

A Study on the Utility of GeneXpert in Cerebrospinal Fluid in the Diagnosis of Tuberculous Meningitis

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ABSTRACT

BACKGROUND

One of the most common forms of central nervous tuberculosis is tubercular meningitis and has high morbidity and mortality. The natural course of TBM is sub-acute in nature; hence, the symptoms may persist for weeks before diagnosis. The diagnosis of tuberculosis is based on clinical presentation and cerebrospinal fluid analysis. GeneXpert is a reliable and rapid diagnostic modality for diagnosing pulmonary tuberculosis. Various studies have shown various sensitivity patterns of GeneXpert in TBM. This study aims to find the utility of GeneXpert in TBM.

METHODS

All adult patients who presented with signs and symptoms of meningitis were included in the study. Detailed history was recorded and physical examination done. All patients were subjected to routine blood investigations, chest X ray, brain imaging along with lumbar puncture for cerebrospinal fluid (CSF) analysis. Apart from routine CSF analysis for cell type, cell count, and biochemical analysis, 3-5 ml of CSF was sent for GeneXpert to intermediate reference laboratory at Government Hospital for Chest Diseases, Pondicherry. On the basis of clinical history, examination, and investigations, composite gold standard for the diagnosis of TBM was defined. The composite gold standard included definite case of TBM, highly probable case of TBM, probable case of TBM and definitely not TBM. Sensitivity and specificity were calculated for GeneXpert for the composite gold standard.

RESULTS

100 patients were included in the study. 64 were males and 36 were females. TBM was detected in 22 cases. Mean age for TBM was 42 ± 19.2 years. Among 22 cases of TBM, only one case was categorized as definite TBM, and the rest 21 were either highly probable TBM (7) or probable TBM cases (14). Common clinical signs and symptoms on presentation were headache (87%), fever (78%), neck rigidity (69%), seizure (52%) and altered sensorium (74%). GeneXpert and CSF culture was positive in only one case with sensitivity of 14% and specificity of 100%. Adenosine deaminase (ADA) was high in 13 cases with sensitivity of 60% and specificity of 100%.

CONCLUSIONS

The utility of GeneXpert in diagnosing tubercular meningitis is very insignificant. Negative GeneXpert in CSF analysis does not rule out TBM as sensitivity is 14% but positive GeneXpert has 100% specificity. In the absence of reliable diagnostic test, clinician should look for specific signs and symptoms of meningitis along with routine CSF analysis and CSF ADA level.

KEYWORDS

Tubercular Meningitis, CSF GeneXpert, Diagnostic Criteria

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BACKGROUND

Tuberculous meningitis (TBM) is undoubtedly one of the most common and serious manifestations of tuberculosis with a mortality rate of 20-50% despite initiation of treatment. Nearly 10% of patients who have tuberculosis subsequently develop neurological disease. The mortality rate of tuberculous meningitis in India is 1.5 per 100,000 populations with higher rates when associated with HIV Co-infection.¹ TBM is almost 100% fatal if not treated and case fatality rates remain high (15-40%) despite effective treatment.² Diagnosis of TBM is based on history, physical examination and CSF studies. Definitive diagnosis of TBM is made by demonstrating *Mycobacterium tuberculosis* in CSF. This can be done by smear microscopy, culture or by use of molecular probes to detect *Mycobacterium tuberculosis* DNA.¹ The definition of TBM when used in clinical research has varied from study to study.^{3,4,5} For the large majority, patients are given a definite, probable, or possible tuberculous meningitis status depending on clinical findings, laboratory tests primarily CSF and radiological findings. Definite Tuberculous meningitis cases usually include patients with AFB on CSF microscopy or MTB cultured from CSF or another CNS source.⁶ Criteria for probable or possible tuberculous meningitis cases differ greatly between studies. Culture is the gold standard for diagnosis of tuberculous meningitis with a sensitivity of up to 77% but is of limited value as it takes six to eight weeks to get results.⁷ The GeneXpert is a multifunctional, automated, closed system that performs real-time PCR to give diagnosis of tuberculosis and assessment of rifampicin resistance within 2 hours. It is able to ascertain a positive diagnosis in 99-100% of patients with smear positive pulmonary TB and 57-83% in smear negative tuberculosis.⁸ In a country like India with limited resources, it is the need of the hour to have diagnostic strategies that are financially feasible, readily available, rapid and sensitive. Rapid diagnosis of the disease and early initiation of treatment is a strong prognostic indicator in reducing neurological complications and death. The tests available for diagnosis of tuberculous meningitis are inadequate mostly due to low bacillary load in CSF. GeneXpert has been approved by the WHO for the diagnosis of pulmonary tuberculosis but there is a lack of data on its use to diagnose tuberculous meningitis. This study will assess the utility of GeneXpert in cerebrospinal fluid in the diagnosis of tuberculous meningitis.

