



REVIEW

UPDATE **Mechanism, spectrum, consequences and management of hyponatremia in tuberculous meningitis [version 2; peer review: 2 approved]**

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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 (130-134mEq/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 euvolemia 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.

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report



report

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Tuberculous meningitis, hyponatremia, cerebral salt wasting, stroke, SIDH, natriuretic peptide



This article is included in the [Tuberculous Meningitis International Research Consortium](#) collection.

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UPDATE Amendment from Version 1

This updated paper differs from the previous version as it highlights the importance of volume status and its role in differentiating SIADH and CSW, and management of Hyponatremia. Hyponatremia is a disorder of water balance. The categorization of Hyponatremia is based on volume status, although the clinical assessment of volume is not foolproof. For differentiating SIADH and CSW saline infusion and furosemide test have been used but these have not been validated and are not considered safe.

In TBM, there is limited information on the management of Hyponatremia hence there is a need to generate more information. The management of hyponatremia in TBM is based on the current guidelines on the treatment of hyponatremia. In patients with moderate to severe Hyponatremia, delay in treatment may lead to brain edema and very rapid correction may lead to central pontine myelinolysis. In a patient with moderate to severe hyponatremia one starts with 150 ml 3% saline iv in 20 min and check serum sodium; and if low, 3% saline bolus is repeated. Lack of improvement after rising of serum sodium by 5 mEq/L should lead to the further investigation including imaging. In the first 24 h, the safe limit of rising of serum sodium 10 mEq/L and 18 mEq/L in 48 h. It is important to manage the patients with Hyponatremia where a facility for repeated monitoring of serum sodium is available. However, if frequent serum sodium monitoring is not possible, after initial treatment with 3% saline and clinical improvement, one may treat with normal saline and sodium chloride 5–12 g in capsule or through a nasogastric tube. The role and limitation of vaptans in the treatment of hyponatremia have been discussed.

Any further responses from the reviewers can be found at the end of the article

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 units¹. Hyponatremia is a disorder of water balance. The severity of hyponatremia has been categorized as mild (130–134 mEq/L), moderate (120–129 mEq/L) and severe (<120 mEq/L)², and serum sodium <125 mEq/L is regarded as an independent

predictor of mortality, especially in critically ill patients³. In a review of hospitalized patients with hyponatremia, mortality increases by 1.5–60 times in the patients with hyponatremia compared to controls³. 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 secretion of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW). 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 trigger⁴. ADH binds to ADH receptors in the kidney tubules, and results in re-absorption of water without re-absorbing sodium. An increase in 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](#). 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:

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

The main causes of hyponatremia are set out in [Table 1](#). There are two important causes of hyponatremia in neurological conditions: SIADH and CSW.

Table 1. Causes of hyponatremia based on volume status.

Normovolemic	Hypovolemic	Hypervolemic
Endocrinal	Diabetes, corticosteroid withdrawal	Heart failure
Hypothyroidism	Sweating, burn	Chronic renal failure
Adrenal insufficiency	Ketone, urea	Cirrhosis of liver
Hypertonic fluid administration	Iatrogenic (hypotonic fluid)	Iatrogenic (hypertonic solution)
SIADH	CSW	SIADH

SIADH = syndrome of inappropriate antidiuretic hormone; **CSW** = cerebral salt wasting.

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 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 dendroaspis natriuretic peptide (DNP) may be responsible for CSW, although BNP is regarded as the most important cause of CSW⁴. 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^{5,6}. 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 response may be responsible for CSW; association of CSW with neuroleptic malignant syndrome suggests the role of the sympathoadrenal system and natriuretic peptides⁷. A direct relationship between ANP and BNP with intracerebral pressure (ICP) has been reported⁴. 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 SIADH⁸. 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 decreased⁹. 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 CSW¹⁰. 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^{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 reabsorption¹³.

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 level^{14,15}. 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-ponine 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^{20–22}. 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%).

Table 2. Studies reporting hyponatremia in tuberculous meningitis patients.

