Deciphering Familiar Conundrum of Cerebral Salt Wasting Syndrome vs Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Establishing Role of Hyponatremia in Patients of Tuberculous Meningitis as a Predictor of Outcome.

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Date of submission: 2nd March 2024 Date of Acceptance: 19th July 2024 Date of publication: 15th August 2024

Abstract

Introduction: Hyponatremia is one of the most common electrolyte abnormalities [35-71%] associated with tuberculous meningitis [TBM]. It is an independent predictor of patient outcome . Cerebral salt wasting syndrome[CSWS] and syndrome of inappropriate secretion of antidiuretic hormones [SIADH] are two common causes of hyponatremia in patients with TBM. This study targets patients with tuberculous meningitis to provide a detailed analysis of hyponatremia in TBM patients and it's predictive value in terms of outcome and also describes the distinguishing features of CSWS and SIADH

Materials and Methods: This was a clinical, prospective study of 31 patients with TBM in which various parameters were analysed. Serial sodium levels were recorded on the day of admission ,day 2, 7 and 28. Patients with hyponatremia were divided into CSWS and SIADH

Results: In this study, 24[77.42%] patients had hyponatremia. In 14 [58%], hyponatremia was due to CSWS and in 10[42%] of the patients with hyponatremia it was SIADH . Hyponatremia was related to disease severity ,GCS score ,hospital stay ,ventilator stay and patient outcome. CSWS was more strongly associated with disease severity than SIADH.

Conclusion: Hyponatremia is a common electrolyte imbalance in patients with TBM and a direct and valid predictor of disease outcome. CSWS should be differentiated from SIADH due to the different treatment strategies.

Keywords : Hyponatremia, Tuberculous Meningitis ,Cerebral Salt Wasting Syndrome, Syndrome of Inappropriate Secretion of Antidiuretic Hormones

Introduction

Tuberculosis (TB) is one of the leading forms of infectious disease that involves several organs of the body, primarily the pulmonary system. Tuberculous meningitis (TBM) is one of the deadliest forms of extra-pulmonary TB. Hyponatremia (serum sodium values less than 135 mEq/L) is the most common electrolyte imbalance associated with TBM (35-71%%), which has a significant impact on mortality and morbidity in patients[1]. Different mechanisms have been proposed to explain hyponatremia in TBM , but cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate secretion of antidiuretic hormones (SIADH) remain the foremost causes of hyponatremia in critically ill neurological patients admitted with TBM[2]. The literature regarding the prognostic significance of hyponatremia in TBM are not well elaborated. This study provides a descriptive analysis of hyponatremia regarding it's clinical implications and the prognostic significance in patients diagnosed with TBM .This study will also discuss the differentiating features between CSWS and SIADH

Access this article online

Website: https://www.nepjol.info/index.php/NJN

DOI: https://10.3126/njn.v21i2.63411

HOW TO CITE
Kulwant Singh, Yadav V. Deciphering Familiar Conundrum of Cerebral Salt Wasting Syndrome vs Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Establishing Role of Hyponatremia in Patients of Tuberculous Meningitis as a Predictor of Outcome. NJNS. 2024;22(2):27-32

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ISSN: 1813-1948 (Print), 1813-1956 (Online)

Material & Methods

This prospective study was conducted over a period of nine months from August 2022 to April 2023. The study was conducted after getting ethical clearance from the institutional ethical committee. A total of 31 patients admitted with a diagnosis of TBM were enrolled .Criteria for the age group were 15-60 years. All patients diagnosed with TBM on the basis of clinical ,biochemical ,radiological criteria were admitted and treated accordingly.. Demographical information about all the patients were recorded. Serum sodium values were recorded at day of admission (day 1) ,day 2 ,day 7, day

28 and analysed. Serum osmolality, urine osmolality, urinary sodium were recorded on the day of admission. A serum sodium level below 135 mEq/L was considered hyponatremia.

