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Tubercular Meningitis: The chronic disease with its emergent foot!

Mohindra Ritin [1], Boparai Sukhmani [2], Sharma Devendra [3], Ghai Santosh [4], Kansra Umesh [5], Nair Deepthi [6]

[1]MD. Internal Medicine, Aassistant Professor, Department of Emergency Medicine, All India Institute Medical Sciences, New Delhi

[2]MBBS, Intern, Vardhman Mahavir Medical College and Safdarjung Hospital,New Delhi

[3]MD. Internal Medicine, Resident, Department of Cardiology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry

[4]MD. Internal Medicine, Junior Resident, Department of Medicine, BLK Hospital, New Delhi

[5]MD. Internal Medicine, Consultant, Department of Medicine, Metro Hospital, Faridabad

[6]MD. Microbiology, Professor, Department of Microbiology, Vardhman Mahavir Medical College and Safdarjung Hospital

ABSTRACT

Context: Tubercular meningitis; the most feared complication of tuberculosis poses significant diagnostic challenges and has a high morbidity and mortality.

Aims: To evaluate clinical, laboratory and radiological parameters in patients with suspected tubercular meningitis.

Settings and Design: This was a cross sectional observational study conducted in a tertiary care health centre in New Delhi, India from 2012-2015.

Material and Methods: Patients ≥ 18 years of age, with a diagnosis of tubercular meningitis according to Marais' case definition criteria underwent detailed history, clinical examination, CSF analysis, culture, Real time polymerase chain reaction, Amplified Mycobacterium tuberculosis Direct Testing and appropriate radiological studies.

Statistical analysis: The correlation between quantitative variables was carried out by Pearson's correlation coefficient (r) / non-parametric Spearmen' rank correlation (ρ) with its statistical significance determined by t test. The qualitative variables were analysed by Student's t-test/ non-parametric Man Whitney's test and the association assessed by chi- square test / Fischer exact test.

Results: Out of 50 patients in this study definite diagnosis of TBM could be made in 74% patients. The sensitivities of ZN staining, culture, AMTDT and RT- PCR in CSF were 15.8%, 31.6%, 53.9%, and 73.7% for diagnosing definite TBM with respect to BacT/Alert as the gold standard while the sensitivities were 8.1%, 19%, 89.2%, 62.7% respectively using Marais' case definition as the gold standard.

Conclusions: This study emphasizes that no single test can definitively rule out TBM. Thus, any suspected patient of TBM should undergo multiple tests to establish an early diagnosis.

Key-words:-Tubercular meningitis, Marais' criteria, Medical Research Council.

1. INTRODUCTION

Tuberculosis, caused by Mycobacterium tuberculosis, a slow growing, acid fast bacilli, has plagued mankind since times immemorial and still remains a major health challenge, particularly in developing countries.

It is the ninth leading cause of death worldwide and the leading cause of mortality from a single infectious agent. [1] Globally, there were an estimated 10.4 million new cases of tuberculosis in 2016 with 1.3 million TB deaths among HIV-negative people and an additional 374000 deaths among HIV-positive people. [1] India has the highest

Corresponding author: Dr Deepthi Nair

tuberculosis burden with an estimated incidence of 211 per 100000 population in 2016. [1]

Tuberculosis primarily affects the lungs but can also affect other organs like lymphatics, bones, gastrointestinal system as well as the central nervous system, most often seen as tubercular meningitis (TBM). [2]

Tubercular meningitis commonly develops within three months of primary tuberculosis as the bacilli spread from the lungs via the lympho-haematogenous route to the meninges leading to an inflammatory reaction and the formation of subpial or subependymal foci of caseous granulomas (Rich focus) which eventually ruptures into the subarachanoid space causing signs and symptoms of meningitis. [2]

Tubercular meningitis is one the most serious complications of tuberculosis which is seen in 1% of people with tuberculosis and has a high mortality ranging from 15-60% and significant neurological sequelae among survivors. [2-5] One reason for the high mortality and morbidity is difficulty in differentiating it from other aetiologies of meningoencephalitis because of overlapping clinical features which leads to a delay in diagnosis and treatment. [6-7]

