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# Role of Cartridge Based Nucleic Acid Amplification Test of Cerebrospinal Fluid in the Diagnosis of Tubercular Meningitis

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## ABSTRACT

**Introduction:** Tubercular meningitis is the commonest form of neurotuberculosis. Diagnosis is challenging because of paucibacillary nature, lack of specific sign and symptoms. CBNAAT is a real time Polymerase Chain Reaction (PCR) test for the diagnosis of tubercular meningitis. So we used this rapid test to assess its role in diagnosis of Tubercular Meningitis(TBM).

**Material and Methods:** This study was done over a period of one year in a tertiary centre. Patients with symptoms suggestive of tubercular meningitis were our study population. Their detailed clinical history, followed by a thorough general physical & systemic examination were done and documented in a predesigned proforma. Chest x-ray as well as neuroimaging were done in patients whose condition permitted. 3ml CSF fluid was drawn by lumbar puncture, 2 ml was sent for routine and bacteriological examination test and 1 ml for CBNAAT.

**Results:** 100 patients were included, with a male to female ratio of 1.7:1. Mean age of the affected population was 37.53 years. 47% had radiological finding suggestive of tuberculosis.18 out of 100 were HIV reactive. MRI brain in 64 patients showed meningeal enhancement as the most common finding (60.93%). In Cerebrospinal Fluid (CSF) analysis mean CSF protein was 136.5 mg/dl, mean CSF glucose was 56.4 mg/dl and CSF cell count was 66.7 cells/microliter. Mean Adenosine Deaminase (ADA) was 11.22 U/L.CSF CBNAAT was positive in 9 patients out of which 8 were sensitive to rifampicin and one resistant to it.

**Conclusion:** Even though CSF cytology gives good estimate of suspected TBM patient the test is not confirmative for bacilli demonstration. CBNAAT being a rapid accurate test would play a major role in the diagnosis, treatment, as well as for estimating rifampicin resistance of one of the common medical emergency in India by clear guidance from WHO.

**Key Words:** CBNAAT, Tubercular Meningitis, Cerebrospinal Fluid, Rifampicin resistance, WHO

## INTRODUCTION

Tuberculosis remains one of the deadliest communicable diseases. Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS)[1]. India is the highest TB burden country in the world, accounting for about 23.3% of the global prevalence and estimated incidence being 2.84 million cases[2]. About 2.2% of new cases and 15% of previously treated cases have MDR-TB in India.

Tuberculosis was first recognized as a clinical entity in the early 19thcentury by schonlein, who used the term tuberculosis in 1830, which was derived from the English term "tubercle" or "lesion of consumption"[3]. According to World Health Organization (WHO), TB is a worldwide pandemic. While pulmonary tuberculosis is the most common presentation, extra-pulmonary tuberculosis (EPTB) is also an important clinical problem[4,5].

CNS Tuberculosis includes three clinical categories, tubercular meningitis, tuberculoma and spinal arachnoiditis[6].

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Tubercular meningitis is the commonest form of neurotuberculosis in Indian subcontinent accounting for 70%-80% of cases[7]. The burden of CNS TB is directly proportional to the prevalence of TB infection. Tubercular meningitis is the most devastating form of extra-pulmonary TB with 30% mortality and disabling neurological sequelae in >25% survivors[7]. Important risk factors includes HIV, overcrowding of urban population, poor nutritional status, appearance of drug resistant strains of tuberculosis[7]

The diagnosis of EPTB is challenging because of its paucibacillary nature, lack of specific signs symptoms and often negative acid fast bacilli smear of biological specimens[8].

Patients who demonstrate a subacute clinical course with headache, vomiting, pyrexia and anorexia should be suspected of having TBM. Diagnosis is based on the clinical symptoms and cerebrospinal fluid changes (increased protein, low glucose and mononuclear pleocytosis)[9].

