GeneXpert: A Rapid and Supplementary Diagnostic Tool for Tuberculous Meningitis, Experience from Tertiary Neurocenter

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Introduction

Tuberculosis (TB) is a pulmonary infection caused by Mycobacterium tuberculosis, which can also cause extrapulmonary TB (EPTB).¹ In 2019, globally, 10 million people were suffered from TB and India was reported as the highest TB burden country in the world with an estimated incidence of 26 lakhs (the World Health Organization [WHO] 2020) cases. TB meningitis (TBM) is the common clinical manifestation of central nervous system tuberculosis (CNS TB) that causes high mortality and morbidity in children and adults. Nonspecific clinical presentation and fewer TB bacilli challenge clinicians resulting in delays in diagnosis and treatment.

Abstract

Background Tuberculous meningitis (TBM) is a highly lethal form of central nervous system tuberculosis (CNS TB) that causes high mortality and morbidity in children and adults. Nonspecific clinical presentation and fewer TB bacilli challenge clinicians resulting in delays in diagnosis and treatment.

Aim This study aimed to evaluate the utility of GeneXpert alone and in combination with culture using 1 mL of cerebrospinal fluid (CSF) in a volume constraint situation.

Methods A total of 125 clinically confirmed TBM and 110 non-TBM cases, comprised of both infectious and noninfectious diseases, were included in the study. Patient details including clinical signs and symptoms, CSF, and imaging data were collected from the case records. CSF samples were obtained from all the patients and were tested by the mycobacterial culture method and GeneXpert test. The performance of both the tests was statistically calculated and reported in the form of sensitivity and specificity.

Results Out of 125 TBM cases, 40 were detected positive by culture and 26 by GeneXpert. All 110 non-TBM cases were identified negative by both methods. The sensitivity and specificity of GeneXpert in comparison with culture were 27 and 100%, respectively. The culture was found to be more sensitive (32%) than GeneXpert. But the assay was able to detect a considerable number of clinically confirmed culture-negative TBM cases.

Conclusion GeneXpert is a rapid test and including this as an adjunctive test along with the culture in routine clinical practice can improve the diagnosis of TBM in volume constraint scenario.
nervous system TB (CNS TB) and is often fatal with long-term neurological consequences. The incidence of TBM is mainly influenced by the overall burden of TB, human immunodeficiency virus (HIV) prevalence, and age criteria.\textsuperscript{2,3} TBM is an inflammatory meningitis syndrome with nonspecific clinical presentation, and paucibacillary cerebrospinal fluid (CSF) makes the diagnosis extremely difficult. Definitive diagnosis relies on a combination of clinical, radiological, and laboratory findings.\textsuperscript{4} Early diagnosis and appropriate treatment are important for the proper management of the disease.\textsuperscript{5} The laboratory diagnostic techniques include observation of acid-fast bacilli (AFB) in CSF smear or isolation of M. tuberculosis in culture. Smear microscopy has a high detection threshold limit and less sensitivity ranging from 0 to 40%.\textsuperscript{6,7} The liquid culture method, that is, mycobacteria growth indicator tube 960 (MGIT 960) has a lesser detection threshold limit, high sensitivity ranging from 30 to 60\% compared with the solid culture method, but results obtain only after weeks of incubation which is too slow to aid in the clinical decision.\textsuperscript{8} Polymerase chain reaction (PCR)-based assays developed in recent years have been reported with 56\% sensitivity and 90\% specificity for TBM diagnosis.\textsuperscript{7,8} The GeneXpert is an automated, real-time PCR that simultaneously detects MTB and resistance to rifampicin (RIF) within 2 hours.\textsuperscript{9,10,11} The detection threshold of GeneXpert is 100 to 130 CFU/mL and was found to be useful in detecting both smear-positive and -negative pulmonary TB (PTB) cases.\textsuperscript{12-14} This assay was endorsed by WHO in 2010 and strongly recommended as the preferential test for TBM diagnosis.\textsuperscript{15} GeneXpert sensitivity for EPTB was shown to range from 50 to 80\%.\textsuperscript{16,17} Previous studies have evaluated the performance of this test using a range of CSF volumes combined with and without centrifugation.\textsuperscript{6,10,18,19} However, studies with a larger population of HIV-positive and -negative cases are needed to confirm the utility of this test in early TBM diagnosis.