The TBM patient commonly presents with headache, fever, and neck-stiffness. Along with this they give a history of previous partial antibiotic therapy; a low concentration of glucose in cerebrospinal fluid (CSF) and neutrophils along with lymphocytes in CSF. [4-7] Also, there are significant limitations in isolation of mycobacterium tuberculosis from the CSF for e.g. the ZN stain is rapid but lacks sensitivity and specificity, culture is slow and tedious, and molecular diagnostic techniques, such as polymerase chain reaction (PCR) have not been completely validated. [4-7]

The diagnosis of TBM relies on correlation of clinical, biochemical, microbiological and radiological modalities as no single modality is capable of a definite diagnosis.

This study was conducted to evaluate all these parameters in patients with suspected TBM and aid in a rapid and accurate diagnostic approach

2. **Material and Methods**

This was a single–centric cross sectional study conducted at a 2100 bedded tertiary care hospital in New Delhi, India from 2012-2015. The study was cleared by the Institute Ethics Committee.

Adult patients, of both sexes, aged ≥ 18 years presenting to the Medicine Emergency with clinical suspicion of tubercular meningitis i.e. signs and symptoms like headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy were further evaluated. Workup included lumbar puncture and cerebrospinal fluid (CSF) biochemical and cytological examination, CSF culture on both conventional (LJ) and liquid automated system media (Bact-Alert 3D, Biomerieux France). CSF was also subjected to Real time polymerase chain reaction (RTPCR) and Amplified Mycobacterium tuberculosis Direct Testing (AMTDT).

Patients were subjected to neuroimaging in the form of either Contrast Enhanced Computerized Tomography (CECT) scan or Magnetic Resonance Imaging (MRI) .Patients also underwent chest X-ray and computerized tomography (CT) scan, MRI and ultrasonography of the abdomen to rule out tuberculosis outside the central nervous system and HIV testing, whenever clinically indicated.

Patients testing seropositive for HIV-I or HIV-II, having received treatment previously for TBM or having an alternate diagnosis after workup were excluded from our study.

Fifty consecutive patients with a diagnosis of tubercular meningitis according to Marais' clinical case definition criteria were included in our study [Table 1]. [7]

The patients were then divided into definite, probable and possible TBM based on clinical, microbiological, CSF features, neuroimaging and evidence of TB elsewhere in the body, in accordance with Marais criteria [Table-1]

Medical research council staging (MRC) was used to assess the severity of disease based on clinical features at the time of presentation. Patients were classified as stage I if they were fully conscious and had no focal deficits; stage II if conscious but with inattention, confusion, lethargy and focal neurological signs; and stage III if patients were stuporous or comatose, had multiple cranial nerve palsies, complete hemiparesis or paralysis. [9]

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Patients were classified into two groups based on their final outcome- alive or expired after completetion of treatment. The mortality was then correlated with MRC staging at presentation.

The data was analyzed by using SPSS statistical software version 22.0 with the level of statistical significance taken as $p < 0.05$.

The data has been presented as mean ± SD for quantitative variables and frequency (%) for qualitative variables. The correlation between quantitative variables was carried out by Pearson's correlation coefficient (r) / non parametric Spearmen' rank correlation (ρ) with its statistical significance by t test.

The qualitative variables were analysed by Student's t test and the non parametric ManWhitney's test was used when the data did not follow normal distribution. The association between qualitative variables under these parameters was assessed by chi- square test / Fischer exact test.

3. **Results**

Out of the 50 patients enrolled in this study, 27 (54%) were males and 23 (46%) were females. The most common age group affected in this study was 18- 27 years. The mean age of patients was 39.26 years (range 18- 87 years).Fever (96%) was the most common symptom followed by altered sensorium (78%). Neck rigidity was the most common sign seen in all patients (100%) followed by Kernig's sign (92%). [Table-2].The CSF characteristics of the patients are as shown in Table-3.[Table-3]

MRC staging of every patient was done at presentation. Mean age in patients presenting in stage I was 35.133 years, in stage II was 37.174 years while patients in stage III had mean age of 48.147 years. Age distribution in MRC staging was found to be highly significant ($p<0.05$).MRC staging was also found to be related to outcome ($p<0.05$). [Table-4]

Out of 50 patients 37(74%) were classified into definite TBM, 8 (16%) had probable TBM and remaining 5(10%) were classified as possible TBM.