Definitive diagnosis of tuberculosis involves demonstration of MTB by microbiological, cytological or histo-pathological methods

Gene Xpert or CBNAAT (Cartridge Based Nucleic Acid Amplification Test) is a real time PCR test approved by WHO Policy in 2010, initially used in diagnosing MDR-TB and HIV associated TB. RNTCP policy update in 2013 expanded its uses, including for the diagnosis of TB in children, on selected specimens for the diagnosis of EPTB and for all individuals suspected of having pulmonary TB.[10] Based on systematic review, WHO recommends Xpert over conventional tests for diagnosis of EPTB which permits rapid TB diagnosis through detection of the DNA of mycobacterium TB and simultaneous identification of a majority of the mutations that confirm Rifampicin resistance which is highly predictive of MDR TB.

In the present study we prospectively determined the utility of this test in detection of MTB in CSF samples obtained from the patients suspected to have tubercular meningitis.

## AIM AND OBJECTIVE

To determine utility of Gene Xpert (CBNAAT) test in detection of MTB in CSF obtained from the patients who are clinically diagnosed case of tubercular meningitis.

## MATERIALS AND METHODS

The present study was conducted for a period of one year at R.N.T. Medical College and attached group of hospitals, Udaipur. After obtaining approval from the institutional ethical committee and written informed consent from patient, 100 patients with symptoms and signs suggestive of TBM were included. Their detailed clinical history, previous history of tuberculosis, history of contact with pulmonary tuberculosis, past history of medical illness were taken. After general physical and central nervous system examination, Chest x-ray as well as neuroimaging (CT / MRI brain) were done if patients condition permitted. Sputum samples from study population, who had cough for any duration, was sent for AFB examination. 3ml CSF fluid was drawn by lumbar puncture, 2 ml was sent for routine biochemical and bacteriological examination and 1 ml for CBNAAT. Bacterial, viral and fungal meningitis were ruled out by clinico-radiological basis & biochemical and bacteriological examination of CSF. All the information was recorded in predesigned proforma formed in Microsoft excel for final analysis.

### Inclusion Criteria

1. All patients with suspicion of TBM admitted in MBG (Maharana Bhupal Government) hospital in medicine and neurology ward.
2. Age group >18yrs.

### Exclusion Criteria

1. Age less than 18yrs
2. Patients with other causes of altered sensorium such as dyselectrolytemia, cerebrovascular accident, bacterial /viral meningitis/meningoencephalitis etc
3. Not willing to give consent.

## RESULTS

In this study of 100 patients 63 patients (63%) were male and 37 patients (37%) were females. Male to female ratio was 1.7:1. Majority of them were in adolescent/early adult age group. Mean value for age was 41.3 years. Most common co-morbidity associated with study population was past history of pulmonary tuberculosis and diabetes mellitus.18 patients were HIV positive. Fever was the most common symptom followed by altered sensorium headache and vomiting. Chest x-ray suggestive of pulmonary tuberculosis was 39 (39%) out of which only 4 patients were positive for sputum AFB.8(8%) patients had x-ray chest suggestive of old healed lesion and 53(53%) patients had a normal chest x-ray. CSF analysis showed mean CSF protein value of 136.5 mg/dl, CSF cell count value of 58.8 cells/microliter (90% lymphocytes) CSF glucose value of 56.4mg/dl and CSF ADA level had a mean value of 11.3 U/L. MTB was detected in 9 CSF samples out of 100 sent for CBNAAT. Out of 9 samples 8 were Rifampicin sensitive and 1 showed resistance. Among 8 positive and rifampicin sensitive result one patient was HIV positive. Neuroimaging (MRI) was done on 64 patients out of which 55(85.97%) was abnormal and normal in 9 patients. Most common finding was meningeal enhancement (60.93%) followed by hydrocephalus(11.76%). 39 patients recovered completely, 20 patients recovered with residual

morbidity and 16 patients had mortality. We lost the track of 25 patients as they did not show up in further follow ups.

**Table 1: Sex distribution in the study population**

| Serial no. | Sex of patients | No. of patients |
|---|---|---|
| 1. | Male | 63 (63%) |
| 2. | Female | 37 (37%) |
| | Total | 100 |

In this study of 100 patients 63 % cases were male and 37% were female. Male to female ratio was 1.7:1.

