Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

CASE REPORT

Hyponatremia in a Patient With Cryptococcal Meningitis: Syndrome of Inappropriate Antidiuretic Hormone (SIADH) or Cerebral Salt Wasting (CSW)?

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Disclosure: No competing interests.

Journal of Hospital Medicine 2010;5:193–195.

KEYWORDS: hyponatremia, cryptococcal meningitis, cerebral salt wasting, syndrome ofinappropriate antidiuretic hormone.

An 83-year-old man admitted for weakness, lethargy, and mental status changes was found to have human immunodeficiency virus (HIV) disease and cryptococcal meningitis. His hospital course was complicated by worsening hyponatremia (sodium < 136 mEq/L). By hospital day 6, the patient's serum sodium had declined to 127 mEq/L from his admission level of 133 mEq/L. The initial impression was that the patient had syndrome of inappropriate antidiuretic hormone (SIADH) and fluid restriction to less than 1500 mL per day was initiated. By hospital day 11, serum sodium continued to decline, to 123 mEq/L, despite fluid restriction.

The past medical history was remarkable for coronary artery disease, hypertension, hyperlipidemia, and anemia, but by self-report he had not been taking any medications. His review of systems was positive for intermittent bouts of diarrhea.

Vital signs on day 11 included a temperature of 37.3°C, blood pressure (BP) of 105/55 mm Hg, and pulse of 90 beats per minute. The BP on admission had been 145/86 mm Hg but had steadily declined with fluid restriction. On physical examination, he appeared thin and cachetic with no evidence of jugular venous distention, rales, or peripheral edema to suggest volume overload. He had been receiving 2 to 4 L of isotonic saline daily for 5 days before the fluid restriction was initiated. The urine output continuously exceeded his intake by at least 500 mL per day throughout his hospital course. His only inpatient medications were amphotericin B and flucytosine. For nutritional supplementation, he was receiving a high-calorie supplement with free-water flushes via a nasogastric tube.

Laboratory results revealed a serum sodium concentration of 123 mEq/L, serum potassium of 4.4 mEq/L, serum creatinine of 0.6 mg/dL, urine sodium of 139 mEq/L, serum osmolality of 272 mOsm/kg, and urine osmolality of 598 mOsm/kg (see Table 1). Urinalysis revealed a specific gravity of 1.030. A random serum cortisol level was 11.1 μg/dL. A thyroid-stimulating hormone (TSH) level was 1.32 μIU/mL. Brain natriuretic peptide (BNP) was elevated, at 686 pg/mL. A fractional excretion of uric acid was also elevated, at 83.8%.

The clinical assessment was volume depletion given the high urine specific gravity, decreasing BP, and a negative fluid balance. The hyponatremia was determined to be due to sodium loss rather than dilution from inappropriate antidiuretic hormone secretion. Intravenous fluid (IVF) hydration with isotonic saline was initiated with a goal to keep the patient in positive fluid balance. The serum sodium level gradually improved to 140 mEq/L over the next 10 days. Attempts to decrease the rate of IVF resulted in a fall in serum sodium and improved when isotonic saline was increased. Eventually, the patient was placed on fludrocortisone, which normalized his urine output and serum sodium.

The response to the treatment regimen supported our diagnosis of cerebral salt wasting (CSW). The patient's serum sodium concentration upon discharge was 135 mEq/L.

Discussion

Our case illustrates the diagnostic challenge presented to physicians when they manage hyponatremia in the setting of a central nervous system (CNS) event. Hyponatremia (sodium < 136 mEq/L) has been associated with confusion, lethargy, seizures, coma, and even death.[1] Hyponatremia has been reported to occur in up to 30% of the patients with subarachnoid hemorrhage.[2,3]

SIADH is frequently the cause of hyponatremia in a patient with a concurrent intracranial process. However, CSW is an important diagnosis to consider and differentiate from SIADH. In a retrospective review of 316 patients with subarachnoid hemorrhage and hyponatremia, 69% were determined to be due to SIADH while 6.5% were from CSW.[4] Both CSW and SIADH have been reported to occur in the setting of head trauma, intracranial or metastatic neoplasm, carcinomatous or infectious meningitis, subarachnoid hemorrhage, and CNS surgery. Cryptococcal meningitis as an etiology of CSW has not been previously reported.

2010 Society of Hospital Medicine DOI 10.1002/jhm.516
Published online in wiley InterScience (www.interscience.wiley.com).

