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ORIGINAL PAPER

Hypovolemia due to cerebral salt wasting may contribute to stroke in tuberculous meningitis

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Summary

Background: Both stroke and cerebral salt wasting (CSW) are common in tuberculous meningitis (TBM), but there is paucity of studies evaluating their combined effect.
Aim: The present study has been undertaken to evaluate the spectrum of stroke in TBM and its relation to CSW.
Design: Hospital-based prospective cohort study.
Methods: Eighty-one patients with TBM diagnosed on the basis of clinical, cerebrospinal fluid and magnetic resonance imaging (MRI) criteria were prospectively included. Stroke was diagnosed on the basis of clinical, MRI findings or both. Stroke risk factors were noted. Patients with hyponatremia were categorized into CSW and other causes. Three and 6 months outcome was defined using modified Rankin Scale (mRS) as good (<2) or poor (≥ 2).
Results: Out of 81 patients with TBM, 32 (39.5%) had ischemic stroke. CSW was the commonest cause of hyponatremia and occurred in 34 (42%) patients. Stroke occurred in tubercular zone in 10, ischemic zone in 15 and both in 7 patients. The patients with ischemic zone infarction were older and had stroke risk factors such as diabetes mellitus, hypertension and hyperlipidemia. Out of 16 (47%) patients with CSW, 10 (62.5%) had stroke during the polyuric phase. The patients with CSW had more frequent deep white matter infarcts ($P = 0.01$) which were in internal border zone in 4 (40%).
Conclusion: In TBM, stroke occurred in 39.5% of the patients, 50% of whom had CSW. Volume contraction due to CSW may contribute to stroke.

Introduction

Tuberculous meningitis (TBM) occurs in 0.9% of patients with tuberculosis.[1] The pathophysiology of TBM includes basal exudates, hydrocephalus, granuloma and infarction.[2] TBM is an important cause of stroke in young in endemic areas.[3,4] Stroke in TBM is reported in 13–67% of patients depending on the method of evaluation.[3,5–13] Recent studies, however, have revealed high frequency of stroke in TBM.[14,15] Magnetic resonance angiography (MRA) has shown two patterns of abnormalities such as (i) disseminated irregular caliber of intracranial arteries with or without reduction in distal branches and (2) localized stenosis of the vessels at the base of brain.[16] In a study, vascular involvement was noted in 44.6% of patients with TBM and was related to hydrocephalous, basal exudates and poor prognosis.[16] High frequency of hyponatremia has been reported in patients with TBM (44.7%) and in stroke (43%), and CSW was the commonest cause of hyponatremia in both.[17,18] In the available literature, there was no study evaluating the relationship between stroke and CSW in TBM. It is possible that stroke in TBM may be associated with more frequent and severe hyponatremia due to

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CSW. The present study has been undertaken to evaluate the spectrum of stroke in TBM and its relation to CSW.

Subjects and methods

This prospective cohort study was conducted in a tertiary care referral teaching hospital in India during August 2014 to October 2016. The study was approved by the Institute Ethics Committee and the patients or their authorized representatives gave consent.

Diagnosis of TBM

The diagnosis of TBM was based on clinical, MRI and CSF criteria.[19]

The presence of acid fast bacilli in CSF smear, positive CSF culture or polymerase chain reaction for *Mycobacterium tuberculosis* was considered definite TBM.[19]

Diagnosis of ischemic stroke

The diagnosis of ischemic stroke was based on MRI showing iso-intense to hypointense on T1W and hyperintense on T2W/FLAIR, and/or restriction on diffusion-weighted imaging (DWI). T1 contrast study was carried out using gadodiamide 0.1 nmol/kg intravenously. Cranial MRI and MRA was carried out using 3 T scanner (Signa GE Medical System, Wisconsin, USA). Cranial MRI was examined for leptomeningeal enhancement, hydrocephalus, tuberculoma and infarctions. New stroke on repeat MRI was also noted.

