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RESEARCH ARTICLE

FOCUS INTO THE CLINICO-PATHOLOGICAL PROFILE OF TUBERCULAR MENINGITIS WHILE PROBING THE DETERMINANT EFFECTS OF HYPONATREMIA IN ASSESSING THE CLINICAL SEVERITY AND OUTCOME

Dr. Kallol Bhattacharjee, *Dr. Dwijen Das, Dr. Tirthankar Roy, Dr. Giridhari Kar and Dr. Prithwiraj Bhattacharjee

Department of Medicine, Silchar Medical College, Silchar, India

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ABSTRACT

Background: Tubercular Meningitis is an important life threatening manifestation of extra pulmonary tuberculosis. It is quite common in the developing countries and can influence the socio economic status as most of the cases occur in the working age group.

Aims and Objectives:

To study:

1. The clinico-pathological profile of patients with tubercular meningitis.
2. To assess the role of hyponatremia in relation to its incidence, impact and prognosis in tubercular meningitis.

Materials and Methods: One year single centered observational study including 45 cases of tubercular meningitis in a tertiary care teaching hospital in north eastern India.

Diagnosis of tubercular meningitis was based on CSF findings as per standard protocol.

Serum sodium was estimated on presentation and repeated based on the clinical status and a value < 135 mmol/L was diagnosed as hyponatremia.

Results and Observations: A male preponderance with a mean age of 31.97 years was observed with a peak in the age group of 21 – 30 years. The average duration of symptoms was 3 weeks and fever, headache, nausea, vomiting, seizures, altered consciousness and neurological deficits mostly cranial nerve palsies are the usual presenting features. Clear to turbid fluid, elevated protein, decreased glucose, increased ADA activity, lymphocytic pleocytosis were salient features in CSF which also showed AFB in few samples and positive PCR for Mycobacterium tuberculosis DNA in a substantial number of cases.

Hyponatremia, seen in 46.6% of cases had a bearing on the clinical severity but was statistically insignificant in relation to mortality. Death was observed in 13.33% of total cases, 83.33% of which had hyponatremia.

Conclusion: The study concluded with the inference that hyponatremia may be an important prognostic indicator in relation to the severity of tubercular meningitis.

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INTRODUCTION

Tubercular meningitis (TBM) which accounts for 70-80% of cases of neurological TB is still an important public health problem in developing countries (Tandon *et al*., 1988, Green, 1836). The first description of clinical picture of tubercular meningitis is credited to Scottish physiologist Sir Robert Whytt. TBM was first described as a distinct pathological entity in 1836 (Green, 1836). TBM is one of the most common clinical and neurological manifestations of extra-pulmonary tuberculosis and remains a serious health threat in developing countries (Berengeuer *et al*., 1992, Mishra and Kalita, 1996). It generally develops after a breakdown of a small initial focus (Rich focus) in the superficial cortex or leptomeninges. This focus discharges caseous material into the cerebrospinal fluid (CSF) (Rich and Mc Cordock, 1933). Such focus can destabilize following years of quiescence due to advanced age, trauma, malnutrition, chronic debilitation and immune suppression. TBM can also result from miliary spread of the

Corresponding author: Dr. Dwijen Das,
Department of Medicine, Silchar Medical College, Silchar, India.

disease. With the emergence of HIV, an alarming increase in TB is reported across the globe. There is a resurgence of neurological TB worldwide, including the developing countries (Kumar *et al*., 1997). Even with the modern anti-tuberculosis treatment, neurological TB continues to have a high mortality and morbidity rate, especially in children (Donald, 998). Disturbances of sodium, intravascular volume, and water are common in TBM. Hyponatremia occurs in 35- 65% of patients with TBM (Singh *et al*., 1994, Narotam *et al*., 1994). In patients with TBM, hyponatremia is an independent predictor of death or severe disability (Singh *et al*., 1994).