**Table 2: Age wise distribution of study population**

| Serial No. | Age group of patients | No. of patients |
|---|---|---|
| 1. | 18-30 yrs | 49 (49%) |
| 2. | 30-60 yrs | 29 (29%) |
| 3. | 60-90 yrs | 22 (22%) |
| Total | | 100 |
| Mean age | 37.53 yrs | |
| S.D. | 17.33 | |

In this study, patients were of age ranging between 18 to 90 yrs, mean age of patients was 37.53 yrs and S.D. was 17.33. Most of the patients were in age the group of 18 to 30 yrs (49%).

**Table 3: Comorbidities in study population**

| Serial no. | Comorbidities | No. of patients | % Population |
|---|---|---|---|
| 1. | Diabetes Mellitus | 18 | 18% |
| 2. | Hypertension | 14 | 14% |
| 3. | Past h/o TB /Contact | 24 | 24% |
| 4. | Bronchial asthma | 2 | 2% |
| Total | | 58 | 58% |

**Table 4: HIV status of study population**

| Serial No. | HIV status | No. of patients |
|---|---|---|
| 1. | Reactive | 18 (18%) |
| 2. | Non reactive | 82 (82%) |
| | Total | 100 |

18% cases had HIV reactive status, which increased the susceptibility to TBM.

**Table 5: Symptomatology of study population**

| Serial no. | Symptoms | No. of Patients |
|---|---|---|
| 1. | Fever | 100(100%) |
| 2. | Headache | 41(41%) |
| 3. | Vomiting | 46(46%) |
| 4. | Altered Sensorium | 58(58%) |
| 5. | Seizure | 30(30%) |
| 6. | Cough | 17(17%) |
| 7. | Focal Neurological Deficit | 9(9%) |
| 8. | Loss Of Consciousness | 5(5%) |

In this study, Patients had different symptoms like fever, headache, vomiting, altered sensorium, seizure, cough, focal neurological deficit and loss of consciousness. Most common symptoms were fever (100%), altered sensorium (58%), vomiting (46%).

**Table 6: Chest radiographic findings in study population**

| Serial no. | Chest radiographic finding | No. of patients |
|---|---|---|
| **1.** | **Suggestive of pulmonary TB** | **39 (39%)** |
| **2.** | **Old healed lesion** | **8 (8%)** |
| **3.** | **Normal** | **53 (53%)** |
| | **Total** | **100** |

In this study of 100 patients, 39% cases had chest x-ray finding which suggested lesion of pulmonary TB and 8% case had old healed lesion while 53% cases had normal finding.

**Table 7: Sputum for AFB in study population**

| Serial no. | Sputum for AFB | No. of patients |
|---|---|---|
| **1.** | **Positive** | **4 (4%)** |
| **2.** | **Negative** | **45 (45%)** |
| **3.** | **Not done** | **51 (51%)** |
| **Total** | | **100** |

In this study of 100 patients, only 4% cases had positive AFB sputum and 45% cases had negative AFB status while 51% patients sputum examination for AFB could not be done.

**Table 8: CSF protein in CSF analysis of study population**

| Serial no. | CSF Protein level | No. of patients |
|---|---|---|
| 1. | 50-100 mg/dl | 36 (36%) |
| 2. | 100-200 mg/dl | 52 (52%) |
| 3. | 200-300 mg/dl | 9 (9%) |
| 4. | >300 mg/dl | 3 (3%) |
| Total | | 100 |
| Mean CSF Protein level | 136.5 mg/dl | |
| S.D. | 69.58 | |

In this study of 100 patients, in 52% cases CSF protein level was in range of 100-200 mg/dl. Mean CSF protein level was 136.5 mg/dl and S.D. for this was 69.58.

**Table 9: CSF glucose in CSF analysis of study population**

| Serial no. | CSF Glucose level (mg/dl) | No. of patients |
|---|---|---|
| 1. | 20-40 mg/dl | 14 (14%) |
| 2. | 40-60 mg/dl | 45 (45%) |
| 3. | 60-80 mg/dl | 36 (36%) |
| 4. | 80-100 mg/dl | 5 (5%) |
| Total | | 100 |
| Mean | 56.4 | |

CSF was analysed for glucose level, in majority of patients (45%) CSF Glucose level was in range of 40-60 mg/dl. Mean CSF Glucose level was 56.4 mg/dl

