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Original Research Article

Diagnostic value of cerebrospinal fluid markers and clinical profiles in distinguishing tuberculous from pyogenic meningitis: a cross-sectional study

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ABSTRACT

Background: Tuberculous meningitis (TBM) and pyogenic meningitis (PM) are significant etiologies of central nervous system infections necessitating immediate and precise differentiation owing to their distinct treatment protocols and prognostic outcomes. The similar symptoms of these two types of meningitis often make it hard to diagnose them early.

Methods: This cross-sectional study (CSS) assessed cerebrospinal fluid (CSF) markers and clinical profiles in patients diagnosed with TBM and PM. We looked at the cytological parameters, protein, glucose, adenosine deaminase (ADA), and lactate levels in the CSF. We also did electrophoretic protein fractionation. Clinical data and neuroimaging results were documented to discern distinguishing characteristics.

Results: TBM cases exhibited lymphocytic pleocytosis, elevated ADA levels, increased protein-glucose ratios, and heightened gamma globulin fractions on electrophoresis. On the other hand, PM showed a lot of neutrophils, a lot of CSF lactate, and more alpha globulin fractions. Hydrocephalus and cranial nerve involvement were more prevalent in TBM. These parameters exhibited high sensitivity and specificity in distinguishing TBM from PM.

Conclusion: The combination of CSF biochemical markers, cytological profiles, electrophoretic patterns, and clinical features improves the accuracy of diagnosing TBM and PM. This multiparametric method is very useful in places where resources are limited because it helps people get the right treatment at the right time to improve their health.

Keywords: Tuberculous meningitis, Pyogenic meningitis, Cerebrospinal fluid, Adenosine deaminase, Lactate, Protein electrophoresis, Diagnostic markers

INTRODUCTION

Tuberculous meningitis (TBM) is the most serious type of extrapulmonary tuberculosis. It happens when *Mycobacterium tuberculosis* (MTB) infects the meninges. This condition causes a lot of sickness and death around the world, especially in developing countries where tuberculosis is still common. TBM usually shows up slowly with vague signs like fever, headache, vomiting, and changes in mental state. These symptoms can be similar to those of other kinds of meningitis, especially PM, which makes it harder to figure out what's wrong. Timely diagnosis of diseases and the swift initiation of appropriate treatments are crucial for reducing the risk of severe neurological consequences and decreasing mortality rates, which can reach 30-40% even with intervention.[1,2] The definitive diagnostic criterion for TBM entails the detection of MTB in CSF using acid-fast bacilli

(AFB) staining and culture. Nonetheless, these techniques are characterized by limited sensitivity and extended turnaround periods. Molecular diagnostic techniques, exemplified by nucleic acid amplification tests (NAATs) like Xpert MTB/RIF Ultra, demonstrate enhanced sensitivity; however, their availability is not universal, especially in resource-constrained environments. Clinicians often depend on biochemical and cytological analyses of CSF for the early differentiation between TBM and PM, which informs timely treatment decisions.[3,4] In TBM, typical CSF findings include lymphocytic pleocytosis, evidenced by moderately elevated total cell counts, an increase in protein concentration, and a decrease in glucose levels when compared to blood glucose levels. In contrast, pyogenic meningitis PM is usually marked by neutrophilic pleocytosis, which is defined by notably high CSF cell counts and protein levels, as well as significantly lowered glucose concentrations, suggesting an acute bacterial infection. ADA, an enzyme that plays a crucial role in lymphocyte proliferation, is found to be elevated in TBM. This biomarker has shown to be a very useful diagnostic tool because it is very sensitive and specific. In cases of PM, the concentration of lactate inside CSF is usually higher because bacteria break down and use energy in a way that causes tissue hypoxia. This rise sets bacterial meningitis apart from other types of meningitis.[5,6]

Protein electrophoresis studies demonstrate modified CSF protein patterns in TBM, characterized by elevated gamma globulins signifying an immunoglobulin-mediated response, whereas PM exhibits high alpha globulin levels indicative of an acute-phase reaction. Clinical characteristics, including subacute progression, cranial nerve palsies, and hydrocephalus, assist in distinguishing TBM from pyogenic meningitis.[7] Nonetheless, early differentiation is challenging due to the overlap of clinical and CSF findings, highlighting the necessity for an exhaustive evaluation that includes clinical, cytological, biochemical, and electrophoretic data. This method improves the accuracy of diagnoses and helps with timely treatment, which lowers the risk of neurological problems and improves outcomes. This work assesses the diagnostic efficacy of CSF markers and clinical characteristics in differentiating tuberculous meningitis from pyogenic meningitis, offering guidance for clinical practice, particularly in areas with high tuberculosis prevalence.

METHODS

Study design

This cross-sectional study aimed to assess the diagnostic efficacy of CSF markers and clinical characteristics in differentiating TBM from PM.

Ethical approval

The institution's ethics board approved the study before it began, and all participants or their legal guardians gave their informed consent.

