Cerebral salt wasting and elevated brain natriuretic peptide levels after traumatic brain injury: 2 case reports

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Abstract

Background: Historically, hyponatremia in patients with varying brain diseases was termed \textit{cerebral salt wasting}. Hyponatremia secondary to CSW was reported to be a distinct entity from SIADH, with the distinguishing feature of decreased extracellular fluid volume. Brain natriuretic peptide, a peptide with natriuretic, vasorelaxant, and aldosterone-inhibiting properties, was recently implicated in aneurysmal SAH patients with CSW. Here, we describe 2 cases of CSW in TBI patients with elevated BNP levels. This phenomenon has not been previously described.

Case Description: Two patients with TBI and hyponatremia were subject to analysis. Central lines were placed to assess volume status. Levels of BNP were measured at the onset of hypertonic saline infusion. Electrocardiogram and cardiac enzyme studies were performed to assess cardiac function. Serial imaging was performed to assess the extent of brain injury.

Conclusions: These patients with TBI had findings consistent with CSW with elevated BNP levels in the setting of normal cardiac function. In both cases, a high BNP level was observed after declining plasma Na levels despite aggressive hypertonic saline infusion. High BNP levels may be associated with CSW. Further studies are necessary to establish a causative role for BNP in TBI-induced CSW.

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1. Introduction

Hyponatremia was reported in the 1950s in a number of patients with various causes of brain disease. As excessive natriuresis was observed, the term \textit{cerebral salt wasting} was coined for this syndrome [3,14,19]. The proposed natriuretic factor was never identified, and with the discovery of ADH, SIADH gained favor as the causal mechanism [2,4,5]. Recently, the concept of CSW was revived and thought of as an entity distinct from SIADH, with the distinguishing feature of decreased extracellular fluid volume compared with normal or increased extracellular volume of SIADH [6]. In recent years, evidence has accumulated implicating CSW as the most common cause of hyponatremia in acute brain disease. This distinction is important, as the treatment of SIADH, namely, fluid restriction, can exacerbate the condition of CSW and further aggravate volume depletion and cerebral ischemia.
The recent discovery of a family of NPs produced by both brain and heart has revolutionized the mechanistic understanding of physiologic and pathologic natriuresis [9]. ANP and BNP are known as the cardiac NPs because of their predominant expression in the atria and ventricles, respectively. ANP is produced by the cardiac atria and the brain. BNP is produced by the brain and the cardiac ventricles. CNP is produced abundantly in the brain but is also present in peripheral tissues, such as vascular endothelial cells [16]. CNP, in contrast to the endocrine action of ANP and BNP, is thought to function in a paracrine manner [15]. BNP has been used most prominently in the evaluation and treatment of congestive heart failure [10]. Brain natriuretic peptide has natriuretic, vasorelaxant, and aldosterone-inhibiting properties. Its secretion is stimulated by increased cardiac volume or pressure, may have an important role in Na and blood pressure homeostasis, and has been popularized as a diagnostic measurement of heart failure by Maisel et al.

In 1997, Berendes et al [1] published a Lancet article implicating BNP in SAH patients with CSW. In this study, BNP has been shown to be correlated with Na excretion in hyponatrexic patients with SAH but unrelated to plasma ADH levels. Moreover, in a separate study in patients with SAH, BNP levels were found to be associated with hyponatremia and predicted the 2-week GCS score [11].

Despite the emerging evidence that elevated BNP levels may play a role in hyponatremia associated with SAH, to date there is no evidence to suggest whether hyponatremia after TBI may be due to elevated BNP levels. This information would be of critical importance in suggesting new avenues toward diagnosis and treatment of TBI-associated hyponatremia. In this article, we report 2 cases of TBI that demonstrate an association between post-TBI CSW and high BNP levels.

2. Case report 1

A 52-year-old male with no significant prior medical history presented after an assault to the head. He was initially confused and then developed tonic-clonic seizure activity, with a GCS score of 4 (E1V1M2) as per EMS. Upon arrival to the San Francisco General Hospital, the patient was intubated for airway protection and was given Ativan (Baxter Health Care; Deerfield, IL, USA) and Dilantin (Pfizer; NY, NY, USA) for seizures. At that time his GCS score was 3, and he had a fixed and dilated right pupil. Head CT revealed a large right holohemispheric SDH with 8-mm midline shift, extensive right frontal contusions, intraventricular hemorrhage, and right uncal herniation (Fig. 1).