Authors, year	Patients, n	Patients with hyponatremia, n (%)	Cause of hyponatremia, n (%)	Comments
²¹ Lee <i>et al.</i> , 2018	TBM: 47; VM: 51	TBM: 37 (78.7); VM: 14 (27.5)		
²² Inamdar <i>et al.</i> , 2016	75	29 (38.7)	CSW: 10; MISC: 19	No patients with SIADH
²⁰ Misra <i>et al.</i> , 2016	76	34 (44.7)	CSW: 17; SIADH: 3; MISC: 14	No relationship reported to outcome
²³ Anderson <i>et al.</i> , 2010	104	51 (49)		
²⁴ Smith <i>et al.</i> , 2000	20	12 (60)		
¹⁸ Singh <i>et al.</i> , 1994	20	13 (65)	SIADH: 13	No effect on outcome after 72 hours
²⁵ Narotam <i>et al.</i> , 1994	24	15 (62.5)		Negative correlation between serum sodium with ANP and no correlation between plasma ADH and plasma sodium
²⁶ Shian <i>et al.</i> , 1993	16	11 (70)		
²⁷ Davis <i>et al.</i> , 1993	54	43 (79)		
²⁸ Karandanis <i>et al.</i> , 1976	11	8 (73)		
²⁹ Busmann <i>et al.</i> , 2001	195	20 (10.3)	SIADH: 7; CSW: 9	Hyponatremia attributable to CSW is at least as frequent in children as SIADH.
Total	642	276 (43)		
A summary of studies that had more than 20 patients and clearly defined CSW and SIADH criteria				
²² Inamdar <i>et al.</i> : 2016	75	29		
²⁰ Misra <i>et al.</i> : 2016	78	34	CSW: 17; SIADH: 3	
¹⁸ Singh <i>et al.</i> : 1994	20	6	CSW: 0; SIADH: 16	
²⁹ Busmann <i>et al.</i> : 2001	195	20	CSW: 9; SIADH: 7	
Total	366	99 (27.1)	CSW: 36 (36.4); SIADH: 26 (26.3)	

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

Relationship between hyponatremia and TBM-related stroke

Hyponatremia is reported in 40% of stroke patients³⁰ and up to 50% of TBM patients may have stroke³¹. 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: at the 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 radiata: 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 exudates^{31,32}.