Therefore, the present study was aimed to assess the efficacy of GeneXpert for TB diagnosis using approximately 1 mL of uncentrifuged CSF in volume constraint situations and to determine its usefulness in combination with culture, that is, MGIT 960 in the routine clinical investigation practice.

Materials and Methods
Study Population and Ethics Statement
A prospective study was conducted between 2017 and 2018, in the department of Neuromicrobiology, National Institute of Mental Health and Neurosciences (NIMHANS), a tertiary neurocare center at Bengaluru in India. A total of 235 patients with characteristic signs and symptoms, CSF findings, and impaired neurological function were enrolled as clinically suspected cases of TBM and other neuroinfections as non-TBM. All the patients history and clinical details were obtained from the case records. The diagnosis of the TBM group was made based on the criteria specified in the uniform case definitions described by Marais et al.\textsuperscript{20} The study was approved by the Institute’s Ethics Committee and the written informed consent forms were sought from all the patients.

Sample Collection
A total of 4- to 5-mL CSF was received in our laboratory and based on the patient’s clinical details and history; relevant investigations were done for all the patients. The leftover volume of 1.5 to 2 mL was used for AFB culture and the GeneXpert test.

Mycobacterial Investigations
Acid-Fast Bacilli Culture
AFB culture was performed by the liquid culture method in an automated MGIT system with all the safety precautions. Briefly, approximately 500 µL of each CSF volume was inoculated into MGIT tube containing 7-mL Middlebrook 7H9 broth and 0.8 mL of lyophilized MGIT PANTA (containing polymyxin B, azlocillin, nalidixic acid, trimethoprim, and amphotericin B) which was reconstituted with MGIT growth supplement OADC (oleic acid, albumin, and dextrose and catalase). The tubes flagged positive by the instrument were observed for the presence of mycobacteria by smear microscopy and further confirmed by immunochromatographic MPT64 card test (Standard Diagnostic Ltd., Korea).\textsuperscript{3,4}

GeneXpert Assay
The GeneXpert MTB/RIF assay (Cepheid, United States) was performed according to the manufacturer’s instructions. In brief, 1 mL CSF of each patient was mixed with 2 mL of sample reagent and incubated for 15 minutes with intermittent shaking. After incubation, 2 mL of the mixture was added into the Xpert cartridge using a sterile pasture pipette and the cartridge was loaded in the instrument. The results were displayed automatically within 2 hours. The reports were given as either “MTB detected” with sensitivity to rifampicin or “MTB not detected.” The cycle threshold (Ct) values will be recorded for each sample with positive test results to assess bacillary load semiquantitatively.\textsuperscript{7}

Statistical Analysis
The statistical analysis was done using Graphpad Prism version 6. The performance of GeneXpert and culture was evaluated in the form of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with a 95\% confidence interval (CI). CSF parameters in TBM were compared statistically with that of non-TBM cases. First, normal distribution of data was assessed by Shapiro–Wilk test; S denotes skewness and K denotes kurtosis. Parametric “t-test or Mann–Whitney U-test (nonparametric) was applied based on the normality distribution to calculate the p-value for assessing the significant differences between the TBM group and control group. A p-value of <0.05 was used to interpret the level of significance.

