oe} = V\left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right) = 3\text{L}\left(1 - \frac{70}{96}\right)$$
$$= 3\text{L}(1 - 0.73) = 810\ \text{mL}$$

where C_{H_2Oe} is electrolyte-free water clearance, V is urine flow rate, U_{Na} is urine sodium level, U_K is urine potassium level, and P_{Na} is plasma sodium level.

Unless a commensurate amount of water is replaced, serum sodium concentration will increase. Nonetheless, the increase in serum sodium level that this patient sustained primarily was a function of the addition of solute, in this case, potassium (Box 1).

Although this has been amply described in the literature,[24,25] the impact of potassium administration in substantially changing serum sodium concentrations is not as widely appreciated as it should be.

What happened to this patient? The clinical picture of deteriorating neurologic status on day 8 of hospitalization, as well as the subsequent radiology studies, pointed to osmotic demyelination. The delay in onset of symptoms is characteristic. The diagnosis is made clinically because radiologic findings may be delayed even further or, in some cases, absent altogether. The pathogenesis of osmotic demyelination is not fully understood. Because it afflicts the brains of patients with established chronic hyponatremia, it is likely that the adaptive process in which solutes, including potassium and organic osmolytes, have been depleted to protect against brain swelling is necessary for the injury to occur. As hyponatremia is corrected, the delayed cerebral redistribution of solutes leads to brain shrinkage, disrupting tight junctions and opening the blood-brain barrier, causing oligodendrocyte damage and demyelination. There is recent evidence that hyponatremia downregulates a neutral amino acid transporter (SNAT2; encoded by the *SLC38A2* gene), impairing cellular reuptake of amino acids, thereby rendering them more susceptible to injury as hyponatremia is corrected.[26] In this patient, the increase in serum sodium levels during 24 hours exceeded the recommended limits. This is compounded by a small, but significant, increase in serum potassium levels of 3.5 mEq/L (3.5 mmol/L).

Box 1. Teaching Points

- Thiazide-induced hyponatremia often is associated with significant hypokalemia
- Correction of hypokalemia is associated with a predictable increase in serum sodium levels
- In chronic hyponatremia (duration >48 h), the increase in serum sodium plus potassium levels should not exceed 12 mEq/L in the first 24 h and 18 mEq/L in the first 48 h
- In patients with a more rapid increase with or without symptoms of osmotic demyelinating syndrome, it is advisable to reverse the process by the use of free water and, if needed, desmopressin

The development of osmotic demyelination in this patient raises another intriguing question regarding the role of potassium in brain shrinkage and the pathogenesis of the disease. It has been observed that the incidence of hypokalemia in patients developing osmotic demyelination is high.[27] If administration of potassium increases serum sodium levels primarily through the entry of potassium into the intracellular space as sodium leaves it, there should be no osmotic gradient or change in cellular volume. Therefore, in contrast to the effect of 3% sodium chloride to alter cell volume, it is surprising that osmotic demyelination should have occurred in this particular clinical setting when only potassium replacement was used as therapy. Cell shrinkage may be a component, but perhaps not the only pathway that underlies the development of osmotic demyelination.

What could have been done differently? In as much as the patient's primary symptom of profound weakness most likely was related to the low potassium level and the prolonged corrected QT interval placed the patient at risk of a serious arrhythmia, potassium repletion was clinically indicated. This patient was at risk of overcorrection because she had 2 of the most common clinical settings in which such overcorrection occurs: thiazide use and hypovolemia. As discussed, when the effects of thiazide diuretics dissipate, urinary sodium and potassium loss decrease, effectively increasing free-water excretion. Likewise, volume resuscitation in hypovole-

mic patients results in suppression of vasopressin, further diluting the urine. Because this patient excreted >3 L in the first 24 hours, some of these processes most likely were operant, resulting in overcorrection of hyponatremia.

Serum sodium should be measured every 4-6 hours, and if the increase has reached 8 mEq/L (8 mmol/L) in the first 12 hours, measures to prevent a further increase should be instituted by matching urine output with 5% dextrose in water. If inadvertent overcorrection has occurred, there is experimental evidence for a window of opportunity to again decrease serum sodium levels using desmopressin to prevent brain lesions[28] and decrease mortality (Box 1).[29] The protective effect of a repeated decrease in serum sodium levels may be independent of preserving the blood-brain barrier permeability because administration of steroids restores such permeability without providing a survival advantage in hyponatremic rats.[29] There also are clinical case reports supporting the salutary effect of a repeated decrease in serum sodium levels[30] even after neurologic symptoms characteristic of osmotic demyelination are evident.[31] A more recent report describes the use of desmopressin (1-2 μg subcutaneously or intravenously) and 5% dextrose in water to prevent and treat overcorrection successfully in 20 patients. This was accompanied by no serious side effects and no episodes of osmotic demyelination.[32] In our patient, when serum sodium level increased >10 mEq/L (10 mmol/L), administration of hypotonic fluids should have been instituted to allow for the safe and necessary continuation of potassium repletion.

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