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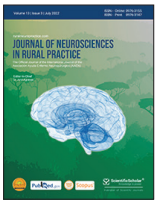

*Original Article*

# The spectrum of cerebrospinal fluid findings in tuberculous meningitis and their relation to severity, radiological features, and outcome

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## ABSTRACT

**Objectives:** The aim of the study was to evaluate cerebrospinal fluid (CSF) findings in tuberculous meningitis (TBM) and correlate it with severity, radiological features, and outcome of TBM.

**Materials and Methods:** In a retrospective study, data from admitted TBM patients were analyzed, and findings of CSF examinations were recorded. The CSF was categorized as typical (protein 50–500 mg/dL, cells 50–500/mm$^3$, and glucose 50% or lower of blood sugar); those above and below these values were categorized as increased or decreased, respectively. The CSF findings were correlated with stage of TBM, and 3-month outcome and radiological features. Paradoxical response was also noted.

**Results:** There were 111 patients with TBM (definite 34, highly probable 77). On admission, 20 patients were in Stage I, 63 in Stage II, and 28 in Stage III TBM. CSF cells were in typical range in 73, low in 27 and increased in 11 patients. Protein was in typical range in 92 patients decreased in 11 patients and increased in eight patients. Sugar was normal in 41 and reduced in 70 patients. CSF cells, glucose, and protein did not correlate with the severity of meningitis. Fifteen patients had normal initial magnetic resonance imaging (MRI). Tuberculomas were present in 53 patients, hydrocephalus in 43 patients, basal exudates in 43 patients, and infarction in 44 patients. Mixed findings were present in 65 patients. The MRI features did not correlate with CSF. Second CSF was available after a median duration of 26 (13–276) days in 50 patients. The CSF cells were decreased in 20 and increased in 30 patients, protein increased in 30 and sugars decreased in 16 patients. Paradoxical worsening occurred in 27 patients. Fifty-one patients recovered completely, 41 partially, 15 had poor, three patients were lost to follow-up, and one died. CSF parameters did not correlate with 3-month outcome or paradoxical worsening. CSF parameters do not differ significantly between baseline and 1 month CSF, but cells and lymphocytes changed significantly between 1$^{st}$ month and 3$^{rd}$ month CSF.

**Conclusion:** Typical CSF findings were present in 66% and did not correlate severity of TBM, radiological features paradoxical worsening or 3-month outcome. CSF cell count decreased within 3 months of treatment.

**Keywords:** Cerebrospinal fluid, Tubercular meningitis, Outcome

## INTRODUCTION

Tuberculous meningitis (TBM) indicates severe form of tuberculosis and occurs in 0.9% patients.[1] Assuming global burden of tuberculosis as 1.4 million, 0.36 million patients with TBM are expected in the world. About 30% of them die and half the survivors have significant disability. In India, an estimated 1.5 people/100,000 dies from TBM each year.[2] A definite diagnosis of TBM is possible in 10–20% of patients only because of low smear or culture positivity of cerebrospinal fluid (CSF). In most patients, therefore, the antitubercular therapy (ATT) is started empirically based on clinical, CSF, and magnetic resonance imaging (MRI) findings. The new molecular and diagnostic techniques have not reached the desired level of sensitivity; moreover, these are expensive and not widely available in the resource poor countries where TBM is prevalent.[3] CSF findings therefore are crucial for the diagnosis of TBM. There are only a few systematically planned studies on the CSF changes in TBM.[4,5] However, none analyzed CSF parameters in comparison with radiological features and paradoxical reactions.

### Objectives

The objectives of the study are as follows:

1. To study the spectrum of CSF findings in patients with TBM and their relationship with the severity of TBM

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2. To study whether CSF examinations help in correlating paradoxical reactions and outcome of TBM patients.

### Subjects

The retrospective data from electronic medical records for patients admitted with definite and highly probable tubercular meningitis of a tertiary care hospital in India during August 2009 to October 2019 were included in the study.

### Diagnosis of TBM

Diagnosis of TBM was based on essential and supportive criteria.

#### *Essential criteria*

Features suggestive of meningitis (headache, irritability, vomiting, fever, weight loss, neck stiffness, convulsions, focal signs, or altered sensorium in isolation or in combination) for more than 5 days.