Location and subtypes of stroke

The infarctions were classified according to the anatomic location and vascular supply as well as into 'tubercular zone' and 'ischemic zone'.[2]

Border zone infarcts

The 'cortical border-zone' was classified as paramedian (between anterior and middle cerebral artery), anterior (between anterior and middle cerebral artery territory) or posterior (between posterior and middle cerebral artery territory). The 'internal border-zone' infarcts included region between lenticulostriate and middle cerebral artery territory, lenticulostriate and anterior cerebral artery, Hubner artery and anterior cerebral artery and anteriorchoroidal and posterior cerebral artery.[20]

Clinical evaluation

History of vomiting, diarrhea and drug intake (carbamazepine, mannitol and acetazolamide) was noted. Consciousness was assessed by Glasgow Coma Scale (GCS). The severity of TBM was categorized as stages I–III using Medical Research Council criteria.[21] The stroke risk factors such as age, gender, smoking (smoking presently or till 2 months back), hypertension (blood pressure $\geq$ 140/90 mmHg, history of hypertension or on antihypertensive treatment), diabetes mellitus (fasting blood sugar $>$126 mg/dl, 2 h postprandial blood sugar $\geq$ 200 mg/dl or on oral hypoglycemic drugs or insulin therapy) and hyperlipidemia (on dietary modification or lipid lowering drugs or abnormal lipid level) were also noted. Alcohol consumption was enquired.

Investigations

The investigations included hemoglobin, blood counts, hematocrit serum bilirubin, alkaline phosphatase, transaminases, creatinine, fasting and postprandial blood sugar, HIV serology, radiograph of chest and abdominal ultrasonography. Echocardiography was done when indicated. Cerebrospinal fluid was examined for protein, cells, glucose, bacteria, fungi, malignant cells; smear and culture for *M.tuberculosis*. Serum osmolality, urine osmolality and urine sodium were measured. Hyponatremia was diagnosed if serum sodium was $<$ 135 mEq/L in two consecutive reports 24 h apart. Hyponatremia was defined by the lowest level of serum sodium. Serum sodium levels were checked on alternate day till the patient was discharged. Extracellular fluid volume status was assessed by tachycardia, dry mucous membranes, edema, tenting of the skin and capillary refill time. Central venous pressure (CVP) was measured if clinically indicated and CVP of 6–10 cm was considered normal. Daily fluid intake and output chart were maintained. Body weight was measured on admission and daily variation in weight was monitored on a special bed (LINET Eleganza3XC, Slaný, Czech Republic). Other causes of hyponatremia such as drugs, diuretics, heart failure, hypothyroidism and Addison's disease were excluded.

Diagnosis of cerebral salt wasting

Cerebral salt wasting (CSW) was considered in the presence of following features:

Essential (all required):

1. Polyuria: urine output more than 3L for at least two consecutive days.
2. Hyponatremia: serum sodium $<$135 mEq/L on two consecutive evaluations 24 h apart.
3. Exclusion of secondary causes such as endocrine abnormalities, renal, cardiac and hepatic failure and diuretics.

Supportive criteria: at least three out of five of the following:

1. Clinical findings of hypovolemia such as hypotension, dry mucous membranes, tachycardia or postural hypotension.
2. Persistent negative fluid balance as determined 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. CVP $<$ 6 cm of water.
5. Urinary sodium $>$40 mEq/L or urine osmolality $>$300 mOsm/L in two consecutive reports.

Management

The patients received four drugs anti tubercular treatment (RHZE) for 6 months followed by RH for 12 months. Rifampicin was prescribed 10 mg/kg ($\sim$450 mg/d), isoniazid 5 mg/kg ($\sim$300 mg/d), pyrazinamide 25 mg/kg ($\sim$1500 mg/d) and ethambutol 15 mg/kg ($\sim$800 mg/d). The patients also received prednisone 0.5 mg/kg ($\sim$40 mg) and aspirin up to 150 mg daily if not contraindicated. The patients were subjected to ventriculoperitoneal shunt or external ventricular drainage or mechanical ventilation if indicated.

