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CASE REPORT

Cerebral salt wasting in tuberculous meningitis: Two cases and review of the literature

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Abstract

Cerebral salt wasting syndrome (CSWS) is characterized by severe natriuresis and volume depletion in the presence of cerebral pathology. In literature, there are few reports about tuberculous meningitis and cerebral CSWS. In this article, we report two tuberculous meningitis cases with CSWS and present a review of the literature on this topic. Cerebral salt wasting diagnosis was based on hyponatraemia associated with high urinary sodium excretion and inappropriately high urine output in the presence of dehydration. Treatment was made with sodium-fluid replacement plus fludrocortisone therapy in both cases. In agreement with the literature we argue that cerebral salt wasting syndrome might be more common than the syndromes of inappropriate antidiuretic hormone secretion (SIADH) in cerebral disorders. Differentiating the cerebral salt wasting syndrome from the SIADH is very important because unrecognized cerebral salt wasting syndrome can lead to inadequate management and result in unnecessary hyponatremia-related morbidity. The electrolyte and hydration status of patients should be monitored closely in patients with tuberculous meningitis.

INTRODUCTION

Tuberculous meningitis (TBM) is the most common severe form of tuberculosis disease. In TBM, many factors lead to poor outcomes: brain ischemia, hydrocephalus, direct parenchymal injury, hyponatremia, and seizures are some of them (Figaji & Fieggen, 2010). Hyponatremia is also the most electrolyte abnormality seen in TBM (Celik *et al.* 2005; Huang *et al.* 2004). Hyponatremia can develop secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt wasting syndrome (CSWS) or adrenal failure (Celik *et al.* 2005; Celik *et al.* 2014; Doczi & Bodosi, 1989). These three settings notably differ in clinical picture, diagnosis and also treatment. Cerebral salt wasting syndrome which was first mentioned by Peters *et al.* (1950) is described by characteristics like hyponatremia, development of natriuresis and subsequent hypovolemic dehydration in patients with intracranial disorders. Jimenez *et al.* (2006) describes various criteria for the diagnosis of CSWS; hyponatremia (plasma sodium <130 mEq/L), accompanied by elevated urine sodium (>120 mEq/L), elevated urine osmolarity (>300 mOsm/kgH_2O), excessive

Tab. 1. Differential diagnosis of CSWS and SIADH.

	Cerebral Salt Wasting	Syndrome of inappropriate antidiuretic hormone secretion
Hyponatremia	+	+
Natriuresis	+	+ (increased, but not high)
Volume	Reduced	normal or increased
Salt wasting	Gross	Self limited
Urine output	Polyuria	Variable
Response to saline treatment	yes	no
Response to fluid and salt restriction	no	yes
Plasma BNP concentration	normal or increased	normal
Plasma ANP concentration	increased	increased
Plasma Antidiuretic hormone concentration	Reduced	increased

urine output (>3 mL/kg/h), and a negative 24-hour fluid balance (Table 1).

We also recently described two cases of CSWS complicating status epilepticus (Celik *et al.* 2014). There are few reports about CSWS in tuberculous meningitis in the literature (Camous *et al.* 2008; Celik *et al.* 2005; Dass *et al.* 2003; Gouveia *et al.* 2009; Huang *et al.* 2004; Jabbar *et al.* 2010; Loo *et al.* 2003; Nagotkar *et al.* 2008; Ravishankar *et al.* 2006; Sakarcan & Bocchini, 1989; Syed *et al.* 2012; Ti *et al.* 1998; Tinggaard *et al.* 2011). Only few reports about CSWS in TBM exist in the literature; herein we report two further cases and present a review of the literature on this topic.

CASE REPORTS

Case 1

A 16-year-old boy was admitted to pediatric intensive care unit with fever, weight loss, lack of appetite, vomiting for 1 month and finally convulsions and unconsciousness for 2 days.

