

Cerebral salt wasting in pediatric critical care; not just a neurosurgical disorder anymore

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Abstract

OBJECTIVE: Cerebral salt-wasting syndrome (CSWS) is a hypovolemic hyponatremia caused by natriuresis and diuresis, of which the exact pathogenesis is unknown. Although CSWS has been more commonly described to be associated with neurosurgical disorders, increasing numbers of patients are diagnosed and new etiological factors are being identified as the awareness of it increases.

METHODS: The files of the patients who had been hospitalized and treated with the diagnosis of CSWS at the pediatric critical care unit during the last three years were retrospectively reviewed.

RESULTS: Totally 9 patients had been treated with the diagnosis of CSWS. The causes of CSWS were identified as tuberculosis meningitis in two patients, status epilepticus in two patients, ketamine infusion in one patient, medulloblastoma in one patient, sepsis in one patient, brain oedema following child abuse in one patient, and cerebral infarct in one patient. All of the patients had received isotonic saline and hypertonic saline while 77.7% of them had received fludrocortisone. The mean time to correction of hyponatremia was 20.37 ± 14.73 days. One patient had died.

CONCLUSION: Cerebral salt-wasting syndrome is increasingly described in the etiology of hyponatremia that is commonly seen in children hospitalized especially at critical care units. Serum sodium, urinary sodium and polyuria should be primarily considered in the diagnosis, and supportive laboratory tests such as uric acid and brain natriuretic peptide (BNP) should not be stipulated. At hospitals providing inpatient care services, clinical and laboratory characteristics of CSWS should be known in detail especially at pediatric critical care units.

INTRODUCTION

Hyponatremia is one of the most common electrolyte disturbances seen in hospitalized children (Oh *et al.* 2015; Celik *et al.* 2014; Kurtoğlu *et al.* 2002; Grant *et al.* 2015; Thompson *et al.* 2012). Most cases are asymptomatic, being discovered on routine blood analyses. The most common causes of hyponatremia in hospitalized children are inappropriate fluid therapy, hypotonic fluid therapy, syndrome of inappropriate anti diuretic hormone (ADH) secretion (SIADH) and Cerebral salt-wasting syndrome (Grant *et al.* 2015; Thompson *et al.* 2012). Although in the past it was considered that SIADH is seen more commonly than CSWS, today CSWS cases increase every year and thought to be more common than supposed (Celik *et al.* 2014; Rivkees 2008; Diringer *et al.* 1989). Some authors suggest that CSWS is seen more commonly than SIADH especially in cerebral diseases (Diringer *et al.* 1989). Various diagnostic criteria have been defined for cerebral salt-wasting syndrome and one of the most commonly criteria has been defined by Jimenez (Celik *et al.* 2014; Jimenez *et al.* 2006). Jimenez's criteria is as follows; hyponatremia (plasma Na<130 mEq/L), increased urinary sodium levels (>120 mEq/L), increased urine osmolarity (>300 mOsm/kgH₂O), increased urine volume (>3 mL/kg/hour) and negative fluid balance during the last 24 hours (Jimenez *et al.* 2006).

MATERIAL AND METHODS

Records of 9 patients who had been hospitalized and treated with the diagnosis of CSWS between 2012 and 2015 at our pediatric critical care unit, which consists of a 12-bed tertiary care unit, were retrospectively reviewed. Firstly the patients' diagnoses at admission to the critical care unit, treatments they had received and demographic data were compiled. For the patients who had developed cerebral salt-wasting syndrome, information was collected about when hyponatremia had occurred after hospitalization, the lowest serum Na level, the highest urine output (ml/kg/hr), urinary sodium and density, serum BNP levels, serum uric acid levels, complete blood count and biochemistry values, the contents of the intravenous fluid they had received, intravenous fluids given after the diagnosis of CSWS (0.9% NaCl, 3% NaCl), whether fludrocortisone therapy had been given, and the duration of the fludrocortisone therapy. Whether the patients had been mechanically ventilated or not, and their mortality and morbidity were investigated.

For the study, ethics committee approval was obtained from the "Adana Numune Training and Research Hospital Non-Interventional Clinical Trials Ethics Committee" on 02/10/2015.

Statistical analysis was performed using "Statistical Package for Social Sciences" version 20.0 (IBM Corp., Armonk, NY, USA). The descriptive statistics of the

study group's variables (number, percentage, mean and standard deviation) were calculated.