For the management of hyponatremia, the offending drugs if any were withdrawn and the underlying medical condition treated. All patients with CSW were treated with oral salt supplementation and intravenous normal saline. Fludrocortisone

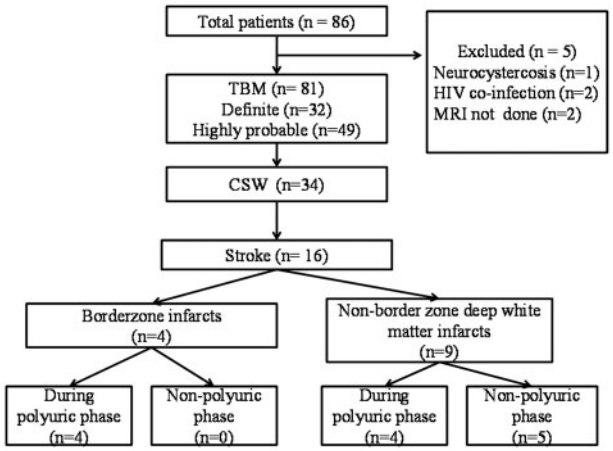

Figure 1. Flow diagram of patients with TBM who developed CSW and infarction in different brain regions. Majority of infarctions occurred in the polyuric phase of CSW.

(0.1–0.4 mg /day) was prescribed if the patient did not respond to saline therapy.

Follow-up and outcome

The patients were followed up at 1, 3 and 6 months and earlier if indicated. Patients or their caregivers were advised to maintain a 24 h intake output chart once every week. During follow-up, the neurological status, modified Rankin Scale (mRS) and intake–output charts were reviewed. Serum and urinary sodium and osmolality were measured. Functional outcome at 3 and 6 months was noted. The patients were considered to have a poor outcome if mRS score was >2 and good if mRS score ≤ 2.

Statistical analysis

Continuous and normally distributed variables were represented as mean $\pm$ SD while continuous but skewed variables were represented as median and range. Statistical significance was defined as two-tailed P values < 0.05. For normally distributed continuous variables, independent t-test and for skewed variables, Mann–Whitney U test was used. $\chi 2$ or Fisher's exact test was used to compare the categorical variables. Statistical analyses were performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

Eighty-six patients were screened, five of whom were excluded (Figure 1). The patients' median age was 27.5 (5–75) years, 36 (44.4%) of whom were males. Extra CNS tuberculosis was present in 17 (21%) patients; pulmonary and abdominal in three each, disseminated and spine TB in five each and lymph node involvement in one. The median duration of illness was 60 (30–120) days.

Location and subtypes of stroke

Thirty-two (39.5%) patients had stroke that was symptomatic in 23 (72%) patients and was noted at the time of admission in 12 (37.5%), within 3 months in 14 (43.7%) and after 3 months in six (18.7%) patients. Twenty patients (62.5%) had multiple infarctions. The median number of infarctions was 2.3 (1–6). The infarctions were cortical in seven patients (22%) and subcortical in the remaining. The location of sub-cortical infarctions was as follows: internal capsule in 23 (72%), basal ganglia in 18 (56%), thalamus in 10 (31%), corona radiata in 13 (40.6%) and infra-tentorial in seven (22%) patients. The infarctions were located in tubercular zone in 10 (31%) (Figure 2), ischemic zone in 15 (47%) and both in seven (22%) patients.

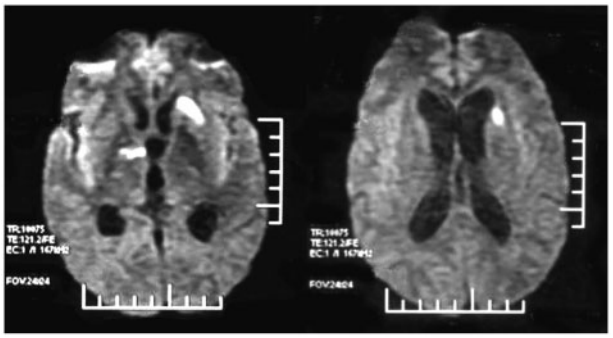

Figure 2. Cranial DWI MRI axial section showing acute infarct in the tubercular zone in a 9-year-old boy with stage II TBM. This patient did not have hyponatremia.

