CASE REPORT

Cerebral salt wasting in a postoperative period

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Abstract

Cerebral salt wasting syndrome (CSW-cerebral salt wasting) was first described in 1950 by Peters. This syndrome can occur in patients who have sustained damage to the central nervous system (e.g. patients with subarachnoid bleeding, bacterial meningitis or after neurosurgery). Patients present with excessive natriuresis and hyponatremic dehydration.
Differentiating this syndrome with the syndrome of inappropriate antidiuretic hormone secretion (SIADH-syndrome of inappropriate antidiuretic hormone secretion), which may occur in the same group of patients, is necessary in order to administer the correct treatment which consists of fluid restriction and sodium replacement in SIADH and fluid and sodium replacement as well as occasional mineralocorticoid therapy in CSW.

INTRODUCTION

Cerebral salt wasting syndrome (CSW) was first described by Peters *et al.* (1950). It consists of hyponatremia, which is accompanied by extracellular volume depletion and renal sodium loss leading to increased diuresis in patients with various neurological disorders, in which disorders of the hypothalamic-pituitary-adrenal and thyroid axis have been excluded (Peters *et al.* 1950). However, after the publication by Schwartz *et al.* (1957) of the first description of syndrome of inappropriate antidiuretic hormone secretion (SIADH-syndrome of inappropriate antidiuretic hormone secretion), which is characterized by hyponatremia, normovolemia and reduced urine output, it was discovered that most of the cases considered CSW so far met the diagnostic criteria for SIADH. Recent studies that have been published in the last years have provided a more precise characterization and a more detailed description of the etiopathogenesis of CSW and thus allowed for its differentiation with SIADH (Sivakumar *et al.* 1994; Damaraju et al.1997;Albanese *et al.* 2001; Palmer 2003; DiIorgi *et al.* 2012). Treatment other than the one recommended for SIADH has also been proposed. CSW syndrome occurs most often in patients with stroke, intracerebral hemorrhage, subarachnoid hemorrhage and in patients after neurosurgical operations. It has also been reported in patients with tuberculous meningitis and increased intracranial pressure. In several pro-

spective studies, it has also been found that CSW may occur more frequently than SIADH in patients after neurosurgical interventions (Palmer 2003). In a retrospective cohort study Hardesty *et al.* (2012) found that CSW occurred in 15/282 (5%) pediatric patients after brain tumor surgery and that there was a high incidence of neurological complications in the form of seizures in 50% of the described patients with this syndrome.

CSW usually occurs within the first 10 days after subarachnoid hemorrhage, trauma, stroke or neurosurgical intervention (Cerda-Esteve *et al.* 2008). Ruiz-Juretschkea *et al.* (2012) have speculated that hydrocephalus may play an important role in the pathogenesis of CSW. It is also believed that CSW due to the reduction of extracellular fluid volume secondary to renal sodium loss, may be a defense mechanism preventing the development of increased intracranial pressure in patients with subarachnoid hemorrhage, cerebral trauma or stroke (Johanson *et al.* 2006; Ruiz-Juretschkea *et al.* 2012) In the differential diagnosis of hyponatremia with polyuria, excessive fluid intake and diuretics use in the postoperative period must be ruled out. It is also important to remember that CSW can coexist with diabetes insipidus (DI-diabetes insipidus), and that polyuria secondary to natriuresis may be erroneously recognized as the result of a too low dose of desmopressin. In such cases, increasing the medication dose may escalate the hyponatremia (Albanese et al.2001). As presented in this case report, CSW can also occur in the course of complex three-phase (DI-DI/CSW-DI) fluid and electrolyte disturbances following central nervous system (CNS) operations.

The relationship between CNS damage and renal salt wasting in CSW is unclear.

