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Case Report

Persistent Hyponatremia in Tuberculous Meningitis- Diagnostic Dilemma.

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Abstract

Hyponatremia has been recognized as a serious complication in patients with tuberculous meningitis (TBM). The differential diagnoses of hyponatremia in TBM are adrenal insufficiency, Syndrome of Inappropriate Anti Diuretic Hormone (SIADH) secretion, and Cerebral Salt Wasting Syndrome (CSWS). Thorough clinical and laboratory examination is important to distinguish between SIADH and CSWS as attention to extracellular volume status is critical. Misdiagnosis of CSWS as SIADH can be fatal, as water restriction is detrimental to patients with CSWS.

Keywords: Tuberculous meningitis (TBM), Syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, Cerebral Salt Wasting Syndrome (CSWS)

Introduction

World Health Organization (WHO) Global Tuberculosis Report 2016 reports an estimated one million new cases of tuberculosis occurred in HIV-negative children in 2015, with 2,00,000 deaths.[1] Central nervous system (CNS) tuberculosis disproportionately afflicts children with a high mortality and neurological morbidity.[2] Hyponatremia occurs in 35–65% of patients with tuberculous meningitis (TBM) and is an independent predictor of death or severe disability.[3,4] Hyponatremia may be due to the Syndrome of Inappropriate Anti Diuretic hormone (SIADH) secretion, cerebral salt wasting syndrome (CSWS), excessive fluid administration in patients with impaired thirst, diuretic therapy such as mannitol, and treatment of transient/permanent diabetes insipidus.[4-6] Diagnosing the cause of hyponatremia among patients with acute cerebral insults can be challenging. We report a case of young female aged 16 year who presented with tuberculous meningitis and persistent hyponatremia.

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Case History

A 16-year-old adolescent female presented with fever, myalgia, vomiting and headache of 15 days duration with h/o contact with tuberculosis. Physical examination revealed signs of meningeal irritation. CSF analysis revealed lymphocytic predominant leucocytosis, hypoglycorrhachia, elevated proteins and CB NAAT positive for Acid Fast Bacilli. Further investigations revealed reduced serum osmolality and hyponatremia. An increase in urinary sodium and osmolality was also noted. CT scan of Brain was normal. Considering TBM with SIADH, anti-tubercular therapy was started along with 3% Sodium Chloride and fluid restriction (2/3rd maintenance). However, hyponatremia persisted. On day 5 of admission, patient developed polyuria and hypotension and serum Sodium (Na) level was 120mEq/L (Tables 1 and 2). In view of the above findings, CSWS was suspected and mineralocorticoid (fludrocortisone at 0.2 mg/kg) was added. The patient responded favourably and was later discharged.

Table 1: Serum Sodium Values.

Serum Sodium Levels(mEq/L)					
Day 1	120	Day 7	127	Day 13	126
Day 2	122	Day 8	128	Day 14	126
Day 3	128	Day 9	128	Day 15	125
Day 4	126	Day 10	126	Day 16	126
Day 5	120	Day 11	126	Day 17	132
Day 6	129	Day 12	128	Day 22	138

Table 2: Serum and Urine Osmolality Values.

	Day 1	**Day 5**
Urinary Sodium (mEq/L)	125	225
Urinary Osmolality (mOsm/L)	527	566
Serum Osmolality (mOsm/L)	225	186

Table 3: Differences between CSWS and SIADH.