METHODS

This study was a cross sectional study of suspected meningitis in adult patients coming to Pondicherry Institute of Medical Sciences (PIMS) during the period of October 2016 to August 2018. All patients of age more than 18 years admitted in PIMS as a suspected case of meningitis showing one of the following clinical features - 1. Headache 2. Fever 3. Neck pain 4. Neck rigidity 5. Altered Sensorium 6. Seizures/Convulsions 7. Photophobia 8. Cranial Nerve

Palsies 9. Weight loss 10. Dysarthria and / or. Lymphocytic predominance in CSF, with high protein and low glucose and / or CT Scan/MRI of brain showing features of Tuberculous meningitis were included in the study. Patient who had contraindication for lumbar puncture like uncorrected coagulopathy, acute spinal cord trauma and brain abscess were excluded from the study. Patients with central nervous system malignancy were also excluded from the study.

All patients who fulfil the inclusion criteria during the study period were recruited in the study. After detail history and examination lumbar puncture was performed under strict aseptic conditions and in case of papilledema, a guarded procedure was done. Around 8-10 ml of CSF was collected in 4 containers. Three of the containers were sent for CSF protein, glucose, Total count, Differential Count, AFB staining (Ziehl Neelsen), conventional culture and for ADA. 3-5 ml of the sample was sent for GeneXpert to an intermediate reference lab at Government Hospital for Chest Diseases, Pondicherry. Apart from CSF analysis other relevant blood investigations were done like complete blood count, erythrocyte sedimentation rate (ESR), Liver function tests, blood urea, creatinine and electrolytes. In case of altered sensorium or seizure, brain imaging (CT scan / MRI) was done along with chest X ray. The following criteria were used as composite Gold standard to diagnose TBM. 1. Clinical Criteria - Fever >2 weeks, Headache, neck stiffness, neck rigidity, neck pain, altered sensorium, convulsions, cranial nerve palsies, photophobia, weight loss, dysarthria. 2. Supportive Criteria - A. CSF findings - Lymphocytic pleocytosis, increased protein, sterile culture and/or CSF ADA more than 10 U/L B. CT/MRI findings suggestive of tuberculous meningitis such as granulomas, basal exudates and hydrocephalus C. Findings of extra neural tuberculosis (chest x-ray suggestive of tuberculosis, sputum AFB positive) D. Response to Treatment. On the basis of the above criteria TBM was classified as definitely TBM, highly probable TBM, probable TBM and definitely not TBM. Definitely TB Meningitis was defined, if clinical criteria plus one or more of the following were present - acid-fast bacilli seen in the CSF; *Mycobacterium tuberculosis* cultured from the CSF. Highly Probable TB Meningitis was defined, if clinical criteria plus three or more of the supportive criteria were present. Probable TB Meningitis was defined, if clinical criteria plus two of the supportive criteria were found. In Case of alternate cause of neurological presentation (toxoplasma, cryptococcus, pyogenic, viral and rickettsial) then it was termed as definitely not TBM.