He was taken to the OR for right decompressive hemicraniectomy, SDH evacuation, and placement of left-sided external ventricular drain. Postoperatively, his GCS score was 4 (E1V1M2); he had bilateral reactive pupils, positive corneal and cough reflexes, and extensor posturing in all extremities to noxious stimuli. To monitor for seizure activity, EEG was placed, which showed diffuse encephalopathic slow delta and superimposed alpha rhythm. On POD 4, he had a temperature spike to 39.0°C, chest x-ray revealed bibasilar pulmonary infiltrates, and blood culture was positive for Klebsiella. Zosyn (Wyeth Pharmaceuticals; Philadelphia, PA) was started for empirical coverage.

Hyponatremia consistent with CSW was observed in this patient. Admission Na was 136, and 3% normal saline was started at 30 mL/h. His Na requirement increased to 70 mL/h by HD 6 for an Na of 133 mmol/L. Preceding this, urine excretion of Na and urine output began to increase on HD 4 (Figs. 2 and 3, respectively). Despite aggressive NaCl infusion, the patient’s Na continued to decline to 131 mmol/L on HD 8. Notably, he had evidence of dehydration, as his admission BUN/Cr ratio was 17:0.9, and after initial fluid resuscitation the BUN/Cr ratio declined to 11:0.9. Over this period, hematocrit also declined from .45 to .36. Furthermore, his initial CVP was 4 mm Hg and increased to 6 to 9 mm Hg after resuscitation.

Serum BNP level was determined to be 81 pg/mL (normal, <15 pg/mL) on HD 7 despite having normal cardiac function during hospitalization. This correlated to a high level of urinary Na excretion (Fig. 2). Electrocardiogram on admission and during hospitalization revealed normal sinus rhythm without any abnormalities. Central venous pressure ranged from 4 to 8 mm Hg without evidence of cardiac failure.

Despite aggressive ICU care, his neurologic status did not improve. Throughout his hospitalization, his ICP was in the 20 mm Hg. On POD 9, his neurologic status declined to minimally reactive pupils and no cough and gag with extensor posturing. Computed tomography and CT angiogram of the head were performed at that time and revealed in all extremities to noxious stimuli. To monitor for seizure activity, EEG was placed, which showed diffuse encephalopathic slow delta and superimposed alpha rhythm. On POD 4, he had a temperature spike to 39.0°C, chest x-ray revealed bibasilar pulmonary infiltrates, and blood culture was positive for Klebsiella. Zosyn (Wyeth Pharmaceuticals; Philadelphia, PA) was started for empirical coverage.

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minimal brain perfusion with diffuse brain swelling, and thereafter he was given comfort care and died on HD 17.

3. Case report 2

A 48-year-old male with a history of alcohol abuse fell from standing and struck his occiput on a concrete sidewalk. He was witnessed to have tonic-clonic seizure after the fall. He was brought by the EMS to our emergency department where he was initially found to be postictal with a GCS score of 9 (E3V2M4), gradually improving to a GCS score of 13 (E4V4M5). Head CT revealed left frontal intraparenchymal hemorrhage with left frontal SDH and no midline shift (Fig. 3). Coagulation panel revealed a hematocrit of .27 a platelet count of 141 × 10^9/L, and an INR of 1.4. He was loaded with Dilantin. Over the course of 30 minutes, his GCS score declined to 5, and repeat head CT revealed increased left SDH and 3 mm of midline shift. Therefore, he was intubated and taken to the OR for left frontotemporal craniectomy, evacuation of SDH, and placement of left external ventricular drain and subdural drain.

Postoperative examination revealed flexion of extremities to pain, pupils sluggish bilaterally, intact corneal reflex, normal oculocephalic reflex, and positive gag/cough. Head CT revealed paramedian infarcts (bilateral ACA and left PCA infarcts) secondary to herniation. Intracranial pressure remained in the 20 mm Hg despite aggressive EVD drainage and propofol sedation. Electroencephalogram was placed to monitor for seizure activity.

Hyponatremia consistent with CSW was also observed in this patient. His admission Na was 136 mmol/L. Despite 2 g of salt tablets given by feeding tube 3 times per day and multiple boluses of 23.4% NaCl for ICP control, the patient’s Na remained less than 140 mmol/L. On HD 4, the patient was started on 3% NaCl at 40 mL/h for an Na of 135 mmol/L. Despite the above interventions. The patient’s urinary excretion and output increased concomitantly on HD 4 (Figs. 1 and 2, respectively). On HD 6, 3% NaCl was increased to 70 mL/h for declining Na of 134 mmol/L.