RESULTS

It was found out that nine patients had been treated with the diagnosis of cerebral salt-wasting syndrome at the pediatric intensive care unit. Two (22.2%) of the patients were girls and 7 (77.8%) were boys (Table 1). Their mean age was 6.16±5.48 years. The diagnoses at admission to the critical care unit were status epilepticus in three patients, tuberculosis meningitis in two patients, cerebral oedema and hyponatremia following child abuse in one patient, medulloblastoma and convulsion in one patient, sepsis in one patient, and convulsion in one patient. None of the patients had received intravenous hypotonic fluid therapy. No diarrhea, vomiting, acute or chronic renal failure, pulmonary disease, adrenal failure, hypothyroidism, congestive heart failure were found that may have caused hyponatremia in the patients.

The etiology of CSWS was described as tuberculosis meningitis in two patients, status epilepticus in two patients, ketamine infusion in one patient, medulloblastoma in one patient, sepsis in one patient, brain oedema following child abuse in one patient, and cerebral infarct in one patient. Dehydration was found in one patient (11.1%) which was also present at admission. With respect to the day of follow-up on which the diagnosis of CSWS had been made, this period was 4±2.12 days on average (minimum: 1 day, maximum: 8 days) (Table 1).

Fluid losses due to polyuria had been compensated in all patients. All of the patients had received isotonic saline and hypertonic saline while 77.7% (7/9) of them had received fludrocortisone. The mean duration of fludrocortisone therapy was 15.14±14.59 days. The mean time to correction of hyponatremia was 20.37±14.73 days (minimum: 8, maximum: 55). The mean urine output was 6.83±2.03 ml/kg/hour. At a rate of 33.3% (3/9) of the patients had been mechanically ventilated and 11.1% (1/9) had died. The laboratory values were as follows; hemoglobin: 10.44±1.89 mg/dl, white blood cells: 13.77±7.05×10³/mm³, platelet: 322.48±260.21×10³/mm³, serum sodium: 120.55±4.24 mg/dl (minimum: 116.9, maximum: 130), BNP: 73.58±86.93 pg/ml (minimum: 5, maximum: 219), uric acid: 0.86±0.26 mg/dl, urinary sodium: 146.33±44.3 (minimum: 98, maximum: 208), urine specific gravity: 1016.5±8.75 (minimum: 1001, maximum: 1030) (Table 2).

DISCUSSION

Cerebral salt-wasting syndrome was first described by Peters in 1950 in three patients who had hyponatremia, renal sodium loss and dehydration had no problems in the hypothalamic, pituitary or adrenal glands and had central nerve system disorders (Oh *et al.* 2015; Thomp-

son *et al.* 2012; Peters *et al.* 1950). Following the definition of SIADH by Schwartz in 1957, CSWS was ignored almost until 1980s (Oh *et al.* 2015; Schwartz *et al.* 1957; Nelson *et al.* 1981). Although CSWS was considered to be a variant of syndrome of inappropriate ADH secretion in the past, it is now recognized as a different disease after the revelation of its pathophysiology during the recent years (Oh *et al.* 2015; Kurtoğlu *et al.* 2002; Thompson *et al.* 2012; Palmer 2003). The etiology of cerebral salt-wasting syndrome includes subarachnoid hemorrhages, brain surgeries, infections, head traumas, brain tumors and strokes (Oh *et al.* 2015; Berkenbosch *et al.* 2002; Celik *et al.* 2005). New etiological factors are increasingly being identified for CSWS, which is a relatively new concept (Celik *et al.* 2014). Cerebral salt-wasting syndrome, which is described mostly following brain surgeries, is a growing problem in pediatric critical care. In our study, CSWS cases were identified associated with status epilepticus in 2 patients, ketamine infusion in 1 patient, sepsis in 1 patient and cerebral infarct in 1 patient in addition to the diseases that are expected to play a role in the etiology of CSWS.

Cerebral salt-wasting syndrome clinically manifests with polyuria, excessive urinary sodium loss resulting in extracellular fluid loss-dehydration and hyponatremia (Rivkees 2008; Jimenez *et al.* 2006). In our study, all patients had hyponatremia and polyuria levels of 6.83 ± 2.03 ml/kg/hour. Urinary sodium loss, one of the criteria defined by Jimenez, was 146.33 ± 44.3 meq/L which meets the criteria (Jimenez *et al.* 2006). Although decreased serum uric acid levels have been reported in syndrome of inappropriate antidiuretic hormone secretion (SIADH) in contrast with CSWS, serum uric acid levels decrease also in CSWS and similarly the fractionated excretion of uric acid increases (Oh *et al.* 2015, Kurtoğlu *et al.* 2002). In our study, serum uric acid levels were 0.86 ± 0.26 mg/dl. Using the uric acid levels to differentiate between CSWS and SIADH may mislead the clinician and is not sufficient by itself.