CSW and its relationship with stroke

Hyponatremia occurred in 46 (57%) patients with TBM and was most commonly due to CSW, which occurred in 34 (42%) patients after a median of 11 (1–191) days of admission. Sixteen (47%) patients had both CSW and stroke, and stroke occurred during the polyuric phase of CSW in 10 (62.5%, $P = 0.03$) (Figure 3). In patients with CSW, systolic blood pressure (SBP) was lower than those in the non CSW group (115 vs. 123 mm Hg; $P = 0.04$), but diastolic blood pressure (DBP) did not show any significant difference (75 vs. 79 mm Hg; $P = 0.09$). Hyponatremia was more severe in patients with stroke (126 vs. 130 mEq/L; $P = 0.02$) and persisted for longer time (median 11 vs. 7 days; $P = 0.02$) compared to those without stroke (Table 1). Despite serum sodium correction, urinary output remained high for longer duration in the patients with stroke (median 67, range = 22—323 days) compared to those without stroke (median 34, range = 12—180 days; $P = 0.01$).

The patients with CSW had more frequent infarctions in the deep white matter (corona radiata) than those without [10(62.5%) vs. 3(19%) patients; $P = 0.01$)] (Table 3). In four (40%) patients, deep white matter infarctions were located in the internal border zone (Figure 4). The clinical and MRI findings between TBM patients with and without CSW are compared in Table 2.

Risk factors and predictors of stroke

On comparing the patients with and without infarction, the significant predictors of stroke were admission stage of TBM ($P < 0.01$), admission GCS score ($P < 0.01$), hydrocephalus ($P = 0.02$) and meningeal enhancement ($P = 0.01$) (Table 1). The patients with infarction in the ischemic zone were older than those in the tubercular zone (40 vs. 16.5 years; $P = 0.05$). The stroke risk factors such as diabetes mellitus, hypertension and hyper-lipidemia were also significantly more frequent in the patients with infarctions in the ischemic zone compared to those in the tubercular zone (Table 3).

Outcome

Eight patients died in the hospital; two (6%) with infarctions and six (12%) without ($P = 0.51$). Three patients lost to follow-up at 3 months, and another one at 6 months, who have been excluded

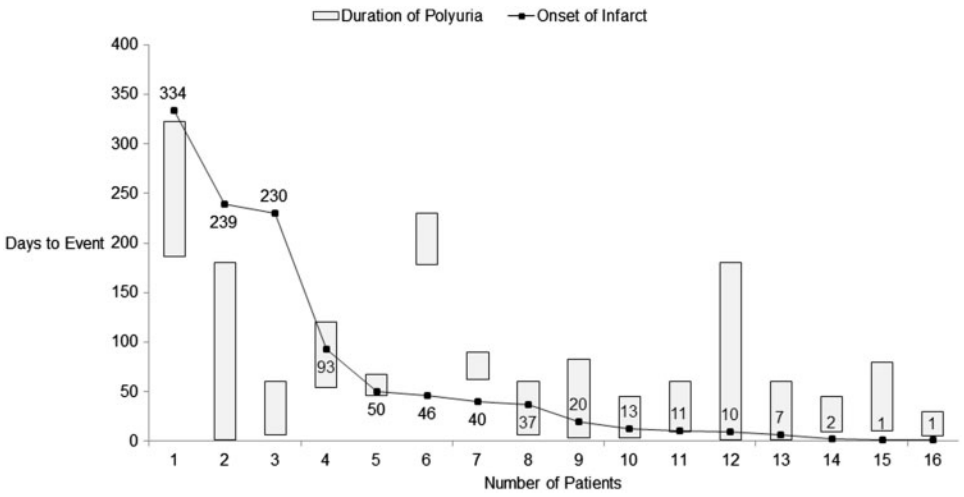

Figure 3. Showing the duration of polyuria and the onset of stroke in patients with CSW. The vertical grey bars denote the onset (lower limit) and subsidence (upper limit) of polyuria in each patient. The black small squares denotes the day of stroke after admission. Ten of 16 patients developed stroke during CSW (high urinary output).