Aim: The aims of the study were

- To study the clinical profile of patients presenting with TBM.
- To estimate the occurrence of hyponatremia in TBM.
- To determine the impact of hyponatremia in clinical status in TBM.
- To know the prognosis of patients with hyponatremia in TBM.

MATERIALS AND METHODS

The one year prospective, single centred observational study was conducted in 45 patients suffering from tubercular meningitis, admitted in the General Medicine ward of Silchar Medical College and Hospital, Silchar, Assam, which is a tertiary care teaching hospital in north eastern India. Necessary institutional ethical committee permission was obtained.

Inclusion criteria

- Patients of either sex above 13 years of age suffering from TBM.

Exclusion criteria

- Other infectious and non-infectious causes presenting with similar features.
- Patients with age less than 13 years.
- Patient not giving consent.

Diagnosis of TBM was based on CSF cytology (pleocytosis with predominant lymphocytosis), CSF biochemistry (glucose less than half of the value of simultaneous blood glucose levels, and increase in proteins), CSF-ADA estimation, detection of acid fast bacilli (AFB) on direct smear examination by Ziehl-Neelsen staining and CSF-PCR for DNA of M. tuberculosis (Shariff and Vidya Pai, 2014). The diagnosis was supported by history of contact, radiological evidence of tuberculosis, positive Mantoux test, and fine needle aspiration of lymph nodes suggestive of caseation and/or presence of AFB. Diagnosis of hyponatremia was kept at serum sodium level <135mEq/L. Serum sodium was assessed by ion selective electrode method and was repeated on day 3 and in between or after 10 days.

RESULTS

The period of study was from June 2014 to May 2015 and included 45 cases of TBM. The age range varied from 14 to 63 years and mean age was 31.97 years. Maximum cases were in the age group 21to 30 years. 29 of the cases were males and the rest 16 were females. The average duration of illness was 3 weeks. Clinical presentation included fever in 36 (80%), nausea and vomiting in 13 (29%) and headache in 29 (64.4%) patients. Decline in awareness and altered sensorium was observed in 24 (53.3%) and seizure in 22 (48.8%) patients. All cases had anorexia, malaise and fatigue. Neurological deficit was seen in 13 patients (28.89%) of whom 10 (22.2%) had cranial nerve palsies and another 4(8.89%) had motor weakness which included one case who had both.

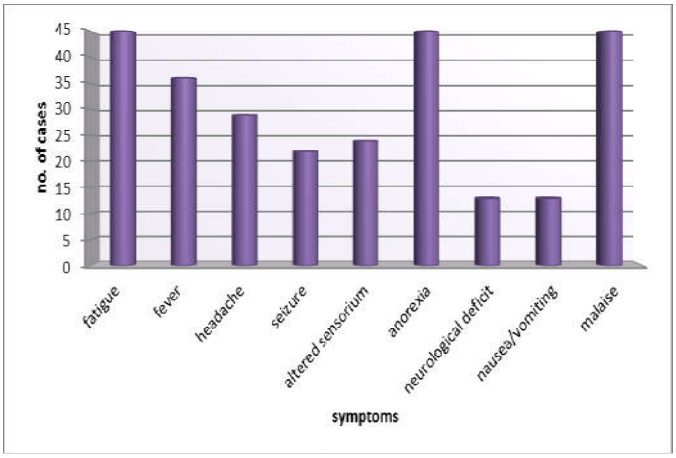


Fig. 1. The distribution of symptoms in patient with TBM

Poor nutritional status was observed in 34 (76%) patients. Past history of TB was noted in 10(22.2%) cases, 8(17.78%) of them had completed treatment while 2(4.44%) cases were on medications. Enlarged lymph nodes were found in 7 (15.56%) cases of which cervical and axillary were seen in 5 and 2 cases respectively. The average temperature was 101.16º F ± 1.54.

