SERUM SODIUM AND OSMOLAL CHANGES IN TUBERCULOUS MENINGITIS

B.S. Singh
A.K. Patwari
Manorama Deb

ABSTRACT

Twenty children from 2 months to 7 years (mean age 2.74 years ± 1.62) diagnosed to have tuberculous meningitis (TBM) were evaluated for serial serum sodium levels and osmolality of cerebrospinal fluid (CSF), serum and urine on admission and the results compared with 20 age and nutritionally matched controls, and these investigations repeated on day 3 and day 10. Mean serum sodium levels (130.7 ± 6.26 mEq/L), and osmolality of CSF (272.0 ±7.0 mOsm/kg) and serum (275.5 ± 6.09 mOsm/kg) were significantly lower (p <0.001) than in controls. Hyponatremia was detected in 65% of cases on admission, 47% on day 3 and in 30.8% on day 10. All the patients with hyponatremia had biochemical evidence of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) on admission. Incidence of SIADH gradually decreased to 41.2% on day 3 and 15.4% on day 10. In some of the cases serum sodium levels and osmolality of serum and CSF took about 3 weeks to return to normal. CSF osmolality was lower than concomitant serum osmolality in patients as well as in controls. In patients with SIADH, CSF osmolality followed the same trend as serum values and returned to normal in 2-3 weeks. Overall mortality was 25%. Two out of 3 patients who expired during first 3 days had SIADH but in those cases who survived there was no correlation with degree of meningeal inflammatory changes or ultimate outcome.

Hypo-osmolality of body fluids in tuberculous meningitis (TBM) has been reported by several workers in the past(l,2). Hyponatremia with or without evidence of inappropriate secretion of antidiuretic hormone (SIADH) has also been observed in association with TBM(3,4). Changes in serum osmolality may be reflected in changes in cerebrospinal fluid (CSF) osmolality during the course of illness. Such changes have been described in non-tubercular bacterial meningitis(5-7). However, there is paucity of such data regarding CSF osmolality changes in TBM. This study was undertaken to evaluate serial serum sodium levels and osmolal changes in CSF, serum and urine in patients suffering from TBM.

Material and Methods

The study was conducted in hospitalized patients in one of the General Pediatric unit

of Kalawati Saran Children's Hospital, New Delhi. Children of either sex below 12 years of age with TBM were studied for their serum sodium levels, and osmolality of CSF, serum and urine on admission and the results compared with age and nutritionally matched children (control group) in whom lumbar puncture was performed on suspicion of CNS pathology and who were eventually found to have febrile convulsions or epilepsy. Diagnosis of TBM was based on CSF cytology (pleocytosis with predominant lymphocytosis/progressive increase in the count of lymphocytes on repeat CSF examination, biochemistry (glucose <40 mg/dl or less than half of the value of simultaneous blood glucose levels, and increase in proteins), detection of acid fast bacilli (AFB) on direct smear examination by Ziehl-Neelson staining and culture for AFB. The diagnosis was supported by history of contact, gastric aspirate for AFB, radiological evidence of tuberculosis, positive Mantoux or BCG reaction, and fine needle aspiration of lymph nodes suggestive of caseation and/or presence of AFB(8). The criteria for diagnosis of SIADH included serum sodium <135 mEq/L, serum osmolality <270 mOsm/kg and inappropriately high urinary osmolality(9). Children with associated conditions known to affect ADH release were excluded from the study. Cases diagnosed to have SIADH were given only 60% of the daily maintenance fluids till all their biochemical parameters returned to normal. Serum sodium estimation was done by using Corning 902 sodium and potassium analyser which uses the method of ion selective electrodes. Osmolality of CSF, serum and urine was estimated by the method of freezing point depression(10) using Roebling's osmometer. Serum sodium, and osmolality of CSF, serum and urine were repeated on day 3 and day 10. These para-

meters were also repeated after 10th day as and when deemed necessary. Statistical analysis was done by Student's 't' test.

Results

This prospective study was conducted from July 1987 to June 1988 and included 20 cases of TBM from 2 months to 7 years (mean age 2.74 years ±1.62) with 12 boys (60%) and 8 girls (40%). Clinical presentation of these cases included fever (90%), altered sensorium (80%), convulsions (55%), neurological deficits (40%), vomiting (25%) and headache (10%). The diagnosis of TBM was mainly based on CSF cytology (20/20), CSF biochemistry (20/20), radiological evidence of primary complex, miliary tuberculosis or non-resolving pneumonia (7/20), positive tuberculin test (5/20), positive BCG reaction (4/20), gastric aspirate for AFB (l/20) and fine needle aspiration cytology (1/20). Ziehl-Neelson staining and CSF culture were negative in all the cases. The results of CSF, serum and urine samples from 20 age and nutritionally matched children finally diagnosed as typical febrile convulsions (n=14) and epilepsy (n=6) were used for comparison as controls. Serum sodium values, and osmolality of CSF, serum and urine of the patients on admission have been compared with controls in *Table I* which suggests that all these parameters were significantly different in TBM except for urinary osmolality. *Table II* shows the comparison of various parameters in patients with and without SIADH. The mean CSF osmolality was observed to be lower than the mean serum osmolality in both the groups as well as in controls though not statistically significant. As expected, the mean serum sodium values, CSF and serum osmolality were significantly lower in patients with SIADH as compared to those without SIADH and controls. The mean

