Mechanism, spectrum, consequences and management of hyponatremia in tuberculous meningitis [version 1; peer review: awaiting peer review]

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Abstract
Hyponatremia is the commonest electrolyte abnormality in hospitalized patients and is associated with poor outcome. Hyponatremia is categorized on the basis of serum sodium into severe (< 120 mEq/L), moderate (120-129 mEq/L) and mild (130-134 mEq/L) groups. Serum sodium has an important role in maintaining serum osmolality, which is maintained by the action of antidiuretic hormone (ADH) secreted from the posterior pituitary, and natriuretic peptides such as atrial natriuretic peptide and brain natriuretic peptide. These peptides act on kidney tubules via the renin angiotensin aldosterone system. Hyponatremia <120mEq/L or a rapid decline in serum sodium can result in neurological manifestations, ranging from confusion to coma and seizure. Cerebral salt wasting (CSW) and syndrome of inappropriate secretion of ADH (SIADH) are important causes of hyponatremia in tuberculosis meningitis (TBM). CSW is more common than SIADH. The differentiation between CSW and SIADH is important because treatment of one may be detrimental for the other; evidence of hypovolemia in CSW and euvoolemia or hypervolemia in SIADH is used for differentiation. In addition, evidence of dehydration, polyuria, negative fluid balance as assessed by intake output chart, weight loss, laboratory evidence and sometimes central venous pressure are helpful in the diagnosis of these disorders. Volume contraction in CSW may be more protracted than hyponatremia and may contribute to border zone infarctions in TBM. Hyponatremia should be promptly and carefully treated by saline and oral salt, while 3% saline should be used in severe hyponatremia with coma and seizure. In refractory patients with hyponatremia, fludrocortisone helps in early normalization of serum sodium without affecting polyuria or functional outcome. In SIADH, V2 receptor antagonist conivaptan or tolvaptan may be used if the patient is not responding to fluid restriction. Fluid restriction in SIADH has not been found to be beneficial in TBM and should be avoided.

Keywords
Tuberculous meningitis, hyponatremia, cerebral salt wasting, stroke, SIDH, natriuretic peptide
Introduction
The human body is composed of 60–70% water, one-third of which is in the extracellular compartment. Sodium is the major electrolyte, which normally ranges between 135 and 145 mEq/L. Hyponatremia is defined as a serum sodium decrease of <135 mEq/L, and is the commonest electrolyte abnormality occurring in 3–35% of hospitalized patients, 50% of neurological admissions, and one-third of patients in intensive care units. The severity of hyponatremia has been categorized as mild (130–134 mEq/L), moderate (120–129 mEq/L), and severe (<120 mEq/L), and serum sodium <125 mEq/L is regarded as an independent predictor of mortality, especially in critically ill patients; mortality increases by 1.5–60 times in the patients with hyponatremia. Consequently, every attempt should be made to maintain a normal serum sodium level. It is important to check serum sodium levels twice to avoid laboratory error and use the lowest level to define the severity of hyponatremia. Hyponatremia in a patient may be due to a number of causes such as poor intake of sodium, drugs, vomiting, diarrhea, liver, kidney or heart failure, endocrine disorders, syndrome of inappropriate section of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). A number of neurological disorders such as stroke, subarachnoid hemorrhage, head injury, neurosurgical operations and central nervous system (CNS) infections may result in hyponatremia. This review will focus on the pathophysiology, diagnosis and management of hyponatremia with an emphasis in tuberculous meningitis (TBM).

Pathophysiology of hyponatremia
Serum sodium has an important role in maintaining serum osmolality, and hyponatremia can be associated with normal, increased or reduced osmolality. In normal individuals, serum osmolality ranges between 280 mOsm/L and 295 mOsm/L, and is calculated by the following formula:

\[ \text{Serum Osmolality} = (\text{Serum sodium} \times 2 + \text{blood glucose/1.8} + \text{blood urea/2.8}) \text{ mEq/L} \]

