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A study of hyponatremia in tuberculous meningitis

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ABSTRACT

Setting: In view of paucity of studies on predictors of hyponatremia in tuberculous meningitis (TBM) and its influence on outcome, this study was undertaken.
Objective: To study the frequency, predictors and prognosis of hyponatremia in TBM.
Design: In this prospective hospital based study, 76 patients with TBM (definite 18 and probable 58) were enrolled. The severity of meningitis was graded as I–III and hyponatremia as severe (<120 mEq/L), moderate (120–129 mEq/L) or mild (130–134 mEq/L). Hospital death was noted and functional outcome was assessed by modified Rankin Scale (mRS) on discharge.
Results: 34 (44.7%) TBM patients had hyponatremia (mild 3, moderate 23 and severe 8). Hyponatremia was due to cerebral salt wasting in 17, syndrome of inappropriate secretion of antidiuretic hormone in 3 and miscellaneous causes in 14 patients. Hyponatremia was related to GCS score and basal exudates. Outcome of TBM was related to duration of hospitalization, GCS score, focal deficit, mechanical ventilation, severity of TBM, age and comorbidities. Cerebral salt wasting was related to severity of TBM.
Conclusion: Hyponatremia occurred in 44.7% of TBM patients. Cerebral salt wasting was the commonest cause of hyponatremia and was related to the severity of TBM.

1. Introduction

Hyponatremia is a common, life threatening electrolyte abnormality in critically ill neurological patients. Amongst the central nervous system disorders, hyponatremia is commonly noted in subarachnoid hemorrhage, encephalitis, meningitis and head injury. Hyponatremia may also be due to recurrent vomiting, diarrhea, nutritional deficiency and drug toxicity such as osmotic agents, diuretics and carbamazepine. Hyponatremia has been reported in 29% patients with subarachnoid hemorrhage [1] and in 53% patients undergoing trans-sphenoidal pituitary surgery [2]. Cerebral salt wasting (CSW) was first reported in 1950. In majority of neurological patients, hyponatremia with normal renal functions was attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) which was described seven years later than CSW [3]. CSW was reintroduced to the medical literature by Nelson et al. in 1981 [4]. Subsequently, there are several reports of CSW as a cause of hyponatremia in neurological patients [4–6]. CSW has been reported to be more common than SIADH in some studies [7]. In the patients with tubercular meningitis (TBM), there may be higher frequency of hyponatremia compared to other CNS infections due to leptomeningeal inflammation, hydrocephalous, raised intracranial pressure and ventriculitis [8]. There are reports of SIADH and CSW in TBM but most of these are case reports or short series. CSW and SIADH have many similarities. Moreover a number of clinical conditions such as poor oral intake, extra renal loss (vomiting, diarrhea), endocrinal abnormalities and heart failure have to be considered before diagnosing CSW or SIADH. Differentiation between CSW and SIADH is based on weight loss, negative fluid balance and low central venous pressure (CVP) in CSW. The differentiation between CSW and SIADH is important, because therapy of one may be detrimental to the other [5]. There is paucity of prospective studies reporting the frequency and predictors of hyponatremia and its prognostic significance in TBM. The aim of the present study is to report the frequency, etiology and predictors of hyponatremia in TBM and its influence on short term prognosis.

2. Patients and methods

This prospective hospital based study was conducted in a tertiary care teaching hospital in North India which caters to a large area of Uttar Pradesh, Madhya Pradesh, Bihar and Nepal. The study was conducted during December 2013 to April 2015 and was approved by the Institute Ethics Committee (2013-83-EMP-72).

2.1. Inclusion criteria

The patients with TBM were included prospectively. The diagnosis of TBM was based on the following criteria:

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2.1.1. Essential criteria

Meningeal symptoms comprising of fever with headache and/or vomiting for 2 weeks or more in whom malaria, septic and fungal meningitis were excluded by peripheral blood smear examination, antigen test (malaria and cryptococcal) and cerebrospinal fluid (CSF) culture for bacteria and fungi.

2.1.2. Supportive criteria

1) Cerebrospinal fluid pleocytosis with lymphocytic predominance and raised protein.
2) Cranial CT scan or MRI evidences of exudates, infarction, hydrocephalus or tuberculoma in isolation or in combination.
3) Evidence of extra CNS tuberculosis.
4) Response to antitubercular treatment.

Presence of essential and 3 of the 4 supportive criteria was considered highly probable and 2 supportive criteria as probable TBM. Patient was considered definite TBM if CSF smear or culture revealed *Mycobacterium tuberculosis*, positive CSF polymerase chain reaction (PCR) or IgM antibody by enzyme linked immunosorbent assay (ELISA) [9].