Table 1. Comparison of demographic, clinical and imaging features of tubercular meningitis patients with and without stroke

Parameters	With stroke ($N = 32$)	Without stroke ($N = 49$)	*P*-value
Age (years)—Median (range)[a]	28.5 (5–62)	26 (8–75)	0.82
Diabetes—*n* (%)	6 (18.8)	5 (10)	0.27
Hypertension—*n* (%)	6 (18.8)	4 (8)	0.16
Smoking—*n* (%)	5 (16)	3 (6)	0.25
Alcohol—*n* (%)	1 (3)	3 (6)	1.0
Stage TBM at admission—*n* (%)			
I	4 (12.5)	18 (36.7)	
II	17 (53)	27 (55)	
III	11 (34.4)	4 (8.2)	<0.01
Admission GCS—median (range)[a]	12.5 (4–15)	15 (6–5)	<0.01
MRI findings—*n* (%)			
Tuberculomas	23 (79.3)	34 (72.3)	0.49
Hydrocephalus	23 (72)	22 (45)	0.02
Exudates	25 (78)	29 (59)	0.07
Enhancement	31 (97)	38 (81)	0.01
Hyponatremia—*n* (%)	20 (62.5)	27 (58.7)	0.48
CSW—*n* (%)	16 (50)	18 (37)	0.24
Days to sodium correction—Median (range)[a]	11 (2–38)	5 (1–54)	0.03
In hospital mortality—*n* (%)	2 (6)	6 (12)	0.47
Outcome at follow-up—*n* (%)			
Mortality at 3 months ($n = 78$)[b]	3 (10)	9 (18.8)	0.35
Disability at 3 months ($n = 66$)[c]	13 (48.1)	7 (17.9)	0.01
Mortality at 6 months ($n = 77$)[b]	3 (10.3)	9 (18.8)	0.52
Disability at 6 months ($n = 65$)[c]	10 (38.5)	7 (17.9)	0.06

CSW = cerebral salt wasting, GCS = Glasgow Coma Scale, MRI = Magnetic resonance imaging.

[a] Range denotes minimum and maximum values.

[b] Excluding lost to follow-p.

[c] Excluding deaths and lost to follow-up.

from the analysis. Four additional patients died at 3 month follow-up; one in infarction and three in the non-infarction group. This difference was not significant ($P = 0.35$). However, significantly higher number of patients with infarctions had poorer outcome (m RS ≥ 2) at 3 months (48.1% vs. 17.9%; $P = 0.01$) compared to those without infarctions, but this difference was not significant at 6 months (38.5% vs. 17.9; $P = 0.06$) (Table 1). On comparing the patients with symptomatic ($n = 9$) and asymptomatic ($n = 23$) infarctions, the in-hospital mortality (0 vs. 2), 3 months mortality (0 vs. 3) and poorer outcome at 3 month [3(37.5%) vs. 13(59%); $P = 0.42$] was insignificantly worse in asymptomatic group. The median GCS score in symptomatic infarction group was 14 (8–15) and in asymptomatic group was 12 (4–15) ($P = 0.05$).

Table 2. Comparison of MRI findings and outcome in patients with TBM with and without CSW

Parameters	CSW ($n = 34$) *n* (%)	Without CSW ($n = 47$) *n* (%)	*P*-value
Infarct on MRI	16 (47)	16 (34)	0.24
Multiple infarcts	11 (69)	9 (56)	0.46
Infarct zone			
BG infarct	11 (69)	7 (44)	0.15
Thalamus	6 (37.5)	4 (25)	0.45
Corona radiate	10 (62.5)	3 (19)	0.01
Lobar infarct	7 (43.8)	0	—
Hydrocephalus	27 (79.4)	18 (42)	0.001
Exudates	28 (82.4)	26 (60.5)	0.04
SBP (mmHg)	115 ± 17.8	123 ± 15.7	0.04
DBP (mmHg)	75 ± 12.5	79 ± 10.6	0.09
Poor m RS score at 3 months	21 (64)	10 (26)	<0.01

Discussion

In TBM, stroke occurred in 39.5% patients, which was mainly in sub-cortical white matter and basal ganglia. The patients with stroke had more severe hyponatremia which was mainly due to CSW and was associated with poor outcome at 3 months. Stroke occurred during the polyuric phase of CSW in 62.5% of patients. We, for the first time, highlight the importance of CSW in TBM-related stroke.