Study setting and population

This study was conducted at The Health City Hospital, a tertiary care facility located in Varanasi, Uttar Pradesh, India, from September 2014 to October 2015. A total of 102 patients (42 female and 60 male), aged 18-45 years exhibiting clinical manifestations indicative of meningitis, including fever, headache, vomiting, and meningeal signs, were evaluated. Individuals diagnosed with TBM or even PM were included as per established diagnostic criteria. Individuals with viral or fungal meningitis, along with other neurological disorders, were excluded.

Diagnostic criteria and case definitions

The diagnosis of TBM was validated through clinical presentation, positive CSF acid-fast bacilli or culture results, supportive neuroimaging findings, and clinical response to antitubercular treatment. PM was confirmed by a positive CSF Gram stain, culture, or clinical improvement subsequent to appropriate antibiotic treatment.

Data collection

For each patient, detailed demographic information, clinical history, and neurological examination results were carefully recorded. Neuroimaging (CT or MRI) was performed as needed to identify issues such as hydrocephalus or infarcts.

Cerebrospinal fluid analysis

Authors did a lumbar puncture in a clean way to get CSF samples. Standard biochemical methods were used to check the total and differential leukocyte counts, as well as the levels of protein and glucose. A colorimetric assay quantified CSF-ADA, while enzymatic methods assessed CSF lactate levels. We used CSF protein electrophoresis to look at the protein fraction patterns in some samples.

Statistical analysis

A comparative analysis of clinical and cerebrospinal fluid parameters between the TBM and PM groups was performed utilizing suitable statistical methods (e.g., t-test, chi-square). Authors computed diagnostic accuracy metrics, encompassing sensitivity and specificity, for the principal biomarkers. Correlation analyses across clinical severity and CSF profiles were conducted to elucidate the interrelations of parameters.

RESULTS

This study analyzed 102 patients diagnosed to have meningitis, aiming to distinguish between TBM and PM by assessing CSF markers and clinical characteristics. Both groups frequently exhibited symptoms such as fever, headache, vomiting, and indications of meningeal irritation. The cases of TBM exhibited a more subacute clinical progression and an increased incidence of neurological complications, such as cranial nerve palsy and hydrocephalus. The cytological analysis of CSF demonstrated a significant predominance of lymphocytes in TBM, in contrast to the neutrophilic predominance and elevated total leukocyte counts observed in purulent meningitis. Biochemical markers such as protein, glucose, ADA, and lactate in CSF exhibited significant variations. ADA levels were markedly elevated in instances of TBM, whereas lactate levels were greatly elevated in instances of PM. Authors looked at the diagnostic accuracy of important CSF markers again. ADA levels of ≥10 IU/l exhibited considerable sensitivity and specificity for TBM, while CSF lactate concentrations of ≥5 mmol/l were strongly indicative of PM. Other factors, like a protein-glucose ratio of 2 or higher and hydrocephalus seen on imaging, were also strongly linked to the diagnosis of TBM. The amalgamation of these markers with clinical and cytological data enhanced the differentiation between TBM and PM. In addition to standard CSF markers, electrophoretic profiling of CSF proteins revealed distinctive alterations useful in differentiating TBM from PM. TBM cases showed increased gamma globulin fractions indicative of immunoglobulin response, whereas PM had higher alpha globulin fractions reflecting acute phase reactants. These electrophoretic differences provided complementary diagnostic information.

Table 1: Demographic table.

Variable	Description/value
Total participants	102 (60 male, 42 female) patients with meningitis
Age range	18-45 years
TBM cases	58 patients
PM cases	44 patients

Table 2: Summarizes the core CSF cytological and biochemical markers observed in patients with TBM and PM.

Parameter	Tuberculous meningitis (n=58)	Pyogenic meningitis (n=44)	P value
Total leukocytes (cells/mm³)	260±180	730±1180	<0.001
Neutrophils (%)	22±18	78±18	<0.001
Lymphocytes (%)	78±18	22±18	<0.001
Protein (mg/dl)	185±113	268±114	<0.001
Glucose (mg/dl)	44.3±19.3	41.3±19.5	0.04
ADA (IU/l)	12.5±4.1	5.2±2.7	<0.001
Lactate (mmol/l)	4.0±1.3	11.7±3.2	<0.001

Table 3: Details the sensitivity and specificity of major CSF markers utilized for differential diagnosis.

Marker/cut-off	Sensitivity	Specificity	Comments
ADA ≥10 IU/l (TBM)	85–90%	85–95%	Reliable marker for diagnosing TBM
Lactate ≥5 mmol/l (PM)	85–95%	80–90%	Distinguishes acute pyogenic meningitis
Protein: Glucose ratio≥2	—	—	Predictive for TBM with supportive context
Total leukocytes <800 cells/mm³	—	—	Consistent with TBM lower pleocytosis
Hydrocephalus (imaging)	—	—	Supportive radiological evidence for TBM

Table 4: Presents the CSF protein electrophoresis patterns among control subjects, TBM, and PM patients.