Result
Patient Details and Clinical and Laboratory Findings
As shown in – Fig. 1, a total of 235 cases were included in the study of which 125 were clinically diagnosed as TBM and 110
as non-TBM (controls). Non-TBM group comprised of infectious diseases, namely, cryptococcosis \( (n = 22) \), pyogenic meningitis \( (n = 12) \), toxoplasmosis \( (n = 3) \), brucellosis \( (n = 1) \), viral meningoencephalitis \( (n = 10) \), Herpes simplex virus \( (n = 3) \), measles \( (n = 1) \), and noninfectious disorders, like epilepsy, migraine, cerebrovascular disease, polyneuropathy, movement disorders \( (n = 52) \), neurodegenerative diseases like multiple sclerosis \( (n = 3) \), and carcinomatous meningitis \( (n = 3) \).

The majority of the patients included in this study were from Karnataka \( (77\%) \) and others from neighboring states which included 7.6% from Andhra Pradesh, 6.8% from Tamil Nadu, 6.3% from West Bengal, 1.2% from Bihar, and 0.4% each from Kerala and Jharkhand. Out of 235 cases, 145 \( (61.70\%) \) were males and 90 \( (38.29\%) \) were females and the age range was 3 to 80 years (►Table 1). The commonly observed signs and symptoms in TBM patients were fever \( (80\%) \), headache \( (75.2\%) \), vomiting \( (55.2\%) \), altered sensorium \( (48\%) \), loss of appetite \( (11.2\%) \), and neck stiffness \( (34.4\%) \). Other unusual clinical findings seen were seizure \( (12.8\%) \), convulsion \( (0.8\%) \), meningeal enhancement \( (10.4\%) \), diplopia \( (4.8\%) \), photophobia \( (5.6\%) \), etc. In some patients, a computed tomography (CT) scan showed hydrocephalus \( (4\%) \), basal exudates \( (11\%) \), and infarction \( (0.8\%) \). Among 125 TBM cases, 4 were also diagnosed as miliary TB with TBM.

In the TBM group, cytological examination showed characteristic CSF findings like lymphocytic predominant pleocytosis, elevated protein, and low glucose concentration which were found to be statistically significant \( (p < 0.0001) \) as compared with the non-TBM (►Table 2).

### Performance of GeneXpert Assay and Culture

As mentioned in the previous section, uniform case definition criteria (Marais and Thwaites, 2010) was followed to ensure the diagnostic certainty of the highest possible standard and to allocate suspected cases of TBM accordingly into the definite, probable, and non-TBM group. Of the total 125 TBM cases, smear microscopy was performed for only 14 cases based on the CSF algorithm followed in the laboratory.

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**Fig. 1** Summary flow chart showing patient recruitment, diagnostic test performed, and test results. CSF, cerebrospinal fluid; MGIT, mycobacteria growth indicator tube; TBM, tuberculous meningitis.

**Table 1** Patient characteristics with in TBM and non-TBM group

| Characteristics                        | TBM \( (n = 125) \) | Non-TBM \( (n = 110) \) |
|----------------------------------------|---------------------|-------------------------|
| Age (y) Mean ± SD                      | 36.24 ± 14.81       | 39.27 ± 17.20           |
| Sex, male/female (%)                   | 75/50 (60/40)       | 70/40 (64/36)           |
| HIV status (P/N/U)                     | 13/30/82            | 43/37/30                |
| Evidence of extra CNS-TB, (Yes/No/U)   | 4/112/9             | 0/110/0                 |
| Duration of illness (>6 days/<6 days/U)| 39/46/40            | 90/18/2                 |
| History of contact (Yes/No/U)          | 15/101/9            | 0/110/0                 |

Abbreviations: N, negative; P, positive; SD, standard deviation; TBM, tuberculous meningitis; U, unknown.
(chronic meningitis workup, high clinical suspicion, etc.) and staining was done by standard Ziehl–Neelsen method. Of these 14 cases, 3 were detected positive (two probable and one definite) and 11 were identified as negative (seven probable and four definite). Out of 125 TBM cases, 40 (32%) were presented with signs and symptoms, CSF changes (→ Table 3), cerebral imaging findings suggestive of meningitis, and MTB were detected in CSF by culture, hence categorized as definite TBM.