Glasgow coma scale

Table 1. The GCS score in TBM patients

GCS	No. of patients	% of Cases
13-15	15	33.33%
8-12	16	35.56%
3-7	14	31.11%

Neck rigidity and Kernig's sign were observed in 38(84.44%) and 34(76%) cases.

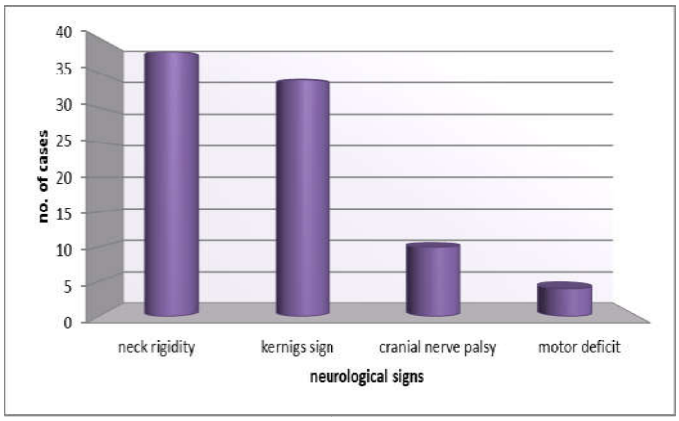


Fig.2. The distribution of Neurological signs in patients with TBM

Blood parameters suggest anaemia in 12(26.6%) patients and the average erythrocyte sedimentation rate (ESR) was 46.33 AEFH. Hyponatremia was seen in 21 (46.66%) cases. The mean value of serum sodium was 131.9mmol/l. 6(28.57%) patients had sodium level <120 mmol/l, 12(57.14%) had sodium between 121- 130mmol/l and remaining 3(14.28%) had between131-135 mmol/l on the day of presentation.