**Table 10: CSF cell count in CSF analysis of study population**

| Serial no. | CSF cell count Cells/microliter | No. of patients |
|---|---|---|
| 1. | 10-50 cells/microliter | 51 (51%) |
| 2. | 50-100 cells/microliter | 42 (42%) |
| 3. | 100-200 cells/microliter | 4 (4%) |
| 4. | >200 cells /microliter | 3 (3%) |
| Total | | 100 |
| Mean | 66.7 cells/microliter | |
| S.D. | 83.01 | |

In majority of patients (51%) cell counts were in range of 10-50 cells/microliter(>90% lymphocytic pleocytosis) Mean CSF cell count was 66.7 cells/microlitre and S.D. for this observation was 83.01.

**Table 11: ADA Level in CSF fluid analysis of study population**

| Serial no. | ADA level in CSF (U/Litre) | No. of patients |
|---|---|---|
| 1. | 0-5 U/Litre | 9 (9%) |
| 2. | 6-10 U/Litre | 37(37%) |
| 3. | 11-15 U/Litre | 43(43%) |
| 4. | 16-20 U/Litre | 11(11%) |
| Total | | 100 |
| Mean | 11.225 U/Litre | |

ADA level in CSF was analysed and observed that majority of the patients had CSF ADA level in range of 11-15U/Litre. Mean ADA level in this study was 11.22 U/Litre and S.D. was 4.8.

**Table 12: CSF CBNAAT in CSF analysis of study population**

| Serial no. | CSF CBNAAT Status | No. of patients |
|---|---|---|
| 1. | Positive | 9 (9%) |
| 2. | Negative | 90(90%) |
| 3. | Error | 1(1%) |
| Total | | 100 |

Out of 100 patients 9 patients CSF CBNAAT analysis turned out to be positive out of which 8 were sensitive and 1 was resistant to rifampicin

**Table 13: MRI brain in study population**

| Serial no. | MRI findings | No. of patients |
|---|---|---|
| 1. | Meningeal enhancement | 39(60.93%) |
| 2. | Hydrocephalus | 8(11.76%) |
| 3. | Vasculitic infarct | 5(7.81%) |
| 4. | Meningoencephalitis | 2(3.12%) |
| 5. | Dural sinus thrombosis | 1(1.56%) |
| 6. | Normal | 9(9%) |
| 7. | Not Done | 36(36%) |
| Total | | 100 |

**Table 14: Outcome in study population**

| Serial no. | Outcome | No. of patients |
|---|---|---|
| 1. | Death | 16(16%) |
| 2. | Lost to follow up | 25(25%) |
| 3. | Recovery | 39(39%) |
| 4. | Morbidity | 20(20%) |
| Total | | 100 |

In this study of 100 patients final outcome was variable, 39% cases were completely recovered from the disease and 20% patients had some residual morbidity, while 16% mortality was observed. 25% cases outcome could not be documented as we lost the follow up.

## DISCUSSION

In this study 63 patients (63%) were male and 37 patients (37%) were females. Male to female ratio was 1.7:1 and mean age of population was 37.53 years, Most of the patients were in the age group of 8 to 30 yrs (49%). In a study by Rakesh Bhatia et al[11]. 20 were males and 14 were females and male to female ratio was 1.4:1. Patients of productive age groups were frequently involved by this clinical entity. Co-morbidities in our study group included 18 patients of diabetes mellitus, 14 of hypertension, 24 with past history of tuberculosis/contact and 2 of bronchial asthma. In Inês Sanches et al study, HIV, DM and cancer were frequent co-morbidities associated with extra-pulmonary tuberculosis and seen in 15.8% (20), 6.3% (8) and 4.8% (6) patients respectively[12]. DM is a well known risk factor for Tuberculosis. depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency have been implicated in the occurrence of tuberculosis in Diabetic patients.

18 (18%) patients out of 100 were HIV positive in our study population. In a Study by Nathan C Bahr et al out of 257 patients with meningitis 105 (40%) patients were HIV positive[13]. HIV is a major risk factor for tuberculosis. Patients with HIV and active tuberculosis have an increased risk of extrapulmonary tuberculosis, and this risk will also increase with declining CD4+ count.