Following patients were excluded from this study –

1)Patients with high cardiac output or cardiac failure who were put on diuretics ,antihypertensives,
2)Patients with renal failures.
3)Patients with metabolic disorders, pituitary hormone deficiencies.
4)Patients who were put on drugs to decrease intracranial pressure like mannitol , hypertonic saline etc.
5)Patients with long history of drug intake of antidepressants, antipsychotics or anticonvulsants
6)Patients with severe diarrhea

BMRC (British Medical Research Council Contemporary Clinical Criteria) grade was used to divide the TBM patients into 3 stages.

1)Stage I is defined as a Glasgow coma scale (GCS) of 15 without focal neurological signs
2)Stage II is defined as a GCS of 15 with neurological deficit or a GCS of 11–14
3)Stage III is defined as a GCS of ≤ 10

Serum sodium values on the day of admission were analysed with different variables i.e., GCS at admission, seizures ,TBM grade, hospital stay (days), ventilator stay (days), Glasgow outcome scale (GOS) at 28 days and 6 months.
Different criteria have been proposed for defining CSWS and SIADH .We divided TBM patients with hyponatremia into three groups on the basis of bedside clinical and biochemical parameters at admission:

1) Cerebral salt wasting syndrome (CSWS)
- Serum sodium level : < 135 mEq/L
- Hypovolemia(CVP <6 mm Hg)
- Polyuria (>3L urine output in 24 hrs)
- Urinary sodium >40 mEq/L
- Urinary osmolality >300mEq/L
- High serum osmolality (>300 mOsm/L)
- Decreased skin turgor
- Increased hematocrit

2)Syndrome of inappropriate secretion of Antidiuretic hormones (SIADH)
- Serum sodium level : <135 mEq/L
- Hypervolemia or Euvolemia(CVP>6 mm Hg)
- Urinary sodium >20 mEq/L
- Low serum osmolality(< 300 mOsm/L)
- High urine osmolality (>300mEq/L)

3)None: patients with normal sodium levels.
A dichotomized analysis was done between the patients categorized into CSWS and SIADH.
A control group of 20 was also taken from normal disease free population [relatives of patients with proper consent] , in which sodium values were recorded and compared with sodium values of patients with TBM in our study.

All patient took antitubercular treatment (ATT) along with tapered doses of steroids .Management of hyponatremia was done accordingly by the use of 3% saline ,fludrocortisone , vaptans.

The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

For statistical significance, a p value of less than 0.05 was considered statistically significant.
The association of the variables that were quantitative and not normally distributed in nature were analysed using the Kruskal Wallis test (for more than two groups) and the variables that were quantitative and normally distributed in nature were analysed using Independent t test (for two groups) and ANOVA (for more than two groups). A Wilcoxon signed rank test was used for comparison across follow up. The association of the variables , which were qualitative in nature, was analysed using Fisher's exact test, as at least one cell had an expected value of less than 5. Spearman rank correlation coefficient was used for the correlation of serum sodium values at admission with different variables.

Results

In this study, out of 31 patients ,74.2% (n=23) were males and 25.8% (n=8) were females. The mean age was 34.5± 11.5 (range 17-55).Most of the patients presented with headaches and vomiting (Table 1).

Table1: Presenting Complaints in patients admitted with Tuberculous meningitis

Presenting complaints	Frequency	Percentage
Headache	16	51.61%
Loss of consciousness	6	19.35%
Headache with vomiting	8	25.81%
Vomiting	1	3.23%
Total	31	100.00%

Five patients had a history of seizures. 25 out of 31 patients had symptoms lasting more than 10 days (Table 2).

Table 2: Duration of Symptoms in patients admitted with Tuberculous meningitis

Duration of symptoms(days)	Frequency	Percentage
<10	6	19.35%
10 to 30	14	45.16%
>30	11	35.48%

On BMRC grade ,13 patients were in the grade 1,12 patients were in the grade 2 and six patients were in the grade 3 at the time of admission . The mean GCS at the time of the admission (day 1) was 12.94 ± 2.74 (range 6-15). The mean GCS at day 2 of the admission was 13.39 ± 2.5 (range 8-15), at day 7 it was 13.65 ± 2.15 (range 9-15) and at day 28 it was 14 ± 2 (range 9-15) (Table 3) .

