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Acid-Base and Electrolyte Teaching Case

Reset Osmostat: The Result of Chronic Desmopressin Abuse?

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A reset osmostat as a cause of hyponatremia can be found in a variety of clinical settings, including pulmonary and neurologic diseases, as well as in physiologic circumstances such as pregnancy. This teaching case describes a 72-year-old white man with a long-standing history of self-medicating with desmopressin acetate (DDAVP) who presented with profound hyponatremia. On discontinuation of DDAVP treatment, he was found to have a reset osmostat. The mild hyponatremia persisted on follow-up. We theorize that the reset osmostat may have developed secondary to long-standing DDAVP use.
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INDEX WORDS: Reset osmostat; hyponatremia; osmolality; vasopressin; desmopressin acetate (DDAVP); serum sodium; osmolality homeostasis.

INTRODUCTION

The most common cause of hyponatremia in hospitalized patients is the syndrome of inappropriate antidiuretic hormone (SIADH).[1] It is diagnosed by inappropriate urinary concentration at some level of hypo-osmolality in the setting of euvolemia[2] and normal kidney, adrenal, and thyroid function.

Four patterns of ADH regulation have been described in SIADH. The first, the classic pattern, is characterized by the erratic release of ADH independent of osmotic control.[3] Malignancy is often implicated in this situation. The second is thought to be the result of dysfunctioning inhibitory neurons in the hypothalamus, leading to a persistent "leak" of vasopressin. The result is inappropriately high plasma vasopressin levels at low plasma osmolalities, but a normal relationship between plasma osmolality and plasma vasopressin levels at physiologic osmolalities.[3]

A clinical picture consistent with SIADH, except that vasopressin levels are not elevated, exemplifies the third pattern.[3] This rare situation, termed the nephrogenic syndrome of inappropriate antidiuresis, has been described in the context of a gain-of-function mutation in the vasopressin receptor and is clinically implicated in both children and adults.[4,5] The fourth pattern occurs when the osmoregulation of vasopressin is preserved, which maintains the collecting duct's concentrating and diluting abilities, but the threshold for ADH release is lowered. This is known as the reset osmostat and can be seen in severe neurologic[6,7] and pulmonary disease,[8,9] as well as with infections,[10] alcoholism, malignancy,[11] and trauma[12] (Box 1).

Distinguishing between classic SIADH and reset osmostat is clinically relevant because there are treatment implications. We present the case of a 72-year-old male physician who developed hyponatremia secondary to desmopressin acetate exposure superimposed on chronic hyponatremia due to a reset osmostat.

CASE REPORT

Clinical History and Initial Laboratory Data

A 72-year-old white male physician presented with palpitations secondary to atrial fibrillation and was found to have a serum sodium level of 115 mEq/L. He had no symptoms that were immediately attributable to hyponatremia. He was admitted for management of atrial fibrillation and hyponatremia.

The patient's medical history was notable for 10 years of "polyuria," for which he self-prescribed oral desmopressin acetate (DDAVP), 100 μg, 3 times per day despite not having formal urinary measurements or water deprivation testing. He adjusted his DDAVP dose to achieve a goal of ∼2 L of urine output per day. He reported having subsequent issues with mild hyponatremia, with unsuccessful attempts to discontinue DDAVP treatment due to recurrent "polyuria" and episodes of self-reported hypotension. He took salt tablets intermittently in an effort to prevent hyponatremia. These steps generally maintained his serum sodium level at ∼130 mEq/L. Prior to these practices, his serum sodium level was normal at 140 mEq/L. Due to his symptom of palpitations, he had increased his water intake and DDAVP dose prior to presentation.

Additional medical history included 2 deep vein thromboses (1990 and 1997) attributed to factor V Leiden deficiency, both of which occurred prior to his DDAVP use. There was no significant surgical or family history. He was married and practiced internal medicine. He used alcohol rarely and did not smoke or use illicit drugs. He denied recent ethanol or toxic alcohol use, as well as exposure to glycine, sorbitol, or mannitol. His medications included oral DDAVP, propafenone, atenolol, warfarin, pyridoxine, and salt tablets. He described no allergies.

On examination, the patient was alert and oriented to person, place, and time. Vital signs included blood pressure of

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Box 1. Teaching Points

- Reset osmostat can be seen in a variety of clinical situations, including severe neurologic or pulmonary disease, as well as in the normal physiology of pregnancy
- Reset osmostat is diagnosed by demonstrating normal urinary dilution and concentration, the latter of which occurs at a lower-than-normal serum osmolality. It requires an euvolemic patient with normal kidney, thyroid, and adrenal function
- Unlike classic SIADH, reset osmostat does not require fluid restriction
- Long-term DDAVP use may induce neurochemical changes involving the brain and/or renal collecting ducts that may precede the development of a reset osmostat

Abbreviations: DDAVP, desmopressin acetate; SIADH, syndrome of inappropriate antidiuretic hormone.