TABLE 1. Biochemical Data During Hospital Course

Parameters	Day 1	Fluid Restriction Initiated: Day 6	Day 8	Fluid Resuscitation Initiated: Day 11	Day 13	Day 15	Day 26	Day 37*	Day 40	Day 44†
Na (mEq/L)	133	127	126	123	131	119	140	131	132	135
K (mEq/L)	4.2									4.2
BUN (mg/dL)	39									36
Cr (mg/dL)	1.1									0.9
U_{Na} (mEq/L)	–			139	–	86	154	138		–
U_{Osm} (mOsm/kg)	–			598	–	362	–	376		–
S_{Osm} (mOsm/kg)	–			272	–	273	–	279		–
BNP (pg/mL)	–			–	–	686	–	900	222	–
S_{UA} (mg/dL)	–			–	–	1.7	2.6	1.6		–
U_{UA} (mg/dL)	–			–	–	38	11	–		–
FE_{UA} (%)	–			–	–	83.82	28.21	–		–
FE_{Na} (%)	–			–	–	3.94	7.33	–		–
BP (mm Hg)	147	136	122	105	101	90	125	132		140
Total input (mL)	700	NR	1285	3320	NR	3040	4030	4240	3120	1900
Urine output (mL)	500	NR	2400	6501	NR	3150	3380	2950	1900	950

Abbreviations: BNP, brain natriuretic peptide, BP, blood pressure; BUN, blood urea nitrogen, Cr, creatinine, FE_{Na}, fractional excretion of sodium; FE_{UA}, fractional excretion of uric acid; K, serum potassium, Na, serum sodium; NR, not recorded; S_{Osm} = serum osmolality, S_{UA} = serum uric acid; U_{Na}, urine sodium, U_{Osm}, urine osmolality, U_{UA}, urine uric acid.

*Fludrocortisone 0.2 mg/day started.

†Day of discharge.

The main differentiating feature between SIADH and CSW is that CSW is a dysfunction of renal sodium absorption whereas in SIADH renal sodium handling is intact. This also leads to a difference in the extracellular volume status. SIADH is associated with an increased to normal volume status whereas CSW is a volume-depleted state. Our patient exhibited a low serum osmolality and a high urine osmolality in the context of hyponatremia, which is present in both CSW and SIADH. However, the clinical course and presentation suggested volume loss, specifically the diarrhea, high urine specific gravity, declining BP, and a negative fluid balance. Some other features that are helpful in determining the volume status may include orthostatic changes, tachycardia, and skin turgor.

Our patient had a low serum uric acid, which is also present in both SIADH and CSW. The key difference between the 2 is that while uric acid will improve with resolution of hyponatremia in SIADH, it will remain low in CSW, as in our patient's uric acid levels, which remained low after normalization of the serum sodium.

Finally, the hyponatremia improved with isotonic fluid repletion, which would not occur in SIADH. The majority of the CSW patients will respond to volume repletion alone, as CSW is a transient condition that will usually resolve in 3 to 4 weeks.[3] However, a few patients may require fludrocortisone, as was needed in our patient.

The renal wasting of sodium in CSW is poorly understood. Some postulated mechanisms cite the disruption of sympathetic neural input to the kidney and natriuresis induced by natriuretic peptides. Natriuretic peptides, in particular BNP, have been reported to be elevated in patients with CSW.[5,6] Natriuretic peptides cause salt wasting by inhibition of sodium reabsorption in renal tubule and intramedullary collecting.[5,6] Renin and aldosterone release can also inhibited by the natriuretic peptides. BNP levels were elevated in our patient despite volume loss and no signs of congestive heart failure. Cardiac congestion is a possible etiology for the elevated BNP levels, which peaked to 900 pg/mL on hospital day 37. However, 3 days later the BNP levels declined to 222 pg/mL despite the fact that he was continually in positive fluid balance, suggesting that the BNP elevation was due to CSW and not heart failure.

Conclusions

Our case illustrates the diagnostic and management challenge of hyponatremia in the setting of a CNS event. Both SIADH and CSW are possible etiologies but it is important to make a differentiation. Levels of natriuretic peptides and changes in fractional excretion of uric acid may help differentiate between the 2 conditions.[6] The key difference mechanistically is that CSW is due to sodium-handling deficits, whereas in SIADH sodium-handling is intact. It is essential to establish volume status since SIADH is a euvolemic to mildly hypervolemic state vs. CSW, which is a volume-depleted state.[7]

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Published online in wiley InterScience (www.interscience.wiley.com).

CSW is well recognized in the neurosurgical arena. The hospitalist will encounter neurosurgical patients with increasing frequency, and thus having an understanding of this disorder, including its diagnosis and treatment, is key.

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