Table 3: Mean GCS in patients of Tuberculous meningitis over time span of 28 days

Glasgow Coma Scale(GCS)	Mean ± SD	Median(25th-75th percentile)	Range
Day 1 of admission	12.94 ± 2.74	14(12-15)	6-15
At day 2	13.39 ± 2.5	15(12.5-15)	8-15
At day 7	13.65 ± 2.15	15(13.5-15)	9-15
At day 28	14 ± 2	15(15-15)	9-15

The mean duration of the hospital stay was 17.45 ± 11.31 (range 10-52 days), and the ventilator stay was 3.65 ± 6.41 days (range 0-24 days).

Serum sodium values at the time of admission were measured in the cases (n=31) and the controls (n=20),there was a significant difference [p <0.0001,Indpendent t test] (Table 4).

Table 4: Comparison of serum sodium values in patients of Tuberculous meningitis with controls (normal disease free population)

Serum sodium at day 1 and TBM grade	Grade 1(n=13)	Grade 2(n=12)	Grade 3(n=6)	Total (n=31)	
Mean ± SD	134.38 ± 3.64	133.17 ± 2.98	123.17 ± 4.31	131.74 ± 5.5	<.0001
Range	129-140	129-139	118-129	118-140	
Serum sodium at day 1 and seizures	Seizures Absent (n=26)	Seizures			
Mean ± SD	133.15 ± 4.42	124.4 ± 4.88		131.74 ± 5.5	0.0004
Range	119-140	118-131		118-140	

TBM: tuberculous meningitis

Table 5: Correlation of serum sodium values at day 1 with TBM grade and seizures

77.42% (n=24) patients had hyponatremia (serum sodium values <135 mEq/L) at the time of admission. The mean urinary sodium level was 68.68 ± 47.5 mEq/L (range 23-176 mEq/L) and the mean urinary osmolality was 249.68 ± 164.22 mOsm/L (range 100-678mOsm/L) (Figure 1,2).

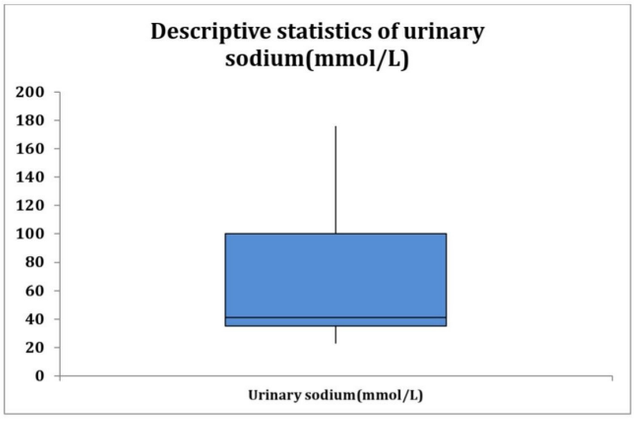

Figure 1 : Urinary sodium values at day of admission

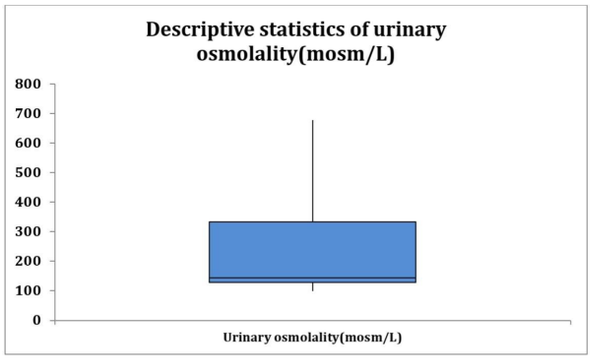

Figure 2: Urinary osmolality at day of admission

13 patients had high serum osmolality (>300 mOsm/L) and 18 patients had low serum osmolality[< 300 mOsm/L]. Mean serum sodium was in increasing trend following treatment ,mean serum sodium values gradually increased from 131.74 ± 5.5 mEq/L at day 1 of admission to 137.65 ± 5.8 mEq/L at the 28th day of admission (Figure 3).

