Clinical Case Report

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Cerebral salt-wasting syndrome in a child with Wernicke encephalopathy treated with fludrocortisone therapy

A case report

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Abstract

Rationale for this case report: Cerebral Salt-Wasting Syndrome (CSWS) is characterized by hyponatremia and sodium wasting in the urine.[1] These conditions are triggered by various neurosurgical disorders such as subarachnoid hemorrhage, brain tumor, head injury, and brain surgery.[2,3] To our knowledge, CSWS caused by Wernicke encephalopathy (WE) has been rarely reported.

Presenting concerns of the patient: A 2-year-old male patient presented to our hospital due to a seizure attack. He had been neglected and refused to take food for a long time (body weight < 3rd percentile). During admission, the patient showed low serum osmolality, high urine osmolality, dehydration state, increased urine output, and negative water balance, a diagnosis of CSWS was made.

Diagnoses, interventions, and outcomes: Brain MRI displayed symmetrical lesions of T2WI and FLAIR high signal intensity in the peri-aqueductal and hypothalamic areas, which suggests Wernicke encephalopathy. For the early diagnosis of WE, neuroimaging studies can be an important marker. Thiamine hydrochloride was administered at a dose of 100 mg/day for 3 weeks. Cerebral salt-wasting syndrome was subsequently diagnosed due to persistent hyponatremia, dehydrated state, and high urine sodium with massive urination.

Main lessons learned from this case: Wernicke encephalopathy is a very rare cause of cerebral salt-wasting syndrome in pediatrics patients. The patient had a good outcome after hypertonic solution and fludrocortisone therapy.

Abbreviations: CSWS = cerebral salt-wasting syndrome, SIADH = syndrome of inappropriate anti-diuretic hormone, WE = Wernicke encephalopathy.

Keywords: cerebral salt-wasting syndrome, hyponatremia, Wernicke encephalopathy

1. Introduction

Hyponatremia can be fatal and is frequently associated with cerebral salt-wasting syndrome (CSWS); Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH); hypothyroidism; renal, hepatic, or adrenal insufficiency; and congestive heart failure.[4] It is also commonly observed in patients with neurologic disorders.[5] If hyponatremia is associated with neurologic disorders, SIADH or CSWS should be considered. Both diseases show hyponatremia with hypoosmality. However, unlike SIADH, which shows dilutional hyponatremia, decreased urine volume, euvolemia, or hypervolemia due to excessive release of antidiuretic hormone, CSWS shows hyponatremia, serum hypoosmality, concentrated urine, and natriuresis with dehydration. In the present case, CSWS was diagnosed on the basis of renal loss of sodium, persistent polyuria, and increased urine osmolality and hypovolemic state. The differential diagnosis between SIADH and CSWS is important because the treatments are the exact opposite; SIADH is treated with fluid restriction, whereas CSWS is treated with replacement fluid and electrolytes. First described by Peter et al.[6] CSWS is defined by the development of extracellular volume depletion due to a renal sodium transport abnormality in patients with intracranial disease and normal adrenal and thyroid function. CSWS commonly occurs in postoperative neurosurgical patients.[7]

The most common cause of WE in adults is chronic alcohol abuse.[8] WE is very rare and underdiagnosed in children.[8] The

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most common admitting diagnosis in children is brain tumor, and the second most common is hydrocephalus, but metabolic causes are rarely reported.[9] WE is a little-known cause of CSWS. Herein, we reported a CSWS patient with WE who had a good outcome after hypertonic solution and fludrocortisone therapy.