Overall, cumulative mortality at the end of 15 day period was 46%.

Out of 50 cases, sputum for AFB was positive in only 8 patients (16%).CSF properties of the patients are shown in table -2. [Table-2]

Chest X- ray was suggestive of pulmonary tuberculosis in 42 % of the patients. CT or MRI features of basal meningitis, hydrocephalus or vasculitis were present in 68% of patients. Of these 34 patients 30 had basal meningitis, 15 had hydrocephalus and 8 had infarcts suggestive of vasculitis.

All the five microbiological tests were analyzed and all diagnostic parameters were calculated using BacT/ Alert [Table-5] and Marais' clinical case definition for tubercular meningitis [Table-6] as gold standard separately. Other variables like true positive (TP), true negative (TN), false positive (FP) and false negative (FN) were compared for CSF stain, CSF culture, AMTDT and RT- PCR taking BacT/Alert as gold standard.[Graph -1]

Taking definite tubercular meningitis by Marais criteria as the gold standard, CSF stain was found to have the highest sensitivity. [Graph-2]

Table1: Marais' clinical case definition criteria for the diagnosis of tubercular meningitis

	Diagnostic score
Clinical criteria	(Max. category score=6)
Symptom duration of more than 5 days	4
Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks	2
History of recent (within past year) close contact with an individual with pulmonary tuberculosis	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1

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Altered consciousness	1
Cerebrospinal fluid criteria(CSF criteria)	(Maximum category score=4)
Clear appearance	1
Cells: 10–500 per µl	1
Lymphocytic predominance (>50%)	1
Protein concentration greater than 1 g/L	1
CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2mmol/L	1

Table 2- Baseline characteristics of patients

Sign and symptoms	Frequency% (n)
Neck Rigidity	100% (50)
Fever	96% (48)
Kernig's Sign	92% (46)
Altered Sensorium	78% (39)
Cough	60% (30)
Headache	54%(27)
Vomiting	50%(25)
Papilledema	34% (17)
Seizures	24% (12)
Cranial nerve Abnormality	18% (9)
Motor abnormality	18%(9)

Table-3: CSF properties of the patients

	Mean and Standard deviation		**Percentage(n)**
CSF Sugar (mg/dL)	36.175 (18.5532)	Patients with low sugar (<2.2mmol/l)	70% (35)
CSF Proteins (mg/ dL)	142.34 (192.5737)	Patients with protein raised(>1g/L)	90% (45)
CSF Cells	81.8 (141.6634)		
CSF Neutrophils (%)	13.6 (15.35)	Patients with neutrophil predominant CSF (>50%)	4% (2)
CSF Lymphocytes (%)	82.6 (22.7282)	Patients with lymphocyte predominant CSF (>50%)	90% (45)

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Table-4: Percentage of patients presenting in each stage of Medical Research Council Staging

Stage	Frequency	Mortality
MRC I	30% (15)	0% (0)
MRC II	46% (23)	52.17% (12)
MRC III	24% (12)	91.66% (11)

Table-5: Depicting sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy and inter- rater agreement (κ) microbiological tests when compared to BacT/ Alert.

	CSF Stain	LJ Media	RT-PCR	AMTDT
Sensitivity	15.79%	31.58%	53.85%	73.68%
Specificity	100%	96.77%	45.95%	70.97%
Positive Likelihood Ratio		9.79	0.99	2.54
Negative Likelihood Ratio	0.84	0.71	1	0.37
Disease prevalence	38%	38%	26%	38%
Positive Predictive Value	100%	85.71%	25.93%	60.87%
Negative Predictive Value	65.96%	69.77%	73.91%	81.48%
Diagnostic accuracy	68%	72%	48%	72%
Inter- rater agreement (κ)	0.189	0.323	0.119	0.429

Table-6: Depicting sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy and inter- rater agreement (κ) microbiological tests when compared to Marais clinical case definition as a gold standard.