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

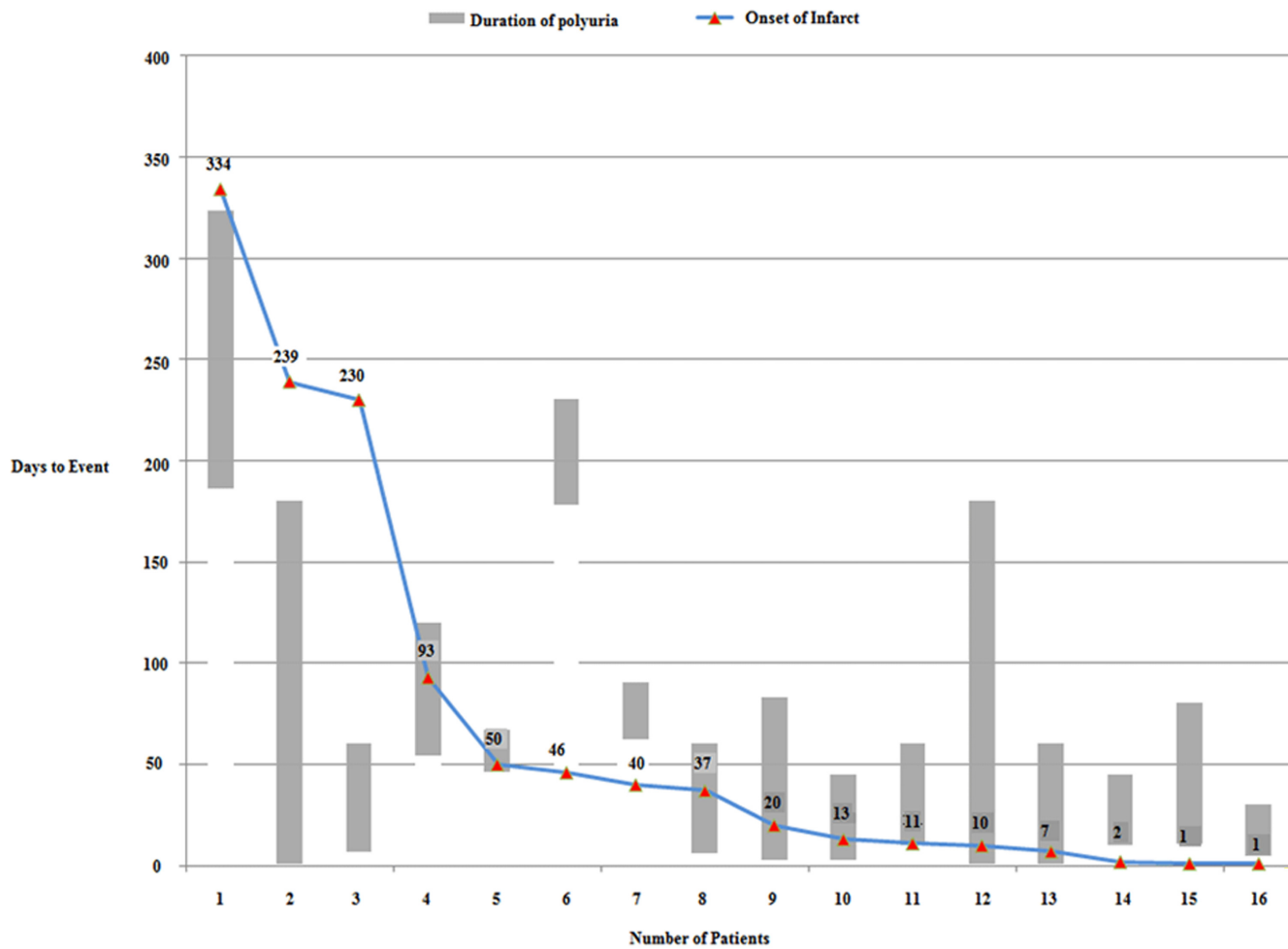


Figure 1. Duration of polyuria and onset of stroke in tuberculous meningitis patients with cerebral salt wasting (CSW). The vertical grey bars denote the onset (lower limit) and subsidence (upper limit) of polyuria in each patient. The red triangles denote the day of stroke after admission. A total of 10 out of 16 patients developed stroke during CSW (high urinary output). (Reproduced from Misra UK, Kalita J, Kumar M, *et al.*: Hypovolemia due to cerebral salt wasting may contribute to stroke in tuberculous meningitis. *QJM*. 2018; 111(7): 455–60. with permission).

(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 in TBM (Figure 1). In a previous study, internal border zone necrosis was reported in 50% children with TBM³³. 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 mmHg³⁴. 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 changes³⁵.

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^{36,37}. The definite diagnosis of the cause of hyponatremia may take some time, but empiric therapy may be started assuming

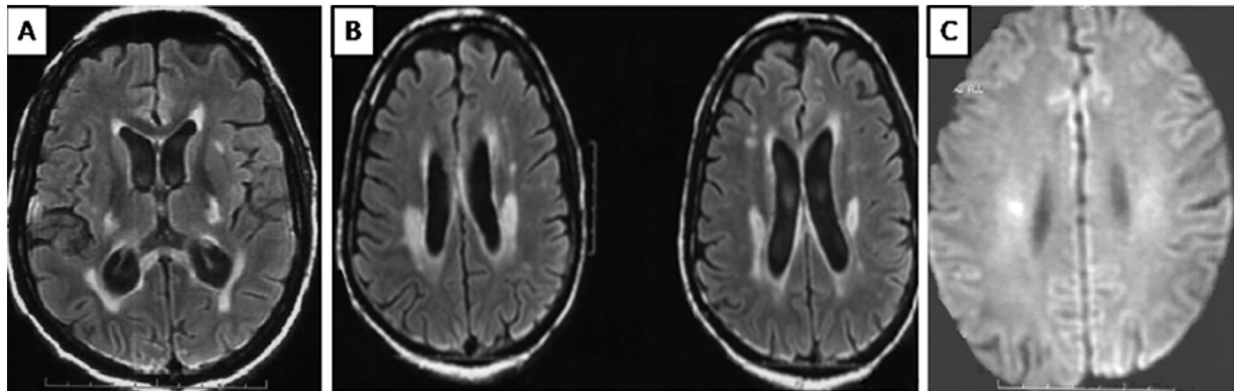


Figure 2. Cranial T2 FLAIR MRI axial sections in a 45- year-old male, stage III tuberculous meningitis (TBM) with type 2 diabetes mellitus and hypertension, and a 15-year-old male, stage III TBM patient. (A and B) Infarcts are shown in the (A) ischemic and (B) peri ventricular region bilaterally (internal border zone) of the 45- year-old male. Cerebral salt wasting (CSW) was diagnosed on Day 40. The patient developed infarctions on Day 68 of admission. Hyponatremia was corrected after 12 days and urinary output normalized after 3 months. (C) 15-year-old male showing asymptomatic infarct in right peri-ventricular white matter (internal border zone) with CSW diagnosed at admission (Day 1). (Reproduced from Misra UK, Kalita J, Kumar M, *et al.*: Hypovolemia due to cerebral salt wasting may contribute to stroke in tuberculous meningitis. *QJM*. 2018; 111(7): 455–60; with permission)³⁸.

Table 3. Differentiating features between CSW and SIADH.

Parameter	CSW	SIADH
Extracellular volume	↓	↑
Body weight	↓	↑
Fluid balance	Negative	Positive
Tachycardia	+	-
Hypotension	+	-
Hematocrit/Blood urea nitrogen/Albumin	↑	Normal
Central venous pressure	↓	Normal or slightly high

CSW = cerebral salt wasting; SIADH = syndrome of inappropriate antidiuretic hormone.

CSW is more common and fluid restriction may be hazardous in CSW, especially in bacterial meningitis^{39–42}.