Cerebral salt-wasting syndrome has been tried to be explained with decreased renal sympathetic tone and increased renal natriuretic peptides. With sympathetic stimuli, renin secretion increases and reabsorption of sodium, uric acid and water increases in the proximal tubules. In the theory of decreased sympathetic stimuli,

Tab. 1. The demographic and clinical findings.

Patient age, sex	CSWS etiology	Serum Na	Urine Na	Urine volume ml/kg/hr	Treatment	Correction period of CSWS	Dehydration	Mortality
1 14 months, male	Cerebral oedema	116	208	4.7	Fluid, S,* HS**, fludrocortisone (5 days)	24 days	No	No
2 10 months, male	Sepsis	116	163	5.8	Fluid, S,* HS**, fludrocortisone (16 days)	28 days	No	No
3 16 years, male	Tbc meningitis	119	98	11	Fluid, S,* HS**, fludrocortisone (47 days)	55 days	No	Yes
4 5 years, female	Tbc meningitis	123	120	6	Fluid, S,* HS**, fludrocortisone (10 days)	18 days	No	No
5 14 months, male	Ketamine infusion	119	100	6	Fluid, S,* HS**, fludrocortisone (5 days)	17 days	No	No
6 12 years, male	Status epilepticus	122	100	7	Fluid, S,* HS**, fludrocortisone (10 days)	13 days	No	No
7 10 years, male	Status epilepticus	120	150	6	Fluid, S,* HS**, fludrocortisone (10 days)	8 days	No	No
8 5 years, female	Cerebral infarkt	130	171	5.6	Fluid, S,* HS**	15 days	No	No
9 7 years, male	Medulloblastoma	120	207	9.39	Fluid, S,* HS**, fludrocortisone (13 days)	13 days	Yes	No

*S: saline, **HS: hypertonic saline

Tab. 2. Laboratory results (mean values).

Hb	Wbc	Plt	CRP	Glu	Ure	Cre	Na	K	Cl	UA	BNP
10.44	13.77	322.48	0.96	107.5	11.55	0.35	120.55	3.71	86.26	0.86	73.58

Hb: hemoglobin (9.6–13.1g/dl), **Wbc:** white blood cell ($6.3-12.6 \times 10^3/\text{mm}^3$), **Plt:** platelet ($214-459 \times 10^3/\text{mm}^3$), **CRP:** C-reactive protein (0–0.5 mg/dl), **Glu:** glucose (60–100 mg/dl), **Ure:** urea (16.6–48.5 mg/dl), **Cre:** creatinine (0.57–0.87 mg/dl), **Na:** sodium (136–145 mmol/L), **K:** potassium (3.5–5.1 mmol/L), **Cl:** chloride (98–107 mmol/L), **UA:** uric acid (mg/dl), **BNP:** brain natriuretic peptide (0–100 pg/ml)

deactivation of these mechanisms and volume loss and sodium loss occur (Oh *et al.* 2015; Celik *et al.* 2014; Kurtoğlu *et al.* 2002). In the pathophysiology of cerebral salt-wasting, natriuretic peptides ANP and BNP stand out. Atrial natriuretic peptide is produced in the atrial cardiomyocytes, and secreted through contraction of the atrial muscle. Brain natriuretic peptide is secreted from ventricular cells which increase especially in heart failure. Atrial Natriuretic Peptide and BNP increases glomerular filtration rate thereby causing diuresis and natriuresis. With the secretion of natriuretic peptides, an increase in stroke volume, acceleration in natriuresis and diuresis, and decrease in renin-aldosterone levels occur (Oh *et al.* 2015; Celik *et al.* 2014; Kurtoğlu *et al.* 2002). In our study, patients whose BNP levels had been measured showed a mean value of 73.58 ± 86.93 , and values were not high in all cases. No single and simple cause is involved in the pathophysiology of cerebral salt-wasting syndrome. With respect to the classical manifestations used in the differential diagnosis of cerebral salt-wasting syndrome and SIADH, not every patient with increased BNP levels should be diagnosed with CSWS and CSWS should not be excluded in patients with decreased uric acid levels.