Table 2. No. of patients with hyponatremia during the course of illness

Sr.Na+ level	Day 1	Day 3	Day 10
110-120	6	6	3
121-130	11	9	6
131-135	4	3	4

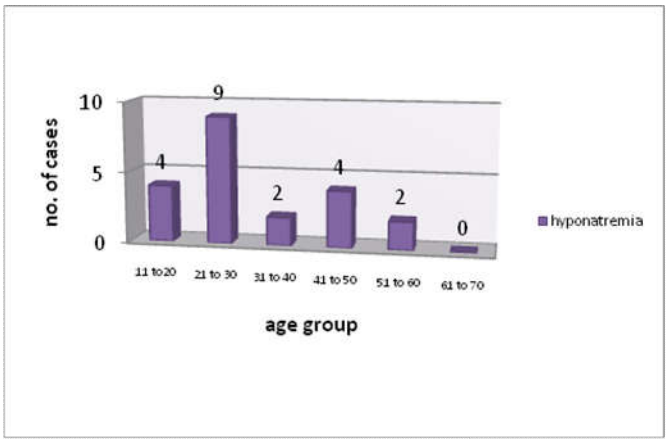


Fig. 3. Hyponatremia in different age group on day of presentation

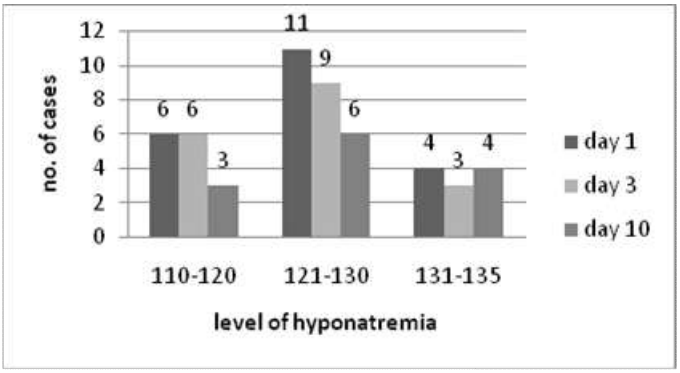


Fig. 4. No. of cases having hyponatremia during the course of illness

Numbers of patients with serum sodium level between110-120 mmol/l were 6 on presentation, 6 on 3rd day of hospital stay and 3 on 10th day of stay. In this group 2 patients died on 5th day. In the other group with serum sodium level between, 121-130 mmol/l, 11cases were detected on presentation, 9 on day 3 and on the 10th day of stay, 6 were still having low serum sodium level (121-130 mmol/l). 2 patients who had initial serum sodium between 121-130 mmol/l, died during the course of illness (on 7th and 11th day). Patients with sodium level between 131-135 mmol/l were 4 on the day of presentation, 3 on day 3 and 4 on day 10. One patient in this group died in the course of illness. Mantoux test was positive in 27 (60%) cases whereas fundoscopic examination revealed papilloedema in 11 cases of whom 5 were associated with hyponatremia. Appearance of CSF was clear in 35(77.77%), turbid in 10(22.22%) and cobweb coagulam in 23 (51.11%) samples. All cases had elevated CSF protein, with a mean value of 180.97± 42.38 mg/dl. The overall range of CSF protein was from 110-300 mg/dl while most of the cases had in the range of 141 to 180 mg/dl. CSF analysis showed marked decrease in glucose levels with the average CSF glucose being 41.96 ± 11.39 mg/dl with a standard deviation of 14.27. The average CSF ADA level was 16.57 ± 4.46 U/L; with a standard deviation of 6.08. The range varied from 6.23 – 32.4 U/L.

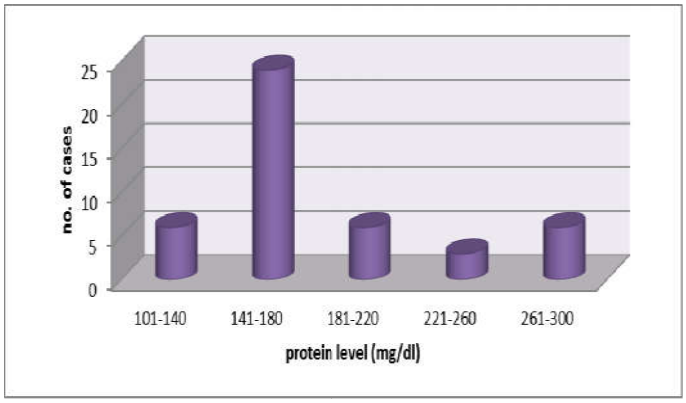
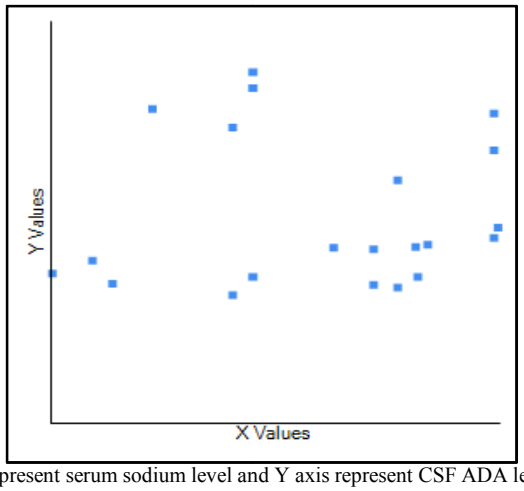


Fig. 5. Number of patients in different protein range in TBM group



X axis represent serum sodium level and Y axis represent CSF ADA level.