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.
2. Persistently 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 on 2 consecutive occasions

Diagnosis of SIADH is based on the following criteria⁴³:

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)

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 SIADH⁴⁴
- *Saline infusion test*: Hyponatremia is aggravated after infusion of 100 ml of normal saline in SIADH

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 extra cellular volume in CSW, which is normal or increased in SIADH.

In SIADH, hyponatremia is aggravated by infusing 100 mL of normal saline, whereas it leads to normalization of serum sodium in CSW. Similarly, 20 mg of furosemide may normalize serum sodium in SIADH but not in CSW⁵. However, the safety or reproducibility of these tests has not been validated. Hence, we have not used saline infusion test⁴⁴. Serum uric acid is likely to be low in SIADH and normal or high in CSW. This relationship has, however, not been well studied. In a study, serum uric acid was unexpectedly low in CSW³. Hyponatremia and high urate excretion might be a common feature of intracranial disease in general⁴⁵.

Some authors do not differentiate between CSW and SIADH and have suggested a term 'hyponatremia natriuretic syndrome'²⁵ or 'cerebral wanting syndrome'⁴⁶. However, using the simple bedside criteria stated above, the authors of the present article feel comfortable in differentiating CSW from 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

Management of hyponatremia: In TBM, there is limited information about the management hyponatremia. There is need to generate more information to rationalize the management of hyponatremia in TBM. However, the management of hyponatremia in TBM is based on the available evidences in other conditions. Urgent treatment of hyponatremia may be life-saving, although sometimes a proper assessment of the patient may not be possible because of shock, sedation or mechanical ventilation in severe meningitis. Mild hyponatremia may corrected by addition of 10–12gm salt/day. In severe or moderately severe hyponatremia, the risk of brain edema may outweigh that of osmotic demyelination. Urgent treatment of hyponatremia is needed in patients with severe clinical manifestations such as coma, convulsions, vomiting, cardiorespiratory distress, or deep somnolence. Treatment is initiated with 3% saline at a rate of 0.5–2ml/kg/hour till symptoms resolve; but resolution of symptoms may nor occur in TBM. The rate of sodium correction should not exceed by 10 mEq/L in first 24 hours, and 8 mEq/L in the next 24 hours (Braun *et al.*, 2015; Sterns *et al.*, 2009^{46,47}. As per European Guideline, 150ml of 3% saline is administered in 20 min and serum sodium is checked every 20min. 3% saline should be repeated till target rise of serum sodium of 5mEq/L is achieved⁴⁸. Frequent monitoring of serum sodium is required to avoid rapid correction and central pontine myelinolysis (CPM). If there is no symptomatic improvement after raising serum sodium by 5 mEq/L during first hour, other causes should be checked including imaging⁴⁸. The management of hyponatremia is presented in [Figure 3](#).

In resource poor setting or if the facilities for frequent serum sodium are not available, one may start with 3% saline, following clinical improvement normal saline and oral salt (10–12 g/day) as salt capsule or through nasogastric tube may be administered. Serum sodium may be monitored as frequently as possible based on above mentioned guidelines.

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 stroke⁴⁹. In TBM, the role of FC in CSW was initially based on an isolated case report or short series^{50–53}. 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 (5–12g/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

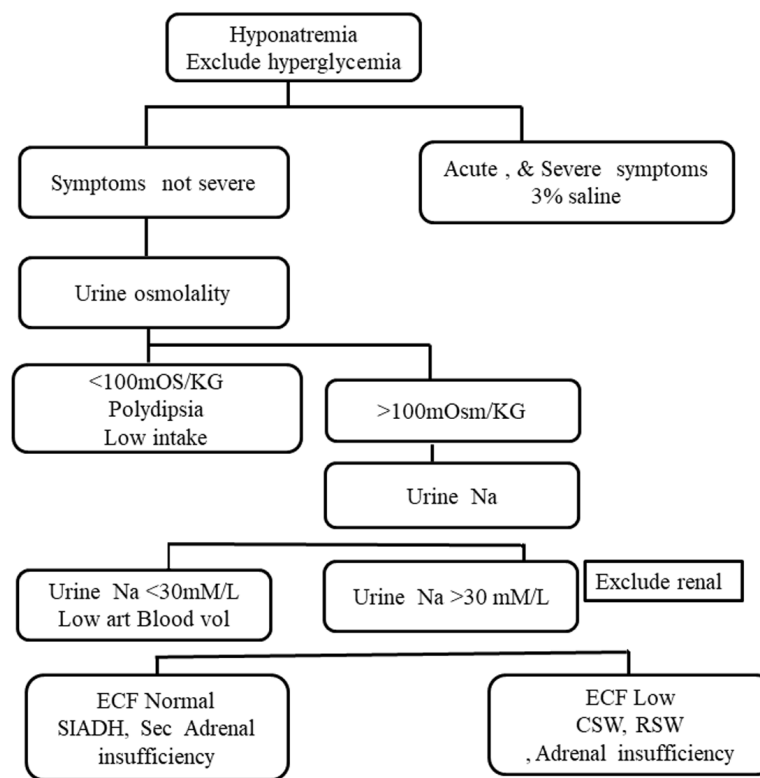


Figure 3. Schematic diagram shows management of hyponatremia. art= arterial.