The remaining 85 (68%) cases showed, clinically, CSF and cerebral imaging criteria indicative of meningitis (diagnostic score of >10–12) without an alternative diagnosis.20 All were identified negative by available diagnostic methods performed in our laboratory which includes smear microscopy or culture. Also, none of these had evidence of AFB in the context of histological changes consistent with TB in the brain or spinal cord together with suggestive signs or symptoms and CSF changes (→ Table 4) or visible meningitis (on autopsy) and therefore designated as probable TBM cases.

All non-TBM cases were detected M. tuberculosis negative by both the methods. Among 40 definite TBM cases, 11 (28%) were detected positive by GeneXpert of which 9 (81%) were RIF sensitive and 1 (19%) each gave resistant and indeterminate results (→ Table 3). Out of 85 probable TBM cases, 15 (18%) were detected positive by GeneXpert of which, 14 (93%) were RIF sensitive and 1 (7%) was detected with indeterminate resistance (→ Table 3). In total 26 (20%) GeneXpert positive cases, 2 (8%) were detected with “low” (Ct: 22–28 cycles) and 24 (92%) with “very low” (Ct: >28 cycles) bacillary load. None of the CSF samples was detected with a “high” or “medium” bacillary load. Machine error was detected in 5 (2%) among 235 CSF samples. GeneXpert Ct values of all the analyzed CSF samples were matching with the semiquantitative bacillary load. As shown in → Table 5, the GeneXpert result was evaluated comparatively and in combination with culture as the standard reference method. Samples with machine errors were not included in the analysis. In our study, culture was found to be more sensitive 32% (95% CI: 23.94–40.93%) than GeneXpert. The specificity was given 100% (95% CI: 96.70–100%) by both methods. The sensitivity and specificity of GeneXpert relative to culture was 27% (95% CI: 14.60–43.89%) and 100% (95% CI: 96.70–100%), respectively.

### Discussion

TB is a medical emergency and is predominantly seen in developing countries like India. Confirmatory diagnosis in the early stages of the infection is very important to effectively control the disease. The problems associated with the currently available conventional and molecular tests demands researchers to look for more rapid and sensitive techniques that could be helpful in the early diagnosis of the disease. GeneXpert assay is now available worldwide and is also currently in use for national TB control programs.21 The study primarily aimed at economizing the CSF volume for TBM diagnosis by GeneXpert in a sample constraint setting. Further, its efficacy in early TBM diagnosis is combined with culture in routine clinical practice. The strength chiefly focused on a large pool of culture-confirmed and probable TBM cases wherein the later, low CSF volume could be relied on as a diagnostic quantity to evaluate the test utility. In the

### Table 2 CSF parameters in TBM and non-TBM group

|        | TBM (n = 125) | Non-TBM (n = 110) | p-Value |
|--------|---------------|--------------------|---------|
| Lymphocytes (cells/μL) | 60 (16–156) | 9(0–35)          | <0.0001 |
| Protein (g/L) | 185 (102–270) | 88 (51–157)      | <0.0001 |
| CSF glucose (mmol/L) | 35 (23–54) | 53 (33–73)     | <0.0001 |
| CSF/serum glucose ratio | 0.3 (0.2–0.4) | 0.3 (0.1–0.5) | –       |

Abbreviations: CC, cerebrospinal fluid; IQR, interquartile range; TBM, tuberculous meningitis.