The clinical diagnosis of stroke in TBM is not easy especially in comatose patients. In an earlier study on 55 patients with

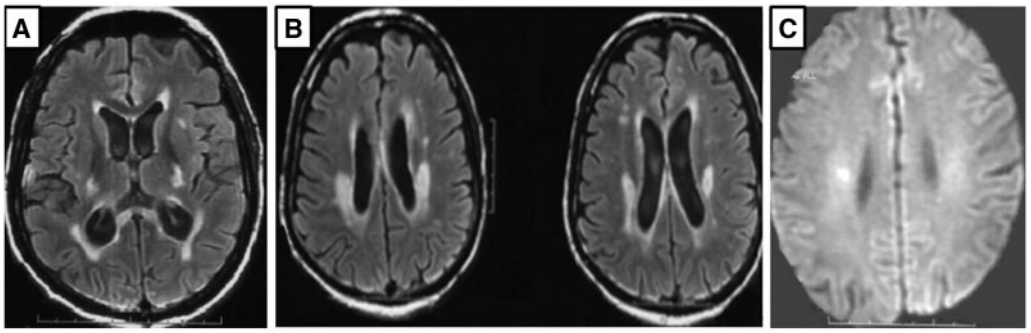

Figure 4. Cranial T2 FLAIR MRI axial sections show infarcts in the ischemic (**A**) and peri ventricular region bilaterally (internal border zone) (**B**) in a 45- year-old male, stage III TBM with type 2 diabetes mellitus and hypertension. CSW was diagnosed on Day 40, he developed infarction on Day 68 of admission. Hyponatremia was corrected after 12 days and urinary output normalized after 3 months. (**C**) Cranial DWI MRI axial section of another 15-year-old male, stage III TBM patient showing asymptomatic infarct in right peri-ventricular white matter (internal border zone) with CSW diagnosed at admission (Day 1).

Table 3. Comparison of stroke risk factors in patients with infarcts in ischemic and tubercular zone (excluding combined infarct patients)

Risk factors	TB zone infarct ($n = 10$)	Ischemic zone infarct ($n = 15$)	*P*-value
Diabetes—*n* (%)	0	6 (40)	0.05
Hypertension—*n* (%)	0	6 (40)	0.05
Age (years) —Median (range)[a]	16.5 (5–55)	40 (6–62)	0.05
Total cholesterol (mg/dl)—mean (SD)	163 (42)	189 (48)	0.04
LDL-cholesterol (mg/dl)—mean (SD)	92 (34)	117 (38)	0.01

LDL =Low density lipoprotein, SD =standard deviation.
[a]Range denotes minimum and maximum values.

TBM, the infarctions were subclinical in 58% of patients and were diagnosed on MRI.[3] The worse 3 month outcome of asymptomatic infarction in our study could be due to difficulty in diagnosing the silent infarctions, especially in comatose patients.

The distribution of infarctions in our study is in agreement with an earlier study in which the infarctions were in the tubercular zone in 8 and ischemic zone in 18 patients. The frequency of caudate involvement was significantly higher in patients with TBM compared to those with ischemic stroke.[3] In the study by Hsieh *et al*., the infarctions in tubercular zone were present in 75%.[22] In another study, however, tubercular zone infarctions were seen in only 2 (6%) patients, and 67% infarctions occurred in both ischemic and tubercular zone.[23] In our study, infarctions were present in tubercular zone in 31% of patients.

In the present study, CSW was associated with corona radiata infarction, hydrocephalus and basal exudates. There are two components of CSW: first, the polyuria leading to hypovolemia and second, natriuresis leading to hyponatremia. Out of 16 patients who had CSW with stroke, infarctions occurred during polyuric phase in 10 when they were having negative fluid balance. Among these 10 patients, 4 (40%) had infarctions in the intrinsic border zone. It is likely that negative fluid balance in patients with CSW may result in volume contraction, hypo perfusion or thrombosis in already compromised vessels.