It seems that the etiology of CSW is multifactorial. Most authors agree that the primary pathogenetic mechanism is renal sodium loss leading to hyponatremia and the reduction of extracellular fluid volume (Yee *et al.* 2010). A reduction in renal sympathetic nervous system activity may affect the reabsorption of sodium (Na^+) in the renal proximal tubule and simultaneously lead to a reduction in the secretion of renin and aldosterone despite a decrease in extracellular fluid volume (Berendes *et al.* 1997; Palmer 2003; Cerda-Esteve *et al.* 2008). Furthermore a possible involvement of natriuretic peptides is being considered in the etiology of CSW as well (Cerda-Esteve *et al.* 2008). They fulfil a regulatory role in the process of ion homeostasis in the cerebrospinal fluid, and several studies using animal models have demonstrated that they have an impact on the reduction of intracranial pressure and cerebral edema (Minamikawa *et al.* 1994; Akdemir *et al.* 1997). Atrial (ANP-atrial natriuretic peptide) and brain (BNP-brain natriuretic peptide) natriuretic peptides directly inhibit Na^+ reabsorption in the proximal tubule and indirectly increase natriuresis by suppressing the renin-angiotensin-aldosterone axis (Steele *et al.* 1991; Levin *et al.* 1998; Yee *et al.* 2010). BNP which is produced in the cardiac ventricles and the hypothalamus is considered the most likely natriuretic peptide mediating CSW (Berendes *et al.* 1997; Levin *et al.* 1998). In patients with subarachnoid hemorrhage and cerebral trauma, increased concentrations of ANP and BNP in the serum and cerebrospinal fluid along with an increase in intracranial pressure were found (Berendes *et al.* 1997; Yamasaki *et al.* 1997; Kirchhoff *et al.* 2006; Sviri *et al.* 2006). Johanson *et al.* (2006) demonstrated that ANP decreases the production of cerebrospinal fluid in acute hydrocephalus. It is not clear whether the determination of serum natriuretic peptides and ADH may be useful in the differential diagnosis of hyponatremia in SIADH and CSW (Berkenbosch *et al.* 2002; Singh *et al.* 2002; Cole *et al.* 2004; Jimenez *et al.* 2006).

In this case report we present a patient who experienced fluid and electrolyte disturbances, including CSW in the postoperative period.

CASE PRESENTATION

A 22-year-old patient with hydrocephalus caused by congenital toxoplasmosis, after multiple ventriculoperitoneal shunt replacements due to the necessity of its extension as a result of the growth of the patient and occlusion was re-admitted to the Neurosurgery Department for his next scheduled shunt replacement.

The operation was complicated by intraventricular bleeding. In the first postoperative day, laboratory results showed a slight hypernatraemia (serum Na: 150 mmol/l (n: 135–145 mmol/l), with a low urine specific gravity (1.0 g/ml), an increased serum osmolality of 298 mOsm/kg H_2O, decreased urine osmolality of 180 mOsm/kg H_2O, increased diuresis 5,200 ml/day and polydipsia. On the basis of these results, the patient was diagnosed with central DI (cDI), and received desmopressin at a dose of 0.1 mg twice a day, resulting in clinical improvement and normalization of fluid and electrolyte abnormalities (serum Na: 140 mmol/l, urine specific gravity: 1.015 g/ml, normalization of serum and urine osmolality and a reduction in diuresis, (Figure 1). On the 13th postoperative day hyponatremia (serum Na: 116 mmol/l) and polyuria (4,900 ml/day) were found. The desmopressin dose was reduced to 0.05 mg p.o. twice a day. In a clinical evaluation the patient was conscious, dehydrated, reporting dizziness upon standing as evidenced by orthostatic hypotension and a blood pressure of 90/60 mmHg. Laboratory tests also showed increased natriuresis: sodium excretion in the urine: 542 mmol/24 hours (N: 40–220), which amounts to 5.8 mmol/kg/day (n: 2.6±0.5), a negative sodium balance: (–) 277 mmol/l/24 h, equal to >3 mmol/kg/24 h, decreased serum osmolality (255 mOsm/kg H_2O), normal urine osmolality (293 mOsm/kg H_2O), and a ratio of urine osmolality to serum osmolality of 1.15. Decreased levels of uric acid (85 mmol/l, n: 180–506), increased hematocrit (54%, n: 41–53), urea level at the upper limit of normal (6.7 mmol/l, n: 3.2–7.1) and

Tab. 1. CSW and SIADH – differential diagnosis (Albanese *et al.* 2001; Hannon & Thompson 2010).

	CSW	SIADH
Central venous pressure	↓	N
Blood pressure	↓, orthostatic hypotension	N
Body weight	N or ↓	N or ↑
Thirst	↑	N
Urine volume	N/↑	N/↓
Creatinine in serum	N/↓	N/↑
[Na+] in serum	↓	↓
[Na+] in urine	↑	↑
urea	N/↑	N/↓
Plasma renine activity	N, ↑, ↓	↓
AVP	↑↑	N/↑
ANP, BNP	↑↑	N/↑

↓-decreased, ↑-increased, N-normal, ANP - atrial natriuretic peptide, BNP - brain natriuretic peptide, AVP - arginine vasopressin