Fig. 6. Relationship between S. Sodium and CSF ADA level

The value of R is 0.0455. Although technically a positive correlation, the relationship between the variables are weak. The value of R2, the coefficient of determination, is 0.0021. An increase in CSF cell count with lymphocytic pleocytosis was noted, with an average count of 194.78 cells/mm^3 of CSF. AFB was detected in 6 (13.33%) cases while another 18(40%) showed positive results for DNA-PCR for M. Tuberculosis. Abnormalities in Chest X-ray was noted in 14(31.11%) cases of whom 11 had hyponatremia. Number of patients having hyponatremia along with abnormal CECT findings were 10 of whom 5 had basal meningeal enhancement and among the remaining 5 cerebral oedema and infarcts were seen in 2 each and hydrocephalus in the other. 6 patients died during the

course of illness of whom 5 had hyponatremia. 2 cases died on 5th day after admission and the remaining 4 died after 10 days of hospital stay. The two patients who died on 5th day of stay had initial serum sodium level below 120 mmol/l ($p > 0.05$).

DISCUSSION

In the present study 42.2% of the cases were in the age group 21 -30 years, similar to that observed by Zafar *et al*. The mean age of patients in the present study was 31.97 years which is comparable to studies by Mishra, Kalita and Zafar *et al*. where a mean age of 29.6 years was reported. Out of 45 cases, 29 (64.4%) were males and 16 (35.56%) females the male to female ratio being 1.8:1. Tarakad S Ramachand in his review of TBM stated that during adulthood, TB infection rates are consistently higher for men than women with a male to female ratio of 2:1. Studies by Kent, *et al*. reveal that most of the patients present within 2 weeks of onset of symptoms which is in contrast to the present study, where the average duration of illness was 3 weeks. Zafar *et al*. reported the mean duration of illness as 29.13 days in their series. The present study revealed a poor nutritional status in 76% of the patients which is similar to the observation of Thwaites and Tran, who noted that, malnutrition is one of the important factors responsible for the increased prevalence of TBM in under privileged world. All patients of the series presented with anorexia, malaise and fatigue which is similar to the observations of Garg. Fever was the main presenting symptom observed in 80% of the cases which was similar to that of Zafar *et al*., who reported an incidence of 82% in their series. Baheti *et al*., Zafar *et al*. reported the incidence of headache in patients with TBM as 47.36% and 57% respectively whereas, in the present study headache was observed in 64.4% of the cases. 29% of the cases in the series presented with nausea and vomiting which was similar to that of Illingworth who reported the same in 32% of cases. Seizure was present in 48.8% of cases and similar results (46.9%) were observed by Mishra and Kalita. The present study showed 53.33% of the cases had a decline in the state of awareness and conscious level, which was similar to the observations made by Thomas MD *et al*. where the same was observed in 52.6% cases. A much higher incidence of 66.7% was noted by Zafar *et al*. Neck rigidity was present in 84% of cases similar to Verdon *et al*. who reported the same in 76% respectively. In the present series, cranial nerve palsies were observed in 10 (22.22%) cases, which was similar to that of Thwaites and Tran who reported an incidence of 22% in their series. Among the cranial nerve palsies, involvement of Abducens nerve is the commonest and found in 60% of cranial nerve involvement which is comparable to the studies by Keane who found cranial nerve involvement in 65% of the patients. Singh *et al*. in their study found motor weakness in 16 (34%) patients of whom 15 (94%) patients had hemiplegia and 1had paraplegia whereas Shukla *et al*. observed hemiparesis in 23% of patients. In the present study, motor weakness was seen in 4(8.89%) cases of whom 3 (75%) had hemiparesis and the other one had left lower limb weakness while none developed para-paresis. In the present study, tubercular lymphadenitis was present in 7 (15.56%) cases of whom 5 had enlarged cervical and 2 had axillary nodes. Goblirsch *et al*. in their study reported lymphadenitis in 11% of patients of TBM.