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 FC⁵⁴.

V2 receptor antagonists

Arginine vasopressin peptide receptor antagonist- intravenous conivaptan and oral tolvaptan have been used in 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^{55–57} 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 polyuria⁵⁵. Conivaptan is administered as 20mg IV over 30 min followed by continuous infusion of 20–40mg up to 96 hours. Adverse reactions of conivaptan are local reaction, edema, hypokalemia, increased urinary output and increased thirst⁵⁵. A review of 20 trials including 2900 patients comparing vasopressin receptor antagonist versus placebo in mild to moderate hyponatremia did not reduce mortality, RR 1.08 (95% CI 0.08–1.46). A subgroup analysis revealed that there was insignificantly increased risk of death in the patients with hypervolemia⁵⁸. Updated analysis of trials after that by Resen Zvi revealed that vasopressin receptor antagonists resulted in

increased serum sodium at 3–7 days and 7 months. There was no difference in adverse events but the risk of rapid rise in serum sodium was 60% higher in VRA group compared to placebo (RR 1.61, 85% CI 1.11 - 2.33) and were consistent in various VRAs (tolvaptan, conivaptan, lixivaptan, and satavaptan) though no patient developed CPM. Subsequently, there are reports of CPM leading to neurological sequelae in patients receiving tolvaptan⁵⁹, leading to drug safety communication by FDA⁶⁰. There are also concerns about high alanine aminotransferase (4.4% vs 1%)⁶¹. 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.

Acknowledgements

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Tuberculosis Meningitis Consortium

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Reviewer Report 20 July 2020

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Ghulamullah Lail 

Department of Medicine and Allied, Jinnah Medical and Dental College, Karachi, Pakistan

Dr Misra and Dr Kalita excellently reviewed a relatively common topic: "Hyponatremia in tuberculous meningitis (TBM)". This review is clear and concise takes in consideration broader viewers almost everyone graduate, postgraduates fellows and seniors may be benefited. Hyponatremia is commonly encountered in our daily clinical practice. Authors have summarized here the basics including pathogenesis, clinical features diagnosis and treatment. Possible reasons of hyponatremia in TBM discussed here with much focus on cerebral salt wasting (CSW) and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Early recognition and prompt response improve outcomes in such situation.

Authors are knowledgeable and given precise review. I have gone through previous peer review report, valuable comments given from Parveen Kumar Sharma, previous peer review has not changed my decision making. Here are few humble suggestion from my side.

Abstract:

"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." These sentences gives reader a thought that in TBM patients SIADH must be managed by vaptans. (First sentence emphasizes if fluid restriction doesn't benefit vaptans may be given, in next sentence recommends avoid fluid restriction in TBM) so a brief overview of the vaptans better be included in abstract. (Spasovski, Eur J Endocrinology 2014¹). Table 2: Shows two totals 642 and 366 reason for two totals is not explained in foot notes of table. Diagnostic criteria for SIADH may be adjusted as more than 30mmol/l (J AmSocNephrol 28: 1340-1349, 2017²) higher urate clearance observed during hyponatremia related to SIADH(CJASN July 2008, 3 (4) 1175-1184³)

No reference given for saline infusion test.

"the authors of the present article feel comfortable in differentiation CSW and SIADH." Better if this sentence is supported by scientific evidence like sensitivity and specificity considering authors

used these simple bedside tests.

Management of hyponatremia in TBM

In asymptomatic patients with SIADH Fluid restriction may be sufficient. While in abstract it is "Fluid restriction in SIADH has not been found to be beneficial in TBM and should be avoided". Symptomatic patients; Hypertonic saline infusion rate not explained. Hypertonic saline (2mL/kg) indicated. (Spasovski, Eur J Endocrinology 2014¹).

I hope these small comments will be helpful for the review paper.

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Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 Feb 2021

USHA KANT MISRA, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Dear Sir,

The above-mentioned changes have been included in the revised version and resubmitted for publication in your esteemed journal.

Ghulamullah Lail

1. Fluid restriction and Vaptans in SIADH in TBM.

Answer: In our experience CSW is much more common than SIADH. In view of hazards of fluid restriction in meningitis, we feel that the patients should be treated with hypertonic saline during emergency which may be followed by normal saline and salt. If one is very sure of the diagnosis, vaptans may be used but in our experience it is not common. We have included discussion on vaptans in the paper.