In symptomatology of our study population, all patients (100%) had fever followed by altered sensorium in 58 (58%) patients. Headache and vomiting had a prevalence of 41 (41%) and 46 (46%) respectively among patients, followed by seizure (30%), cough (17%), focal neurological deficit (9%,one with facial nerve involvement) and loss of consciousness(5%). In study by Modi M et al[14] out of 209 patients 195 patients had fever followed by headache (199), vomiting(169), loss of appetite(139), altered sensorium (101), loss of weight (94), focal deficit (67) and seizure (49).

In our study chest x-ray suggestive of pulmonary tuberculosis was 39, out of which only 4 patients were positive for sputum AFB. 8 patients had x-ray chest suggestive of old healed lesion and 53(53%) patients had a normal chest x-ray. Chest x-ray lesions included apical infiltrates (unilateral >bilateral), miliary infiltrate and old healed calcified lesion and pleural thickening. In a study conducted by Solomons R S et al out of 84 children 37 (44%) TBM patients had CXR findings suggestive of TB, 9 (11%) with disseminated (miliary) TB.

In a study conducted by Sidra Aurangzeb et al[15] out of 100 TBM patients radiographic findings of pulmonary TB was found only in 30(30%) patients .The predominant patterns on CXR were apical infiltration (26.6%), miliary mottling (20%) and hilar enlargement (16.6%).The relationship between pulmonary and cranial miliary lesions is controversial and there is a paucity of work done on adults in this regard.

CSF analysis conducted in our study population had mean CSF protein value of 136.5 mg/dl and CSF cell count value of 58.8 cells/microliter ( 90% lymphocytes) and CSF glucose value of 56.4mg/d. In the study conducted by Modi M et al[14] out of 203 patients 179 (88%) patients had lymphocytic predominant (>90%) pleocytosis,101 (44%) patients had glucose <30mg/dl. In a study by Moghtaderi et al[16] mean CSF protein was 80 mg/dl, mean CSF glucose was 34 mg/dl and lymphocyte predominance (80%) mean value being 18 cells/microliter. In the study conducted by Kumar K et al[17], 156 patients had lymphocyte predominance (>50%). High protein (>45mg/dL) was seen in 173 patients. Characteristic CSF findings of TBM include the following: (i)lymphocytic-predominant pleocytosis. Total white cell counts are usually between 100 and 500 cells/µL. Very early in the disease, lower counts and neutrophil predominance may be present, (ii)elevated protein levels, typically between 100 and 500 mg/dL, (iii)low glucose, usually less than 45 mg/dL or CSF: plasma ratio <0.5[18]

CSF ADA level in our study population had a mean value of 11.3 U/L (range 10-20 U/Litre).In the study conducted by Lely solari et al[19]**.** The validity of cerebrospinal fluid parameters for the diagnosis of tuberculous meningitis , ADA level >6 U/l had a sensitivity of 60% and was 94% specific. ADA is released by T cells during cell mediated immune response (CMI) to the tubercle bacilli. Raised levels of ADA in CSF are not specific to meningeal inflammatory disease but it can be a test for confirming its etiology with good predictive value. CSF ADA level 10 µ/L is sensitive and can suggest the diagnosis of TBM, especially if the clinical suspicion is high[20,21].

In this study MTB was detected in 9 CSF samples out of 100 sent for Gene Xpert technique and 1 with error. Out of 9 samples 8 were Rifampicin sensitive and 1 showed resistance. Among 8 positive and rifampicin sensitive result, one patient was HIV positive.

In study by Nguyen Thi Quynh Nhu et al[22] X-pert MTB/ RIF was positive in 108 (59.3%) patients with sensitivity of 59.3% and specificity 99.5%. 4 cases of RIF resistance(4/108) was identified by Xpert. Patel and colleagues[23] report the diagnostic performance of the Gene Xpert system's Xpert MTB/

RIF assay for the diagnosis of TBM assay's overall sensitivity was 62%, and specificity was 95%.