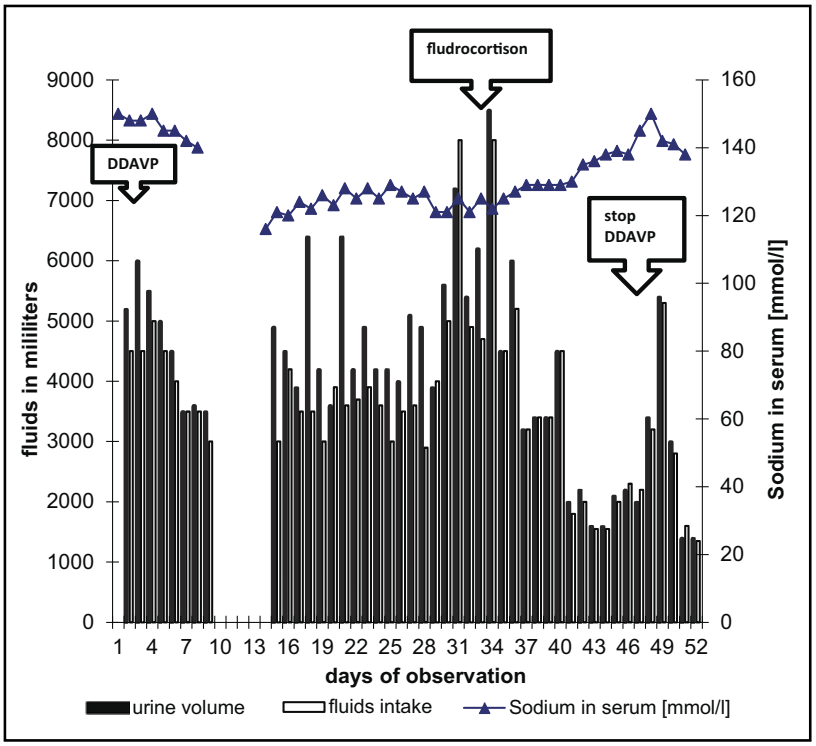

Fig. 1. Clinical and biochemical observation of patient. DDAVP, desmopressin. Arrows present start or stop of therapy.

decreased levels of aldosterone (38 pg/ml, n: 55–160) were also found.

Due to normal plasma renin activity: 0.38 pg/ml/h (n: 0.2–2.8) and cortisol levels: 137.2 ng/ml (n: 50–230) adrenal insufficiency was excluded. Normal TSH (1.87 mIU/mL, n: 0.4–4.2) and fT4 levels (16.7 pmol/l, n: 10–25) allowed the exclusion of hypothyroidism as a cause of hyponatremia as well. Until adrenal insufficiency was ultimately excluded the patient was treated for 2 days with hydrocortisone, during this time we did not observe any significant changes in natremia or an increased urine volume. Desmopressin was maintained at a reduced dose (0.05 mg twice a day), fluids and electrolytes were supplemented. In the absence of improvement with fluid and sodium supplementation alone, fludrocortisone was introduced at a dose of 0.05 mg twice a day resulting in clinical improvement and normalisation of biochemical parameters. The patient was discharged home on postoperative day 40. Outpatient fludrocortisone was discontinued after a month, without any changes in natremia, however an attempt to withdraw desmopressin resulted in an increase in diuresis and a tendency towards hypernatremia, which indicated persistent DI in our patient (Figure 1).

DISCUSSION

This case describes a 22 year-old patient with a rare three-phase fluid and electrolyte disorder which occurred after neurosurgery comprising of: Central DI in the first phase, then the coincidence of CSW and DI in the second phase and persistent DI in the last phase [Fig. 1]. The diagnosis of central DI was based on the following criteria: (1) polydipsia and polyuria found in a 24 hour fluid balance, (2) hypernatremia and plasma hyperosmolality, (3) decreased urine osmolality which was lower than serum osmolality, (4) low urine specific gravity and clinical and biochemical improvement after the administration of desmopressin (DiIorgi *et al.* 2012). In the differential diagnosis of hyponatremia (which occurred in the second phase) we ruled out excessive fluid intake in the postoperative period, too high of a dose of desmopressin in the treatment of transient DI, liver failure, heart failure, adrenal insufficiency, hypothyroidism and side effects of antiepileptic drugs (Albanese *et al.* 2001). In the differential diagnosis of hyponatremic hypovolemia which was reported in the patient at a later stage, extrarenal loss of extracellular fluid, diuretics, nephropathy with the loss of sodium and osmotic diuresis were taken into account (Di Iorgi *et al.* 2012). In the broader differential diagnosis of natriuresis SIADH, CSW and the coincidence of CSW and DI were included (Albanese *et al.* 2001; Beukhof *et al.* 2007; Rahman & Friedman 2009) (Table 1).

SIADH and CSW occur as a complication of the same type of damage to the CNS and in a similar time period (3–10 days after neurosurgery or trauma to the CNS) (Di Iorgi *et al.* 2012). Patients in these two disorders present with hyponatremia and increased natriuresis, and the differences between the two syn-

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dromes are minimal. It is important to answer the question if the primary reason for low sodium in the serum is water intoxication in the course of SIADH (relative hyponatremia) or severe loss of sodium ions in the urine (absolute hyponatremia) in the course of CSW (Di Iorgi *et al.* 2012). Diuresis is increased in CSW (Table 1) and SIADH, but in this second disorder it may also be normal or reduced, and therefore the absence or presence of polyuria cannot be the main criterion for differentiating these two states. The concentration of uric acid is decreased in both diseases. It is believed that increased fractional excretion of uric acid in CSW is a result of impaired reabsorption of Na^+ in the proximal tubule, while in SIADH it is due to an increase in extracellular fluid volume (Maesaka *et al.* 1992; Palmer *et al.* 2003; Sterns & Silver 2008; Bitew *et al.* 2009).

