Int. J. Curr. Res. Med. Sci. (2018). 4(2): 59-65

International Journal of Current Research in Medical Sciences

ISSN: 2454-5716

P-ISJN: A4372-3064, E -ISJN: A4372-3061

www.ijcrims.com

Original Research Article

Volume 4, Issue 2 -2018

DOI: http://dx.doi.org/10.22192/ijcrms.2018.04.02.011

Role of CBNAAT in diagnosis of Tuberculous Meningitis

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Abstract

Tuberculous meningitis is one of the most severe forms of tuberculosis associated with high incidence of death and disability. Due to paucibacillary nature of CSF, it is difficult to demonstrate tubercle bacilli by the standard staining procedures which is the gold standard for diagnosis, thus leading to a large number of cases being undiagnosed or misdiagnosed. Now, it has further been complicated by the emergence of multidrug resistance. So, this study was done with the aim to know the role of CBNAAT in the diagnosis of tubercular meningitis. 62 patients were included in the study who had features suggestive of tubercular meningitis. According to the universal case definition, the patients were divided into probable, possible and definitive TBM. Out of 62 patients included in the study, 6(4%) were Definite TBM, 33(58%) were probable TB, 17(30%) were possible TBM and 5 (8%) were not TBM. Total 22 patients had M. TB detected in their CSF on CBNAAT, out of a total of 57 TBM patients. Out of these 22,1 was detected with Rifampicin resistance. The sensitivity of CBNAAT in our study was 38.6%. Hence because of its rapidity, simplicity, and sensitivity, CBNAAT(Gene Xpert MTB/RIF) technology is emerging as a novel and promising technique to diagnose tuberculous meningitis and rifampicin resistance, which was undiagnosed most of the time.

Keywords: CBNAAT, GeneXpert, Tubercular meningitis, CSF.

Introduction

The first description of TBM dates back to 1836 when six cases of acute hydrocephalus in children characterized by 'an inflammation of the meninges, with the deposit of tubercular matter in the form of granulations, or cheesy matter' were described in the Lancet.[1] Among various forms of extrapulmonary TB, tuberculous meningitis (TBM) is the most severe form and remains a major global health problem with the case fatality rate for untreated TBM reaching almost 100 %,[2] even after more than 100 years.

Early recognition of TB meningitis is of paramount importance because the clinical outcome depends greatly upon the stage at which the therapy is initiated,[3] and delay in treatment often leads to permanent neurological damage.

The diagnosis of TBM has been a continuous challenge. Definitive diagnosis requires demonstration of tubercle bacilli in CSF, which can be done either by smear microscopy or culture. Smear microscopy is inexpensive and rapid but insensitive (0–20 %) due to low microorganism densities in CSF, while culture techniques are unacceptably slow which makes it unsuitable as a routine technique for rapid confirmatory diagnosis.[2,4] Thus, diagnosis of tubercular meningitis basically remains presumptive and is based on clinical symptoms, neurologic signs, CSF findings, CT scans, and response to anti-TB drugs.

Cartridge Based Nucleic acid-based amplification test(CBNAAT) or GeneXpert has now emerged as potentially important tool for diagnosing TBM. The GeneXpert System (Cepheid) is a single use cartridge-based real-time PCR fully automated system that performs sample decontamination, sonication, automated nucleic acid amplification, and fluorescence-based quantitative PCR.[5-7]

The published Xpert MTB/RIF detection threshold is approximately 100 - 130 colony forming units (cfu)/ml of sample.[5,6] In comparison, the detection threshold is <10 cfu/ml for mycobacterial liquid culture and is >5,000 cfu/ml for Ziehl-Neelsen staining for acid fast bacilli (AFB) via standard microscopy in sputum.[7-9]

According to recent WHO guidelines, Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis in order to reach quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase yield.[10]

So, the present study was undertaken to evaluate the role of CBNAAT in early detection of tubercular meningitis and to also detect rifampin resistance in this era of alarming rise of multi-drug resistant strains of mycobacterium.

Materials and Methods

This prospective study was carried out in the Dept of Tuberculosis and Respiratory Diseases, Govt. Medical College, Amritsar after approval from the institution's ethical committee.