1. Diagnostic criteria for SIADH may be adjusted as more than 30mmol/l (J AmSocNephrol 28: 1340–1349, 2017) higher urate clearance observed during hyponatremia related to SIADH (CJASN July2008, 3 (4) 1175-1184)

Answer: We have kept the diagnosis of CSW and SIADH based on simple bedside criteria avoiding lab estimations which may not be widely available. We agree that the utility of our criteria need to be confirmed by other investigators.

1. No reference given for saline infusion test.

Answer: In SIADH, hyponatremia is aggravated by infusing 100 mL of normal saline, whereas it leads to normalization of serum sodium in CSW. Similarly, 20 mg of furosemide may normalize serum sodium in SIADH but not in CSW. However, the safety or reproducibility of these tests has not been validated. Hence, we have not used saline infusion test (Casulari et al 2004)

Competing Interests: None

Reviewer Report 24 February 2020

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Praveen Kumar Sharma 

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This article gives concise and very informative coverage of all aspects of hyponatremia, a commonly encountered problem in patients of tuberculous meningitis. Dr. Misra et al. provided some basics pertaining to hyponatremia followed by its pathophysiology in terms of any underlying cause and clinical features along with the importance of its early recognition and timely treatment to avoid the poor outcome. Subsequently, authors have summarized knowledge about hyponatremia associated with TBM which included a brief review of previous studies, its relationship with stroke, an approach to diagnosing the cause of hyponatremia and treatment. This article also tells about the importance of differentiating CSW from SIADH to avoid incorrect and at times potentially deleterious treatment.

Overall, this article is clearly written, concise, crisp and gives valuable knowledge for practitioners to apply in the management of the patients of TBM to improve outcomes as well as for researchers to find new avenues. I have the following small comments to consider.

1. Hypovolemia is a cardinal feature of CSW, and it acts as a stimulus for ADH secretion too. So, there is a theoretical possibility as well as studies also to support that sometimes they both coexist in the same patient wherein the cause is labelled as mixed. Possibly, miscellaneous causes of hyponatremia in a few previous studies as summarized here might have included mixed cases too^{1,2}. I suggest little elaboration of the mixed cause and strategy of its management should have been included as well.
2. Exclusion of endocrine dysfunction is important for the diagnosis of both CSW and SIADH. Here I wish to add since endocrine dysfunction is not uncommon in TBM and can be central in origin, Hypercortisolism and Hypothyroidism which can cause hypo-osmolar hyponatremia, should have been stressed upon for the exclusion with appropriate tests³.
3. I suggest including fractional excretion of Urate as lab support for the diagnosis of SIADH since the criteria given here for its diagnosis are fine in a clearly hypervolemic patient but become confusing in euvolemic mildly hypervolemic cases⁴.

At the last, I must say that Dr. Misra et al. have given a very clear view of a complicated but frequently encountered problem in clinical practice particularly in tropical countries like India. This is going to be of immense value to the practitioners and food for thought to researchers.

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Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: I have been a student of both the authors in the past and know them but this has not affected my ability to provide an unbiased review

Reviewer Expertise: Epilepsy, Stroke & Neuro-infections

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 Feb 2021

USHA KANT MISRA, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Dear Sir,

The above-mentioned changes have been included in the revised version and resubmitted for publication in your esteemed journal.

1. elaboration of the mixed cause and strategy of its management should have been included as well.

Answer: The miscellaneous causes refer to other causes of hyponatremia and our comments are targeted to clearly defined cases. Using our criteria we feel that a clear diagnosis is possible. However some authors have emphasized that it is difficult to differentiate these conditions clearly and they suggest the term salt wanting syndrome and treat it with saline when in doubt.

1. Exclusion of endocrine dysfunction is important for the diagnosis of both CSW and SIADH. Here I wish to add since endocrine dysfunction is not uncommon in TBM and can be central in origin, Hypercortisolism and Hypothyroidism which can cause hypo-osmolar hyponatremia, should have been stressed upon for the exclusion with appropriate tests .

Answer: We agree that endocrinal disorders should be excluded before diagnosis of CSW and SIADH. If present these have to be managed as usual.

1. Suggest including fractional excretion of Urate as lab support for the diagnosis of SIADH since the criteria given here for its diagnosis are fine in a clearly hypervolemic patient but become confusing in euvolemic mildly hypervolemic cases

Answer: Serum uric acid is likely to be low in SIADH and normal or high in CSW. This relationship has, however, not been well studied. In a study, serum uric acid was unexpectedly low in CSW.3 Hyponatremia and high urate excretion might be a common feature of intracranial disease in general (Maesaka et al 1998)

Competing Interests: None

Comments on this article

Version 1

Author Response 11 Feb 2021

USHA KANT MISRA, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

Dear Sir,

The above-mentioned changes have been included in the revised version and resubmitted for publication in your esteemed journal.