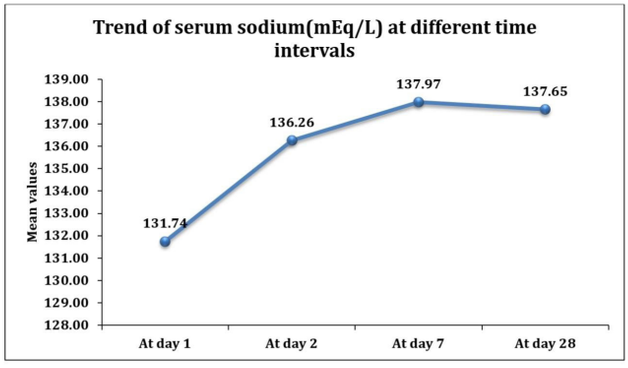

Figure 3 : Trend of serum sodium values with time

Serum sodium levels at the admission were significantly related to TBM grade (p<0.0001) and seizures (p=0.0004) (Table 5).Serum sodium levels at the admission were significantly associated with mean GCS at the admission, duration of the total hospital stay , ventilator stay and GOS at 28 days (Table 6,Figure 4,5,6,7).

Variables	Glasgow Coma Scale at admission	Duration of hospital	Duration of	Glasgow outcome scale at 28 days
Serum sodium (mEq/L) on day 1				
Correlation coefficient	0.635	-0.455	-0.484	0.557
P value	0.0002	0.011	0.006	0.001

Spearman rank correlation coefficient

Table 6: Correlation of Glasgow Coma Scale at admission, duration of hospital stay(days), duration of ventilation(days) and Glasgow outcome scale at 28 days with serum sodium (mEq/L) on day 1.

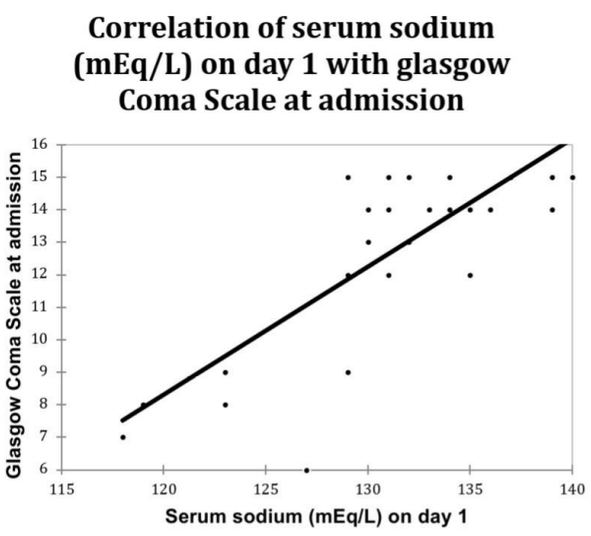

Figure 4 :Correlation of serum sodium (mEq/L) on day 1 with Glasgow Coma Scale at admission.