Statistical Analysis

Data collected were analysed by using SPSS v. 17.0. Mean and standard deviation were used for continuous variables. Number and percentage were used for categorical variables. Sensitivity, Specificity and was calculated taking the total number of patients with definite, highly probable and probable TBM. Subgroup analysis was done by taking patients who were categorized as definite and highly probable TBM.

Ethical Considerations

Prior approval from the institute ethics committee was obtained (IEC no.: RC/16/122). Informed consent was obtained from all the participants before the data collection.

RESULTS

107 patients presented to medicine department with symptom suggestive of meningitis during the study period, out of which only 100 patients fulfilled the inclusion criteria, hence they were recruited for the study. Out of 100 participants 64 were males and 36 were females with mean age of 55.8±10.02 and 51.6±8.78 respectively. Common presenting symptoms were headache followed by fever and neck rigidity. Co-morbid condition that was commonly present was type 2 diabetes mellitus and hypertension. (Table 1)

Variables	Characteristics (n=100)
Gender	
Male	64%
Female	36%
Age	
Male	55.8 ± 10.02
Female	51.6 ± 8.78
Sign & Symptoms	
Headache	92%
Fever	76%
Neck rigidity	71%
Altered sensorium	71%
Seizures	52%
Cranial nerve palsy	0%
Comorbid Condition	
Type 2 DM	45%
Systemic Hypertension	36%
PLHA	1%
CSF Analysis	
Normal	58%
Abnormal	42%

Table 1. Clinical Features of Participants Who Presented with Meningitis (n = 100)

DM: Diabetes Mellitus, PLHA: People Living with HIV & AIDS, CSF: Cerebrospinal Fluid

Among the abnormal CSF 22(52.4%) had features of TBM, 8(19%) had pyogenic meningitis, 11 (26%) had viral meningitis and 1(2%) had cryptococcal meningitis.

Among 22 cases of TBM, 10 (46%) were male and 12 (54%) were female. Maximum age of presentation was between 21 to 60 years of age with mean age of 42±19.2 years. Among the TBM cases, 87% had headache, 78% had fever, 69% had neck rigidity, 52% had seizure and 74% had altered sensorium. Out of the 22 patients with TBM, 7 (31.8%) had a chest X-ray suggestive of PTB. Out of the 7 patients, two (28%) had military TB. Sputum AFB smear was positive in 4 (57%). 4 patients (18%) had tuberculoma in the brain on imaging and another 4 patients (18%) had hydrocephalus on imaging. According to the criteria for composite Gold standard, 1 out of 100 (1%) participant had a definite diagnosis for TBM, 7(7%), and 14 (14%) were highly probable and probable TBM respectively. 78 (78%) had no evidence for TBM. Among the TBM cases, GeneXpert was positive in only 1 case with definite diagnosis of TBM and it was negative in all the cases of highly probable and probable TBM. GeneXpert was negative in definitely not TBM

cases. Sensitivity and specificity of GeneXpert in TBM cases was 4.7% and 100%. (Table 2)

	TBM +ve (Composite Gold Standard)	No TBM	
GeneXpert +ve	1	0	1
GeneXpert -ve	21	78	99
	22	78	100

Table 2. Sensitivity (4.7%) and Specificity (100%) of GeneXpert in Tubercular Meningitis
TBM positive: Definitely TBM, Highly probable TBM, Probable TBM.
No TBM: Definitely not TBM (pyogenic, Viral, cryptococcal)

In subgroup analysis of definitely and highly probable TBM, there were only eight cases, out of which only 1 case was positive and 7 were negative for GeneXpert. In this subgroup GeneXpert had 14% and 100% sensitivity and specificity respectively. (Table 3)

	TBM +ve (Definite + Highly probable)	No TBM	
GeneXpert +ve	1	0	1
GeneXpert -ve	7	92	99
	8	92	100