The stroke in TBM is multifactorial and is contributed by all three components of Virchow's triad; endothelial injury, stasis of blood and hypercoagulability. We have not evaluated the procoagulant state in this study, but it has been reported.[24] The basal exudates are associated with periarteritis and panarteritis resulting in endothelial injury.[25,26] Organization of basal exudates results in compromise of vessel lumen. CSW is associated with a negative fluid balance, which persists for longer period in the patients with stroke. Prolonged hypovolemia may lead to hypoperfusion, and in the background of vasculitis, could result in ischemia and infarctions. In our patients with CSW, there was significant reduction of SBP. The involvement of internal border-zone underscores the role of hypoperfusion and hypotension in TBM-related stroke. Moreover, the collaterals that are natural defense mechanism during vascular occlusion and hypotension may be also be compromised in TBM thereby rendering the internal border zone more vulnerable. In a MRI-based study, border zone necrosis was found in 50% of children with TBM, which was associated with basal exudates.[27] When infarcts occur adjacent to severe meningeal and cisternal inflammation, the areas are considered 'border-zone' infarction.[28] Maintaining euvolemia in CSW is difficult because increasing the intake results in corresponding increase in urinary output, and the negative fluid balance persists. Fludrocortisone therapy normalizes the sodium balance in TBM but polyuria persists (unpublished observation), although both negative fluid balance and polyuria responded to fludrocortisone in subarachnoid haemorrhage.[29]

Limitations of the study

Our study is limited by small sample size, single center experience from a tertiary care hospital with a referral bias for more severe and advanced patients. Our results therefore cannot be extrapolated to TBM in general. These preliminary results need to be confirmed by further studies. We have used simple bedside criteria for CSW which have not been validated against a gold standard. Our aim, however, was to provide simple criteria, which may have wider application especially in the resource poor countries where TBM is common.

Conclusion

It can be concluded that TBM results in infarctions in 39.5% of patients and volume contraction due to CSW may contribute to stroke.

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Ethical approval: This study was approved by Institutional Ethics Committee (2013-83-EMP-72), SGPGIMS, Lucknow, India.

Conflict of interest: None declared.

