ORIGINAL ARTICLE

# Cerebrospinal Fluid Lactate in Tubercular Meningitis: Diagnostic or Prognostic Marker?

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## Abstract

**Introduction/Background**: Diagnosis of tubercular meningitis (TBM) continues to be a clinical challenge and available microbiological tests fail to attain the required accuracy standards. As a result, most guidelines for the diagnosis and management of TBM depend on clinical setting, cerebrospinal fluid (CSF) analyses including adenosine deaminase activity (ADA), and imaging to guide decision-making. Delay in diagnosis leads to high mortality and morbidity. As there is scarcity of data on CSF lactate in TBM and its role as a diagnostic and prognostic marker, study of CSF Lactate in TBM Patients was undertaken.

**Methods**: In this hospital based cross sectional study all admitted patients of meningo-encephalitis aged more than 15 years who fulfilled the diagnostic criteria for TBM were included. Routine haematological and biochemical investigations were done in all the patients. The CSF analysis was done including all routine microscopic parameters, lactate, Gram's stain, AFB and culture. Patients included were classified as definite, probable, or possible TBM as per WHO diagnostic criteria and were classified into three clinical stages using criteria laid down by the British Medical Research Council.

**Results**: Fifty five patients fulfilling the diagnostic criteria for tubercular meningitis were studied. Most of the patients were in stage II according to severity. An increase in CSF lactate and CSF ADA levels with increase in severity of clinical stage of TBM was observed. Other CSF parameters and imaging were not significantly different in various groups.

**Conclusion**: CSF lactate levels of study patients were higher than normal and showed increasing trend from possible to definite diagnosis of TBM suggesting that CSF lactate could be a predictor of definite diagnostic class of TBM though more studies with large number of patients are needed to prove its utility as prognostic tool.


## Introduction

World Health Organization (WHO) has estimated an annual incidence of 9.27 million new cases of TB worldwide, the number of prevalent cases being 13.7 million and most of the disease burden lies in Africa and South East Asia, amounting to an annual incidence rate of 356 and 182 cases per 10,000 populations respectively.[1] Tubercular meningitis (TBM) is the most serious form of neurotuberculosis. India is among the nations with high incidence of TB. Usually there are 20% of extra pulmonary cases of whom 15% are neurotuberculosis.[2] TBM is associated with a high frequency of neurologic sequelae and mortality if not treated promptly.[3-7] In recent times, even after the advent of molecular testing, diagnosis of tubercular meningitis (TBM) continues to be a clinical challenge in which disproportionate inflammatory exudates rather than numbers of circulating bacteria make bacteriological diagnosis difficult, and the available microbiological tests fail to attain the accuracy standards required. As a result, most guidelines for the diagnosis and management of TBM depend on clinical setting, cerebrospinal fluid (CSF) analysis including adenosine deaminase activity (ADA), computed tomography (CT) scans and magnetic resonance imaging (MRI) to guide decision-making. Delay in seeking medical care, diagnosis, and initiation of treatment are contributing factors to the high mortality and morbidity, especially in resource-limited regions. When diagnosed promptly, TBM can be cured with supervised medication administration and supportive care.

The culture of M. tuberculosis from CSF is the gold standard but it is time consuming. Polymerase Chain Reaction (PCR) has low sensitivity (40-60%) is expensive and is not routinely available in developing countries.[8,9] Looking at the huge disease burden, there is a need for simple, cost effective and reliable marker.

One such diagnostic marker may be CSF lactate which is easy to estimate, is relatively less costly that may aid in early recognition of TBM. CSF lactate is produced by anaerobic metabolism and its level increases in any condition which causes decrease in oxygen supply to the brain. The few studies that have addressed the predictive value of this test have primarily focused on acute bacterial meningitis or differentiating it with viral and aseptic meningitis.

There is scarcity of studies of CSF lactate in TBM and its role as a diagnostic and prognostic marker has not been elucidated, hence this study of CSF lactate in TBM patients was undertaken.

## Methods

This was a hospital based cross sectional study, which was prospectively

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**Table 1: Diagnostic criteria for classification of definite, probable, and possible Tubercular meningitis**

**Definite Tubercular Meningitis**

Patients should fulfil following criterion A or B:

A: Clinical entry criteria plus one or more of the following: Acid-fast bacilli seen in the cerebrospinal fluid (CSF), Mycobacterium tuberculosis cultured from the CSF or a CSF positive polymerase chain reaction test for TB (TB PCR).

