Case Report

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Hyponatremia-Associated Rhabdomyolysis

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Key Words

Hyponatremia · Rhabdomyolysis · Thiazide diuretics · Creatine phosphokinase · Myoglobin · Myoglobinuria

Abstract

Background: Hyponatremia is the most frequent electrolyte disorder. However, hyponatremia rarely results from excessive water intake, unless the kidney is unable to excrete free water, such as in patients on thiazide diuretics; in addition, hyponatremia is an uncommon cause of rhabdomyolysis. ***Methods:*** We present a 51-year-old hypertensive woman on chronic hydrochlorothiazide therapy who developed acute water intoxication and severe myalgias. ***Results:*** The patient developed acute hypotonic hyponatremia and subsequent rhabdomyolysis. We discuss the mechanisms responsible for the development of hyponatremia and its association with rhabdomyolysis. ***Conclusion:*** Muscle enzymes should be monitored in patients with acute hyponatremia who develop muscle pain, and hyponatremia-induced rhabdomyolysis must be considered in patients with myalgias receiving thiazide diuretics.

Introduction

Hyponatremia, defined as a plasma sodium level <130 mEq/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice with an incidence of 1–2% in hospitalized patients [1, 2]. However, hyponatremia is a rare cause of rhabdomyolysis, and, to our knowledge, only 24 cases have been reported [3–15].

We present a case with hypotonic hyponatremia and subsequent development of rhabdomyolysis. We also reviewed the previous reported cases of hyponatremia and rhabdomyolysis and discuss the possible pathogenetic mechanisms.

Case Report

A 51-year-old Caucasian hypertensive woman was admitted because of weakness and light-headedness. Four days prior to admission, she started with diarrhea and frequent episodes of nausea, for both of which she was advised to force fluid intake. Thereafter, she drank at least ten glasses of water daily; however, her symptoms worsened, requiring hospitalization. Daily medication included hydrochlorothiazide 25 mg/day; she denied tobacco use and alcohol intake. Physical examination revealed an oriented woman with orthostatic hypotension (blood pressure 105/80 mm Hg supine; 80/50 mm Hg erect), heart rate 100 beats/min, respiratory rate 16/minute, afebrile. Skin and mucous membranes were dry, and the rest of the physical examination was unremarkable.

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Chest X-ray was normal; an electrocardiogram revealed sinus tachycardia; sodium 115 mEq/l; potassium 3.3 mEq/l; plasma osmolality 260 mosm/kg; urine osmolality 884 mosm/kg; urine analysis showed specific gravity 1.010, pH 7.5; urinary sodium 1 mEq/l; urinary potassium 74 mEq/l. Additional laboratory data are summarized in table 1.

Intravenous infusion containing 0.9% sodium chloride with 20 mmol/l potassium chloride was started at a rate of 100 ml/h, accompanied by oral fluid restriction. On the 3rd day, the patient developed worsening myalgias; the intravenous infusion rate was reduced to 85 ml/h with discontinuation of potassium. One day later, her blood pressure normalized, but myalgias worsened, predominantly affecting the lower extremities. The creatine phosphokinase level was 21,285 U/l; plasma myoglobin was 179 μg/l; urinary myoglobin was 15.2 μg/day; a serum protein electrophoresis displayed a moderate decrease in serum proteins; a human immunodeficiency virus test was negative; thyroid-stimulating hormone and complement levels were within normal limits. Her myalgias progressively and spontaneously improved, and by the 12th day, she was discharged.

Table 1. Selected laboratory values

Blood results	Time, days				
	1	2	4	5	12
Na, mEq/l	115	119	122	129	137
K, mEq/l	3.3	5.5	6.2	5.4	3.4
Cl, mEq/l	81	89	98	98	99
HCO_3, mEq/l	31	22	20	26	27
Ca, mg/dl	9.2	9.2		9.1	9.2
P, mg/dl	3.5	3.7		4.9	4.4
Mg, mg/dl	2.1	2.1		2.1	2.1
Hct, %	51	47			33
WBC/mm^3	12.3	13.3			12.0
Platelets/mm^3	263,000	19,100			410,000
Albumin, g/l	6.3	6.2		2.3	3.9
CPK, U/l			21,285	20,899	2,228
Urea, mg/dl	11	16	27	15	9
Creatinine, mg/dl	0.8	0.8	0.6	0.5	0.6
Uric acid, mg/dl	3			3	
Glucose, mg/dl	149		124	108	104

Na = Sodium; K = potassium; Cl = chloride; HCO_3 = bicarbonate; Ca = calcium; P = phosphorus; Mg = magnesium; Hct = hematocrit; WBC = white blood cells; CPK = creatine phosphokinase.

Discussion

Our patient presented with hypotonic hyponatremia. This condition can be classified into three main categories. First, disorders in which there is a deficit of total-body water and a larger deficit of total-body sodium, i.e., volume depletion, including diuretic intake, mineralocorticoid deficiency, vomiting, and diarrhea, among others. Second, disorders of excess total-body water, such as inappropriate secretion of vasopressin. Third, disorders of excess total-body sodium and larger excess of total-body water (nephrotic syndrome, cirrhosis, cardiac failure, renal failure) [16].

Hyponatremia rarely occurs after water intake, due to the high efficiency of the normal kidney in excreting free water. However, when it is impaired, i.e., by thiazide therapy, renal insufficiency, hypothyroidism, cortisol deficiency, or inappropriate secretion of vasopressin, excessive water intake results in hyponatremia [17].