Initial vital signs were heart rate of 120/min, respiratory rate 18/min, central temperature 37.7 °C and blood pressure 100/70 mmHg. On examination, normal pupillary reflexes, unconciousness, neck stiffness with positive signs of meningeal irritability and bilateral Babinski responses were noted. Glasgow coma scale (GCS) was 5/15.

Initial laboratory tests of white blood cells (WBCs) were 8 100 mm^3, with a differential count of 50% neutrophils, 40% lymphocytes, 10% monocytes and serum sodium as following: 125 mEq/L, potassium: 4.5 mEq/L, blood ure nitrogen: 28 mg/dl creatinine: 0.6 mg/dl.

Chest X-ray of the patient revealed mild left pleural effusion. Brain computerised tomography (CT) imaging showed diffusely increased leptomeningeal enhancement, basal arachnoiditis and enlargement of ventricules. Thorax CT revealed mild left pleural effusion and mediastenal and hilar lymphadenopathy. Purified protein derivative (PPD) test was 15 mm. Lumbar puncture revealed an initial pressure of >250 mmH_2O, WBCs 100 mm^3 (all of lymphocytes), protein 151 mg/dl, glucose 28 mg/dl (simultaneously serum glucose: 85 mg/dl). No pathogen was found in acid-fast stain of the cerebrospinal fluid (CSF). Pleurocentesis accompanied by ultrasound was done but no fluid could be taken. A diagnosis of TBM was made on pulmonary findings, positive result of PPD test, neurological and neuroradiological findings and hypoglycorrhachia. Antituberculous therapy with isoniazid, rifampine, pyrazinamide, streptomycine and prednisone were started. Due to raised intracranial pressure findings, brain CT was repeated. The brain CT revealed moderate ventricular dilatation. Therefore, an external ventricular drain was inserted which was later replaced by a ventriculoperitoneal shunt. On the 4th day of treatment, serum sodium concentration was as following: 124 mEg/L, serum osmolality 270 mOsmol/kg, urine sodium 98 mmol/L and urine output was high (9 ml/kg/h). The case was evaluated as CSWS. Volume replacement was given and 3% saline added treatment was applied but serum sodium remained low at 122 mmol/L and urine output high at (11 ml/kg/h). On day 8, fludrocortisone 0.1 mg was commenced. Following the shunt replacement, there was no change of his mental status, GCS of 5/15. Blockage of the ventriculoperitoneal shunt and shunt infection developed after one month of treatment. Vancomycin and cefotaxime were started. External ventricular drainage was done. At this time, the patient had hyponatremia with serum sodium value of 125 mEq/L which deteriorated to a value of 119 mEq/L. Despite aggressive fluid, saline and fludrocortisone replacement, sodium level and urine output did not improve until a shunt revision on day 55. There was no improvement in the patients' level of consciousness. Overall health condition deteriorated

on the fourth month of treatment. The possibility of a septic shock was taken into consideration as the patient had fever and hypotension. Antifungal treatment combined with antibiotics and inotropic support was started. Both blood and the CSF cultures were positive for *Candida albicans*. Unfortunately on the fifth month of treatment, the patient died due to a septic shock.

Case 2

A 5-year-old girl was admitted to pediatric intensive care unit with fever, headache and vomiting for 1 month. Her father had been diagnosed with pulmonary tuberculosis 3 months before. On admission to the pediatric intensive care unit, she was malnourished, alert and had neck stiffness with positive signs of meningeal irritability.

On laboratory examination, WBCs were 9 600 mm^3 with a differential count of 45% neutrophil, 40% lymphocytes, 15% monocytes. Serum sodium values were as following: 130 mEq/L, potassium: 3 mEq/L, blood ure nitrogen: 16 mg/dl creatinine: 0.6 mg/dl. Chest X-ray showed miliar dissemination. Thorax magnetic resonans imaging (MRI) showed diffuse nodular infiltration (tuberculoma), increased leptomeningeal enhancement and mild dilatation of ventricules. PPD test was negative. Lumbar puncture revealed an initial pressure of >250 mmH_2O, WBCs 40 lymphocytes, protein 232 mg/dl, glucose 15 mg/dl (simultaneously serum glucose: 100 mg/dl). No pathogen was found in acid-fast stain of the CSF. A diagnosis of TBM was made based on the contact history, pulmonary findings (miliar dissemination), neurological signs and hypoglycorrhachia and MRI findings. Antituberculous therapy and prednisone were started. Daily lumbar punction was made.