### Table 3 Details of GeneXpert positive cases among culture-positive cases

| Sr. no. | Age (y) | Sex | CC | Poly | Lympho | Deg | Protein | Glucose | GeneXpert | RIF S |
|---------|---------|-----|----|------|--------|-----|---------|---------|-----------|-------|
| Case 1  | 23      | F   | 260 | 26   | 234    | 0   | 250     | 11      | MTB detected very low | I     |
| Case 2  | 17      | F   | 102 | 0    | 100    | 2   | 887     | 19      | MTB detected very low | S     |
| Case 3  | 28      | F   | 120 | 36   | 78     | 6   | 211     | 51      | MTB detected very low | R     |
| Case 4  | 2       | M   | 212 | 22   | 186    | 4   | 370     | 50      | MTB detected very low | S     |
| Case 5  | 42      | M   | 1,200 | 900 | 300    | 0   | 181     | 33      | MTB detected very low | S     |
| Case 6  | 42      | M   | 70  | 20   | 50     | 0   | 490     | 26      | MTB detected very low | S     |
| Case 7  | 63      | M   | 190 | 114  | 76     | 0   | 316     | 15      | MTB detected low      | S     |
| Case 8  | 19      | F   | 180 | 126  | 54     | 0   | 135     | 26      | MTB detected very low | S     |
| Case 9  | 27      | M   | 162 | 33   | 1      | 0   | 157     | 14      | MTB detected very low | S     |
| Case 10 | 31      | M   | 240 | 0    | 216    | 0   | 149     | 18      | MTB detected very low | S     |
| Case 11 | 11      | M   | 50  | 10   | 40     | 0   | 157     | 14      | MTB detected very low | S     |

Abbreviations: CC, CSF cell count; CSF, cerebrospinal fluid; Deg, degenerated; F, female; I, indeterminate; Lympho, lymphocytes; M, male; MTB, Mycobacterium tuberculosis; Poly, polymorphs; R, resistant; RIF S, rifampicin sensitivity; S, sensitive.
present study, male predominance was observed in the TBM population similar to other studies.\textsuperscript{7,12,22,23} The median age among TBM cases for males and females was 35 and 38 years, respectively, revealing the economically productive age group being more vulnerable to TBM.\textsuperscript{3,5} There was no statistical difference found between the two groups concerning age (\( p = 0.08 \)) and gender (\( p = 0.56 \)).\textsuperscript{5} The signs and symptoms observed in this study were complementary to another study on TBM patients.\textsuperscript{6} In biochemical parameters, derangement in glucose and protein concentrations was found.\textsuperscript{6} CSF pleiocytosis with a lymphocytic predominance was observed and the median value of the cell count was 60 cells/mm\textsuperscript{3}.\textsuperscript{3,4} The number of HIV-negative cases was more than HIV-positive cases in the TBM population, and this is in agreement with the study population in another part of India.\textsuperscript{7} This could be due to a lack of information on the HIV status of the patients because for many cases with the infectious disease, the HIV test was not done and some of them were discharged before HIV testing. Previous studies have assessed the performance of GeneXpert for TBM diagnosis with a range of CSF volume and also reported its diagnostic results with a combination of tests can give more confirmatory results than with a single diagnostic test. Hence, 1 mL CSF can be recommended for TBM diagnosis in routine clinical practice against the volume constraint of neuroinfections with a combination of tests can give more confirming results than with a single diagnostic test. Hence, 1 mL CSF can be recommended for TBM diagnosis in routine clinical practice against the volume constraint of neuroinfections with a combination of tests can give more confirming results than with a single diagnostic test.