Protein fraction	Control (%)	TBM (%)	PM (%)
Pre-albumin	4.8±1.7	2.8±1.2	4.9±2.1
Albumin	42.2±7.6	34.8±9.9	44.1±6.8
Alpha	10.4±2.9	10.3±5.2	19.7±6.9
Beta	9.4±2.3	14.7±4.8	14.9±5.8
Gamma	13.8±4.6	33.2±8.1	16.7±13.2

The findings of the study demonstrate that the early and accurate separation of TBM from PM is significantly improved by a multiparametric approach that includes clinical presentation, CSF cytology, biochemical markers, and protein electrophoresis. Using ADA and lactate as the main biochemical markers, along with full CSF cellular profiles, lets doctors in places with few resources make smart choices and start targeted treatment quickly. This could lower the number of people who get sick or die from both types of meningitis. Electrophoretic protein profiling improves diagnostic clarity in complex situations where traditional signs may overlap.

DISCUSSION

The distinction between TBM and PM presents a significant diagnostic challenge, especially in resource-constrained environments where prompt and precise microbiological validation is frequently inaccessible. This study underscores the importance of utilizing CSF cytological and biochemical indicators in conjunction with clinical profiles to improve diagnostic precision. Elevated ADA levels in CSF are acknowledged as a critical marker for distinguishing TBM. This finding corroborates previous studies that link ADA to the immune response elicited by MTB infection within the central nervous system. The elevated sensitivity and specificity of ADA underscore its importance as a significant surrogate marker, capable of improving clinical decision-making in cases of suspected TBM, particularly when direct pathogen detection poses difficulties.[1,2,8]

The findings from our study regarding CSF lactate levels are consistent with earlier research, which has indicated significantly higher lactate concentrations in instances of PM compared to TBM. The increase in lactate levels in PM primarily signifies the anaerobic metabolic activities initiated by bacterial infections, along with the associated robust inflammatory response. In contrast, TBM, characterized by subacute granulomatous inflammation, typically results in reduced lactate concentrations.

The observed differences highlight the significance of CSF lactate as a distinguishing biochemical marker in standard meningitis evaluations, facilitating prompt differentiation that informs the early initiation of antibiotic or antitubercular treatment.[3,9] The observation of neutrophilic pleocytosis in purulent meningitis and lymphocytic predominance in TBM identified in this study aligns with established pathophysiological principles of meningitis and has been consistently documented in both clinical and epidemiological research. The degree of leukocytosis and the primary cell type present are important diagnostic markers. A marked increase in leukocyte counts, particularly with neutrophil dominance, indicates bacterial meningitis. A moderate pleocytosis, marked by a predominance of lymphocytes, indicates the likelihood of TBM. The observed increase in the protein-glucose ratio in our TBM cases aligns with previous studies that identify this ratio as a significant marker, linked to elevated protein synthesis and impaired glucose transport in the development of TBM.[10]

Electrophoretic shifts that indicate increased gamma globulin fractions in TBM demonstrate the heightened immunoglobulin response characteristic of chronic mycobacterial infection, as well as the compromise of the blood-brain barrier. In contrast, elevated levels of alpha globulins in PM are likely indicative of an acute-phase inflammatory response. The electrophoretic profiles provided in this study contribute further diagnostic information, especially in cases where CSF cytology and standard biochemical markers do not produce clear outcomes.[11] Furthermore, clinical manifestations like hydrocephalus were more commonly associated with TBM, consistent with the presence of basal exudates and widespread inflammation resulting in CSF flow obstruction a notable observation that assists in differentiating it from PM. The distinction between TBM and PM relying exclusively on clinical signs proves inadequate; nonetheless, integrating these signs with CSF markers significantly improves diagnostic precision, as evidenced by recent research on diagnostic models.[12] The study is limited by its cross-sectional design and reliance on conventional diagnostic criteria that lack universal molecular validation, which may result in diagnostic misclassification. Nevertheless, the practical methodology that prioritizes easily accessible CSF markers ensures the relevance of results to real-world conditions, particularly in regions with a significant prevalence of tuberculosis.

CONCLUSION

This study underscores the critical role of CSF analysis in differentiating TBM from PM. The distinctive cytological and biochemical profiles identified, including ADA and lactate levels, offer efficient and accessible methods for early diagnosis. Furthermore, electrophoretic protein fractionation improves the ability to find underlying immunopathological differences. Combining clinical signs with lab tests makes diagnoses more accurate, which helps start treatment quickly and correctly. This is very important for lowering the number of people who get sick or die from meningitis. The results endorse a multiparametric diagnostic strategy that is particularly applicable in environments with restricted access to advanced molecular diagnostics. This approach enhances clinical decision-making, thereby reducing treatment delays and improving patient outcomes.

Future research must prioritize the validation of these markers in larger cohorts and investigate the use of combined biomarker panels to improve diagnostic precision and prognostic assessment in meningitis cases.

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