2. Case report

A 25-month-old male was admitted to the hospital with generalized tonic clonic seizure and loss of consciousness that continued for longer than 1 week. The patient had been diagnosed with communicating hydrocephalus at 19 months of age and delayed development. He could only turn inside. His past admission history was pneumonia at 3 month ago. Of his family, there is no one who had neurologic, metabolic, or cerebrovascular disease. On examination, his mental status was drowsy, and the muscle strength of his lower extremities was decreased to grade 2/5 with spasticity. He could not sit up by himself, and his deep tendon reflexes were accelerated. He also had microcephaly (44 cm < 3rd percentile). His nutritional state was very poor and cachectic (body weight 10 kg <3rd percentile). His first sodium–potassium–chloride level was 132–4.6–98 mmol/L checked. Complete blood count was 8800–14.1–382 K with C-reactive protein negative. Serum pH was 7.32, bicarbonate 16.9. Total protein, albumin, creatinine, and glucose levels were normal. All test results were normal. However, further brain evaluations were conducted because his mental status was gradually worsened. EEG revealed depressed background activities with moderately increased slow waves in the right hemisphere and frequent sharp waves in the left frontal area.

Brain MRI showed high-signal intensity in the peri-aqueductal and hypothalamic areas on T2/FLAIR-weighted images and lateral ventricle dilatation (Fig. 1). These findings are consistent with Wernicke encephalopathy. To support this diagnosis, we measured urine organic acid, lactic acid, pyruvic acid, and lactic/pyruvic acid ratio, but we could not determine the serum thiamine level because thiamine therapy was initiated before sampling. The lactic acid level in the serum and urine was elevated, and the lactic acid/pyruvic acid ratio was 13890, which is also observed with WE. We prescribed anti-epileptics and 50 mg of thiamine per day for 3 weeks. Additionally, we administrated mannitol, methylprednisolone (2 mg/kg/day), phenytoin, and oxcarbamazepine for seizure control and hydrocephalus treatment not using diuretics.

Because his initial volume state euvolemic, we did not check blood pressure and follow-up electrolyte level during first 1 week. On the 6th hospital day, although his seizure attacks progressively improved, he started projectile vomiting 7 times per day. On the 7th hospital day, he had dark-colored loose stool. We decided that he needed a total parenteral nutrition (TPN) time of about 3 days. We supplied combination TPN material (350 kcal/day) and 1:4 SD fluid (100 cc/kg/day contained sodium 2.87 mEq/kg/day). Regardless of the sufficient fluid supplementation, the follow-up lab 3 days later (i.e., day 10) revealed a seriously decreased serum sodium level (96 mmol/L). Fortunately, the patient was in a light drowsy mental state. Simultaneously, we could suggest decreased "effective arterial blood volume," because mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC) count, and BUN was elevated (MCHC – 40.5 g/dL, WBC-43000/μL, BUN 21 mg/dL).[10] That day, his urine osmolality decreased to 129 mOsm/kg with a normal serum osmolality of 290 mOsm/kg. His 24-hour urine output was 516 mL (2.15 mL/kg/h) with a measured fluid intake of 343 mL. Because of the decreased urine osmolality, we considered the possibility that hyponatremia had induced GI bleeding or 3rd space sodium loss. To rule out other causes of hyponatremia, we examined sodium regulating hormone, for example, ACTH, ADH, cortisol, renin, aldosterone, and thyroid hormone. Except the low range of TSH, all hormone study revealed normal results. Massive sodium replacement was performed for 3 days, after which, the serum sodium level gradually recovered to 139 mmol/L. Other lab finding also recovered, MCHC, WBC and BUN were dramatically decreased after one day hydration therapy (MCHC 41.1 g/dL, WBC 19540/mL, BUN 10 mg/dL).

However, on the 3rd day after recovery (i.e., day 13), the patient's serum sodium level suddenly decreased again to 117 mmol/L. At this stage, the urine osmolality was 512 mOsm/kg, and serum osmolality had decreased (273 mOsm/kg).The 24-hour urine output was 1198 mL (5 mL/kg/h) with a fluid supply of 1221 mL. On the basis of low serum osmolality, high urine osmolality, dehydration state, increased urine output, and negative water balance, a diagnosis of CSWS was made, and a 3% NaCl supply regimen was started. During the next 24 hour (i.e., day 14), serum osmolality decreased to 251 mOsm/kg, and urine osmolality increased to 1189 mOsm/kg (Fig. 2).