On the 5th day of the treatment, serum sodium values were as following: 123 mEg/l, serum osmolarity 265 mOsmol/kg, urine sodium 120 mmol/L and urine output was high (6 ml/kg/h). CSWS was diagnosed. Volume replacement and 3% saline was given but serum sodium values remained low, being 122 mmol/L and urine output was too high. On day 8, fludrocortisone 0.1 mg was commenced. Hydrocephalus was arrested on day 15.

On the 18th day of treatment, serum sodium level of the patient was raised (133 mEq/L) and urine output decreased. Fludrocortisone was stopped. The patient discharged without neurological sequelae with antituberculous therapy and oral prednisolone treatment after a month.

DISCUSSION

Serious sequelae and mortality occur in about 50% of patients with TBM despite anti-tuberculosis treatment (Figaji & Fieggen, 2010). Neurological and systemic complications are important causes of morbidity and deaths in TBM. Hyponatremia occurs in up to 85% of patients with TBM and is an independent predictor of death or severe disability (Celik *et al.* 2005; Huang *et al.* 2004). Hyponatremia also may increase the severity of neurological symptoms due to cerebral ischemia and edema. The syndrome of inappropriate secretion of antidiuretic hormone and the CSWS have been reported as the major causes of hyponatremia. However, the therapeutic approach for these syndromes is different because of the total volume status (Table 1).

Cerebral salt wasting syndrome is frequently associated with cerebral diseases but only a few cases of CSWS in TBM have been reported in literature. Previous reports of CSWS in TBM are listed in Table 2. There are nineteen TBM patients with CSWS in the literature (Table 2). Fourteen of the patients are children. The minimum and maximum initial Na levels of them were 104–128 mEq/L respectively. Minimum and maximum urinary sodium levels of the patients were 84–541 mEq/L respectively. Minimum and maximum serum osmolarity levels were 236–286 mOsm/kg H_2O and urinary osmolarity levels were 260–659 mOsm/kg H_2O respectively. Hydrocephalus was observed in 12 of the pediatric patients.

Hyponatremia often follows and develops by the first week following the insult. If the underlying disease that is causing CSWS is remedied, CSWS resolves within three to four weeks. In the cases reported in literature, recovery time under treatment is approximately 13.6±3.6 days. Minimum time was reported to be 2 days and maximum time was 55 days.

The pathogenesis of CSWS remains unclear. Excessive secretion of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and a direct neural influence on renal function are involved in the pathogenesis (Berendes *et al.* 1997; Celik *et al.* 2014; Doczi & Bodosi, 1989). Berendes *et al.* (1997) have provided evidence that the BNP might be a more likely candidate to mediate the renal salt wasting. The BNP in humans is found primarily in the cardiac ventricles, and in the brain as well. Increased release of cardiac BNP could be part of a generalized stress response to the underlying illness, whereas increased intracranial pressure could provide a signal for the brain BNP release. Doczi and Bodosi (1989) reported a linear correlation between the intracranial pressure and ANP concentrations in CSF of patients with subarachnoid hemorrhage. Reduced intracranial pressure may result in reduced concentrations of ANP in CSF and lead to a decrease in natriuresis. Huang *et al.* (2004) suggested that lowering the intracranial pressure with VP shunt or external lumbar drain might be an effective treatment of CSWS in addition to supplements of salt and fluid. Our clinical observations were similar. In our first patient, shunt dysfunction may have caused to severe and prolonged hyponatremia.