Serum osmolality is regulated by antidiuretic hormone (ADH) and kidney. Antidiuretic hormone is released from the posterior pituitary in response to an increase in serum osmolality. It is also released in response to reduced intravascular volume, although serum osmolality is the main trigger. ADH binds to ADH receptors in the kidney tubules, and results in re-absorption of water without re-absorbing sodium. An increase of ADH in the presence of normal or low serum osmolality is regarded as inappropriate, which results in continued absorption of water by the kidney resulting in hyponatremia and natriuresis. The kidneys are able to excrete sodium normally because sodium excretion is regulated by aldosterone and atrial natriuretic peptide (ANP). The main causes of hyponatremia are set out in Table 1. There are two important causes of hyponatremia in neurological conditions: SIADH or CSW.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
The underlying mechanism of SIADH is inappropriate release of ADH or arginine vasopressin resulting in low serum osmolality and water absorption. This leads to expansion of extra-cellular volume and dilutional hypotonic hyponatremia despite normal renal sodium handling. Although SIADH is a volume expanded state, most patients do not show the clinical evidence of hypervolemia, because only one-third of total retained water is in extracellular space. The causes of SIADH are as follows:
- CNS disorders: Meningitis, encephalitis, subarachnoid hemorrhage or trans-sphenoidal pituitary surgery.
- Pulmonary disorders: Pneumonia, bronchogenic carcinoma.
- Malignancy
- Surgery
- Drugs: carbamazepine, oxcarbazepine, cyclophosphamide, selective serotonin reuptake inhibitors

Cerebral salt wasting (CSW)
CSW refers to primary natriuresis leading to hypovolemia and sodium depletion without known stimulus to excrete a large amount of sodium. It is suggested that natriuretic factors such as ANP, brain natriuretic peptide (BNP), C type natriuretic peptide and dendraospis natriuretic peptide (DNP) may be responsible for CSW, although BNP is regarded as the most important cause of CSW. The release of ANP is mainly from cardiac atria and BNP from ventricles, hypothalamus, sympathetic projections and adrenal medulla. Release of ANP and BNP is mostly due to distension of the atria or ventricles in addition to various sympathetic and hormonal influences. The effect of natriuretic peptides is well documented in nephrons, but less clear in the CNS and autonomic nervous system. It has, however, been suggested that dysregulation of the sympathetic

<table>
<thead>
<tr>
<th>Normovolemic</th>
<th>Hypovolemic</th>
<th>Hypervolemic</th>
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</thead>
<tbody>
<tr>
<td>Endocrinial</td>
<td>Diabetes, corticosteroid withdrawal</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Sweating, burn</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Ketone, urea</td>
<td>Cirrhosis of liver</td>
</tr>
<tr>
<td>Hypertonic fluid administration</td>
<td>Iatrogenic (hypotonic fluid)</td>
<td>Iatrogenic (hypertonic solution)</td>
</tr>
<tr>
<td>SIADH</td>
<td>CSW</td>
<td>SIADH</td>
</tr>
</tbody>
</table>

SIADH = syndrome of inappropriate antidiuretic hormone; CSW = cerebral salt wasting.
response may be responsible for CSW; association of CSW with neuroleptic malignant syndrome suggests the role of the sympathoadrenal system and natriuretic peptides'. A direct relationship between ANP and BNP with intracerebral pressure (ICP) has been reported'. CSW may be a protective mechanism in response to excessive rise in ICP, vasospasm in subarachnoid hemorrhage or meningitis. Some studies, however, have not found such a direct relationship between BNP and CSW. In a study on TBM, ANP and BNP were elevated at the time of hyponatremia compared to basal values, and remained elevated even after correction of hyponatremia. ANP and BNP, however, did not differentiate between CSW and SIADH'.

The patients with SIADH had increased volume and sodium excretion in 24 hours compared to those without SIADH and subdural hemorrhage, but their BNP did not change and ANP decreased'. In nine children with features of CSW, hyponatremia normalized by two weeks, but polyuria and natriuresis increased. The potential cause of CSW in these children was elevated ANP in 1 out of 6, and BNP in 2 out of 7 suggesting their limited role in CSW' 9. Apart from ANP and BNP, other natriuretic peptides have also been studied. An elevated DNP level was associated with negative fluid balance and hyponatremia in patients with SIADH and head injury 10,11,12. Dysregulated sympathetic activity may cause an increase in renal blood flow and glomerular filtration rate, and a decrease in renin release and renal tubular reabsorption 13.