Variable	**CSWS**	**SIADH**
Weight	Reduced	Increased
Postural Hypotension	Present	Absent
Serum Osmolality	Reduced	Reduced
Serum Uric acid	Normal/increased	Reduced
Plasma Urea	Normal/increased	Reduced
Urine Sodium	Markedly/increased	Reduced
Urine Volume	Markedly/increased	Reduced

Discussion

Hyponatraemia associated TBM has three main differential diagnoses: Adrenal insufficiency, SIADH and CSWS. Clinical manifestations of these conditions may be similar, but their pathogenesis and management protocols are different.[5,6]

Absence of hyperkalaemia and negative Synacten test suffice to eliminate adrenal insufficiency. Diminished extracellular volume associated with natriuretic hyponatraemia excludes the diagnosis of SIADH. We entertained diagnosis of Cerebral Salt Wasting Syndrome (CSWS) based on the following parameters: Severe volume depletion (postural hypotension with tachycardia), high urinary sodium excretion, and correction of hyponatraemia and volume status with saline and fludrocortisone therapy. Furthermore, demonstration of elevated brain natriuretic peptide levels in TBM supports the diagnosis but it could not be evaluated in our case.

CSWS is defined as loss of sodium through kidney during intracranial diseases, leading to hyponatraemia, volume depletion with clinical response to volume and salt replacement. It was first described by Peters et al. in 1950, 7 years before the identification of SIADH.[7] As early as 1951, Rapoport et al. described a salt-losing state as a possible cause for hyponatraemia in TBM.[8]

A variety of processes have been linked with CSWS, including CNS injury, subarachnoid haemorrhage, encephalitis, TBM, craniotomy, poliomyelitis, and pituitary adenoma, among others. It occurs between 6 months and 65 years of age, and the exact underlying pathophysiology is unclear. [9]

The main mechanisms involved in the pathophysiology of CSWS are a decrease in the sympathetic nervous system outflow during intracranial the disease leading to decrease Sodium (Na) reabsorption in the proximal tubules, inhibition of the Renin Angiotensin System (RAS), and also release of some natriuretic factors such as BNP, Atrial natriuretic peptide (ANP) and other natriuretic proteins. The net effect of the above changes is the induction of natriuresis, which in turn cause polyuria and also the decrease in the effective circulating volume, thus leading to hypotension and hyponatraemia.[10-12]

The main differential diagnosis is SIADH. A thorough clinical examination and laboratory investigation is necessary to diffrentiate between the two and attention to extracellular volume status is critical. Despite apparent similarities, the pathophysiology, biochemistry and treatment are quite different among the two conditions. The major difference between SIADH and CSWS is that, CSWS involves renal salt loss, resulting in hyponatraemia and decrease in extracellular fluid volume, whereas SIADH involves physiologically inappropriate secretion of ADH or increased renal sensitivity to ADH, leading to renal conservation of water and euvolaemic hyponatraemia (Table 3). Conversely, an elevated serum ADH does not exclude a diagnosis of CSWS as it may be raised physiologically in response to hypovolaemia. Misdiagnosis of CSWS as SIADH can be fatal, as water restriction is detrimental to patients with CSWS.

Therapy of CSWS and SIADH is diagonally opposed, i.e. volume restriction in SIADH versus the volume and salt replacement in CSWS. Volume restriction in CSWS would be potentially disastrous, in causing a further decrease in the cerebral perfusion pressure. The volume replacement achieved with 0.9% (or 3% sodium chloride if necessary) is the cornerstone of treatment of CSWS. The rapidity of salt replacement depends on the rate at which hyponatraemia develops. Hyponatraemia developing at a rate of 0.5 mEql/L/hr should be treated aggressively as it is a life-threatening complication and may cause mortality from severe cerebral oedema and cerebral herniation. As ANP can inhibit mineralocorticoid secretion in patients with CSWS, administration of an agent with mineralocorticoid activity, such as fludrocortisone, has also been proved to be effective in returning serum sodium levels to normal, by acting directly on the renal distal tubules to enhance sodium reabsorption. Adverse effects of fludrocortisone including hypertension, hypokalaemia and pulmonary oedema should be monitored.

This case reported highlights the difference between CSWS and SIADH, and the importance of correct diagnosis and treatment. Mineralocorticoid supplementation seems to be an effective and a safe treatment for CSWS, whereas hypertonic and normal saline could be a temporary measure. However, serum sodium level normalization is obtained only with TBM disease control.

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