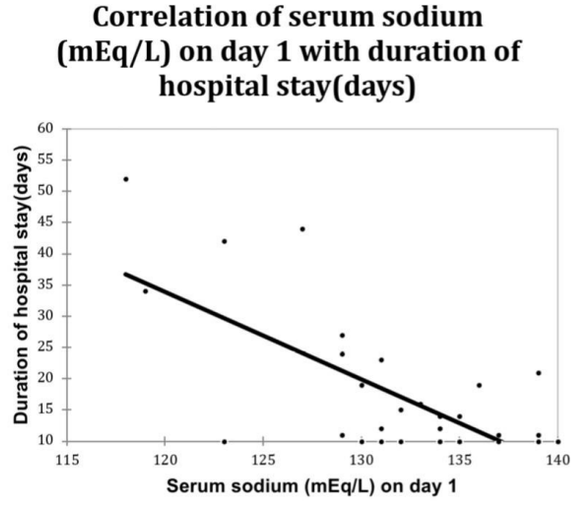

Figure 5 : Correlation of serum sodium (mEq/L) on day 1 with duration of hospital stay(days)

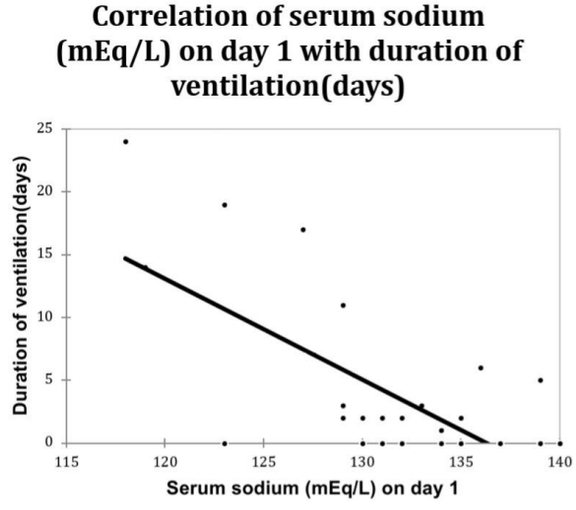

Figure 6 :Correlation of serum sodium (mEq/L) on day 1 with duration of ventilation(days).

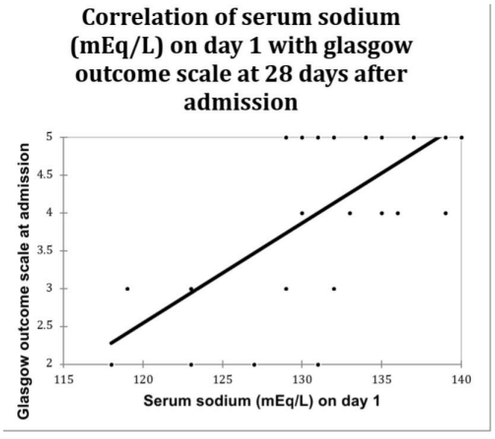

Figure 7 :Correlation of serum sodium (mEq/L) on day 1 with Glasgow outcome scale at 28 days after admission.

Serum sodium values were also significantly related to the Glasgow outcome scale at six months ($p<0.0001$). In this study ,on the basis of criteria mentioned previously , 14 patients (45.16%) were diagnosed with CSWS and 10 patients (32.26%) were diagnosed with SIADH.

Dichotomized analysis was done by dividing the patient with hyponatremia into two groups of CSWS and SIADH (Table 7).

Table 7:Comparison of parameters between CSWS and SIADH

Parameters	CSWS(n=14)	SIADH(n=10)	Total	P value
Gender				
Female	5 (35.71%)	1 (10%)	6 (25%)	0.341
Male	9 (64.29%)	9 (90%)	18 (75%)	
Duration of symptoms(days)				
<10	1 (7.14%)	2 (20%)	3 (12.50%)	0.724
10 to 30	7 (50%)	4 (40%)	11 (45.83%)	
>30	6 (42.86%)	4 (40%)	10 (41.67%)	
TBM grade				
Grade 1	2 (14.29%)	6 (60%)	8 (33.33%)	0.018
Grade 2	6 (42.86%)	4 (40%)	10 (41.67%)	
Grade 3	6 (42.86%)	0 (0%)	6 (25%)	
Age(years)				
Mean ± SD	38.57 ± 13.51	32.3 ± 6.55	35.96 ± 11.4	0.148
Range	17-55	20-44	17-55	
Serum sodium(mEq/L) on day 1				
Mean ± SD	127.93 ± 5.36	132.6 ± 1.58	129.88± 4.77	0.007
Range	118-135	131-135	118-135	
Glasgow Coma Scale at admission				
Mean ± SD	11.21 ± 3.26	14.1 ± 0.99	12.42 ± 2.92	0.007
Range	6-15	12-15	6-15	
Duration of hospital stay(days)				
Mean ± SD	22.64 ± 14.85	13.2 ± 4.1	18.71 ± 12.4	0.241
Range	10-52	10-23	10-52	
Duration of ventilation(days)				
Mean ± SD	6.86 ± 8.37	0.6 ± 1.07	4.25 ± 7.07	0.02
Range	0-24	0-3	0-24	