In the present study hyponatremia was seen in 21 (46.66%) cases of whom 6 (28.6%) had sodium level below 120mmol/l. Anderson *et al*. in their study found 49% of cases had hyponatremia and identified it as a serious complication of TBM. Narotam *et al*. observed hyponatremia in 62.5% whereas Singh *et al*. reported the same in 35% of cases with TBM respectively. The CSF was clear in 77.7% of cases in the present series similar to the observation of Swash (22) where the incidence was in 80% of cases. Gray and Discombe stated that cobweb coagulam was very suggestive of TBM which is in agreement with the present study. On evaluation of CSF protein, a mean value of 180.97± 42.38 mg/dl was observed. The findings were similar to, Verdon *et al*., Mishra and Kalita who observed a finding of 182 ± 36.32 mg/dl, 179 ± 21.2 mg/dl, respectively in their series. The range of CSF glucose was found to be 20-74 mg/dl, with a mean value of 41.9 ± 11.39 which was comparable to the observations of Kennedy. The average cell was found to be 194.8 cells/mm^3 of CSF. There was lymphocytic predominance and the finding was similar to that of Kennedy. In the present study, it was found that the CSF ADA was significantly raised with a mean of 16.57 ± 4.46 U/L. Moghtaderi *et al*., Shariff and Vidya Pai found high CSF ADA activity with mean value of 23.05 ± 13.1 U/L and 16.324 ± 0.0706 U/L respectively in their series. Chacko *et al*. observed sensitivity of 44.5% for CSF-PCR for M. Tuberculosis similar to the present study showing a sensitivity of 40%. In the present study Chest X ray showed abnormalities consistent with tuberculosis in 14 (31.11%) cases, similar to that of Kennedy (32%) and Verdon *et al*. (30%) respectively. 11(78.57%) out of the 14 cases with X-ray abnormalities, presented with hyponatremia. However, these observations could not be compared with other researchers due to paucity of literature in this field. Abnormal CT findings were noted in 10 cases, all of whom had hyponatremia. The abnormalities included basal meningeal enhancement in 50% of cases and cerebral oedema, infarct and hydrocephalus in the rest. These observations could not be compared with other researchers due to lack of works in this area.

According to Singh *et al*. the overall mortality was quite high but was not entirely related to hyponatremia since multiple factors plays a vital role in the ultimate outcome in TBM. However mortality during the first 72 hours was strongly related to hyponatremia. In patients with hyponatremia who had survived beyond 72 hours, outcome was favourable with fluid restriction. This would further support the need for awareness for relatively high incidence of hyponatremia in TBM, early diagnosis and appropriate fluid management. Alarcón *et al*. in their study did not consider hyponatremia as a significant predictor of mortality and morbidity. In the present study, 6 patients died during the course of illness and 5 were having hyponatremia. 2 of them with initial serum sodium concentration between 110 – 120 mmol/l died on the 5th day and other two died on 7th and 11th day. One patient with initial sodium between 131 -135 mmol/l died on the 11th day. However, due to paucity of works in this field mortality contributed by hyponatremia in TBM could not be compared with studies by other researchers. Hence, final outcome in relation to hyponatremia in TBM is a grey area for further research.

Conclusion

Tubercular Meningitis is an important life threatening manifestation of extra pulmonary tuberculosis which is common in the developing countries and influences the socio economic status. A male preponderance in relatively younger population was observed in which the average duration of symptoms was 3 weeks and constitutional features with seizures, altered level of consciousness, neurological deficits are usual manifestations with variable positive chest radiography and tubercular lymphadenits. CSF abnormalities include cobweb coagulum with elevated protein, reduced glucose, increased ADA activity and CSF pleocytosis with lymphocytic preponderance, considerable positivity in PCR for mycobacterial DNA and scanty AFB positivity. Hyponatremia was seen in nearly half of the cases. Severe hyponatremia was observed in more than a quarter of cases which persisted beyond 3rdday and had maximum clinical severity. Mortality was observed in 13.33% of cases, most of which had sustained hyponatremia. The study concluded with the inference that hyponatremia may be an important prognostic indicator in relation to the severity of tubercular meningitis and more number of multicentric research works involving larger number of patients are necessary in this field to establish a clear relationship.

Limitation of this study

It was a short term single centred study including small numbers of population.

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