The diagnosis of extra CNS tuberculosis was considered if the patient had fibro-cavitary lesions or miliary shadow on chest radiograph, lymphadenopathy on clinical examination, ultrasonography or CT abdomen, or Pott's spine on MRI with consistent fine needle aspiration cytology or histology.

2.2. Hyponatremia

Hyponatremia was diagnosed if serum sodium was <135 mEq/L in 2 consecutive reports 24 h apart during their hospital stay.

2.3. Exclusion criteria

Primary renal, hepatic or cardiac failure patients were excluded; however if TBM patients developed hepatic or renal function derangement during treatment, they were not excluded.

2.4. Evaluation

A detailed history was taken and physical examination was done. Duration of illness, presenting symptoms, seizures, focal deficit and features of raised intracranial pressure were noted. History of vomiting, diarrhea and use of carbamazepine, mannitol and glycerine were recorded. Consciousness was assessed by Glasgow Coma Scale (GCS). The severity of TBM was categorized as stage I (meningitis only), stage II (meningitis with focal neurological deficit or GCS score between 11 and 14) and stage III (meningitis with GCS score <11) using Medical Research Council criteria [10]. Comorbidities such as diabetes, hypertension, bronchial asthma and coronary artery disease were noted. Patients were examined for cranial nerve palsy and papilloedema. Muscle power, muscle tone and reflexes were noted. Co-ordination and sensations of pin prick, touch, joint position and vibration were also tested.

2.5. Investigations

Blood counts, hemoglobin, erythrocyte sedimentation rate and serum chemistry were done. Serum osmolality, urine osmolality and urine sodium were measured. Serum sodium levels were checked alternate day for 14 days or until the patient was discharged, whichever was earlier. A serum sodium level below 135 mEq/L twice 24 h apart was considered hyponatremia and was categorized as severe (<120 mEq/L), moderate (120–129 mEq/L) and mild (130–134 mEq/L). The lowest level of serum sodium was used for defining the severity of hyponatremia. Extracellular fluid volume status was assessed on the basis of tachycardia, dry mucous membranes, edema, tenting of the skin and capillary refill time. Central venous pressure (CVP) was measured in some patients. The central venous pressure of 6 to 10 cm was considered normal. Daily fluid intake and output chart was maintained and total fluid balance was calculated. Body weight was measured on admission and daily variation of weight was monitored on a special bed (LINET Eleganza3XC). The change in body weight was considered as indicator of negative or positive fluid balance.

2.6. Cerebral salt wasting (CSW)

CSW was considered in the presence of at least 2 out of 4 following features in a patient with hyponatremia

1. Clinical findings of hypovolemia such as hypotension, dry mucous membranes, tachycardia or postural hypotension.
2. Laboratory evidence of dehydration such as elevated hematocrit, hemoglobin, serum albumin or blood urea nitrogen.
3. Negative fluid balance as determined by intake output chart and/or weight loss.
4. CVP < 6 cm of water.

2.7. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Presence of at least 2 out of 4 following features in a patient with hyponatremia was needed for the diagnosis of SIADH.

1. No signs of hypovolemia such as hypotension, dry mucous membrane, tachycardia or postural hypotension.
2. No laboratory evidence of dehydration such as elevated hematocrit, hemoglobin, serum albumin or blood urea nitrogen.
3. Normal or positive fluid balance with absence of weight loss.
4. CVP > 6 cm of water.

2.8. Management

The offending drugs if any were withdrawn and the underlying pathology was treated. All CSW patients were treated with oral salt supplementation and intravenous normal saline. Fludrocortisone was used in refractory patients. Fluid restriction was done in the patients with SIADH.

2.9. Outcome

The patients' outcomes were defined on discharge and at 1 month follow up. The patients were considered to have a poor outcome if mRS score was >2 and good if mRS score <2. Death in the hospital and its possible causes were noted.

2.10. Statistical analysis

The baseline parameters (demographic, clinical, laboratory and outcome) between the two groups (TBM patients with and without hyponatremia and TBM patients with and without CSW) were compared using Fisher exact test for categorical and independent *t*-test or Mann–Whiney *U* test for continuous variables. For evaluating the effect of hyponatremia on outcome, univariate analysis was done and the variables having a p value of less than 0.1 were included in multivariate analysis. The variable with a two tailed p value <0.05 was considered significant. The statistical analysis was done using SPSS version 16 software and GraphPad Prism 5.

3. Results

Seventy six patients with TBM were included whose median age was 36 (7–80) years and 37 (48.7%) were females. The severity of meningitis was stage I in 7 (9.2%), stage II in 46 (60.5%) and stage III in 23 (30.3%) patients. The diagnosis was definite in 18 (23.7%), highly probable in 44 (57.9%) and probable in 14 (18.4%) patients. 34 (44.7%) patients had hyponatremia which was mild in 3, moderate in 23 and severe in 8