**Clinical manifestations of hyponatremia**

The clinical manifestations of hyponatremia are related to its severity and rate of decline in serum sodium. Symptoms generally appear when serum sodium decreases to 120 mEq/L or lower; however, a rapid decline in serum sodium may manifest at higher sodium level14,15. Headache, nausea, vomiting, anorexia, muscle cramps, myalgia, restlessness, confusion, lethargy and coma may ensue as serum sodium level declines. Neurological examination reveals changes in mentation and reduced tendon reflexes. In an advanced stage, cerebral edema develops, which may be associated with seizures, apnea, coma and death16. In slowly developing hyponatremia, there may not be clinical symptoms and signs even with a very low serum sodium level, as the brain becomes adapted to hypo-tonicity by extruding solute to extracellular space. This process may ameliorate cellular swelling. The drawback of this adaptive process is that it may predispose to osmotic demyelination if hyponatremia is corrected rapidly. Osmotic demyelination typically affects pons and extra-pontine areas.

**Hyponatremia in tuberculous meningitis (TBM)**

TBM is the commonest cause of sub-acute and chronic meningitis, and occurs in ~0.9% of the patients with tuberculosis. TBM is associated with basal exudates, hydrocephalous, tuberculoma and stroke, and is an important cause of stroke in young individuals in India17. Hyponatremia in TBM is multifactorial and may be due to anorexia, nausea, vomiting, poor intake of sodium, diarrhea, drugs (diuretic, osmotic agents, carbamazepine, oxcarbazepine) and associated comorbidities.

Hyponatremia in TBM has been evaluated in only a few studies. In 20 children with TBM, hyponatremia was present in 65% on admission, 47% on day three and 30.8% on day 10. The cause of hyponatremia was diagnosed as SIADH. The outcome was not related to severity of meningeal inflammation. Two out of the 3 children who died within three days had SIADH18. Another study in 115 TBM patients reported endocrinal dysfunctions in 53% and SIADH in 9.6%19. In a prospective study on 76 TBM patients, 34 (44.7%) had hyponatremia, which was mild in 3, moderate in 23 and severe in 8 patients. CSW was the most frequent cause of hyponatremia in 17, SIADH in 3 and there were miscellaneous causes in 14 patients. Hyponatremia was related to the Glasgow Coma Scale score, severity of TBM, focal weakness, mechanical ventilation, age and comorbidities, while CSW was related to the severity of TBM20. There are many short series and case reports on SIADH and CSW in TBM. Studies that comprise of more than 10 patients have been included in Table 2. Out of a total of 11 studies comprising 642 (16–195 patients in each study) patients with TBM, 276 (44.3%) had hyponatremia. Only four studies, including 99 patients characterized CSW and SIADH, found CSW a more common cause of hyponatremia (36 patients; 36.4%) than SIADH (26 patients; 26.3%).

**Relationship between hyponatremia and TBM-related stroke**

Hyponatremia is reported in 40% of stroke patients21 and up to 50% of TBM patients may have stroke22. The relationship between TBM-related stroke and hyponatremia has been recently evaluated in a study of 81 patients with TBM, of which 32 (39.5%) had ischemic stroke. Stroke occurred at different time points: time of admission in 12 patients, within 3 months in 14 patients and after 3 months in 6 patients. Multiple infarctions were present in 20 (62.5%) patients, which were cortical in 7 and subcortical in 29 (capsular: 3, basal ganglia: 18, thalamus: 10, corona radiate: 13 and infra-tentorial: 4) patients. The infarctions were present in the tubercular zone in 10, ischemic zone in 15 and both in 7 patients. Hyponatremia occurred in 46 (57%) patients with TBM and was mainly due to CSW. A total of 16 patients with CSW had stroke, 10 of whom developed stroke during the poly-uric phase of CSW (Figure 1). CSW patients with stroke had lower systolic blood pressure than those without CSW (115 vs 123 mm Hg; P = 0.04). Hyponatremia and polyuria were more severe and persisted for a longer time in stroke patients compared to those without stroke. Deep white matter infarction was more common in CSW (Figure 2) compared to those without. It is possible that hypovolemia associated with CSW may result in hypo-perfusion and may contribute to infarction in a patient with basal exudate with compromised vascular lumen due to vasculitis. The additional contributing factors of stroke in TBM are endothelial injury due to vasculitis, prothrombotic state and strangulation of vessels by exudates22,23.