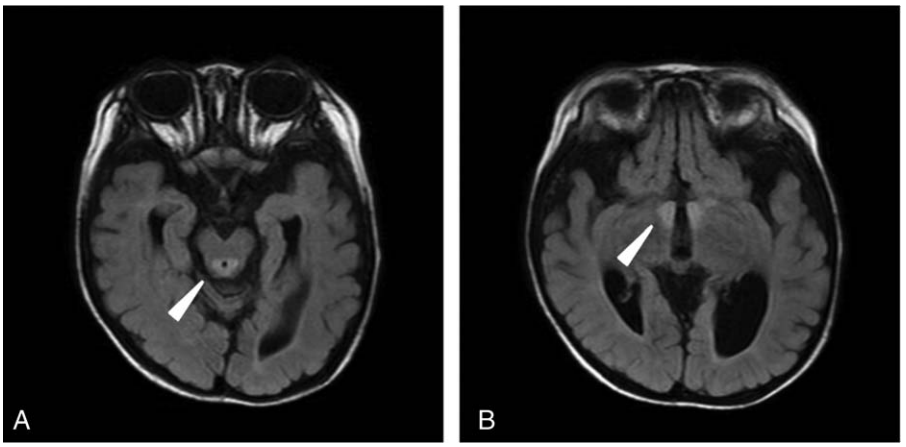

Figure 1. Brain MRI (FLAIR: TR = 9000, TE=99) of a 25-month-old male demonstrating the symmetric lesions of hyperintensity at the peri-aqueductal (A, arrow) and hypothalamic areas (B, arrow). MRI also shows ventriculomegaly with loss of periventricular white matter. MRI = magnetic resonance imaging.

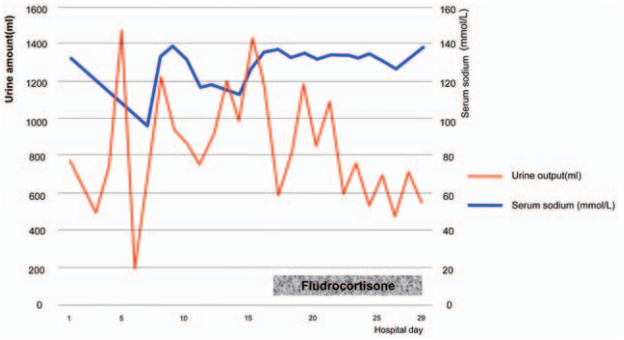

Figure 2. Time course of serum sodium value and urine volume.

The urinary output continued to be high, varying between 50 and 60 mL/kg/h during the next 3 days. On day 17, we changed the treatment plan to 0.2 mg fludrocortisone orally in an attempt to reduce the urinary sodium excretion.

This treatment resulted in a decrease in urine output (i.e., 24–39 mL/h) and a plasma sodium increase to 137 mmol/L. There was also a reduction in urinary sodium osmolality from 1189 to 281 mOsm/kg (i.e., day 20). Similar to findings from other CSWS cases, fludrocortisone was an effective treatment for urinary sodium loss (Table 1).[11,12].

From day 20 to day 30, the patient maintained a serum sodium level between 131 and 138 mmol/L. However, thiamine supplementation and electrolyte correction could not recovery his neurologic condition with lactate accumulation up to 17 mmol/L. He was discharged on the 30th day with well-controlled serum sodium level and seizures.

3. Discussion

Cerebral salt-wasting syndrome was first reported in the 1950s by Peter et al.[6] The most remarkable finding of CSWS is hyponatremia or massive urine output. It is effective to use normal saline or hypertonic saline and fludrocortisone in contrast to treatment for SIADH. Since the 1950s, many cases of CSWS have been reported. The most common admitting diagnosis is brain tumor, with rare cases of acute brain injury and meningoencephalitis. However, there are no reported cases of Wernicke encephalopathy as the primary admitting diagnosis.