#### *Supportive criteria*

a. CSF cells of 10–500/μL, with lymphocytes predominating (>50%), protein 50–500 mg/L and sterile bacterial and fungal culture
b. Cranial computed tomography (CT) or MRI imaging showing evidence of basal exudates, infarct, tuberculoma, or hydrocephalus in isolation or in combinations
c. Evidence of extra central nervous system (CNS) tuberculosis (on chest X-ray consistent with tuberculosis or cranial CT, MRI or ultrasound suggestive of tuberculosis or Acid-Fast Bacillus identified or *Mycobacterium tuberculosis* cultured from sputum, lymph node, gastric aspirate, or urine).
d. Exclusion of alternative diagnoses highly probable TBM.

Essential criteria with two supportive criteria were categorized as; and presence of acid-fast bacilli in CSF smear, positive CSF culture, or polymerase chain reaction for *M. tuberculosis* was considered definite.

The severity of TBM was categorized as Stage I (meningitis only), Stage II (meningitis with focal neurological deficit or Glasgow Coma Scale (GCS) score between 11 and 14), and Stage III (meningitis with GCS score <11).[6]

### Exclusion criteria

The patients below 10 years of age, pregnant or lactating women and those with malaria, septic, fungal or carcinomatous meningitis, head injury, brain tumor, primary renal, hepatic or cardiac failure, endocrinal disorders, malignancy, or any condition limiting the life expectancy to 1 year or less was excluded from the study.

## MATERIALS AND METHODS

CSF examination results on admission and repeated any time were recorded. All the CSF findings were recorded including protein, cells, glucose, smear, and culture for *M. tuberculosis.* Cranial CT scan or MRI findings or both which were done in all the patients on admission and repeated if clinically indicated also was recorded.

CSF was considered typical if the cells were 50–500/mm$^3$, protein 50–500 mg/dL range, and Glucose <50% of the blood sugar. CSF cells was divided into encephalitic type if cells are 5–49 and pseudopyogenic if cells were >500/dL. CSF protein was also divided into mild if it is <50 mg/dL, typical if between 50 and 500 and severe if >500. CSF was considered as lymphocytic predominant if lymphocytes percentage was more than 50%.CSF glycorrhachia was defined as CSF glucose <50% of serum glucose.

Paradoxical reaction to antitubercular treatment during 3 months of ATT was noted which included increase in the size of hydrocephalus, increase in exudates, new appearance of tuberculomas or increase in the size of tuberculoma or abscess formation, and appearance of new stroke.

### Outcome

Death during hospital stay and at 3 months was noted. The outcome at 3 months was evaluated by modified Rankin scale (mRS) and categorized as good (mRS≤2) poor (mRS>2).

### Statistical analysis

Sample size according to prevalence was calculated as 73. Continuous and normally distributed variables were represented as mean ± standard deviation while continuous but skewed variables were represented as median and range. The CSF parameters on admission and at 3 months were compared using one way analysis of variance and stratified according to the stage of TBM. Chi-square or Fisher's exact tests were used to compare relation between categorical variables. The variable was considered significant if the two tailed $P$ value was < 0.05. Statistical analysis was performed using SPSS version 23 software (SPSS Inc., Chicago, IL, USA).

## RESULTS

One hundred and eleven patients were identified of which 34 had definite and 77 had highly probable TBM. The median age of the patients was 33 (13–75) years and 44 were females. At the time of admission, 20 patients were in Stage 1, 63 in Stage 2, and 28 in Stage 3. Focal weakness was present in 65 patients: Hemiplegia in 20, paraplegia in seven, and monoplegia in 20 patients. Cranial nerve palsies were present in 48, optic atrophy in six patients,

bulbar weakness in 22. Extra CNS tuberculosis was present in 40 patients such as lymphadenopathy in 25, pulmonary in 28, abdominal in eight, and bone tuberculosis in 18 patients.

### First CSF

The analysis of individual components of CSF revealed that cells were typical in 73, encephalitic in 27, and pseudo-pyogenic in 11 patients. Ninety-five patients had lymphocyte-predominant CSF, while 16 had polymorph-predominant CSF. Protein was in typical in 92 patients, decreased in 11, and increased in eight patients. Glycorrhachia was present in 70 patients and normal in 41 patients. Overall, first CSF was typical in 48 patients and atypical in 63. CSF pyogenic response (cells >500/mm$^3$ was present in 11 patients.