	CSF Stain	CSF Culture	RT- PCR	AMTDT
Sensitivity	8.11%	18.92%	89.19%	62.16%
Specificity	100%	100%	100%	59.09%
Positive Likelihood Ratio				1.52
Negative Likelihood Ratio	0.92	0.81	0.11	0.64
Disease prevalence	74%	74%	74%	62.71%
Positive Predictive Value	100%	100%	100%	71.88%
Negative Predictive Value	27.66%	30.23%	76.47%	48.15%
Diagnostic Accuracy	32%	40%	92%	72%
Inter-rater Agreement (κ)	0.044	0.108	0.811	0.461

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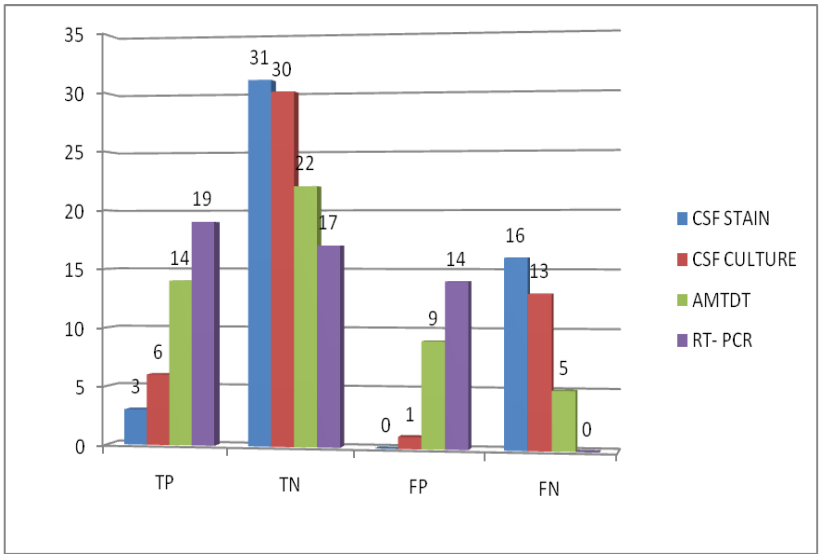
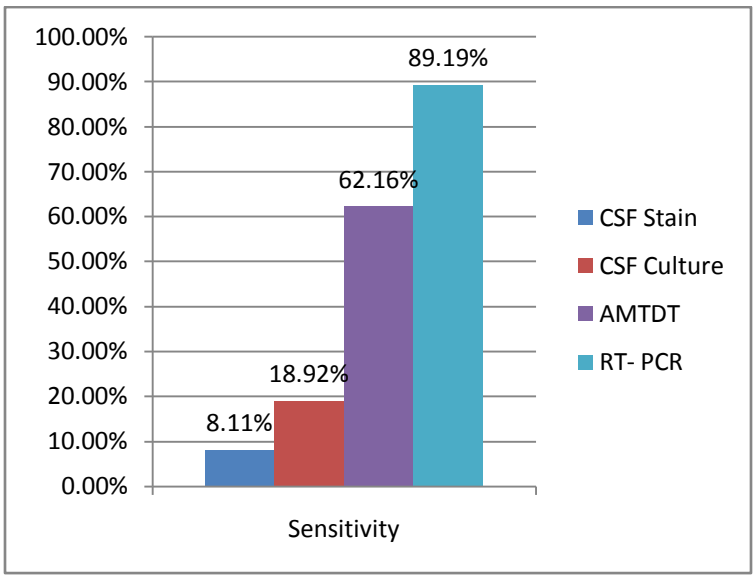


Graph-1: Depicting true positive (TP), true negative (TN) ,false positive (FP) and false negative (FN) of CSF stain, CSF culture, AMTDT and RT- PCR tests



Graph-2: Depicting sensitivity of CSF stain, CSF culture, AMTDT and RT- PCR against Marais' clinical case definition for TBM as gold standard

4. **Discussion**

Tuberculosis (TB) and its sequelae is a major cause of morbidity and mortaliy worldwide which, can be prevented by timely diagnosis and correct treatment.

