Recurrent Hyponatremia After Traumatic Brain Injury

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ABSTRACT: Dysregulation of the neuroendocrine system is a frequent complication after traumatic brain injury (TBI). Symptoms of these hormonal abnormalities might be subtle and thus easily ignored. Hyponatremia usually indicates underlying disorders that disrupt fluid homeostasis. In most patients with TBI, hyponatremia is a feature of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion due to pituitary dysfunction after head injury. Usually TBI-associated hyponatremia is transient and reversible. We report the case of a 48-year-old man with TBI-associated hyponatremia with delayed recovery and recurrent hyponatremia precipitated by subsequent surgery. In this report, we emphasize the importance of identifying patients with slow recovery of the injured brain, which could complicate with SIADH and acute hyponatremia. Differentiating TBI-associated SIADH from other important causes of hyponatremia such as cerebral salt wasting, and hypocortisonism are also reviewed. Prevention of its recurrence by avoiding further risk is mandatory in managing patients with TBI. **KEY INDEXING TERMS:** Hyponatremia; Head injury; Syndrome of inappropriate antidiuretic hormone secretion. **[Am J Med Sci 2008;335(5):390–393.]**

Hyponatremia is a common disorder encountered in various settings.[1] In most cases, hyponatremia manifests as an underlying disease and degree of hyponatremia usually indicates severity of etiology, and can even correlate with patient outcome.[2] Clinical features of hyponatremia are confined to most neurological manifestations, but vary with severity and rate of progression. Hyponatremia is one of the clues for diagnosing disease that might not be detected directly. Moreover, in certain circumstances, hyponatremia can even provide significant prognostic implications.[1]

Traumatic brain injury (TBI) may severely impair brain function. In addition to structural damage, neuroendocrine dysfunction is an important complication.[3] The pituitary insult can manifest with any hormone dysregulation involving either the anterior or posterior pituitary gland.[4,5] Most TBI-associated hyponatremia is mild and asymptomatic, and lasts only a short time. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) commonly underlies acute hyponatremia in these patients.[6] Because the neurological manifestations of hyponatremia and acute brain injury are quite similar, differentiation may be difficult. Furthermore, unresolved recurrent hyponatremia with obvious clinical manifestations has rarely been described. We report here a patient with recurrent symptomatic hyponatremia after head injury.

Case Report

A 48-year-old man was sent to our emergency department because of an accidental fall, and head injury 4 days before admission. He had originally been admitted to a local hospital where brain computed tomography revealed no intracranial hemorrhage or skull fracture. However, he developed progressive headaches, deteriorated consciousness, and vomiting that were refractory to medical treatment. Repeated brain computed tomography at our institution disclosed minimal bilateral frontal subdural hematoma. Biochemical examination found a rapid drop in serum sodium level to 122 mEq/L 2 days after admission. On examination, the patient was euvolemic without signs of volume deficit. He had normal blood pressure throughout hospitalization, and no decrease in body weight. Serum biochemistry panel drawn at admission showed glucose 117 mg/dL, sodium 122 mEq/L, osmolality 263 mOsm/kg H_2O, blood urea nitrogen 13 mg/dL, and creatinine 0.7 mg/dL. No other electrolyte abnormalities were found. Urine biochemistry showed sodium 159 mEq/L and osmolality 710 mOsm/kg H_2O. Adrenal and thyroid function tests showed cortisol level 10.3 μg/dL (normal, 3–13 μg/dL); thyroid stimulating hormone 1.75 μIU/mL (normal, 0.25–4.0 μIU/mL); and free T4 1.85 ng/dL (normal, 0.79–2.01 ng/dL). He denied a history of hyponatremia and no medication-related hyponatremia was noted. A diagnosis of hyponatremia due to SIADH was thus made.
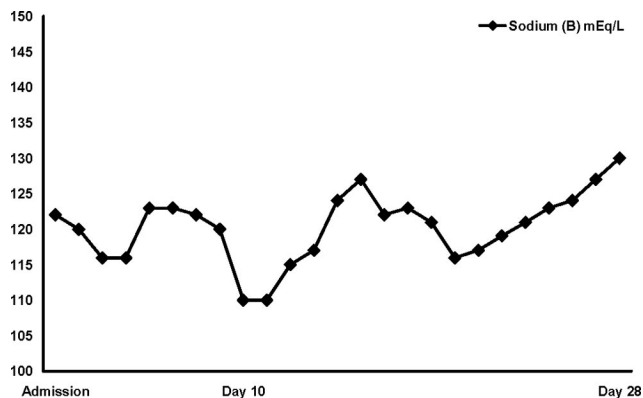
Figure 1. Changes in plasma sodium level during hospitalization for first hyponatremia episode.
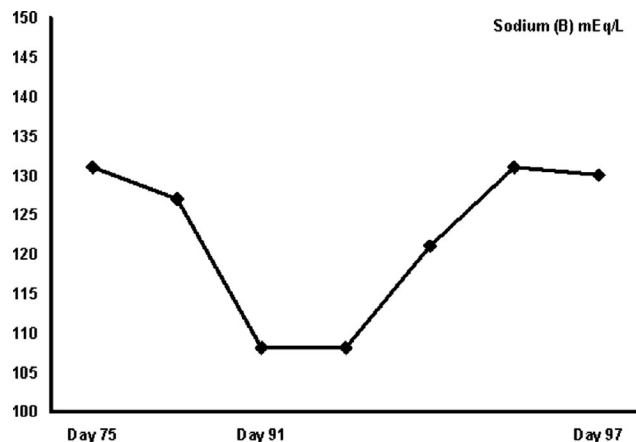