References

1. Ducomble T, Tolksdorf K, Karagiannis I, Hauer B, Brodhun B, Haas W, *et al*. The burden of extra pulmonary and meningitis tuberculosis: an investigation of national surveillance data, Germany, 2002 to 2009. *Euro Surveill* 2013; **18**: pii: 20436
2. Nair PP, Kalita J, Kumar S, Misra UK. MRI pattern of infarcts in basal ganglia region in patients with tuberculous meningitis. *Neuroradiology* 2009; **51**:221–5.
3. Kalita J, Misra UK, Nair PP. Predictors of stroke and its significance in the outcome of tuberculous meningitis. *J Stroke Cerebrovasc Dis* 2009; **18**:251–8.
4. Dalal PM, Dalal KP. Cerebrovascular manifestations of infectious disease. In: Toole JF, ed. *Handbook of Clinical Neurology. Vascular Diseases Part III*. Amsterdam, Elsevier, 1989, 411–41.
5. Thomas MD, Chopra JS, Walia BNS. Tuberculous meningitis (TBM): a clinical study of 232 cases. *J Assoc Physicians India* 1977; **25**:633–9.
6. Dalal PM. Observations on the involvement of cerebral vessels in tuberculous meningitis in adults. *Adv Neurol* 1979; **25**:149–59.
7. Bullock MR, Welchman JM. Diagnostic and prognostic features of tuberculous meningitis on CT scanning. *J Neurol Neurosurg Psychiatr* 1982; **45**:1098–101.
8. Kingsley DP, Hendrickse WA, Kendall BE, Swash M, Singh V. Tuberculous meningitis: role of CT in management and prognosis. *J Neurol Neurosurg Psychiatr* 1987; **50**:30–6.
9. Shukla R, Abbas A, Kumar P, Gupta RK, Jha S, Prasad KN. Evaluation of cerebral infarction in tuberculous meningitis by diffusion weighted imaging. *J Infect* 2008; **57**:298–306.
10. Tai MS, Viswanathan S, Rahmat K, Nor HM, Kadir KA, Goh KJ, *et al*. Cerebral infarction pattern in tuberculous meningitis. *Sci Rep* 2016; **6**:38802.
11. Deshpande DH, Bharucha EP, Mondkar VP. Tuberculous meningitis in adults. (A clinico-pathological study of 18 cases). *NeurolIndia* 1969; **17**:28–34.
12. Dastur DK, Lalitha VS, Udani PM, Parekh U. The brain and meninges in tuberculous meningitis-gross pathology in 100 cases and pathogenesis. *Neurol India* 1970; **18**:86–100.
13. Poltera AA, Templeton AC. Intracranial tuberculosis in Uganda: a post-mortem survey. *Afr J Med Sci* 1973; **4**: 343–9.
14. Vasishta RK, Banerjee AK. CNS tuberculosis–pathology. In: Chopra JS, Sawhney IMS, eds. *Neurology in Tropics*. New Delhi, Churchill Livingstone 1999, 391–8.
15. Shankar SK, Santosh V, Mahadevan A, Yasha TC, Satishchandra P. Pathology of cerebral vasculature in neurotuberculosis-some observations. In: Mehta VS, Misra UK, eds. *Progress in Neurosciences*. New Delhi, Neurological Society of India, 2001, 134–41.
16. Lu TT, Lin XQ, Zhang L, Cai W, Dai YQ, Lu ZZ, *et al*. Magnetic resonance angiography manifestations and prognostic significance in HIV-negative tuberculosis meningitis. *Int J Tuberc Lung Dis* 2015; **19**:1448–54.
17. Misra UK, Kalita J, Bhoi SK, Singh RK. A study of hyponatremia in tuberculous meningitis. *J Neurol Sci* 2016; **367**:152–7.
18. Kalita J, Singh RK, Misra UK. Cerebral salt wasting is the most common cause of hyponatremia in stroke. *J Stroke Cerebrovasc Dis* 2017; **26**:1026–32.
19. Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, *et al*. Tuberculous meningitis: a uniform case definition for use in clinical research. *Lancet Infect Dis* 2010; **10**: 803–12.
20. Mangla R, Kolar B, Almast J, Ekholm SE. Border zone infarcts: pathophysiologic and imaging characteristics. *Radiographics* 2011; **31**:1201–14.
21. British Medical Research Council. Streptomycin in tuberculosis trials committee: streptomycin treatment of tuberculous meningitis. *Lancet* 1948; **1**:582–96.
22. Hsieh FY, Chia LG, Shen WC. Locations of cerebral infarctions in tuberculous meningitis. *Neuroradiology* 1992; **34**: 197–9.
23. Tai MS, Viswanathan S, Rahmat K, Nor HM, Kadir KA, Goh KJ *et al*. Cerebral infarction pattern in tuberculous meningitis. *Sci Rep* 2016; **6**:38802.
24. Schoeman J, Mansvelt E, Springer P, van Rensburg AJ, Carlini S, Fourie E. Coagulant and fibrinolytic status in tuberculous meningitis. *Pediatr Infect Dis J* 2007; **26**:428–31.
25. Misra UK, Kalita J, Srivastava M, Mandal SK. Prognosis of tuberculous meningitis: a multivariate analysis. *J Neurol Sci* 1996; **137**:57–61.
26. Lammie GA, Hewlett RH, Schoeman JF, Donald PR. Tuberculous cerebrovascular disease: a review. *J Infect* 2009; **59**:156–66.
27. Omar N, Andronikou S, van Toorn R, Pienaar M. Diffusion-weighted magnetic resonance imaging of borderzone necrosis in paediatric tuberculous meningitis. *J Med Imaging Radiat Oncol* 2011; **55**:563–70.
28. Andronikou S, Wieselthaler N. Modern imaging of tuberculosis in children: thoracic, central nervous system and abdominal tuberculosis. *Pediatr Radiol* 2004; **34**:861–75.
29. Hasan D, Lindsay KW, Wijdicks EF, Murray GD, Brouwers PJ, Bakker WH, *et al*. Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. *Stroke* 1989; **20**: 1156–61.