Tubercular meningitis, particularly, is a diagnostic dilemma as none of its presenting features are pathognomic of the disease. In this study, males were affected more than females (54% vs 46%). The mean age of patients was 39.26 years with 38% of patients within 18- 27 years of age. Fever was the most common presenting symptom present in 96 % of the patients, which was also associated with altered sensorium (78%), cough (60%), headache (54%), vomiting (50%) and seizures (24%). On examination neck rigidity was present in all (100%) of the patients. Kernig's sign (92%), cranial nerve weakness (18%), motor abnormality (18%) and papilledema (34%) were other common findings.

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These features are consistent with other studies. [6, 7, 10, 11]

A past history of tuberculosis was present in 26% of the patients in this study and a recent history of contact with a person infected with TB was present in 20% of the patients. Yaşar K et al in a study of 160 adults found past history of TB in 27% and 19% had close contact with person with TB. [11]

MRC staging was used to describe the severity of disease based on clinical features. In this study 70 % patients were found to have stage II or III (46 % stage II and 24% stage III) according to the MRC grading. Mortality correlated well with the stage of disease, being 52.17% in stage II and 91.66% in stage III. The overall mortality in our study was 46% at the end of 15 day period. Yaşar K et al reported 84 % patients presenting in stage II or III while Hosoglu S et al reported that 68 % patients presented in stage II or III. [11-12] Sutlas et al in a study of 61 Turkish adults reported a mortality of 27.8%.[13] Heemskerk et al also reported a mortality of 27.8% in their patients.[5] Several other studies have estimated mortality to be between 15 to 60 %.[2-4] This known variation in the mortality may be reflecting basic health and nutrition of the population studied, patient age, and severity of illness at the time of presentation, delay in diagnosing due to varying standards used and starting anti-tuberculosis therapy for tubercular meningitis. The higher mortality in this study can be due to large number of patients presenting in stage II (46%) and III (24%).

Characteristic CSF findings of TBM includes lymphocyte predominant pleocytosis (>50%) with raised proteins (>1g/L) and low glucose (CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2mmol/L). The CSF parameters in the current study were CSF sugar 36.175 ±18.5532 mg/ dL, CSF proteins 142. 34 ± 19.2573 mg/ dL, CSF cells 81.8 ±14.1663, CSF lymphocytes 82.4 ±22.728 %, CSF neutrophils 13.6 ±15.35. In this study, 90% of the patients had a lymphocyte predominant pleocytosis. Proteins were above the reference value in 90% of the patients and sugar was below the reference level in 70% of the patients. Sultas et al in a adult case-series of CNS tuberculosis in Turkey found a CSF lymphocyte predominance in 85%, neutrophil predominance in 15%, high protein levels in 77% and hypoglycorrachia in 67.2%. [13]

ZN smear was positive in 6% of our patients. Its sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy against BacT/Alert as gold standard for diagnosing TBM were 15.79%, 100%, 100%, 65.96% and 68% respectively while using Marais' case definition for TBM as the gold standard its sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy was 8.11%, 100%, 100%, 27.66%, and 32% . Sarkar DN et al reported a sensitivity of 0% in 30 TBM cases. [14] Christensen et al reported a sensitivity of 9.52% in a study of 42 adult TBM patients. [6] These recent studies are consistent with result of current study. Older case series have reported sensitivity as high as 91%. These variable results reflect the differences in staining techniques, interobserver variations, amount of CSF and paucibacillary nature of CSF examined.