We found that a lower GCS score [11.21 vs 14.1,p=0.007, independent t test] ,a higher TBM stage [p<0.0.01, Fisher's exact test], a longer duration of ventilator stay [6.86 vs 0.6 days, p=0.02) and a lower serum sodium level at admission [127.93 vs 132.6 mEq/L] ,(p = 0.007) were associated with CSWS. Four patient died within six months with TBM having CSWS and none patient died with TBM having SIADH.
GOS at 28 days was not related (p=0.183) to both CSWS and SIADH but at 6 month it was lower in CSW (p<0.001) than SIADH.

Discussion

TBM is the most devastating form of TB and continues to cause high morbidity and mortality, with an estimated 50% of patients dying or suffering neurological sequelae and complications [3].Hyponatremia is one of the common electrolyte abnormality (35%-71%) encountered in TBM patients , which has a significant impact on patient outcome[1]. In this study , 77.42 % patients had hyponatremia at the time of admission. Serum sodium values can be regarded as independent predictors of mortality and morbidity[1,2,3]. Hyponatremia is directly correlated with the sensorium of the patients , as in this study, the patients with lower serum sodium values had poor GCS at admission. Hyponatremia is considered an important form of electrolyte

imbalance causing seizures[4]. Hyponatremia and alterations in the osmolality can lead to encephalopathy , characterised by depression in the neuronal activity leading to acute symptomatic seizures. Patients with lower serum sodium values had a longer hospital stay , and the ventilator period also associated with a poor long term outcome. The most common causes of hyponatremia in patients admitted with TBM is CSWS and SIADH[2,5]. Misra et al. (2021) analysed different studies and showed that 36.4% patients of hyponatremia in TBM were attributed to CSWS ; SIADH was causative factor in 26.3% patients [4]. In this study CSWS attributed to 58% (n=14) and SIADH attributed to 42% (n=10) of total patients with hyponatremia based on bedside criteria.

The pathophysiology of CSWS is debatable. Hypothalamic damage during cerebral injury in TBM leads to the release of brain natriuretic peptides (BNP) in the circulation. BNP causes inhibition of sodium resorption. Others factors includes arterial natriuretic peptide (ANP),C-type natriuretic factor (CNP) and dendroaspis natriuretic peptide (DNP), and adrenomedullin [1,5,6]. Dysregulated sympathetic activity also leads to a decrease in renin release which causes deranged renal tubular absorption[5,6,7]. It is a hypovolemic and hyponatremic state. so fluid and sodium correction is mandatory. SIADH is due to the inappropriate release of antidiuretic hormone (ADH) which leads to hyponatremia due to water retention , so fluid restriction is an integral part of management[5].
CSWS is very difficult to differentiate from SIADH ,but it should be distinguished (Figure 8)