In our patient, several factors contributed to the development of hyponatremia: thiazide therapy, hypotension, nausea, and exaggerated water intake. Chronic thiazide diuretic therapy is a common cause of hyponatremia. Unlike loop diuretics, these agents act in the distal nephron and, therefore, do not dissipate medullary tonicity; thus, vasopressin-induced water retention is not modified. Additional factors that predispose to hyponatremia are chronic natriuresis and bodily potassium deficit. Older women are known to be at higher risk of thiazide-induced hyponatremia [18] and to have a tendency to increased water intake [19].

In our case, diuretic intake led to volume depletion; physical findings, high hematocrit, elevated albumin, metabolic alkalosis, and low urinary sodium support such impression. Hypovolemia, severe enough to cause hypotension, even in the presence of a low plasma osmolality, stimulates the sympathetic nervous system and vasopressin secretion [16, 20]. Baroreceptors in the carotid sinus mediate vasopressin release [21]. Moreover, thirst is stimulated by angiotensin II, also increased due to volume contraction [22], and, if water intake is exaggerated or not accompanied by salt intake, hyponatremia ensues. Finally, hyponatremia caused nausea, an independent potent stimulus to vasopressin release [23].

Metabolic alkalosis on admission could be explained by volume contraction and diuretic use. As in our patient, in an initial volume-contracted state, hyperuricemia and high urea levels were not present, this phenomenon could be due to increased uricosuria [24] and the urinary urea wasting [25] that follows the volume-expanded state that developed after excessive water intake and the intravenously administered solution during hospitalization. This effect is presumably due to vasopressin, mediated through V_1 receptors [26]. The low urinary sodium level can be attributed to volume depletion and diminished total-body sodium.

Table 2. Previous reported cases of hyponatremia-induced rhabdomyolysis (in chronological order)

Authors	Year of publication	Cases	Etiology of hyponatremia	Onset of CPK peak levels, h	Outcome
Di Bona and Morens [5]	1977	1	influenza A	120	recovery
Browne [6][a]	1979	1	psychogenic polydipsia	36	reversible ARF
Adler [7]	1980	1	benzodiazepines	72	reversible ARF
Mor et al. [8]	1987	1	psychogenic polydipsia, benzodiazepines	not reported	not reported
Cronin [9][a]	1987	11	psychogenic polydipsia, alcohol	not reported	recovery
Alamartine et al. [10]	1987	1	loop diuretics, spironolactone	not reported	recovery
Mitnick and Bell [11]	1990	1	prostate surgery	96	recovery
Tomiyama et al. [4]	1990	1	psychogenic polydipsia, alcohol, benzodiazepines	96	recovery
Putterman [3][a]	1993	1	psychogenic polydipsia, physical exertion	72	recovery
Egan et al. [12]	1994	1	Addison's disease	not reported	recovery
Fernandez-Real et al. [13][a]	1994	2	benzodiazepines	48	recovery
Rizzieri [14]	1995	1	psychogenic polydipsia	48	recovery
Korzets et al. [15][a]	1996	1	psychogenic polydipsia	48	recovery

CPK = Creatine phosphokinase; ARF = acute renal failure.

[a] Hypokalemia also present.

In this setting of volume depletion, vasopressin is released; nevertheless, water can be retained by independent mechanisms of vasopressin. It is seen in elderly people, in whom the ability to excrete a water load is impaired, and is more prevalent among those who have previously developed thiazide-induced hyponatremia; decreased prostaglandin synthesis is involved [27].

Hyponatremia has been reported as a cause of rhabdomyolysis, presumably because of the hypo-osmolality of the extracellular fluid, leading to cell swelling [3, 28]. After several hours, cellular swelling is reduced, and the volume normalizes, as a result of extrusion of intracellular potassium causing increased blood flow to the area [29, 30]. Potassium-depleted muscle cells fail to release potassium, and blood flow becomes insufficient. Furthermore, in potassium-deficient cells, the cellular transmembrane potential is decreased, leading to rhabdomyolysis and release of creatine phosphokinase and myoglobin and subsequent myoglobinuria [30]. Noteworthy, of the 24 reported cases of hyponatremia-induced rhabdomyolysis, 12 had coexisting hypokalemia [3, 6, 9, 13, 15] (table 2), and, as in our case and these previously reported ones, potassium depletion could have certainly played an additional role in the development of rhabdomyolysis. In our patient, creatine phosphokinase blood levels were measured 4 days after presentation, when important myalgias developed, and we regrettably lack previous levels. As previously stated, a delayed creatine phosphokinase peak level could suggest hyponatremia as a possible etiologic factor for rhabdomyolysis [4]. Our patient developed anemia, thrombocytopenia, and leukocytosis (table 1), features previously associated with rhabdomyolysis [31, 32].

In our patient, rhabdomyolysis was not followed by acute renal failure which complicates 30% of the cases of rhabdomyolysis of other etiologies, although the exact mechanism remains unclear [28]. Excessive water intake and intravenous fluid administration could have played a protective role, since hypovolemia predisposes to pigment-induced tubular necrosis [33].

In summary, we present a patient with a history of chronic thiazide intake and volume depletion. After forcing water intake, she became hyponatremic. Hyponatremia was further complicated by rhabdomyolysis, as creatine phosphokinase and plasma and urinary myoglobin levels were elevated. Thiazides should be avoided in

elderly individuals, but, if indicated, patients should be instructed to limit their fluid intake. Finally, we emphasize the need to monitor muscle enzymes in hyponatremic patients if muscle weakness or pain develop [3].

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