It is important to note that polyuria and negative fluid balance may persist for several months in TBM although hyponatremia improves earlier. Prolonged hypovolemia may lead to some beneficial (reducing intracranial pressure) and harmful effects (hypoperfusion and infarction). In TBM, the collaterals may also be affected, which are a natural defense mechanism to vascular occlusion, and internal border-zone may be more vulnerable.
Table 2. Studies reporting hyponatremia in tuberculous meningitis patients.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Patients, n</th>
<th>Patients with hyponatremia, n (%)</th>
<th>Cause of hyponatremia, n (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al., 2018</td>
<td>TBM: 47; VM: 51</td>
<td>TBM: 37 (78.7); VM: 14 (27.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inamdar et al., 2016</td>
<td>75</td>
<td>29 (38.7)</td>
<td>CSW: 10; MISC: 19</td>
<td>No patients with SIADH</td>
</tr>
<tr>
<td>Misra et al., 2016</td>
<td>76</td>
<td>34 (44.7)</td>
<td>CSW: 17; SIADH: 3; MISC: 14</td>
<td>No relationship reported to outcome</td>
</tr>
<tr>
<td>Anderson et al., 2010</td>
<td>104</td>
<td>51 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al., 2000</td>
<td>20</td>
<td>12 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh et al., 1994</td>
<td>20</td>
<td>13 (65)</td>
<td>SIADH: 13</td>
<td>No effect on outcome after 72 hours</td>
</tr>
<tr>
<td>Narotam et al., 1994</td>
<td>24</td>
<td>15 (62.5)</td>
<td>SIADH: 13</td>
<td>Negative correlation between serum sodium with ANP and no correlation between plasma ADH and plasma sodium</td>
</tr>
<tr>
<td>Shian et al., 1993</td>
<td>16</td>
<td>11 (70)</td>
<td></td>
<td></td>
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<tr>
<td>Davis et al., 1993</td>
<td>54</td>
<td>43 (79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karandanis et al., 1976</td>
<td>11</td>
<td>8 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bussmann et al., 2001</td>
<td>195</td>
<td>20 (10.3)</td>
<td>SIADH: 7; CSW: 9</td>
<td>Hyponatremia attributable to CSW is at least as frequent in children as SIADH.</td>
</tr>
<tr>
<td>Total</td>
<td>642</td>
<td>276 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inamdar et al.: 2016</td>
<td>75</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misra et al.: 2016</td>
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<td>34</td>
<td>CSW: 17; SIADH: 3</td>
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<tr>
<td>Singh et al.: 1994</td>
<td>20</td>
<td>6</td>
<td>CSW: 0; SIADH: 16</td>
<td></td>
</tr>
<tr>
<td>Bussmann et al.: 2001</td>
<td>195</td>
<td>20</td>
<td>CSW: 9; SIADH: 7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>366</td>
<td>99 (27.1)</td>
<td>CSW: 36 (36.4); SIADH: 26 (26.3)</td>
<td></td>
</tr>
</tbody>
</table>

TBM = tuberculous meningitis; VM = viral meningitis; CSW = cerebral salt wasting; MISC = miscellaneous; SIADH = syndrome of inappropriate antidiuretic hormone; ANP = atrial natriuretic peptide; ADH = antidiuretic hormone.

in TBM (Figure 1). In a previous study, internal border zone necrosis was reported in 50% children with TBM	extsuperscript{3}. There is a pressure gradient from the large artery to arterioles; blood pressure in brachial artery is 117/75 mm Hg, thalamostriate artery 101/79 mm Hg, and perforators 59/38 mmHg	extsuperscript{34}. The pressure gradient in subcortical and perforators may render these regions especially vulnerable in the event of hypovolemia and hypotension associated with CSW. A dynamic state between lacunar infarction and white matter hyperintensity has been reported, leading to improvement or worsening in blood flow changes	extsuperscript{35}.