Conventional culture by LJ method (solid media) was positive in 14% of our patients. With BacT/ Alert as gold standard, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for diagnosing TBM were 31.58%, 96.77%, 85.71%, 69.77% and 72% respectively. Sutlas et al reported a sensitivity of 11% in a study of TBM adults. [13] Sarkar et al reported a sensitivity 36.65% for CSF culture.[14] Hosogulu et al in a study of 374 adults reported sensitivity as low as 13.1 % for conventional culture. [12] These studies are consistent with low sensitivity results seen in this study. Low sensitivity results of conventional culture reflect the pauci- bacillary nature of tubercular bacilli in CSF, low sample volume, delay in transportation to laboratory, improper handling, poor centrifugation technique, exposure to sunlight etc.

BacT/ Alert culture was positive in 38% of the patients. Out of 7 positive samples detected on conventional culture 1 turned out to be negative on BacT/ Alert. This difference may be explained due to lack of some growth factors in BacT/ ALERT media when compared to conventional media. Panicker et al in a study of 60 TBM cases found a sensitivity of 66.66% for liquid BACTEC systemThe results of this study are consistent with the study of Panicker et al. [15] Hence though BacT/ ALERT system has a better

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sensitivity for diagnosis of TBM as compared to solid medium, both solid and liquid media are necessary to maximize the sensitivity of detection.

AMTDT was positive in 46% of the patients, taking BacT/ Alert as gold standard its sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for diagnosing TBM were 73.68%, 70.97%, 60.87%, 81.48% and 72% respectively. Gamboa F et al, Ehlers S et al and Baker C et al have reported sensitivity of AMTDT for TBM as 63%, 67% and 56% respectively. [16-18]

RT- PCR was positive in 66% of the patients and its sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for diagnosing TBM were 100.00%, 54.89%, 57.88% ,100% and 72% respectively taking BacT/ Alert as gold standard. Lee et alin a study found sensitivity and specificity of 100% and 38% respectively of PCR in diagnosing TBM. [19] Narayanan S et al in a study found sensitivity and specificity of 91% and 76% respectively for PCR in diagnosing TBM. [20] In a study from north-west India, Panagariya et al found PCR to be a valuable early test with a sensitivity of 68%.[21]

These high levels of sensitivity are in accordance with the results of the current study. The high sensitivity of PCR makes it a useful initial test.

Neuroimaging was positive for TBM in 34 patients which shows a sensitivity of 68% for diagnosis of TBM. This is similar to sensitivity seen in other studies by Hosoglu (69%) and Pehlivanoglu et al (78%).[12, 22] The variations can be explained by variations in interpreting neuroimaging scans. Basal meningitis was the common neuroimaging features observed were basal meningitis (88%), hydrocephalus (44%) and infarcts (23%). Sengoz et al in a study of 121 patients found basal meningitis, hydrocephalus and infarcts in 37%, 17% and 5% patients respectively. [23] El Sahly et al in their study found the incidence of hydrocephalus to be 28.3%.[24] These variations in the frequency of various neuro-radiological features can be explained by differences in the immune status of the study populations, imaging modality used (CT or MRI) and differences in interpretation of the scans.

Out of 50 patients taking part in this study definite diagnosis of TBM based on positive ZN smear, positive culture or positive nucleic acid amplification in CSF could be made in 74% patients. Based on clinical, CSF criteria, neuroimaging and evidence of tuberculosis elsewhere remaining patients were classified into probable (16%) or possible (10%) TBM. The sensitivities of ZN stain, CSF culture by LJ conventional, AMTDT and RT- PCR were 15.8%, 31.6%, 53.9%, and 73.7% for diagnosing definite TBM with respect to BacT/Alert as the gold standard while the sensitivities were 8.1%, 19%, 89.2%, 62.7% respectively using CRS as the gold standard. Inter- rater agreement (κ) between different tests was also found to be very low. Hence it should be emphasized that no single test can rule out the diagnosis of TBM. Given the high morbidity and mortality associated with the disease, any patient presenting with signs and symptoms of TBM should be subjected to appropriate microbiological and radiological tests to establish a diagnosis to initiate appropriate antitubercular therapy, early in the course of the disease i.e within 15 days.

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