135/93 mm Hg and heart rate of 110 beats/min. Cardiovascular examination revealed an irregularly irregular rhythm without murmurs or rubs. Pulmonary and abdominal examination findings were unremarkable. He had moist mucous membranes, normal skin turgor, and no edema. His cranial nerves were intact and he had normal deep tendon reflexes. He ambulated without difficulty.

Blood tests on admission, while the patient was self-medicating with DDAVP, are shown in Table 1. Additional laboratory measurements included the following values: albumin, 3.3 g/dL; uric acid, 5.1 mg/dL; total cholesterol, 116 mg/dL; low-density lipoprotein cholesterol, 63 mg/dL; high-density lipoprotein cholesterol, 35 mg/dL; and triglycerides, 97 mg/dL. Complete blood count and liver profile results were normal. Thyroid-stimulating hormone and morning serum cortisol levels were normal.

Additional Investigations

DDAVP and salt tablets were discontinued on admission. Dextrose 5% in water was given intravenously at 200 mL/h to temper the expected brisk increase in serum sodium concentration. Magnetic resonance imaging of the brain did not show pituitary abnormalities. A urine diuretic screen also gave negative results. Vasopressin levels were not checked.

Table 1. Laboratory Results

Parameter	Values			
	10 y Prior	Admission	Discharge	1 y Post
Serum				
Sodium, mEq/L	140	115	132	131
Potassium, mEq/L	4.4	4.6	4.7	4.5
Chloride, mEq/L	106	90	101	100
Bicarbonate, mEq/L	26	18	24	23
Urea nitrogen, mg/dL	12	9	11	12
Creatinine, mg/dL	1.0	0.7	0.8	0.7
eGFR,[a] mL/min/1.73 m^2	90	94	89	94
Glucose, mg/dL	106	102	124	103
Osmolality, mEq/L		260	278	
Urine				
Osmolality, mOsm/kg		759	382	
Sodium, mEq/L		63	47	

Abbreviation: eGFR, estimated glomerular filtration rate.
[a]Calculated using the MDRD equation.

The patient's serum sodium level was monitored every 4 to 6 hours, in addition to daily urine osmolality and urine sodium levels. By day 1 of admission, serum sodium level and urine osmolality were 121 mEq/L and 110 mOsm/kg, respectively. When an appropriate rate of correction of serum sodium level was achieved, the rate at which 5% dextrose in water was given was reduced and eventually discontinued. DDAVP treatment continued to be withheld.

Two days into the patient's admission, his serum sodium and urine osmolality values were 127 mEq/L and 142 mOsm/kg, respectively. He underwent a 12-hour water deprivation test, upon which his daily urine output decreased from 5 L to 1 L with an increase in urine osmolality to 685 mOsm/kg, while his serum sodium level stayed constant at 130 mEq/L (see Figs 1 and 2).

Diagnosis

Acute hyponatremia from DDAVP use, superimposed on chronic hyponatremia secondary to a reset osmostat.

Clinical Follow-up

The patient remained off treatment with DDAVP and salt tablets. He was instructed to allow thirst to guide his water intake. Serum sodium levels remained stable between 129 and 132 mEq/L for the rest of the hospitalization and at 1-year follow-up.

DISCUSSION

The osmostat is the regulatory center in the hypothalamus responsible for controlling extracellular fluid osmolality.[13] In healthy individuals, plasma osmolality is kept within a narrow range of 280 to 290 mOsm/kg. Vasopressin secretion increases linearly when plasma osmolality increases[14]; if plasma osmolality decreases to <275 mOsm/kg, vasopressin secretion stops.[15] This underscores the role of plasma osmolality as the major stimulus for ADH release. A "reset" osmostat occurs when ADH release occurs at a lower threshold, resulting in a form of chronic hyponatremia considered to be a variant of SIADH. It differs from classic SIADH in that urinary diluting and concentrating capabilities are preserved.

We present an unusual case of a euvolemic man with profound hyponatremia for whom a reset osmostat was ultimately diagnosed. His severe hyponatremia on admission was attributed to excess free water intake combined with a recently increased DDAVP dose. Because there was an osmolal gap, we cannot definitively exclude the presence of an osmotically active substance. However, he had no exposure to mannitol, sorbitol, or glycine and denied recent ethanol or toxic alcohol use.

The patient was taking DDAVP because he thought he had diabetes insipidus; this diagnosis was ruled out when he demonstrated an ability to concentrate his urine on fluid restriction. His dilute urine (osmolality, 100-150 mOsm/kg) at a serum sodium level of 125 mEq/L excluded SIADH in its classic pattern because those with SIADH would be inappropriately concentrating urine at this level of serum osmolality. A reset osmostat was diagnosed by demonstrating: (1) normal urinary dilution with a DDAVP-induced