The CSF cells, protein, glucose, or lymphocytes did not correlate with the severity of TBM [Table 1].

### Radiological features

Initial MRI was normal in 15 patients. Tuberculomas were seen in 53 patients, hydrocephalus in 43, basal exudates in 43, and infarcts in 44. Mixed combination was present in 65 patients [Figure 1].

Presence of tuberculomas, hydrocephalus, basal exudates, and infarction did not correlate with CSF cells, protein, glucose, and lymphocytes level [Table 2].

### Second CSF examination

Repeat CSF was available in 50 patients after a median duration of 26 (3–276) days. Of this 27 was done for paradoxical worsening, rest were done for analyzing response to treatment.

On comparison with the initial CSF, cells decreased in 20 and increased in 30 patients. Protein increased in 36 patients and decreased in 14 patients. CSF sugar level was increased in 16 patients. Lymphocyte predominant CSF pleocytosis was present in 43 patients in the second CSF. No changes were significant [Table 3].

### Paradoxical reactions

Paradoxical response was present in 27 patients. Nine had increase in the size of hydrocephalus, 10 had increase in exudates, three had new onset stroke, 21 had new tuberculomas, and four had increase in size of tuberculomas. Of these cell counts increased in two patients, protein increased in seven, and CSF glucose levels decreased in three patients. These change in CSF cells ($P = 0.534$), protein ($P = 0.846$), and change in glucose ($P = 0.916$) had no significant relation with paradoxical reactions [Figure 2].

### Three-month outcome

Follow-up data revealed good outcome (mRS 0–2) in 51 patients and bad outcome (mRS 3 and above) in 57. No follow-up data were available for three patients. The baseline CSF and second CSF did not correlate with 3-month outcome. At 3 months, CSF findings were available in 45 patients. Cells became normal (<10) in 10 patients: encephalitic in 29, typical in five, and pseudo pyogenic in one patient. Protein: Normal in 15 patients, typical in 28, and severe in 2 patients. Hypoglycorrhachia was still noted in 28 patients. Three-month outcome was not correlated with initial CSF parameters: Cells ($P = 0.92$), protein ($P = 0.69$), and glucose ($P = 0.206$). CSF cells and lymphocytes changed significantly compared to 1$^{st}$ month CSF [Table 4].

## DISCUSSION

The results of this study reveal a wide spectrum of CSF findings in TBM. It was typical in 48 (36.3%) and atypical in majority (63.7%). The baseline CSF findings did not correlate with severity or radiological features and 3-month outcome. A second CSF also did not correlate with paradoxical worsening. All though first and second CSF did not differ significantly, cells and percentage of lymphocytes changed significantly between 2$^{nd}$ and 3$^{rd}$ month CSF.

CSF studies are considered a gold standard in the diagnosis of TBM.[6] Our results agree with Patel *et al.*[5] who showed typical CSF findings in 34% patients only and the typical CSF changes were restricted to some components only. In another study by Donald *et al.*[7] on children with TBM;

**Table 1:** Distribution of TBM stage with first CSF parameters.

| First CSF | Stage I *n*=20 | Stage II *n*=63 | Stage III *n*=28 | *P*-value |
|---|---|---|---|---|
| Cells (per mm$^3$) Mean±SD | 195±304.1 | 100.0±182.9 | 100.0±1113.2 | 0.249 |
| Protein (mg/dL) | 134.5±92.5 | 181±188.2 | 109±148.7 | 0.184 |
| Lymphocytes (% of total cells) | 82.5±26.05 | 95±16.3 | 90±34.1 | 0.868 |
| Glucose (mg/dL) | 37.0±45.0 | 38±530.1 | 39±27.9 | 0.111 |