Table 4 Details of GeneXpert positive cases among culture negative cases

| Sr. no. | Age (y) | Sex | CC | Poly | Lympho | Deg | Protein | Glucose | GeneXpert | RIF S |
|---------|---------|-----|----|------|--------|-----|---------|---------|-----------|-------|
| Case 1  | 43      | F   | 24 | 13   | 11     | 0   | 121     | 49      | MTB detected very low | S     |
| Case 2  | 36      | M   | 16 | 0    | 16     | 0   | 163     | 33      | MTB detected very low | S     |
| Case 3  | 27      | M   | 162| 32   | 130    | 0   | 157     | 14      | MTB detected very low | S     |
| Case 4  | 33      | M   | 0  | 0    | 0      | 0   | 104     | 29      | MTB detected very low | S     |
| Case 5  | 51      | M   | 154| 3    | 146    | 5   | 252     | 35      | MTB detected very low | S     |
| Case 6  | 31      | M   | 770| 308  | 462    | 0   | 249     | 28      | MTB detected very low | S     |
| Case 7  | 24      | F   | 260| 0    | 26     | 234| 250     | 11      | MTB detected very low | I     |
| Case 8  | 19      | F   | 180| 126  | 54     | 0   | 135     | 26      | MTB detected very low | S     |
| Case 9  | 35      | F   | 29 | 0    | 19     | 10  | 190     | 3       | MTB detected very low | S     |
| Case 10 | 58      | M   | 240| 120  | 108    | 12  | 465     | 32      | MTB detected low      | S     |
| Case 11 | 38      | F   | 280| 0    | 6      | 274| 220     | 17      | MTB detected very low | S     |
| Case 12 | 49      | M   | 8  | 0    | 4      | 4   | 269     | 31      | MTB detected very low | S     |
| Case 13 | 39      | F   | 220| 88   | 132    | 0   | 830     | 4       | MTB detected very low | S     |
| Case 14 | 42      | M   | 430| 43   | 387    | 0   | 199     | 25      | MTB detected very low | S     |
| Case 15 | 35      | M   | 110| 33   | 77     | 0   | 347     | 47      | MTB detected very low | S     |

Abbreviations: CC, CSF cell count; CSF, cerebrospinal fluid; Deg, degenerated; F, female; I, indeterminate; Lympho, lymphocytes; M, male; MTB, Mycobacterium tuberculosis; Poly, polymorphs; R, resistant; RIF S, rifampicin sensitivity; S, sensitive.

Table 5 Diagnostic performance of GeneXpert in comparison with culture

| Test               | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|--------------------|----------------------|----------------------|--------------|--------------|
| Culture            | 32% (40/125; 23–40%) | 100% (110/110; 96–100%) | 100%         | 56.41% (53–59%) |
| GeneXpert V/S culture | 27% (11/40; 14–43%) | 100% (110/110; 96.70–100%) | 100%         | 79.14% (75–82%) |

Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
volume used in their study was relatively more (2 mL) as compared with our study. The Sensitivity of GeneXpert found in our study is comparable to a study by Rufai et al in which the test was done using approximately similar CSF volume but the number of TBM cases was more and the study did not include CSF from any non-TBM cases. As stated earlier, GeneXpert is a good rule in testing HIV-infected TBM population because of the higher bacterial load in their CSF compared with HIV uninfected. In our study, of total TBM cases, the overlap of both GeneXpert positive and culture positive was only 8.8% (11/125). All 3 of 11 HIV coinfected TBM cases were positive by both these methods. Information was not available for the remaining eight cases. About 29 (72.5%) of total culture-positive cases were not detected by GeneXpert and the reason could be due to not enough bacteria to reach the detection threshold limit. Detection is possible only when the required threshold is reached. Out of 85 probable TBM cases, 15 (17%) were detected positive by GeneXpert despite a higher analytical detection threshold with false-positive results.

**Limitations**

This study has some limitations that we could not find clinical details for all the patients, and drug susceptibility testing was not performed to confirm the rifampicin sensitivity pattern for culture and GeneXpert positive cases.

**Conclusion**

In conclusion, the GeneXpert test is highly user friendly which does not require expert handling. Although the test performed well in high CSF volume, CSF sample should be used in priority for GeneXpert in sample volume constraint, as sensitivity depends on the volume of the sample subjected to the test. In our study, in addition to culture-confirmed cases, this assay could detect a considerable number of clinically confirmed culture-negative TBM cases which indicates that it can be a rapid, supplementary test that aids in the early detection of culture-negative cases. Also, the test can be useful where a culture facility is not available.

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**Conflict of Interest**

None declared.

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