Figure 2. Changes in plasma sodium level during hospitalization for secondary hyponatremia episode.

The patient's clinical course was uneventful, with treatment including hypertonic saline (3% NaCl) infusion and fluid restriction. His hyponatremia progressed after admission, with the lowest sodium level of 110 mEq/L on hospital day 10. With gradual improvement, the sodium level returned to 130 mEq/L on day 28 (Figure 1). No surgery was performed for his small subdural hemorrhage and he was discharged thereafter. Unexpectedly, another 2 episodes of hyponatremia developed within months. The second episode occurred 2 months later, after surgery for a lumbar spine compression fracture, with the patient experienced severe headaches, vomiting, and epigastric burning. Routine blood tests showed a preoperation sodium level of 131 mEq/L. No symptoms were recorded at that time. There was no medicine use attributed to hyponatremia. His cortisol level was 24.9 μg/dL (normal, 9–23 μg/dL, morning). There was no intravenous free water administration in pre- and postoperative periods. Physical examination and biochemical study supported the diagnosis of recurrent SIADH (Table 1). During hospitalization, the patient's hyponatremia progressed to a nadir at day 14 with sodium level 108 mEq/L. Conservative treatment with water restriction was given and sodium level increased rather rapidly, accompanied by improvement in symptoms within 1 week. Sodium level increased to 130 mEq/L (Figure 2). The third episode occurred 20 days after the second discharge. The patient was readmitted for surgery for a displaced transpedicle screw. The preoperation sodium level was normal at 143 mEq/L. However, the patient experienced recurrent headaches 1 week later and his sodium level went as low as 117 mEq/L. Hormonal study revealed normal thyroid and adrenal functions (thyroid stimulating hormone, 2.34 μIU/mL; cortisol, 23.9 μg/dL). No intravenous free water was given while he was hospitalized. His hyponatremia was normalized with conservative treatment only. No later episodes of hyponatremia were identified, and the patient had no further hyponatremia-related symptoms or signs.

Discussion

Hyponatremia is a common electrolyte disorder frequently observed in patients with a variety of central nervous system disorders and after many different neurosurgical procedures.[7] Clinical symptoms are mainly neurological, in addition to nonspecific complaints. It is therefore necessary to be aware of this overlap and treat patients accordingly. Acute hyponatremia caused by SIADH in the setting of traumatic cerebral injury has a reported prevalence rate ranging from 2.3% to 36.6%, depending on selection criteria, time of study, and follow-up period.[8] Among all etiologies, SIADH accounts for more than 90% of cases of post-TBI hyponatremia.[9] SIADH is thought to be caused by central nervous system disorders because of disorganized inputs from the osmoreceptor cells of the anterior hypothalamus and brainstem cardiovascular regulatory centers.[10] Most TBI-associated hyponatremia occurs within 1 week after head injury and returns to normal within 6 months. Post-TBI hyponatremia is not related to severity of brain insult (ie, as measured by the Glasgow coma scale) or presence of brain edema.[6]

The development of recurrent severe hyponatremia with alternation in consciousness in our patient was unexpected. The first hyponatremia progressed

Table 1. Summary of Traumatic Brain Injury (TBI)-associated Hyponatremia

	Days After TBI	Duration[a] (d)	Blood		Urine	
			Sodium (mEq/L)	Osmolality (mOsm/kg H$_2$O)	Sodium (mEq/L)	Osmolality (mOsm/kg H$_2$O)
First hyponatremia	4	28	122	263	159	710
Secondary hyponatremia	75	22	121	249	84	532
Third hyponatremia	125	14	128	259	151	472

TBI, traumatic brain injury.