Table 3. Sensitivity (14%) and Specificity (100%) of GeneXpert In Tubercular Meningitis
TBM positive: Definitely TBM, Highly probable TBM, No TBM: Probable TBM and Definitely not TBM (pyogenic, Viral, cryptococcal)

CSF culture and Acid fast bacilli staining had similar sensitivity and specificity in both the groups. Adenosine deaminase level was elevated in one, five and seven cases in the definitely TB meningitis group, highly probable group and in probable group respectively. ADA was not positive in any of the definitely not TBM category. ADA had sensitivity of 60% and specificity of 100%. (Table 4) In sub group analysis ADA was positive in six cases and negative in 2 cases with sensitivity of 75% and specificity of 100%.

	TBM +ve (Definite + Highly Probable + Probable Cases)	No TBM	
ADA +ve	13	0	13
ADA -ve	9	78	87
	22	78	100

Table 4. Sensitivity (60%) and Specificity (100%) for ADA in Cases of Tubercular Meningitis
ADA: Adenosine Deaminase

DISCUSSION

Tuberculous meningitis is an important cause of morbidity and mortality. Due to the high prevalence of TB in India, there is need of rapid diagnostic method to initiate early treatment and cure of the diseased individuals thereby to reduce the TB burden. The diagnosis of TBM remains a challenge because of its non- specific presentation, the low sensitivity of smear microscopy in central nervous system samples and the slow growth of M. tuberculosis in culture. This cross sectional study was done to assess the utility of GeneXpert in diagnosing TBM in a total of 100 patients with suspected meningitis who fulfilled the inclusion criteria.

In this study the mean age of presentation was 42±19.2 years, which was similar in the study conducted by Yosry et al, where the presentation of meningitis was between the age of 30 and 60 years.⁹ Diabetes mellitus is a major risk

factor for the development of various infections including meningitis. Approximately one-third of our study population had diabetes mellitus. Several aspects of the immunity are altered in patients with diabetes. Joshi et al., reported that the functions of polymorph nuclear leukocytes is suppressed in the presence of diabetes mellitus, particularly when acidosis is also present. Moreover, leukocytic adherence, chemotaxis, and phagocytosis are also affected. Antioxidant systems involved in the bactericidal activity may also be impaired in patients with diabetes mellitus.¹⁰ In the present study, 31 patients had type 2 diabetes (31%), 22 patients had systemic hypertension. 14 patients had both diabetes and hypertension. 1 patient was retroviral positive.

In our study, out of a total of 100 patients, 42 patients had abnormal CSF values. Out of the 42, 22 were from TB Meningitis patients, 8 patients from pyogenic meningitis, 11 from viral meningitis and 1 Cryptococcal meningitis. Similarly, Yerramilli et al. in 2017 studied 147 cases of suspected meningitis in a tertiary hospital in India and found the incidence of TBM to be around 28%.¹¹ Out of 100 suspected cases of meningitis, 22 were diagnosed as TBM in our study. Clinical findings on presentation were headache (87%), fever (78%), neck rigidity (69%), seizure (52%) and 74% had altered sensorium. Mihaja Raberahona et al reported similar clinical findings in TBM patients on admission.¹² In our study GeneXpert was positive in only one definitely TBM case and was negative in all highly probable or probable cases. The sensitivity was 4.7% and it increased to 14% when only cases of definitely and highly probable TBM were included. Various studies has also shown very sensitivity ranging from 14% to 30%. Fuladi AB, Gupta PP et al in their study in 2017 recruited a total of 108 extra pulmonary Tuberculosis cases out of which 7 were TB Meningitis. GeneXpert was negative in all 7 cases and suggested that a negative result does not rule out the diagnosis of TB meningitis and that the decision should be made on the basis of clinical features and CSF profile.¹³ A total of 267 TBM patients were recruited and their CSF was sent for GeneXpert by Rufai SB, Singh A et al in their study. Out of 267 samples, GeneXpert was positive in only 38 cases again showing very low yield and a sensitivity of 14%.¹⁴ Singh UB, Pandey P et al assessed the efficacy of GeneXpert in 761 extra pulmonary tuberculosis patients out of which 117 CSF samples were sent from patients who had TB meningitis. GeneXpert was found to have a sensitivity of 30%.¹⁵