The pathogenesis of CSWS is still unknown. Some reports have shown that atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) affect the CSWS mechanism.[13–15] Cerda-Esteve et al[16] reported that ANP, BNP, C-type natriuretic peptide, and dendroaspis natriuretic peptide from damaged CNS tissues induce CSWS. However, there is no definitive proof. Elevated levels of the natriuretic peptides can promote CSWS, but this might not be applicable in all patients.

This case is very rare. The patient had only one of the triads of typical clinical features of Wernicke encephalopathy: mental status change, opthalmoplegia, and ataxia. He complained of both extremity spasticity and gait disturbance but did not initially demonstrate ocular signs or mental changes. According to a report, the triad of WE occurs less frequently in nonalcoholic than alcoholics ($P < 0.005$).[17] In many nonalcoholic WE cases, causes of thiamine deficiency can vary. The main causes are cancer, gastrointestinal surgery, hyperemesis gravidarum, starvation, and fasting.[18] In the present case, a diagnosis was difficult because there was no definitive cause of thiamine deficiency. To support the WE diagnosis, we used high-signal MRI density and high lactate level. In WE, the thiamine-dependent enzymes pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase cannot play a role in inhibiting the Krebs cycle. These nonfunctional enzymes lead to reduced ATP synthesis, which can promote cell damage and intracellular accumulation of lactate and alanine.[19] For this reason, areas of high oxidative metabolism such as the medial thalami, the periaqueductal area, the mammillary bodies, and the tectal plate of the midbrain are sensitive to thiamine deficiency, showing intra- and extra-cellular edema and cytotoxic edema swelling.[8,20] On brain MR imaging, these regions show a pathologic alteration presenting on T2-weighted images and as FLAIR hyperintensities.

In response to an unknown trigger, the patient experienced severe hyponatremia with massive urine output on the 7th hospital day, although serum and urine osmolality were in the normal range. We corrected the remediable CSWS using fludrocortisone and a hypertonic solution treatment. In spite

Table 1

Comparison of cerebral salt-wasting syndrome progression in reported cases[10,11] and our patient.

Patient	Day	Plasma Na	U/Na	Uosm	I/O
This case	7	96	40	129	343/516
	14	118	257	1189	1301/1189
	16	113	195		1390/1428
	24	135	32		960/1102
1	6	124	108	408	3300/3900
	11	128			5100/5200
	27	138			2300/2600
2	1	128			3650/4950
	13	132	183	439	2520/3600
	19				2900/2100
3	1	132			1864/940
	4	126	108	408	3920/4430
	12				2600/1500
4	10	124	173	525	600/680
	13	132		222	6300/5600
	16	136	54	218	2300/2600

Etiology of Case 1: subdural hematoma, Case 2: cannabis addiction, Case 3: middle cerebral artery infarction, Case 4: anterior cerebral artery aneurysm operation, Blue line: fludrocortisone start.
I/O = total amount of input/output (mL), serum Na = serum sodium (mmol/L), U/Na = urine sodium (mmol/L), Uosm = urine osmolality (mOsm/kg).

of the recovery from the hyponatremic condition, the patient could not recover from metabolic acidosis despite the thiamine supplementation. There is no standard treatment for CSWS, with no consensus on optimal dose of thiamine, duration of treatment, or preparation form. According to many case reports, in nonalcoholics, treatment with either 100 mg or 200 mg intravenously can be effective.[21] For some reason, in this case, the patient had no response to the thiamine treatment.

4. Conclusion

For the many cases of CSWS that have been reported, the focus was on the differentiation between SIADH and CSWS or a good prognosis resulting from correction of the hyponatremia. Conversely, our report tried to highlight other rare cases of CSWS and the importance of CNS disease control. Normalization of the hyponatremia condition induced by CSWS improved the prognosis of our patient.

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