Mineralocorticoid supplementation seems to be a safe and effective treatment for CSWS (Celik *et al.* 2005; Celik *et al.* 2014). Since natriuretic peptides can inhibit

Tab. 2. Patients with CSWS accompanying tuberculous meningitis.

Author	Year	Patient age, sex	Initial Na/ Urine Na	Initial serum osmol/Urine osmol	Initial urine volume	Treatment	Correction period of CSWS (day)	Presence of Hydrocephalus	Comorbidity
Jabbar A, *et al.*	2010	70 y, female	122/167	?/?	High	Fluid, S,* HS**, fludrocortisone	Unknown	–	No
Nagotkar L, *et al.*	2008	4 y, male	120/84	?/?	10ml/kg/h	Fluid, S,	Unknown	+	No
		6 y, female	119/146	?/?	6 ml/kg/h	Fluid, HS, fludrocortisone	28	+	No
Ravinshankar B, *et al.*	2006	65 y, male	120/541	250/260	10Litre/day	Fluid, S, fludrocortisone	14	–	No
Celik US, *et al.*	2005	8 y, male	127/118	270/513	10ml/kg/h	Fluid, HS, fludrocortisone	6	+	No
		13 y, male	128/221	236/593	9 ml/kg/h	Fluid, HS, fludrocortisone	4	+	No
		5 y, female	124/109	252/425	10ml/kg/h	Fluid, HS, fludrocortisone	6	+	No
Huang SM, *et al.*	2004	3 y, male	121/126	264/659	>4ml/kg/h	Fluid, HS	unknown	+	Thalassemia
Loo KL, *et al.*	2003	38 y, female	112/148	276/280	2800 ml/day	Fluid, S	20	–	SLE, cerebral infarction
Dass R, *et al.*	2003	12 y, male	104/133	280/?	>5 ml/kg/h	Fluid, S, HS, fludrocortisone	3	+	No
Sakarcan A, *et al.*	1998	29 months, male	120/176	273/413	4.8 ml/kg/h	Fluid, HS, fludrocortisone	4	+	No
Ti LK, *et al.*	1998	30 y, male	122/124	261/518	3615 ml	Fluid, HS	2	+	HIV
Syed A, *et al.*	2012	6 month, female	126/104	?/?	8,6 ml/kg/h	Fluid, HS, fludrocortisone	17	–	No
Camous L, *et al.*	2008	42 y, male	117/143	260/650	5 litre/day	Fluid, HS, fludrocortisone	21	–	HIV
Gouveia R, *et al.*	2009	9 y, male	127/90	286/?	6ml/kg/h	Fluid, HS	Few days	+	Renal transplantation
Present cases	2015	16 y, male	124/98	270/550	9 ml/kg/h	Fluid, HS,S fludrocortisone	55	+	No
		5 y, female	123/120	265/480	6 ml/kg/h	Fluid, HS,S fludrocortisone	18	+	No
Tingaard J, *et al.*	2014	2 y, 2y	114/164 112/208	260/? 253/?	?	Fluid, S, HS Fluid, S, HS	2–3 2–3	– +	No

*S:saline, **HS:hypertonic saline

mineralocorticoid secretion in patients with CSWS, administration of an agent with mineralocorticoid activity was effective in returning serum sodium levels to normal (Celik *et al.* 2005; Celik *et al.* 2014). Adverse effects of fludrocortisone should be monitored. In literature, serum sodium and fluid balance was corrected with only hypertonic saline (3%) and fluid treatment in 4 patients. Mineralocorticoid treatment was applied to 8 patients.

SUMMARY

In agreement with the literature we argue that CSWS might be more common than the SIADH in cerebral disorders (Diringer *et al.* 1989). In our patients, CSWS was detected in their follow ups. Differentiating the CSWS from the SIADH is very important because unrecognized CSWS can lead to inadequate management and result in unnecessary hyponatremia-related morbidity. The electrolyte and hydration status of patients should be monitored closely in patients with TBM.

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