B: Acid-fast bacilli seen in the context of histological changes consistent with tuberculosis in the brain or Spinal cord with suggestive symptoms or signs and CSF changes or visible Meningitis (on autopsy)

**Probable Tubercular Meningitis**

Clinical entry criteria plus a total diagnostic score of 10 or more points (when cerebral imaging is not available) or 12 or more points (when cerebral imaging is available) plus exclusion of alternative diagnoses. At least 2 points should come either from CSF or cerebral imaging criteria.

**Possible Tubercular Meningitis**

Clinical entry criteria plus a total diagnostic score of 6-9 points (when cerebral imaging is not available) or 6-11 points (when cerebral imaging is available) plus exclusion of alternative diagnoses.

*Clinical entry criteria comprise of Symptoms and signs of meningitis including one or more of the following: Headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness.

conducted in Era's Lucknow Medical College, Lucknow between January 2013 to June 2014. All admitted patients of meningo-encephalitis more than 15 years who fulfilled the diagnostic criteria for TBM were included. Patients who had seizures, malignancy, metabolic disorder or HIV infection were excluded. Patients with tuberculoma without evidence of meningeal involvement and old cases of TBM treated outside the hospital were also excluded.

All included patients, or a direct/close relative of those with altered consciousness, gave informed consent to participate in the study. The Institutional ethics committees approved the study.

Patients fulfilling the inclusion criteria were subjected to CT scan brain before lumbar puncture. The CSF analysis was done for lactate, protein, glucose, cell count, Gram's stain, AFB and culture. CSF lactate levels were done by Enzymatic Colorimetric Method (Randox Laboratories, India )and 1.6-2.4 mmol/l (28.8-43.2 ml/dl) was taken as reference range. Routine haematological and biochemical investigations were done in all the patients.

**Table 2: Comparison of diagnostic class and clinical stages in study population**

| | Total | Definite (n=17) | | Probable (n=16) | | Possible (n=22) | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| Stage I | 3 | 0 | 0.00 | 0 | 0.00 | 3 | 100.00 |
| Stage II | 36 | 9 | 25.00 | 9 | 25.00 | 18 | 50.00 |
| Stage III | 16 | 8 | 50.00 | 7 | 43.75 | 1 | 6.25 |

$\chi^2$=13.639; p=0.009.

Patients included were classified as 'definite', 'probable', or 'possible' TBM depending on clinical, laboratory and radiological findings as per WHO diagnostic criteria of TBM (Table 1). They were also classified into following three clinical stages using the British Medical Research Council.[10]

Stage I (Early): Nonspecific symptoms and signs with no clouding of consciousness or neurological deficits.

Stage II (Intermediate): Lethargy or alteration of behaviour, meningeal irritation or minor neurological deficits.

Stage III (Advanced): Abnormal movements, convulsions, and stupor or coma.

### Statistical analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Numbers (%) and Mean±SD. The ANOVA (Analysis of Variance) test was used to compare the within group and between group variances amongst the study groups

## Results

Fifty five patients out of two hundred and twenty patients of meningo-encephalitis, aged 15 years or more, fulfilling the diagnostic criteria for tubercular meningitis were studied. Patients were classified into three clinical stages according to clinical severity at admission using the British Medical Research Council (Table 1).

Out of 55 patients included in the study, majority (n=36; 65.45%) belonged to Stage II followed by Stage III (n=16; 29.09%), only 3 (5.45%) patients belonged to Stage I (Table 2). No significant difference in weight, height and BMI of the patients of different clinical stages of TBM was found. Prevalence of fever, headache and vomiting in different clinical stages of TBM was not different but presence altered sensorium was significantly higher in Stage II and Stage III as compared to Stage I (p< 0.001).

Prevalence of other symptoms (eg cough) was higher in stage II. Family history was found to be positive in only Stage II patients. Proportion of patients with positive history was higher in Stage II as compared to Stage I and Stage III. Past history of tuberculosis was positive in 5 (9.09%) patients.

Proportion of patients with abnormal respiratory findings (tuberculosis of lung in 6 and pleural effusion in 13 patients) was significantly higher in Stage III (93.75%) as compared to Stage I (33.33%) and Stage II (27.78%).

CT suggestive of TBM (hydrocephalus, basal meningeal thickening, tuberculoma, cerebral infarct) was detected in 4 (11.11%) patients of Stage II and in 5 (31.25%) of Stage III. MR imaging of brain was done in 24 cases revealing abnormalities in 2 (8.33%) patients of Stage II and 1 (12.50%) of Stage III.