In the study conducted by Sharma Kusum et al[24] multiplex PCR was positive in 84.78% cases. The overall sensitivity and specificity was 86.63% and 100 % respectively**.** In CSF, the pooled sensitivity from metaanalysis of Xpert MTB/RIF compared against culture as a reference standard was 79.5% (95% CI, 62.0-90.2%) (16 studies, 709 specimens)**[25].** Various studies conducted worldwide has varied sensitivity and specificity depending on various factors such as volume, centrifugation. Despite improved diagnostic accuracy using centrifuged CSF for Xpert compared with un-centrifuged CSF, the ideal CSF volume to collect is unknown. Xpert has an analytical sensitivity detection threshold of approximately ~100 CFU/mL *M. tuberculosis* organisms.

In our study neuroimaging (MRI) was done on 64 patients out of which 55(85.97%) showed abnormalities, 39 (60.93%) had meningeal enhancement, 8 patients (11.76%) had hydrocephalus, 5 patients (7.81%) had vasculitic infarct, 2 patients(3.12%) had meningoencephalitis and 1 patient (1.56%) had dural sinus thrombosis.MRI brain was normal in 9 patients.

In study conducted by Modi M et al**[14]**. Exudates were present in 82.3% patients Hydrocephalus was present in 52.1% and infarcts were seen in 23.9% of patients. Tuberculomas were present in 45.9% of patients. R. Abdelmalek et al**[16]** in their retrospective study reviewed 29 patients out of which 26 patients showed abnormalities in their MRI and concluded that Cerebrospinal MRI performed when TBM is suspected aids in its diagnosis and is also a useful means of monitoring the course of the disease under treatment. Common findings on imaging are abnormal meningeal enhancement in the basal cisterns, hydrocephalus, and vascular complications.

Out of 100 patients in our study population 39 patients (39%) recovered completely, 20 patients (29%) recovered with residual morbidity and 16 patients(16%) had mortality. We lost the track of 25 patients as they did not show up in further follow ups. Prognosis of TBM largely depends on neurologic status at the time of presentation, and time-to-treatment initiation. While the course of TBM is generally not as rapid or fulminant as meningitis due to pyogenic bacteria, empiric treatment should be initiated as soon as the diagnosis is suspected as any delay in treatment can worsen outcome**[18]** Mortality risk is highest in those with comorbidities, severe neurologic involvement on admission, rapid progression of disease, and advanced or very young age.

## LIMITATIONS

The main limitation of our study was a small study population and a significant loss of case follow up. The other being overburden of number of samples (both pulmonary and extrapulmonary) as the test was facilitated by a single machine for a tertiary centre. Due to which there was delay in processing of the sample and hence a high false negative result. The third limitation being our inability to repeat CSF samples for comparing different factors such as volume and centrifugation which could have further decreased false negative result of CSF samples study population.

## CONCLUSION

In order to reach a quick diagnosis using CSF specimens, CBNAAT should be preferentially used as rapid diagnosis and treatment is a strong prognostic indicator for reduced death and neurologic deficit. Eventhough CSF cytology gives good estimate of suspected TBM patient the test is not confirmative for bacilli demonstration. Hence CBNAAT has to be endorsed in every centres as the test gives rapid result and also detects rifampicin resistance which is the major concern for every clinician. To increase the value of this test which has gained popularities in detection of MTB and its resistance in sputum samples, a good amount as well as centrifuged CSF sample has to be considered. Clear guidance should be given by WHO regarding CBNAAT testing of CSF samples in suspected TBM patients so that this rapid test would play a major role in diagnosis and treatment of one of the most common medical emergency in India.

## Abbreviations

TBM-Tubercular Meningitis

CSF-Cerebrospinal Fluid

CBNAAT-Cartridge Based Nucleic Acid Test

WHO-World Health Organisation

HIV-Human Immunodeficiency Virus

MRI-Magnetic Resonance Imaging

AIDS-Acquired Immune Deficiency Syndrome

MDR-TB-Multi Drug Resistant Tuberculosis

ADA-Adenosine Deaminase

CT-Computerised Tomography

PLHA-People living With HIV/AIDS

EPTB-Extra Pulmonary Tuberculosis

MTB/RIF-Mycobacterium Tuberculosis/Rifampicin resistance

RNTCP-Revised National Tuberculosis Control Programme

CFU-Colony Forming Unit

DM-Diabetes Mellitus

CXR-Chest Xray

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