SD: Standard deviation, TBM: Tuberculous meningitis, CSF: Cerebrospinal fluid

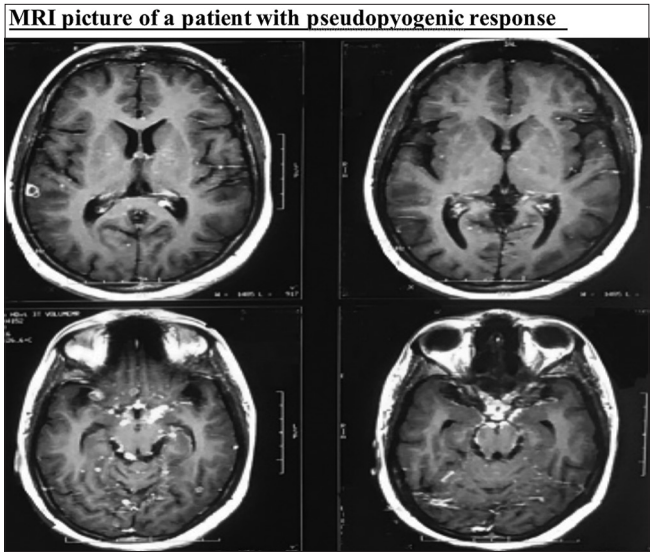


**Figure 1:** T1 contrast magnetic resonance imaging axial section showing multiple tuberculomas with basal exudates and meningeal enhancement in a 38-year-old female with a history of fever and headache for 1 month with highly probable Stage 2 TBM on day 35 of illness, cerebrospinal fluid cells 2400/mm$^3$ with 84% polymorphs, and protein174 sugar 20. At 3-month, the patient had good outcome (modified Rankin scale 0).

**Table 2:** Comparison of various MRI patterns in relation to the type of CSF.

| MRI | Encephalitic *n* (%) | Typical *n* (%) | Pseudo pyogenic *n* (%) | *P*-value |
|---|---|---|---|---|
| Tuberculoma | | | | |
| Present | 13 (56.5) | 37 (56.1) | 3 (42.9) | 0.792 |
| Absent | 10 (43.5) | 29 (43.9) | 4 (57.1) | |
| Hydrocephalus | | | | |
| Present | 10 (43.5) | 33 (49.3) | 3 (37.5) | 0.763 |
| Absent | 13 (56.5) | 34 (50.7) | 5 (62.5) | |
| Exudate | | | | |
| Present | 8 (34.8) | 34 (51.5) | 4 (57.1) | 0.338 |
| Absent | 15 (65.2) | 32 (48.5) | 3 (42.9) | |
| Infarction | | | | |
| Present | 10 (43.5) | 30 (45.5) | 4 (45.8) | 0.812 |
| Absent | 13 (56.5) | 36 (54.2) | 3 (42.9) | |

MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid

**Table 3:** Change in CSF parameters between first and second CSF.

| CSF parameters | 1st CSF | 2ndCSF | *P*-value |
|---|---|---|---|
| Cells (per mm$^3$) | 206.3±253.1 | 173.0±331.1 | 0.537 |
| Protein (mg/dL) | 166.9±101.4 | 257.9±775.5 | 0.401 |
| Lymphocytes (% of total cells) | 82.2±24.5 | 85.7±19.03 | 0.407 |
| Glucose (mg/dL) | 46.12±37.8 | 48.6±40.06 | 0.702 |