Difference in CSF levels of different clinical stages of TBM was found to be statistically significant for CSF lactate and CSF ADA. In present study, CSF lactate levels were far more differentiating in different stages than CSF ADA levels (P value <0.001). Mean CSF lactate values were 21.93±8.21, 42.34±18.84 and 78.77±12.05 mg/dl correspondingly 1.22, 2.35 and 4.38 m mol/L in TBM stage 1, 2 and 3 respectively. Thus an increase in CSF lactate with increase in severity of clinical stage of TBM was observed. When different diagnostic classes were considered, mean levels of CSF lactate with 'possible' class were minimum (33.65±14.42) followed by 'probable' class (54.49±24.89) lastly followed by 'definite' diagnostic class (72.83±15.28 units) thus showing a significant class difference (p=0.001) (Table 3). This observation represents diagnostic predictability of CSF lactate in TBM. CSF-lactate levels of patients in non survivor group were higher as compared to that of patients who survived though difference was not significant (p=0.066).

Differences in CSF sugar, protein and cells were not found to be

**Table 3: Comparison of CSF levels in different diagnostic classes**

| | Definite | | | Probable | | | Possible | | | Statistical significance | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | n | Mean | SD | F | P |
| CSF TLC | 15 | 141.33 | 60.19 | 16 | 157.31 | 80.05 | 22 | 137.50 | 110.04 | 0.240 | 0.787 |
| CSF P | 17 | 10.94 | 8.37 | 16 | 17.63 | 16.48 | 22 | 20.64 | 19.02 | 1.866 | 0.165 |
| CSF L | 17 | 87.88 | 9.55 | 16 | 82.38 | 16.48 | 22 | 79.36 | 19.02 | 1.389 | 0.258 |
| CSF E | 17 | 0.00 | 0.00 | 16 | 0.00 | 0.00 | 22 | 0.00 | 0.00 | | |
| CSF M | 17 | 0.00 | 0.00 | 16 | 0.00 | 0.00 | 22 | 0.00 | 0.00 | | |
| CSF Sugar | 17 | 51.06 | 13.04 | 16 | 65.44 | 16.38 | 22 | 59.82 | 15.31 | 3.891 | 0.027 |
| CSF Protein | 17 | 221.15 | 93.61 | 16 | 191.69 | 76.73 | 22 | 151.90 | 60.52 | 4.005 | 0.024 |
| CSF Lactate (mg/dl) | 17 | 72.83 | 15.28 | 16 | 54.49 | 24.89 | 22 | 33.65 | 14.42 | 22.247 | <0.001 |
| CSF ADA (mg/dl) | 17 | 21.00 | 15.76 | 16 | 18.11 | 15.60 | 21 | 8.97 | 5.76 | 4.668 | 0.014 |

statistically significant among different diagnostic classes. CSF PCR positivity was seen in 87.5% of "definite" cases as compared to none of the "probable" and "possible" cases, thus showing a significant association between definite diagnostic class and PCR positivity.

## Discussion

Tuberculosis remains the single largest infectious disease causing high mortality leading to 3 million deaths annually, about five deaths every minute. India is the highest TB burden country with World Health Organization (WHO) statistics for 2011 giving an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 8.7 million cases.[11] In India, an estimated 2.76 lakh deaths occur from tuberculosis every year and more than 900 people die of tuberculosis that is approximately two deaths every three minutes.[12] An estimated 15% of all tubercular infections are extra-pulmonary consisting of TB lymphadenitis, genitourinary TB, central nervous system TB and others.[13] Extra pulmonary involvement can occur in isolation or along with a pulmonary TB in the patients with disseminated tuberculosis. Central nervous system tuberculosis is the most severe form of extra-pulmonary tuberculosis. It includes Tubercular meningitis (TBM) which occurs in 4% of all cases.[14-16]

The diagnosis of TB meningitis is difficult because TB meningitis presents with nonspecific symptoms and signs.[15-17] Bacterial yield is poor. Other sophisticated investigation and imaging are expensive. Early diagnosis and treatment of the disease is very important as the disease can result in mortality if left untreated.[18] However, the other factor that makes diagnosis difficult is the small number of bacilli in the CSF which reduce the sensitivity of conventional bacteriology.[19] In recent years, new diagnostic assays, in particular molecular techniques like GeneXpert MTB/RIF, have been developed, and these could contribute to the diagnosis of extra pulmonary forms of tuberculosis.[20] With an objective of establishment of a simple cost effective marker for diagnosis and prognostication of TB meningitis our study was planned and conducted in a setting of medical college hospital.