Diagnosis of cause of hyponatremia in TBM

In a patient with hyponatremia, assessment of volume status is the most important step that differentiates SIADH from CSW (Table 3). This differentiation is crucial because the treatment of one can be deleterious for the other condition. Clinical signs and laboratory results should be considered together to judge the volume status. Electrolytes and osmolality of serum and urine are important. Serum renin, ADH, ANP and BNP are not easily available, and usually do not differentiate CSW from SIADH. Serum potassium is normal in SIADH, but may be high in CSW. Serum uric acid is low in both SIADH and CSW, and on correction of serum sodium it rises in SIADH but remains low in CSW	extsuperscript{36,37}. The definite diagnosis of the cause of hyponatremia may take some time, but empiric therapy may be started assuming CSW is more common and fluid restriction may be hazardous in CSW, especially in bacterial meningitis	extsuperscript{38–41}.

CSW diagnosis should be considered in the presence of the following features:

**Essential:** (all required)

1. Polyuria (24 hour urine output > 3L for at least 2 consecutive days).
2. Hyponatremia: serum sodium < 135 mEq/L on 2 occasions 24 hours apart.
3. Exclusion of secondary causes of hyponatremia such as endocrine abnormalities, renal, cardiac or hepatic failure, or diuretics.

**Supportive criteria (at least 3 out of 5):**

1. Clinical evidence of hypovolemia such as hypotension, dry mucous membrane, tachycardia or postural hypotension.
Figure 1. Duration of polyuria and onset of stroke in tuberculous meningitis patients with cerebral salt wasting (CSW). The vertical grey bars denote the onset (lower limit) and subsidence (upper limit) of polyuria in each patient. The black small squares denote the day of stroke after admission. A total of 10 out of 16 patients developed stroke during CSW (high urinary output).

**Misra UK, Kalita J, Kumar M, Neyaz Z. Hypovolemia due to cerebral salt wasting may contribute to stroke in tuberculous meningitis, QJM: An International Journal of Medicine 2018; 111 (7): 455–460, doi:10.1093/qjmed/hcy072.** Reprinted by permission of Oxford University Press on behalf of the Association of Physicians of Great Britain and Ireland. (c) The Author(s) 2018. All rights reserved. For permissions, please email: journals.permissions@oup.com. This figure is not included under the Open Access license of this publication. Disclaimer: “OUP and the AOP are not responsible or in any way liable for the accuracy of the adaptation. F1000 Research Limited is solely responsible for the translation in this publication/reprint.”

2. Persistent negative fluid balance as revealed by intake output chart and/or weight loss.

3. Laboratory evidence of dehydration such as elevated hematocrit, hemoglobin, serum albumin or blood urea nitrogen.

4. Central venous pressure (CVP) < 6 cm of water.

5. Urinary sodium > 40 mEq/L or urine osmolality > 300 mOsm/L in 2 consecutive occasions.

**Daily sodium balance, intake-output and body weight chart should be maintained. When hyponatremia is refractory to IV saline and oral salt; water and salt intake should be carefully increased after reassessing the diagnosis.**

Some tests have been recommended to differentiate CSW from SIADH:

- **Frusemide test:** Infusion of 20mg of frusemide normalizes serum sodium in the patients with SIADH.
- **Saline infusion test:** Hyponatremia is aggravated after infusion of 100 ml of normal saline in SIADH.

**Diagnosis of SIADH is based on the following criteria**:

1. Hyponatremia
2. Low serum osmolality
3. High urinary osmolality > 100mOsm/Kg.
4. Urinary sodium > 20mMol/L
5. Exclusion of endocrinal diseases, renal causes, and disorders of non-osmotic release of ADH such as hypovolemia, hypotension, pain, stress, drugs (narcotic, carbamazepine, cyclophosphamide, Selective serotonin reuptake inhibitors)
The safety and validity of these tests have not been proven. SIADH and CSW may have overlapping clinical and laboratory features such as hyponatremia, low serum osmolality, high urinary sodium and osmolality. The most reliable differentiating feature is evidence of low extracellular volume in CSW, which is normal or increased in SIADH.