Increased intracranial pressure is thought to cause CSWS by increasing natriuretic peptides in the cerebrospinal fluid (Doczi *et al.* 1995; Berendes *et al.* 1997). Therefore, reduction of intracranial pressure (insertion of ventriculoperitoneal shunt or external drainage) is essential especially in patients with hydrocephalus (Doczi *et al.* 1995; Berendes *et al.* 1997; Celik *et al.* 2015). The case with with tbc meningitis in our study (Table 1, case 4), despite aggressive fluid, saline and fludrocortisone replacement, sodium level and urine output did not improve until a shunt revision. Huang *et al.* also suggested reduction of intracranial pressure through ventriculoperitoneal shunt or external drainage of cerebrospinal fluid as an effective treatment in addition to fluid and sodium replacement in CSWS (Huang *et al.* 2004).

Differential diagnosis of cerebral salt-wasting syndrome and SIADH is not always easy because clinical and laboratory findings may show similarity (Oh *et al.* 2015). Hyponatremia is present in both syndromes, and hypovolemia is seen in CSWS while SIADH is frequently euvoletic, even hypervolemic. However, these findings may not be observed in every patient or every stage. Increased urine volume leading to hypovolemia may help in differential diagnosis. Variable urine volumes are seen in syndrome of inappropriate ADH secretion while significantly increased urine volumes are observed in CSWS. With respect to laboratory analyses, the effects of hypovolemia (increased blood urea nitrogen, increased hematocrit levels etc.) may support the diagnosis of CSWS. Urinary sodium loss is also used in differential diagnosis. Urinary sodium loss may exceed 20 mEq/L in syndrome of inappropriate ADH secretion while being more than 100–120 mEq/L

in CSWS. Patients' response to treatment allows the clinician to confirm the diagnosis. Hyponatremia may be corrected by fluid restriction in syndrome of inappropriate ADH secretion while on the contrary significant fluid support should be made and fluids containing hypertonic sodium should be used in CSWS. In our study, dehydration was observed in only one patient, who showed dehydration symptoms also at admission. The negative fluid balance was only 11.1% in our study, which is in fact expected to be high in CSWS patients, may be explained by the close monitoring of the fluid statuses at the critical care unit and by early treatment of the patients before dehydration occurred. Absence of dehydration or hypovolemia symptoms in patients who are hospitalized at pediatric critical care unit or hospital and whose fluid statuses are closely monitored and fluid losses are replaced should not exclude the diagnosis of CSWS.

The first intervention in the treatment of cerebral salt-wasting should be to compensate the fluid deficiency. Sodium levels should be increased along with the correction of dehydration. For this purpose isotonic saline (0.9% NaCl) or hypertonic saline (3% NaCl) is used. Hypotonic fluids should not be used in the treatment. In our study, all patients had received isotonic saline and hypertonic saline and this treatment had been sufficient in 23.3% (2/9) of the patients.

Natriuretic peptides are known to suppress the mineralocorticoid secretion in patients with CSWS. Based on this, use of an agent having mineralocorticoid activity such as fludrocortisone was considered and observed to normalize the serum sodium levels (Celik *et al.* 2014; Sakarcan *et al.* 1998). In our study, fludrocortisone had been given and had corrected the hyponatremia in the 7 patients (77.7%, 7/9) who had persistent hyponatremia despite the use of isotonic saline and hypertonic saline.

SUMMARY

Cerebral salt-wasting syndrome is increasingly described in the etiology of hyponatremia that is commonly seen in children hospitalized especially in critical care units. Cerebral salt-wasting syndrome and SIADH are frequently confused with each other. Although these two syndromes have several characteristics in common, their treatments are quite different. Fluid restriction, which is critically important in syndrome of inappropriate ADH secretion, deepens the existing hypovolemia, increases cerebral ischemia and leads to vasospasm and even to death when used in cerebral salt-wasting syndrome. While the etiology of CSWS classically includes subarachnoid hemorrhages, brain surgeries, infections, head traumas, brain tumors, new etiological factors are increasingly being identified for CSWS. In hospitalized patients, hyponatremia (plasma $\text{Na} < 130$ mEq/L), urinary sodium loss (> 100 mEq/L) and increased urine volume (> 4 ml/kg/hr) should be firstly investigated as CSWS diagnostic criteria, and absence of negative

fluid balance or observation of decreased uric acid and BNP levels should not exclude the diagnosis of CSWS. Physicians who work at hospitals providing inpatient care services, especially at pediatric critical care units, should know the clinical and laboratory characteristics cerebral salt-wasting syndrome and syndrome of inappropriate ADH secretion in order to differentiate these disorders. Cerebral salt-wasting syndrome is not just a neurosurgical disorder anymore.