TABLE I —*Mean Values of Serum Sodium and CSF, Serum and Urinary Osmolality*

Parameters	Cases (n=20)			Contols (n=20)			p value
	Range	mean	SD	Range	Mean	SD	
Serum sodium (mEq/L)	116-143	130.7	6.26	135-143	137.4	1.9	<0.001
CSF osmolality (mOsm/Kg)	256-286	272.0	7.0	278-306	288.2	7.89	<0.001
Serum osmolality (mOsm/Kg)	286-288	275.5	6.09	280-316	293.0	114.0	<0.001
Urinary osmola-lity (mOsm/Kg)	250-780	480.6	60.8	208.-627	412.8	202.5	>0.5

TABLE II– *Comparison of Serum Sodium and CSF, Serum and Urinary Osmolality in Cases with and Without SIADH (on Admission)*

Parameters	Cases with SIADH (n=20)		Contols without SIADH (n=20)		Controls	
	Mean	SD	Mean	SD	Mean	SD
Serum sodium (mEq/L)	127.0	4.2	137.0	2.5	137.4	1.9
CSF osmolality (mOsm/Kg)	269.0	5.1	28.0	2.8	288.2	7.89
Serum osmolality (mOsm/Kg)	271.0	2.6	283.0	2.8	293.0	11.4
Urinary osmolality (mOsm/Kg)	520.0	101.9	433.5	73.0	412.8	202.5

value of urinary osmolality was significantly higher in cases with SIADH than the group without SIADII and controls.

Hyponatremia was detected in 13 cases (65%) on admission and all of them had evidence of SIADH. Within first 72 hours, 2 cases with hyponatremia (with SIADH) and 1 case with no evidence of hyponatremia or SIADH expired. Out of 11 cases with hyponatremia, 8/17 cases (47.0%) continued to have hyponatremia on 3rd day. One case with hyponatremia (but without SIADH) and 1 case without hyponatremia expired before the 10th day. Two cases left against medical advice. By 10th day, 4 out of 13 hospitalized cases (30.8%) had evidence of hyponatremia. Even though all the 13 cases with hyponatremia had supportive evidence of SIADH on admission with an

overall incidence of 65%, only 7/17 cases (41.2%) and 2/13 cases (15.4%) had SIADH on 3rd and 10th day, respectively. On day 3, 1 out of 17 cases and on day 10, 2 out of 13 cases continued to have hyponatremia (without SIADH). Serial mean values of serum sodium and osmolality of CSF, serum and urine in patients with and without SIADH *(Table III)* suggested that the mean values of these parameters remained unchanged till about 10 days. Biochemical parameters suggestive of SIADH returned to normal range only in 4/11 cases who survived beyond 72 hours. By 10th day all the parameters returned to normal in all but 2 of these cases. In both the patients who continued to have biochemical evidence of SIADH on 10th day, all the parameters returned to normal values by the end of 3rd week. It was further observed that degree of meningeal inflammatory changes was not related to incidence of SIADH as only 3/13 (23.1%) cases with SIADH had severe

meningeal inflammatory changes manifested as CSF proteins <400 mg/dl and CSF leucocyte count >400 cells/cu mm.

Overall mortality was 25%. Three patients, including 2 cases with SIADH, expired within first 72 hours and 2 children died during the first week of hospitalization though none of them had SIADH. Two cases left against medical advice on 7th and 9th day, respectively and hence could not be followed. Even though 2/3rd of the early deaths (within first 72 hours) were associated with SIADH, the subsequent outcome beyond 72 hours was quite favorable. No statistically significant correlation was observed between SIADH and overall mortality.