All the patients being admitted in the wards from July 2016 to June 2017, with signs and symptoms suggestive of tubercular meningitis were included in the study after taking their or guardian's (in case of unconscious patients or children) informed consent.

Inclusion criteria:

1. Patients having clinical features of meningitis with or without signs of meningeal irritation.
2. Patients with a subacute onset of symptoms(>5 days) or a positive contact history.
3. MRI brain findings suggestive of tubercular meningitis.
4. CSF showing features of pleocytosis, predominantly lymphocytosis, decreased glucose levels, high protein levels and an ADA >10 IU/L.
5. Presence of tuberculosis elsewhere(eg miliary tuberculosis or abdominal TB).

Exclusion criteria:

1. Patients with features suggestive of pyogenic meningitis.
2. Patients refusing to give consent for the study.

Diagnostic Criteria in the Uniform Tuberculous Meningitis Research Case Definition

Criteria	Diagnostic Score
Clinical criteria (maximum category score = 6)	
Symptom duration of >5 days	4
Systemic symptoms suggestive of tuberculosis (≥1): weight loss/(poor weight gain in children), night sweats, or persistent cough >2 week	2
History of recent close contact with an individual with pulmonary tuberculosis or a positive TST/IGRA in a child aged <10 yr	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
CSF criteria (maximum category score = 4)	
Clear appearance	1
Cells: 10–500/µL	1
Lymphocytic predominance (>50%)	1
Protein concentration >1 g/L	1
CSF: plasma glucose ratio of <50% or an absolute CSF glucose concentration <2.2 mmol/L	1
Cerebral imaging criteria (maximum category score = 6)	
Hydrocephalus (CT and/or MRI)	1
Basal meningeal enhancement (CT and/or MRI)	2
Tuberculoma (CT and/or MRI)	2
Infarct (CT and/or MRI)	1
Precontrast basal hyperdensity (CT)	2
Evidence of tuberculosis elsewhere (maximum category score = 4)	
Chest radiograph suggestive of active tuberculosis (excludes miliary tuberculosis)	2
Chest radiograph suggestive of miliary tuberculosis	4
CT/MRI/US evidence for tuberculosis outside the CNS	2
AFB identified or *Mycobacterium tuberculosis* cultured from another source, ie, sputum, lymph node, gastric washing, urine, blood culture	4

Abbreviations: AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; IGRA, interferon-γ release assay; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification test; TBM, tuberculous meningitis; TST, tuberculin skin test; US, ultrasound.

Complete history including past or family history of tuberculosis was taken. Complete physical examination was done including level of consciousness, signs of meningeal irritation (neck stiffness, Kernig's sign, Brudzinski's sign), cranial nerve involvement, etc.

Lumbar Puncture was done after ruling out papilloedema after taking consent and CSF was subjected to cytology, biochemistry, ADA, fungalstain, smear for AFB, culture and CBNAAT. Other investigations like TLC, DLC, ESR, blood culture, mantoux, HIV etc were done. Chest Xray and MRI were done in relevant cases.

Then, the cases were divided into probable TBM, possible TBM and definitive TBM according to Diagnostic Criteria in the Uniform Tuberculous Meningitis Research Case Definition as given by Suzaan Marais et al as published in The Lancet.[12]

Xpert MTB/RIF results were not included in the case definition, because it was the test under evaluation. Definite TBM was defined as a clinical syndrome consistent with TBM, with acid-fast bacilli seen on CSF smear or *M. tuberculosis* isolated in CSF MGIT culture. Patients in the "probable TBM" group had a diagnostic score of 10 or more without cerebral imaging (MRI or CT scan) or 12 or more with cerebral imaging, with at least 2 points from CSF or cerebral imaging criteria. Patients in the "possible TBM" group had a diagnostic score of between 6 and 9 if cerebral imaging was not performed or between 6 and 11 if cerebral imaging was performed.[12] All patients who had a score below 5 were classified as not having TBM.

Results

62 patients were included in the study who had features suggestive of tubercular meningitis. Out of these, 39 (63%) were male and 23(37%) were female. 24 patients were of age group 0-15 years, 16 patients were in age group 16-30 years and 22 patients were aged > 30 years.