1. also includes vomiting, cardiorespiratory distress and abnormal and deep somnolence. Treatment does not necessarily involve a central venous catheter. Subsequent management should depend on the diagnosis. For diagnosis, a clear algorithm is provided in Hoorn & Zietse (J Am Soc Nephrol 2017) or the afore mentioned guideline (figure 6).

Answer: The indications for treatment with 3% saline have been included as per European Guideline. And an algorithm for treatment of hyponatremia has been included.

1. Close monitoring, should prevent too rapid changes. The suggested upper limit of 2 mEq/L in the first 24 h in the paper is on the high side. For example the aforementioned guideline suggests 8-10 mmol/L in the first 24h (Spasovski, Eur J Endocrinology)

Answer: Repeated monitoring may prevent overcorrection of hyponatremia but is sometime overlooked resulting in severe complications of osmotic demyelination; hence we recommend slower correction after initial urgent tidng over the crisis, and have included the limit to 10mmol /L rather than 12.

1. It would be good to show more clearly that there the distinction between SIADH and CSW is hard to make. In my opinion the tone of the paper is now overconfident when it comes to this distinction: criterium 1, 2, 3 and 4. In the provided definition for SIADH are necessarily also fulfilled in CSW.

Answer: The basic difference between CSW and SIADH is the assessment of volume status by history, examination and investigations. However in certain situations, it may be difficult and has been mentioned.

1. Although tolvaptan and conivaptan are effective in increasing serum sodium levels, their use is discouraged in the European guidelines because of the risk of overcorrection (Spasovski, Eur J Endocrinology 2014). It would be good to acknowledge this

Answer: The comments about tolvaptan have been modified adding additional references

1. In general, the paper would benefit by starting off from the fact that we do not know most of diagnosis and management of the causes of hyponatremia in tuberculous meningitis, and by including a section on data that the field should try to obtain to improve that knowledge. For the management of hyponatremia per se, it would be good to mostly refer to international guideline (including management of symptomatic hyponatraemia, see above). The level of evidence in treating hyponatremia leaves room for improvement. It would therefore be nice if the management section was concluded by a paragraph that explicitly represents the author's opinion on how in their elaborate expertise hyponatremia in tuberculous meningitis

is best handled (i.e. the sentences starting with 'Normal saline ... may be sufficient', would make part of it.

Answer:: Management of hyponatremia has been modified keeping the European Guidelines and a comment about our policy of management added as per suggestion

1. Removing duplication with Introduction: the classification based on sodium levels

move to move to Introduction: pathophysiology (ADH, ANP, BNP production)

Answer: Shifted to introduction

1. The sentence "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." Should perhaps be omitted (see above)

Answer: Modified

1. The introduction should stress that hyponatremia is primarily a water dis-balance disorder

Answer: Hyponatremia is primarily a disorder of water balance.

1. "especially in critically ill patients; mortality increases by 1.5–60 times in the patients with hyponatremia". Does the part of the sentence behind the semi-colon refer to patients with sodium <125 mEq/L? And specifically, to critically ill patients? Perhaps reformulate

Answer: Corrected

Perhaps clarify that the serum osmolality is actually measured, rather than calculated.

1. Perhaps clarify that the serum osmolality is actually measured, rather than calculated.

Answer: Serum osmolality should be measured rather than calculated.

1. It would help to order the columns into 'Normovolemic', 'Hypovolemic' and 'Hypervolemic'. More importantly, it is now acknowledged that the distinction between these causes cannot be reliably made based on physical examination. See for example Spasovski, Eur J Endocrinology 2014.

Answer: The limitation of assessing volume status is acknowledged especially in early cases

1. Table 2: How is hyponatremia defined here? Why are two totals (642 and 366) given? Page

Answer: Table 2 has been modified providing the details about the studies. The lower section includes the studies of more than 20 patients and defined CSW and SIADH

1. Figure 1:

The figure looks rather pixelated. Suggest replacing by a vector file if possible? Do the red triangles (rather than black small squares) denote the day of stroke after admission? X-axis label should

probably read 'Patient number' rather than 'Number of Patients'

Answer: The figure has been modified as suggested.

Competing Interests: none

Reviewer Response 04 Feb 2020

Arjan van Laarhoven, Radboud University Nijmegen Medical Centre, The Netherlands

Prof. Misra and dr. Kalita discuss the important topic of hyponatraemia in tuberculous meningitis in their paper. Hyponatraemia is a common phenomenon in the course of tuberculous meningitis, although much is unknown about the exact pathogenesis and the best management strategies. It is apparent that the authors are very knowledgeable when it comes to the body of literature on this topic, to which they contributed to a great extent.