Some authors do not differentiate between CSW and SIADH and have suggested a term ‘hyponatremia natriuretic syndrome’ or ‘cerebral wanting syndrome’. However, using the simple bedside criteria stated above, the authors of the present article feel comfortable in differentiation CSW and SIADH.

**Management of hyponatremia in TBM**

**Asymptomatic hyponatremia**

In a patient with asymptomatic hyponatremia with volume contraction, ADH level is increased as a compensatory response. Normal saline should be administered to restore intravascular volume and free water should be avoided. As the intravascular volume is normalized, the stimulus for ADH release is eliminated and excess water is excreted leading to correction of hyponatremia. In CSW, polyuria continues and fluid has to be administered as long as hyponatremia persists. In patients with SIADH, fluid restriction may be sufficient.

**Symptomatic hyponatremia**

In mild to moderate hyponatremia, normal saline may be started. Hypertonic saline (3%) through a central venous catheter is indicated in case of severe hyponatremia with coma or convulsion. Once the emergency situation is tided over, normal saline in a dose of 50 ml/kg/h may be sufficient to correct hypovolemia. Alternately oral salt 5–12 g/d may be given as salt capsules or through a nasogastric tube. In addition, 1.5% saline may also be administered intravenously. One should be cautious to avoid rapid correction of serum sodium more than 12 mEq/L/24 hours or 19 mEq/L/48 hours. In the first two hours, correction should not exceed 1–2mEq/L/hour.
Fludrocortisone (FC)
There is inhibition of renin angiotensin-aldosterone system in CSW; therefore, FC has been used in patients who are refractory to saline and oral salt treatment. There are however very few studies evaluating the role of FC in CSW. In a randomized controlled trial in SIADH, FC resulted in restoration of sodium balance and reduction in delayed stroke. In TBM, the role of FC in CSW was initially based on an isolated case report or short series. In a recent randomized controlled trial of patients with TBM-associated CSW, 18 patients each were randomized to oral FC (0.4–1 mg daily) and no FC groups. In addition, both the groups received normal saline and oral salt (5–12 g/d). Serum sodium level was normalized earlier in the FC group compared to the no-FC group (4 vs 15 d; \( P = 0.04 \)). Hospital mortality and 3 and 6 month disability did not differ, but there were fewer infarctions in internal border zone in the FC group (6% vs 33%; \( P = 0.04 \)). FC was associated with severe hypokalemia and hypertension in two patients each and pulmonary edema in one patient. In two patients, FC had to be withdrawn because of adverse events. This study concluded that FC results in earlier normalization of serum sodium and fewer infarctions in deep white matter in patients with TBM-related CSW. Polyuria however was not influenced by FC.

V2 receptor antagonists
Arginine vasopressin peptide receptor antagonist intravenous conivaptan and oral tolvaptan are useful for the management of hyponatremia in SIADH. The V2 receptor antagonists bind to V2 receptors in the collecting tubule of the kidney and prevent binding of ADH. This results in excretion of water (aquaresis) leading to increased urinary output and decreased urinary tonicity. Both conivaptan and tolvaptan have been studied in patients with SIADH and are both effective in increasing serum sodium. The dose of tolvaptan is 15, 30, or 60 mg depending on serum sodium level. Side effects of tolvaptan include dryness of mouth, increased thirst, constipation and polyuria. Conivaptan is administered as 20 mg IV over 30 min followed by continuous infusion of 20–40 mg up to 96 hours. Adverse reactions of conivaptan are local reaction, edema, hypokalemia, increased urinary output and increased thirst. Vasopressin antagonists are contraindicated in CSW.

Conclusion
Hyponatremia is common in TBM and occurs most frequently due to CSW. Volume contraction associated with CSW may contribute to border zone infarction. Fludrocortisone treatment may normalize serum sodium earlier than those on saline and salt treatment only, but polyuria persists. Further studies are needed to develop strategies to manage volume contraction in CSW.

Data availability
No data are associated with this article.

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References