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REFERENCES

- Berendes E, Walter M, Cullen P, Prien T, Van Aken H, Horsthemke J, et al. (1997). Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. *Lancet*. **349**: 245–249.
- Berkenbosch JW, Lentz CW, Jimenez DF, Tobias JD (2002). Cerebral salt wasting syndrome following brain injury in three pediatric patients: suggestions for rapid diagnosis and therapy. *Pediatr Neurosurg*. **36**: 75–79.
- Celik T, Tolunay O, Tolunay I, Celik U (2014). Cerebral Salt Wasting in Status Epilepticus: Two Cases and Review of the Literature. *Pediatr Neurol*. **50**: 397–99.
- Celik U, Celik T, Tolunay O, Başpınar H, Kömür M, Levent F (2015). Cerebral salt wasting in tuberculous meningitis: Two cases and review of the literature. *Case Report. Neuro Endocrinol Lett*. **36**: 306–310.
- Celik US, Alabaz D, Yıldızdas D, Alhan E, Kocabas E, Ulutan S (2005). Cerebral salt wasting in tuberculous meningitis: treatment with fludrocortisone. *Ann Trop Paediatr*. **25**: 297–302.
- Diringer M, Ladenson W, Borel C, Hart GK, Kirsch JR, Hanley DF (1989). Sodium and water regulation in a patient with cerebral salt wasting. *Arch Neurol*. **46**: 928–930.
- Doczi TP, Joo F, Balas I (1995). Atrial natriuretic peptide (ANP) attenuates brain oedema accompanying experimental subarachnoid haemorrhage. *Acta Neurochir (Wien)*. **132**: 87–91.
- Grant P, Ayuk J, Bouloux PM, Cohen M, Cranston I, Murray RD, et al (2015). The diagnosis and management of inpatient hyponatraemia and SIADH. *Eur J Clin Invest*. 2015 May 20. doi: 10.1111/eci.12465. [Epub ahead of print]
- Huang SM, Chen CC, Chiu PC, Cheng MF, Chiu CL, HsiehKS (2004). Tuberculous meningitis complicated with hydrocephalus and cerebral salt wasting syndrome in a three-year-old boy. *Pediatr Infect Dis J*. **23**: 884–886.
- Jimenez R, Casado-Flores J, Nieto M, García-Teresa MA (2006). Cerebral salt wasting syndrome in children with acute central nervous system injury. *Pediatr Neurol*. **35**: 261–263.
- Kurtoğlu S, Akçavuş M, Per H, Güneş T, Öztürk M.A., Gümüş H (2002). Cerebral salt wasting in children: Report of two cases and review of literature. *Erciyes Medical Journal*. **24**: 91–95.
- Nelson PB, Seif SM, Maroon JC, Robinson AG (1981). Hyponatremia in intracranial disease: perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). *J Neurosurg*. **55**: 938–41.
- Oh JY, Shin JI (2015). Syndrome of inappropriate antidiuretic hormone secretion and cerebral/renal salt wasting syndrome: similarities and differences. *Front Pediatr*. **22**:146.
- Palmer, B.F (2003). Hyponatremia in patients with central nervous system disease: SIADH versus CSW. *Trends Endocrinol Metab*. **14**: 182–187.
- Peters JP, Welt LG, Sims EA, Orloff J, Needham J (1950). A salt-wasting syndrome associated with cerebral disease. *Trans. Assoc. Am. Physicians*. **63**: 57–64.
- Rivkees SA (2008). Differentiating appropriate antidiuretic hormone secretion, inappropriate antidiuretic hormone secretion and cerebral salt wasting: the common, uncommon, and misnamed. *Curr Opin Pediatr*. **20**: 448–52.
- Sakarcan A, Bocchini J (1998). The role of fludrocortisone in a child with cerebral salt wasting. *Nephrol*. **12**: 769–771.
- Schwartz WB, Bennett W, Curelop S, Bartter FC (1957). A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med*. **23**: 529–42.
- Thompson C, Berl T, Tejedor A, Johannsson G (2012). Differential diagnosis of hyponatraemia. *Best Pract Res Clin Endocrinol Metab*. **26**: 7–15.