Discussion

Hypo-osmolality of body fluids in association 'with tuberculous meningitis documented in earlier studies(1,2) was believed

TABLE III– *Serial Mean Values of Serum Sodium and Osmolality of Serum, CSF and Urine in Cases With and Without SIADH*

Parameters	Cases with SIADH			Cases without SIADH		
	Day 1 (n=13/20)	Day 3 (n=7/17)*	Day 10 (n=2/13)**	Day 1 (n=7/20)	Day 3 (n=10/17)*	Day 10 (n=11/13)**
Serum sodium (mEq/L)	127.0 ±4.2	127.0 ±3.5	126.8 ±3.5	137.0 ±2.5	136.0 ±16.4	135.8 ±1.1
Serum osmolality (mOsm/Kg)	271.0 ±2.6	269.0 ±4.8	274.0 ±7.4	283.0 ±2.8	282.0 ±2.4	283.0 ±2.4
CSF osmolality (mOsm/Kg)	269.0 ±5.1	268.0 ±5.3	271.0 ±4.6	280.0 ±2.8	276.0 ±1.6	276.0 ±2.6
Urinary osmolality (mOsm/Kg)	520.0 . ±101.9	583.0 ±73.0	609.0 ±85.0	433.5 ±73.0	389.2 ±76.0	446.5 ±78.0

* 3 cases expired within first 72 hours.
** 2 cases expired and 2 cases left against medical advice before 10th day.

to be due to renal salt loss. Hyponatremia in children with TBM is due to increased water reabsorption by the kidneys(ll) which has been related to hypotonic expansion of extra cellular fluid space. Sixty five per cent of our cases had hyponatremia on admission, 47% on day 3 and 30.8% on 10th day. Even though some studies(12) have shown a much lower incidence of hyponatremia in similar patient population, a high incidence of hyponatremia has been reported by others(3,4). Serum sodium levels took a longer time to return to normal values. In 4 cases, hyponatremia continued beyond 10th day and serum sodium values came back to normal during 3rd week. Menon *et al.* (4) also observed similar findings.

Association of SIADII in TBM has been related to excessive ADH secretion from tubercular granuloma(13). Other factors which may be associated are meningeal inflammation resulting in ADH leak from posterior pituitary, stress reaction or hypoxic insult. Our results highlight that SIADH is quite common in children with TBM as 65% our cases fulfilled the criteria of SIADH on admission. Smith and Godwin(3), and Menon *et al.* (4) have also observed a high incidence of SIADII in their series. However, some cases had only hyponatremia without any supportive evidence of SIADH. Hyponatremia in those cases might have been due to vomiting, fever or restricted oral intake. High incidence of SIADH was not related to severe meningeal inflammatory changes. Clinical manifestations of SIADH are primarily due to hyponatremia because most of the cases may be asymptomatic till serum sodium levels fall below 120 mEq/L(14). Therefore, a diagnosis of SIADII may be missed unless suspected, because clinical features of hyponatremia like convulsions, altered sensorium, confusion and personality changes

are also common manifestations of TBM. The personality changes are also common manifestation of TBM. The biochemical parameters suggesting SIADH followed the same trend as hyponatremia and took a long time to return to normal values. Menon *et al.* (4) also observed these parameters to return to normal by 3-4 weeks. This observation would suggest that fluid restriction may be necessary not only during first 24 hours of hospitalization in a majority of cases of TBM like in acute bacterial meningitis(15) but in some cases fluids may have to be restricted for a longer time.

Osmolality of brain tissue and CSF has been related to plasma osmolality. Thus serum sodium levels are believed to determine CSF osmolality(16). Experimental studies(6) have shown that 0.338 mOsm/L change in CSF osmolality occurs per unit mOsm/L change in serum osmolality. But alteration in the serum osmolality may not always correlate with CSF osmolality in a predictable fashion. Acute fall in serum sodium below 135 mEq/L can cause much higher percentage of increase in brain volume than in chronic hyponatremia(5). Moreover, a fall in intracellular potassium in chronic hyponatremia may help in maintaining osmolality of nervous tissue in the face of falling serum osmolality. Our observations suggest that CSF osmolality was significantly lower (p <0.001) in patients with TBM as compared to controls. Even though there was no statistically significant difference, mean CSF osmolality was lower than the mean serum osmolality within the patient groups as well as in controls. CSF osmolality was observed to be lower than serum osmolality even in cases with SIADH and this trend continued through day 1, 3 and 10. This is in contrast to the changes observed in the presence of SIADII in acute bacterial meningitis where mean CSF

osmolality may remain higher than serum osmolality because the fall in CSF osmolality is not of the same degree as that of serum(5-7). Our observations suggest that hypo-osmolality of serum may eventually result in hypo-osmolality of CSF as well in long standing hyponatremia as is the case in TBM, and it may take 3 weeks or more for the serum sodium and osmolality of CSF and serum to return to normal levels.

Overall mortality was quite high but was not related to presence of SIADH since multiple factors play a vital role in the ultimate outcome in TBM. However, mortality during first 72 hours was strongly related to SIADH. In patients initially diagnosed as SIADH who survived beyond 72 hours, outcome was favorable with fluid restriction from the beginning even though biochemical parameters of SIADH continued beyond 10th day in some of the cases. This would further support the need for awareness of high incidence of SIADH in TBM, early diagnosis and appropriate fluid restriction from the beginning.

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