Central venous pressure monitoring to evaluate volume status revealed that CVP was elevated to up to 18 mm Hg after fluid resuscitation and transfusions in the perioperative period, but after HD 3, his CVP ranged from 4 to 8 mm Hg.

On HD 4, his BNP was determined to be 78 pg/mL (normal, <15 pg/mL). There was no evidence of cardiac dysfunction during hospitalization. Blood pressure was supported without any need for pressors. Electrocardiogram showed normal sinus rhythm without any abnormalities. Despite aggressive care, his neurologic status declined, with no response to central pain. On HD 12, he was given comfort care and died.

4. Discussion

We present 2 cases of patients with TBI with findings consistent with CSW with elevated BNP levels in the setting of normal cardiac function. The BNP range deemed normal for this age range (40-50 years) is less than 10 pg/mL[18]. In both cases, a high BNP level was observed after declining plasma Na levels despite aggressive hypertonic saline infusion.

Cerebral salt-wasting syndrome is characterized by hyponatremia with low plasma volume[6]. In both cases, there were signs of low plasma volume (high BUN/Cr ratio and/or low/normal CVPs) treated with intravenous fluid and Na replacement. Patients presented with high hematocrit despite intracranial hemorrhage, a low CVP, and high BUN/Cr ratio. Case 1 presented with persistently low CVP after the initial resuscitation period. These findings are more consistent with CSW than SIADH. Patients with SIADH exhibit a volume-expanded state: high CVP, low serum osmolality, and low hematocrit[6]. Anti-diuretic hormone levels are known to be highly variable, depending on severe pain, nausea, stress, or hypotension without clear correlation with the extent of hyponatremia [6,12]; therefore, we did not obtain ADH levels on these patients.

In previous studies of BNP levels in the population of patients presenting with acute SAH, the mean admission
BNP level was 15 pg/mL for patients with aneurysmal SAH compared with the control of 3 pg/mL in patients with tumor [1]. In our patients, we cannot rule out the possibility that TBI-associated SAH is responsible for the rise in BNP levels. In addition, we cannot exclude the possibility that surgery contributed to an increase in SAH and ultimately to high BNP levels. However, based on a review of CT scans, the amount of SAH in our patients is low compared with that in patients with aneurysmal SAH, therefore making SAH an unlikely explanation for the rise in BNP levels. The levels of BNP in our patients are much higher than that in patients with aneurysmal SAH and still higher compared with the highest levels observed in patients with SAH (70 pg/mL vs 30 pg/mL) [11]. The comparisons above argue for a distinct mechanism in TBI that induces a rise in BNP levels when compared with patients with SAH.

The action of BNP in cardiac failure is well characterized. Brain natriuretic peptide is produced by ventricular myocytes in response to wall stress. Brain natriuretic peptide was initially isolated in 1988 from extracts of porcine brain, but subsequently the primary sites of production were found to be the cardiac atria and ventricles [7,17] because the focus of BNP has been in cardiac failure. Brain natriuretic peptide is synthesized as prepro-BNP, which is processed intracellularly to pro-BNP, then proteolytically cleaved by furin and subsequently secreted as the biologically inactive N-terminal fragment N-BNP1-76 and lyrically cleaved by furin and subsequently secreted as the biologically active 32-amino acid BNP77-108. Intravenous injection of BNP into rats led to natriuresis and increased urine output. In retrospect, these symptoms were consistent with CSW [17].

Natriuretic peptides such as BNP stimulate production of intracellular second messenger cGMP via binding to NPR and activating guanylyl cyclase/cGMP second messenger signaling [13]. The different tissue distribution of NPR underlies the differential effects of NP (as well as the differential tissue distribution of NPs themselves). ANP and BNP represent selective ligands for NPR-A and CNP is a selective agonist at NPR-C. Natriuretic peptide receptor-A is predominantly expressed in the vasculature (ANP and BNP), and NPR-B is predominantly expressed in the brain. Natriuretic peptide receptor-C (the “clearance receptor”) is a single transmembrane receptor with a short C-terminal tail that lacks GC activity. It is the most abundantly expressed NPR (95% of total NPR population) and has similar affinity for all NP [8]. The primary role of NPR-C is to modulate the availability of NP by binding and removing them from the circulation [3]. If BNP is responsible for CSW, various inhibitors of this pathway are available, and patients can be treated before hyponatremia. However, confirmation of BNP-CSW link awaits further prospective clinical studies and laboratory studies.

References