Originally asked to review the paper, but later identified as not-eligible as a reviewer as member Tuberculous Meningitis International Research Consortium, I'll leave my comments here, and hope they are of any help. Because the paper will be used by colleagues in the field to diagnose and treat hyponatraemia in the context of tuberculous meningitis, I did suggest to the editorial board to invite a reviewer, i.e. an internist-nephrologist, who is more knowledgeable than I am on the topic of hyponatraemia itself.

I would like to make the following main recommendations:

- Align the proposed management of hyponatremia with international guidelines, for example the European guideline (Spasovski, Eur J Endocrinology 2014), in which the most important first decision is to decide whether the hyponatremia is considered symptomatic with severe symptoms, and then to treat with 3% hypertonic saline (2mL/kg) indicated. Of note, these symptoms, apart from the suggested coma and seizures, also includes vomiting, cardiorespiratory distress and abnormal and deep somnolence. Treatment does not necessarily involve a central venous catheter. Subsequent management should depend on the diagnosis. For diagnosis, a clear algorithm is provided in Hoorn & Zietse (J Am Soc Nephrol 2017) or the afore mentioned guideline (figure 6).
- Next, because theory and practice are often far apart, the key to hyponatremia management in my view is close patient monitoring. Close monitoring, should prevent too rapid changes. The suggested upper limit of 12 mEq/L in the first 24 h in the paper is on the high side. For example the afore mentioned guideline suggests 8-10 mmol/L in the first 24h (Spasovski, Eur J Endocrinology 2014). I would suggest to avoid mentioning specific volumes or infusion speeds. Certainly, the mentioned speed of infusion of 50 ml/kg/h normal saline needs revision as it could lead to dangerous situations.
- It would be good to show more clearly that there the distinction between SIADH and CSW is hard to make. In my opinion the tone of the paper is now overconfident when it comes to this distinction: criterium 1., 2., 3. and 4. in the provided definition for SIADH are necessarily also fulfilled in CSW.
- Although tolvaptan and conivaptan are effective in increasing serum sodium levels, their use

is discouraged in the European guidelines because of the risk of overcorrection (Spasovski, Eur J Endocrinology 2014). It would be good to acknowledge this.

- In general, the paper would benefit by starting off from the fact that we do not know most of diagnosis and management of the causes of hyponatremia in tuberculous meningitis, and by including a section on data that the field should try to obtain to improve that knowledge. For the management of hyponatremia per se, it would be good to mostly refer to international guidelines (including management of symptomatic hyponatraemia, see above). The level of evidence in treating hyponatremia leaves room for improvement. It would therefore be nice if the management section was concluded by a paragraph that explicitly represents the author's opinion on how in their elaborate expertise hyponatremia in tuberculous meningitis is best handled (i.e. the sentences starting with 'Normal saline ... may be sufficient', would make part of it.

Some small further recommendations:

Abstract: the abstract could win by being more concise. Consider:

- removing duplication with Introduction: the classification based on sodium levels
- move to Introduction: pathophysiology (ADH, ANP, BNP production)
- the sentence "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." Should perhaps be omitted (see above)

Introduction:

- the introduction should stress that hyponatremia is primarily a water disbalance disorder.
- "especially in critically ill patients; mortality increases by 1.5–60 times in the patients with hyponatremia". Does the part of the sentence behind the semi-colon refer to patients with sodium <125 mEq/L? And specifically, to critically ill patients? Perhaps reformulate.

Pathophysiology of hyponatremia

- Perhaps clarify that the serum osmolality is actually measured, rather than calculated.

Table 1:

- It would help to order the columns into 'Normovolemic', 'Hypovolemic' and 'Hypervolemic'. More importantly, it is now acknowledged that the distinction between these causes cannot be reliably made based on physical examination. See for example Spasovski, Eur J Endocrinology 2014.
- How does infusion of hypertonic solution lead to hypervolemic hyponatremia?

Table 2:

- How is hyponatremia defined here?

- Why are two totals (642 and 366) given?

Figure 1:

- The figure looks rather pixelated. Suggest to replace by a vector file if possible?
- Do the red triangles (rather than black small squares) denote the day of stroke after admission?
- X-axis label should probably read 'Patient number' rather than 'Number of Patients'.

Please see these as suggestions to further improve this paper on an important topic, very much relevant to clinical practice in tuberculous meningitis.

Nijmegen, February 8th 2020

Yours sincerely,

Arjan van Laarhoven

Competing Interests: no competing interest