CSF: Cerebrospinal fluid

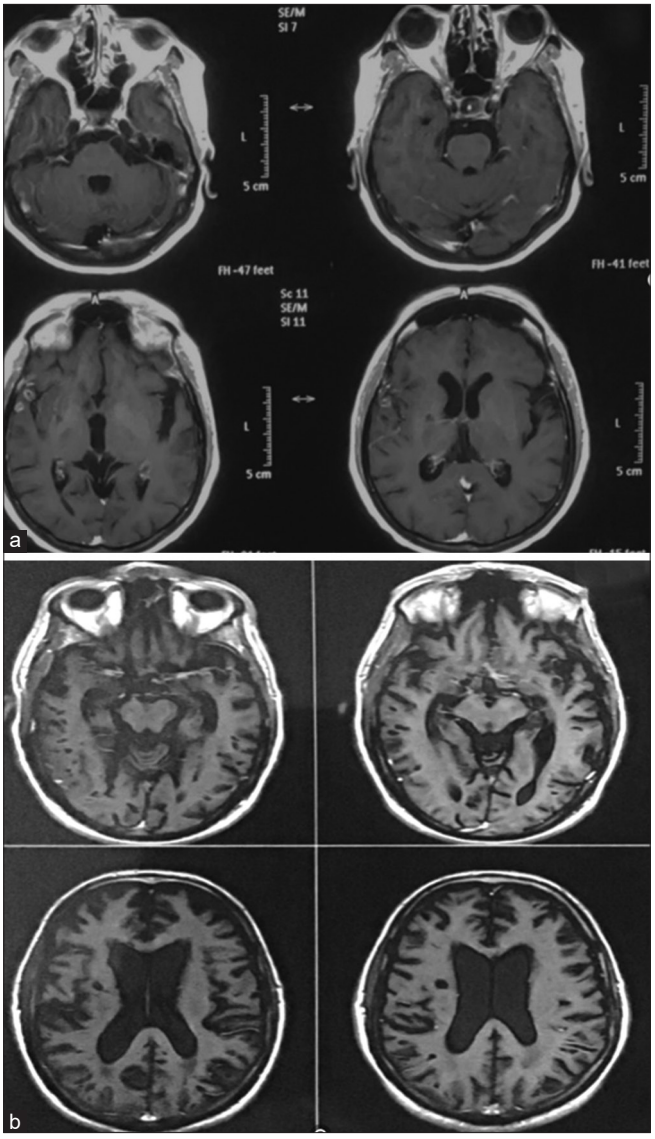


**Figure 2:** (a) Contrast magnetic resonance imaging axial section showing multiple tuberculomas with meningeal enhancement and with dilated ventricle in a 56 male with definite tuberculous meningitis Stage 3 presented on day 50 of illness, cerebrospinal fluid cells 10/mm$^3$ with all lymphocytes, and protein 60 sugar 45. (b) At 1 month, the patient had paradoxical worsening in the form of increased hydrocephalus.

**Table 4:** Changes in CSF parameters between 2nd and 3rd month CSF.

| CSF parameters | 2nd CSF | 3rd CSF | *P*-value |
|---|---|---|---|
| Cells (per mm$^3$) | 173±331.2 | 53.8±119.7 | 0.018 |
| Protein (mg/dL) | 257.9±775.5 | 133.6±160.1 | 0.269 |
| Lymphocytes (% of total cells) | 85.7±19.03 | 96.3±12.04 | 0.005 |
| Glucose (mg/dL) | 48.6±40.1 | 47.9±15.1 | 0.903 |

CSF: Cerebrospinal fluid

mild CSF protein rise (<0.89 g/L) were seen in 18% and mild pleocytosis in 44%.

When CSF shows marked pleocytosis, protein rise with hypoglycorrhachia the possibility of partially treated bacterial meningitis is considered and the patient may receive combined ATT and anti-pyogenic treatment. In such a situation, CSF examination is repeated to confirm the suitability of therapy.[8] Polymorphonuclear predominant response is sometimes found in TBM especially in first 2 weeks and the CSF protein may also rise in first 2–4 weeks.[9] In our study, the CSF findings neither correlated with the severity of TBM nor with 3-month outcome. In the study of Patel *et al*., also there was no correlation between the rate of change in CSF and clinical severity of TBM or its clinical response. However, a study by Thwaites *et al*. showed low CSF white cell counts, in particular neutrophils, and hypoglycorrhachia correlated with death in TBM patients.[10]

We have used oral prednisolone with ATT which could have altered the CSF findings in our patients. There are contradictory reports on the role of corticosteroids on CSF. O'Toole and Hockady have reported that the cells in CSF increased initially[11,12] whereas Bernard and Ashby reported decrease of cells and glucose.[13,14] But Marais *et al*. found no significant effect on cell count.[15] The CSF changes reflects intrathecal tuberculin reaction and depend on amount of antigen and sensitivity of the patients. In patients with decreased sensitivity, CSF cell count may be like viral encephalitis. When mycobacteria multiply inside CSF host inflammatory response is triggered and releases tumor necrosis factor alpha, interleulin-1 beta. Interleukins further activates the cascade of inflammatory mediators including matrix metalloproteins, prostaglandins, and reactive oxygen species and promotes entry of neutrophils into CSF. This neutrophil extravasation in bacterial meningitis is measured as CSF pleocytosis (Jeren and Beus, 1992).[16] CSF in TBM usually have moderate degree of pleocytosis.

### Limitations

The study is limited by a retrospective design, referral bias of a tertiary care hospital where advance or severe cases are referred. The result of this study therefore cannot be extrapolated to TBM in general. Few patients had received ATT before coming to our hospital which could have influence the CSF findings.

## CONCLUSION

CSF findings in TBM are quite variable and typical findings are found in 36.3% of patients. CSF findings do not correlate with severity of TBM or predict its outcome or paradoxical worsening.

### Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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