Vadwai et al in 2011 studied a total of 547 extra pulmonary TB patients in which 7 were TB meningitis. GeneXpert was positive in 2 out of 7 cases yielding a sensitivity of 30%.¹⁶ Metcalf T, Soria J et al in 2018 studied the CSF of total of 37 patients with presumed TB meningitis. Out of these 30 were definite TB meningitis and GeneXpert had a sensitivity of only 23%.¹⁷

In our study, GeneXpert had a specificity of 100%. There were no false positives from the definitely not TB meningitis group. Subgroup analysis specificity was also 100%. This is in keeping with other studies. Nhu et al. in 2014 evaluated 379 presumptive TB meningitis and

GeneXpert had a specificity of 99.5% with one false positive result.¹⁸ Maynard Smith et al conducted a meta-analysis of 6206 patients with extra pulmonary TB of which 20% were TBM and had a specificity of 98%.¹⁹ ADA was able to detect 1 case in the definitely TB meningitis group, 5 in highly probable and 7 in probable cases of TBM. When compared to the gold standard, ADA had a sensitivity of 60% and specificity of 100%. In subgroup analysis with only definite and highly probable TBM, Culture had sensitivity of 75% (positive in 6 out of 8 cases) and specificity of 100%. Similarly, Kothari et al in 2017 studied CSF of 86 patients with TBM and estimated the sensitivity of ADA to be 64% and 97% respectively. (97) Study done in 2014 in SKIMS institute in Kashmir studied 61 patients out of which 53 had tuberculous meningitis and found that ADA had a sensitivity of 67%.²⁰ Culture was able to detect 1 case in the definitely TB meningitis group. It was negative in all other 7 highly probable and 14 probable cases. When compared to the gold standard, GeneXpert had a sensitivity of 4.7% and specificity of 100%. In subgroup analysis with only definite and highly probable TBM, GeneXpert had sensitivity of 14% and specificity of 100%. Similarly, a study done in India in 2010, Thakur R et al analysed 164 CSF samples and found that sensitivity is only 10% with the Lowenstein Jensen Medium.²¹ Venkataswamy MM et al in 2007 analysed 256 samples of CSF from patients with TBM and yield by LJ medium was only 7%.²² In our study, culture was done using only LJ medium and no liquid culture was employed. Studies have shown that liquid culture (MGIT) yields better results than the conventional LJ medium. Thakur et al in 2010 found that when compared to LJ medium, MGIT had a slightly better yield of 27% vs. 10% from 49 CSF samples of patients with TBM.²³

Limitations

One potential drawback affecting the yield was the amount of CSF which was sent. The quantity of CSF sent varied between 3-5 ml. Nhu NT et al in 2014 analysed a total of 62 CSF samples from TB Meningitis patients and found that large quantities (around 8 ml) were associated with more positive results.¹⁸ Bahr et al. in 2016 published a review article detailing a meeting between 54 experts from 10 countries regarding the use of GeneXpert for Tuberculous Meningitis. They concluded that GeneXpert cannot be used a sole test and often large quantities are needed (8-10ml) and this is associated with difficulties in obtaining such a large quantity of CSF.¹⁷ Bahr NC et al. in 2018 studied the utility of GeneXpert in 23 TB meningitis patients who were HIV positive and also opined that a median amount of 8 ml of CSF was needed.²³

CONCLUSIONS

Despite recent advances in the diagnosis of tuberculosis with GeneXpert, its utility in diagnosing TBM is low as sensitivity is only 14%, hence negative test does not exclude TBM but if positive then 100% confirms TBM as specificity is 100%.

Clinician should rely on clinical features of meningitis, CSF cell count and biochemical parameters along with CSF adenosine deaminase to diagnose TBM.

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