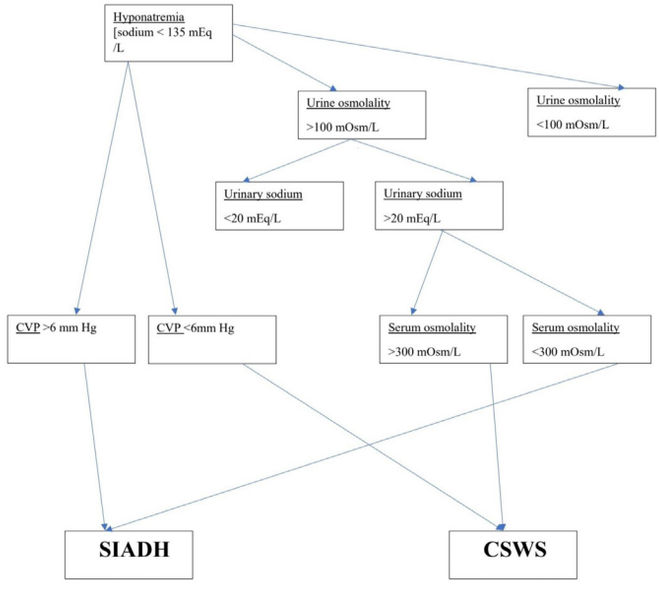

Figure 8 : Algorithm to clinically and biochemically differentiate CSWS and SIADH

because both have different treatment strategies. Although CSWS and SIADH are collectively referred to as cerebral wanting syndrome by some authors [8], CSWS is a relatively more severe entity than SIADH[1,5]. In our study , patients with CSWS had a lower GCS and a more severe grade of TBM at admission. Patients with CSWS also had the lower serum values of sodium at the time of admission than SIADH. Ventilator stay was also greater in patients with CSWS. Six month outcome was poor in patients with CSWS as four patients with CSWS died within six months although GOS at 28 days was not relatable, so we can conclude that CSWS is associated with a poor long term outcome.

Management of hyponatremia in TBM is challenging , as stated above. Start a 3% saline infusion at the rate of 1-2 mL per kg body weight per hour . Infusion rates may be doubled in comatose patients. Do not exceed the rate of correction by 8-10 mEq/L in first 24 hours[5,8,9].Rapid correction is avoided as it may lead to osmotic demyelination of pons[5].Fluid correction done in CSWS but restricted in SIADH. Fludrocortisone acetate, which acts directly on the renal tubules to increase the sodium absorption, is found to be useful in the management of CSWS[10]. Demeclocycline ,which partially antagonizes the effects of ADH on renal tubules, can be used in SIADH at the dose of 300-600 mg twice a day[11].Nonpeptide antagonists of vasopressin receptors, Vaptans , have also been used in hospitalised patients with SIADH. A loading dose of conivaptan (20 IV mg) over 30 minutes, followed by an infusion of 20 mg over 24 hours, is done for 3-4 days. Vaptans are contraindicated in CSWS[4,5].

Conclusion

Hyponatremia is one of the most common electrolyte abnormality associated with TBM. It is an independent and valid predictor of mortality and morbidity. CSWS contributes

most of the times to hyponatremia in patients with TBM. CSWS is related to the severity of TBM. The differentiation of CSWS from SIADH is of utmost importance when deciding treatment strategies.

Abbreviations

TB: Tuberculosis ,TBM: Tuberculous Meningitis ,CSWS: Cerebral Salt Wasting Syndrome, SIADH: Syndrome of Inappropriate Secretion of Antidiuretic Hormones, BMRC: British Medical Research Council, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale.

Ethics approval and consent to participate

This study was conducted after getting ethical clearance from local institutional ethical committee members. Consent for participation was obtained from each patient prior to the study.

Consent for publication

Not applicable. We confirm that all data incorporated into this study are anonymized.

Availability of data and materials

All data that support the findings of this study are available from the neurosurgery department of Institute of Medical Sciences, Banaras Hindu University. Data are however available from the author when requested with permission.

Competing Interests

The authors declare that they have no competing interests

Funding

All patients evaluated in this study were investigated and managed in the hospital for free.

Acknowledgement

Special gratitude to Dr Anurag Sahu for his immaculate guidance in preparing this article

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