Present study demonstrated that CSF lactate levels were higher than normal in patients with TB meningitis. It had positive correlation with severity of stages of TB meningitis. The stage profile of patients in present study indicates a delay in seeking medical attention. One reason for this could be attributed to the fact that our facility is a tertiary care centre. The TBM stage profile of patients in present study matched with the stage profile of patients in other tertiary care facilities too. In a study by Sher et al., maximum number of patients of TBM had clinical stage II (46.6%) at the time of admission followed by stage III (33.3%) and stage I (20%) respectively.[21] In another study, Saleem et al., 50% of patients had TBM stage II, 39.47% had stage III and 10.53% had stage I of disease at the time of admission.[22]

In present study, radiological/ imaging features (hydrocephalus, basal meningeal thickening, tuberculoma, infarction) did not show a significant difference among different TBM stage groups. Similar to present study, Sher et al. did not find any significant association between radiological/ imaging features and TBM staging but found radiological abnormalities to be higher in TBM stages II and III as compared to TBM stage I.[22]

Except for CSF lactate and ADA levels for none of the CSF parameters a significant association with TBM stage could be observed. CSF lactate and ADA levels showed an incremental trend with increasing TBM stage. In present study, the mean CSF ADA levels in Stage 1, 2 and 3 of TBM were 9.45, 10.84 and 26.70 IU/ml respectively, thus showing values in stage 1 and 2 to be of lower order than those in stage 3. ADA has been extensively studied in tuberculosis and in TBM but its levels in different studies exhibit a wide range and that is why majority of studies could not find any correlation between its levels with clinical stages thereby precluding it to serve as prognostic marker.[23-25]

In this study, CSF lactate levels of patients were higher than normal and showed increasing trend from the 'possible' group of TBM patients to the 'definite' group suggesting that CSF lactate could be a predictor of the 'definite' diagnostic class of TBM.

Cerebrospinal fluid lactate assay has been a subject of research since 1925. The increased catabolism of glucose through glycolysis to pyruvate, and its conversion to alanine and predominantly lactate, reflects a metabolic burst as seen in the CSF profile of TBM patients. The greatly elevated levels of lactate, most likely leads to immune activation in the TB-infected microglial cells as suggested by Nareika et al in their study.[26] In addition, the increased levels of monocarboxylates such as lactate and pyruvate, the presence of branched-chain keto acids derived from leucine, valine and isoleucine, and ketone bodies such as acetoacetate, 3-hydroxybutyrate and acetate suggests functional down regulation of the neuron-associated monocarboxylate transporter-1 (MCT-1), resulting in decreased neuronal energy supply, which manifests in the coma-related clinical symptoms seen in the TBM patients.[27]

Most of the studies evaluating the role of CSF lactate levels have focussed on differentiating it from bacterial and non-bacterial meningitis. A systematic review by Huy and colleagues summarizes data from 25 studies evaluating the role of CSF lactate in the differential diagnosis between acute bacterial and aseptic meningitis. The authors concluded that CSF lactate is a good single indicator and a better marker compared with conventional markers.[28]

Probably this is the first study that has evaluated the role of CSF lactate levels within TBM patients with a reasonable sample size that has correlated lactate levels with TBM clinical stage and found a significant association. Tang et al., in their study did not find a significant association of TBM clinical stage and CSF lactate levels.[29] However, the reason for this could be attributed to a small sample size consisting of only 21 TBM patients.

On exploring the relation of CSF lactate levels with mortality it was observed that the mean value of CSF lactate levels was higher in non survivors as compared to survivors although this difference could not achieve statistical significance. Thus despite being indicated as a useful indicator of clinical stage, CSF lactate levels lacked efficacy in terms of prediction of mortality. However, it might be pointed out that in present study TBM clinical staging too did not show a significant association with mortality. One of the reasons for our inability to find such association could be the small sample size.

The predictive role of CSF lactate has been assessed in a more useful manner by Genton and Berger, who evaluated efficacy of CSF lactate by using serial measurement methods and indicated that a decreasing trend of CSF lactate levels might indicate a good prognosis.[30] In present study, these assessments were done only once and hence no such possibility could be explored.

The findings in present study are probably among the premier ones in the direction of exploring and establishing a correlation of CSF lactate with clinical stages and different diagnostic classes of TBM. Our study had certain limitations. Important ones were relatively small sample size (viz. Inability to carry out test in pyogenic Meningitis, inclusion of only TBM cases, lack of control/other diagnoses, fewer number of cases in each clinical stage).The results of our study have been encouraging hence we recommend further clinical studies on large number of patients in order to evaluate the prognostic value and correlation with severity of disease in TBM patients.

### Conclusion

The findings of present study indicated that CSF lactate had a positive association with both the stage as well as diagnostic class of TBM and thus can reliably predict the stage III and 'definite' diagnostic class of TBM. More studies with large number of the patients are needed to further substantiate the observation made by this study; and to further explore the role of CSF lactate in TBM.

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