Table 1: Age distribution of patients

Age group	No. of patients	Percentage
0-15 years	24	39%
16-30 years	16	26%
>30 years	22	35%

According to the universal case definition, the patients were divided into probable, possible and definitive TBM. Out of 62 patients included in the study, 6(10%) were Definite TBM, 34(55%) were probable TB, 17(27%) were possible TBM and 5 (8%) were not TBM.

Table 2: Categorisation of patients according to the diagnostic criteria in the uniform tuberculous meningitis research case definition

Category	No. Of patients	Percentage
Definitive TBM	6	10%
Probable TBM	34	55%
Possible TBM	17	27%
Not TBM	5	8%

According to the categories, M. TB was detected on GeneXpert as following
:

Table 3: No. of patients with MTB detected on CBNAAT

Category	Total no	Mtb detected	MTB not detected
Definitive TBM	6	4(66%)	2(34%)
Probable TBM	34	11(32%)	23(68%)
Possible TBM	17	7(41%)	10(59%)
Not TBM	5	0	5

To calculate statistical values, Definitive, probable and possible TBM were grouped together. So, total study patients were divided into two groups: TBM and Not TBM.

Total 22 patients had M. TB detected in their CSF on CBNAAT, out of a total of 57 TBM patients.

Table 3(a): No. of patients with MTB detected on CBNAAT

Category	Total no	MTB detected	MTB not detected
TBM	57	22	35
Not TBM	5	0	5

According to statistical analysis, sensitivity was 38.6% and specificity was 100%.Positive predictive value was 100%, Negative predictive value was 12.5% and negative likelihood ratio was 0.61.

Out of these 22 patients with M. TB detected in their CSF on CBNAAT,1 was detected with Rifampicin resistance.

Table 4: No. of patients with R- resistance on CBNAAT

Category	Total no	MTB detected	MTB not detected	Rifampicin resistance detected
TBM	57	22	35	1
Not TBM	5	0	5	0

Discussion

Tuberculosis (TB) is a global health concern. India is highest TB burden country in the world and accounts for one fourth of the global TB burden cases. In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB.[13]

Extrapulmonary Tuberculosis (EPTB) accounts for about 15 to 20% of all cases of Tuberculosis in India. The percentage may be higher in children and in HIV infected individuals. In HIV positive patients, EPTB accounts for more than 50 per cent of all cases of TB.[14]

Exact prevalence of CNS TB in India is not known, but it accounts for an estimated 1% of all cases of TB, which equates to around 17 000 cases in India in2014 (WHO, 2015). Case fatality rates for the most common form of CNS TB, i.e. TB meningitis, are high[15].A definitive diagnosis of mycobacterium infection depends on detection of the Mycobacterium Tuberculosis in CSF. It can be either done by smear microscopy which has very low sensitivity in CSF sample or by culture which has good sensitivity but takes too long to give the results. So, CBNAAT was proposed as a promising tool to detect M. TB early with increased sensitivity as compared to smear microscopy.

Sensitivity of CBNAAT in CSF has been variable among various studies. The pooled sensitivity of CBNAAT in CSF in a meta-analysis was 80.9%.[16] Other studies showed sensitity ranging from 40%[17] to 59.3%[18]. Its use for diagnosis of TBM has also been endorsed by INDEX TB guidelines. Thus, this study was planned to determine the sensitivity and utility of CBNAAT in diagnosis of TBM at a tertiary care centre in Punjab.

The sensitivity of CBNAAT in our study was 38.6% which is comparable with results of other studies. Also, resistance was detected in 1 patient. Thus, Gene Xpert MTB/RIF assay is an efficient and reliable technique for detection of M. TB in CSF samples. Its simplicity, speed and automation, and detection of resistance at the same time makes this technique a very attractive tool for the rapid diagnosis of TB meningitis, especially in suspected cases.

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	Subject: Medical Sciences

How to cite this article:
Ashi Singh, Amarendra K. Shukla, Rajwinder Kaur, N.C. Kajal , Nadia, Lakhvir Kaur, N.S.Neki. (2018). Role of CBNAAT in diagnosis of Tuberculous Meningitis. Int. J. Curr. Res. Med. Sci. 4(2): 59-65.
DOI: http://dx.doi.org/10.22192/ijcrms.2018.04.02.011