[a] The duration was calculated from the onset of hyponatremia until the highest sodium level was noted during that episode.

slowly and sodium level increased gradually. However, the second and third episodes were noted immediately after operations without other remarkable etiology. Because we know experiencing an operation is among the most common causes of SIADH in hospitalized patients, it is reasonable to speculate that our patient had not recovered completely from the initial insult and was susceptible when confronted with further surgery, provoking the SIADH. The lowest sodium level (108 mEq/L) was detected during the secondary episode but a rather modest decline was found in the third episode. Although most insults are transient, one patient was reported to have TBI-associated SIADH at 1 year after injury.[11] Our patient experienced recurrent hyponatremia precipitated by surgery (the apparent precipitating factor). This clinical feature illustrates a delayed recovery of pituitary function, and external stimuli, such as those produced by surgery, could induce SIADH with resulting hyponatremia.

In addition to SIADH, other causes of hyponatremia after head injury include cerebral salt wasting (CSW), glucocorticoid deficiency, medications, and aggressive use of intravenous fluids.[9,12] By definition, SIADH is a syndrome with normal to mild increased volume with resultant hyponatremia. The excessive ADH, acting on collecting ducts, enhances water reabsorption. Without volume deficit and in the absence of hypofunction of the thyroid and adrenal glands, hypo-osmolality with urine osmolality greater than maximal dilution and elevated urine sodium excretion are cardinal figures of SIADH. Our patient demonstrated typical laboratory abnormalities in 3 hyponatremia episodes and improved spontaneously solely with fluid restriction. The recently discovered arginine vasopressin receptor antagonist may be a potential therapeutic agent to treat TBI-associated SIADH, especially in patients with prolonged and symptomatic hyponatremia as observed in our patient.[13,14] Another specific, rare, but important cause of post-TBI-associated hyponatremia is CSW. This syndrome is characterized by central nervous system lesions with association of renal sodium and chloride loss. Peters et al[15] first described patients with neurological disorders complicated with increased renal sodium excretion and hyponatremia. Intact pituitary and adrenal function but renal defect in preserving sodium and chloride was found in later studies.[16,17] Natriuresis and volume depletion with increased vasopressin secretion are typical presentations in CSW patients. There are several factors contributing to the development of CSW. Natriuretic substances from central nervous systems origin such as brain natriuretic peptide, atrial natriuretic peptide, and digitalis-like peptides can exert natriuretic effect directly on the kidney.[18] Furthermore, the decrease in sympathetic nervous system outflow with resultant inhibition of

renal tubular sodium reabsorption and aldosterone secretion aggravates urinary sodium loss.[19] In the presence of volume deficit, vasopressin is elevated in response to hypovolemia. Differentiating between these 2 disorders is critical because treatments are quite different. The most reliable way to differentiate the 2 is to assess effective circulating volume in these patients, as laboratory features are similar.[19]

Impact of TBI on pituitary hormone secretion is distributed evenly between the anterior and posterior parts. The prevalence of anterior pituitary hormone deficiency has been estimated to be 28.4%, with two-thirds of cases involving an isolated hormonal axis.[20] The most commonly affected hormones are adrenocorticotropic hormone, gonadotropin, and growth hormone. Although we did not check adrenocorticotropic hormone, this patient had normal cortisol levels in 3 subsequent measurements and did not manifest with typical feature of acute adrenal failure as described.[9] These data did not support coexisting hypocortisonism in association with SIADH. On the other hand, about one-third of patients have complications with posterior pituitary dysfunction.[6] Interestingly, TBI can elicit excessive excretion, as well as deficiency, of ADH. In a large cohort study of post-TBI patients, incidence of diabetes insipidus was more common than SIADH.[6] Both disorders result from posterior pituitary dysfunction associated with disturbance in sodium homeostasis. In severe diabetes insipidus, hypernatremia rather than hyponatremia is a common laboratory finding. Most pituitary hormones are reduced in TBI-induced pituitary dysfunction except for elevation of prolactine and ADH. The reason is currently unknown. The clinical course of post-TBI pituitary dysfunction is not universal for all hormones involved. Some abnormalities can develop soon after brain insult, whereas others may present as late as 1 year later, and disease duration can vary.[21]

In conclusion, we reported a TBI patient with recurrent hyponatremia accompanied by neurological symptoms. The SIADH-related hyponatremia had a prolonged, gradual recovery and was provoked repeatedly by subsequent surgical procedures. This case report highlights the clinical significance of recurrent trauma-associated SIADH and the severity of hyponatremia. Continuous evaluation for hyponatremia is necessary for all patients post TBI.

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