In clinical practice, the most important criterion differentiating CSW from SIADH remains extracellular fluid volume assessment (ECF, extracellular fluid), which is increased in SIADH and decreased in CSW. In order to accurately assess the ECF volume and establish the diagnosis of CSW invasive central venous pressure monitoring is recommended (Damaraju *et al.* 1997; Albanese *et al.* 2001; Cerda-Esteve *et al.* 2008; Rahman & Friedman 2009). Invasive methods of assessing volemia however are not routinely used in the postoperative period, since usually, at least in our centre, the patient is no longer in the intensive care unit 48–72 hours after neurosurgery. According to some authors it may be helpful to assess hematocrit and urea levels which are elevated in CSW and indicate dehydration in the patient and normal in SIADH where normovolemia is common (Brook & Brown 2008).

The diagnosis of CSW in this patient was based on clinical features such as dehydration, low blood pressure, symptoms of orthostatic hypotension, elevated hematocrit, and urea levels (indirectly indicating a reduction in extracellular fluid volume), increased diuresis and biochemical indicators such as hyponatremia with natriuresis and a negative sodium balance (Table 1).

An argument against the diagnosis of SIADH in this patient was the presence of dehydration. In contrast to SIADH, which is caused by the inadequate secretion of ADH or hyperactive vasopressin receptors in the kidneys, leading to water retention and euvolemic or hypervolemic hyponatremia, in CSW hypovolemic hyponatremia is due to the loss of both sodium ions and water (Kinik *et al.* 2001; Yee *et al.* 2010; Ozdemir *et al.* 2010).

Determining the cause of hyponatremia was important in this case because of the differences in treatment regimens. In SIADH therapy is based on fluid restriction and the slow administration of hypertonic saline solution. Fluid restriction is contraindicated in CSW as it may worsen hypovolemia and cause hypotension, cerebral vasospasm, ischemia and/or infarction of the brain tissue (Hickey 2009). In CSW fluids are supplemented with 0.9% and 3% sodium chloride. 3% sodium chloride solution should be administered slowly, not exceeding the maximum limit of correction of sodium <12 mmol/l/day, as a rapid correction of hyponatremia can cause myelinolysis syndrome of the CNS (Hickey 2009; Mortimer & Jancik 2006; Ozdemir *et al.* 2010). When possible, fluids and electrolytes should be supplemented orally as it was done in this patient.

Additional tests also showed a decrease in aldosterone levels. The patient received fludrocortisone yielding an improvement in his fluid, electrolyte and clinical status. Fludrocortisone is a synthetic corticosteroid with moderate glucocorticoid and predominant mineralocorticoid potency which reduces the loss of renal sodium by increasing its resorption in the renal proximal tubule (Ishikawa *et al.* 1987; Rahman & Friedman 2009; Momi *et al.* 2010). Fludrocortisone is used for aldosterone substitution in various forms of primary adrenal insufficiency such as Addison's disease, classic salt-wasting form of congenital adrenal hyperplasia and isolated adrenal mineralocorticoid deficiency. The benefits of fludrocortisone in CSW have also been described (Ishikawa *et al.* 1987; Momi *et al.* 2010). Fludrocortisone doses range from 0.05 to 0.1 mg, with the possibility of increasing the dose to 0.4 mg a day in divided doses (Albanese *et al.* 2001; Taplin *et al.* 2006; Min Jeong Choi *et al.* 2012).

Because of persistent polyuria in this patient (Figure 1), we suspected the possibility of coincidence of CSW and DI, which is why the treatment in the second phase of the electrolyte disturbances consisted of desmopressin maintained at lower dose as well as oral supplementation of sodium and fluids (Albanese *et al.* 2001).

SUMMARY

Hyponatremia is the most common electrolyte disorder in hospitalised patients with various neurosurgical disorders appearing in about 15% of them (Palmer 2003; Mirski & Verales 2008; Hardesty *et al.* 2012). Hyponatremia in the postoperative neurosurgical patient may lead to a lower threshold for seizures. Given that seizures in neurosurgical patients can lead to further damage to the brain tissue increasing morbidity and mortality in the postoperative course, determining the cause of hyponatremia is important because of the different therapeutic approaches. The differential diagnosis should also take into account the occurrence of the rare cerebral salt wasting syndrome.

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