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DIAGNOSTIC USEFULNESS OF CBNAAT IN DIAGNOSING PEDIATRIC TUBERCULOSIS: A COMPARATIVE STUDY.

Dr. Vivek Kumar[1], Dr. Manoj Kumar[2], Dr. Gopal Shankar Sahni[3]
[1]Senior Resident, Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India.
[2]Senior Resident, Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzafferpur, Bihar, India.
[3]Associate Prof & Head, Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India.

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Corresponding author: Dr. Manoj Kumar
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Abstract

Introduction: Tuberculosis (TB) caused by the bacterium Mycobacterium tuberculosis, remains one of the major health problems in India. The recent introduction of Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) also known as Gene Xpert MTB/ RIF assay has significantly transformed the diagnostics of TB. The present study aimed diagnostic usefulness of CBNAAT for diagnosing pediatric tuberculosis in our hospital setting.

Material and Methods: This study was carried out at department of Pediatric, Skmch Bihar India from oct 2018 to Nov 2019. Total 447 patients showing symptoms and signs of suspected localized and/or disseminated tuberculosis or having history of close contact with diagnosed tuberculosis patients admitted in our hospital during the study period were included in this study. Samples (pulmonary and extrapulmonary) were collected from the subjects and put to test for CBNAAT, Zeihl-Neelsen (ZN) smear and culture.

Results: Among the pulmonary samples, CBNAAT detected MTB in 23 of the 108 sputum/induced sputum samples (21.29%), 89 of the 248 gastric lavage/aspirate samples (35.88%) and 0 of the 5 bronchoalveolar lavage samples (0%). Among the extrapulmonary samples, CBNAAT detected MTB in 9 of the 63 CSF samples (14.28%), 1 of the 13 pleural fluid samples (7.69%), 0 of the 6 ascitic fluid samples (0%) and 3 of the 4 lymph node aspirate samples obtained by FNAC(75%). Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT in reference to culture are 90.15%, 98.09%, 95.2%and 95.2%respectively. Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT in reference to ZN smear are 100%, 91.47%, 76% and 100% respectively.

Conclusion: CBNAAT assay is a rapid test which identifies both the presence of Mycobacterium tuberculosis (MTB) (with high sensitivity, specificity, positive predictive value and negative predictive value) and rifampicin resistance associated with mutation of rpoB gene in a single test. It also helps to avoid injudicious use of anti-tuberculosis drugs.

Keywords: CBNAAT; MTB; ZN smear; Culture

Introduction

Pulmonary Tuberculosis (PTB) continues to be an important cause of preventable mortality in both developing and developed nations. Early diagnosis and treatment remains the cornerstone of TB control.[1] According to Global TB Report-2018, 10.0 million people (range, 9.0-11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children.[2] Smear microscopy is the cornerstone for the diagnosis of TB in resource-limited settings; it has only modest (35-80%) sensitivity and a poor Positive Predictive Value (PPV).[3] Mycobacterial culture, though is gold standard, usually takes 2-6 weeks for final result and requires technical expertise.[4] Chest X-ray is useful but is not specific for diagnosing PTB. Also, TB may show symptoms and atypical radiologic findings, indistinguishable from those of community-acquired pneumonia.[5] Quick and accurate detection of the pathogen with its drug susceptibility patterns is vital for treatment initiation and disease control.[6] Rapid molecular tests are recent diagnostic tools that can be used to simultaneously test for PTB and RIF resistance with higher sensitivity than sputum smear microscopy and which could replace conventional culture-based drug susceptibility testing.[7] The CBNAAT detects the presence of TB bacilli and also tests for resistance to RIF. CBNAAT, as it is a very cost-effective and rapid test is likely to revolutionize the diagnosis and treatment of PTB.[8] CBNAAT is a highly specific test as it uses 3 specific primers and 5 unique molecular probes to target the rpoB gene of Mycobacterium tuberculosis, which is the critical gene associated with RIF resistance.[9]

We aimed to study the diagnostic usefulness of CBNAAT (sensitivity, specificity, positive predictive value and

negative predictive value) for diagnosing pediatric tuberculosis in our hospital setting.

Materials and Methods

The present study was carried out at department of Paediatric, skmch of Bihar, India. After taking institutional ethics committee approval from Oct 2018 to Nov 2019. Total 447 patients showing symptoms and signs of suspected localized and/or disseminated tuberculosis or having history of close contact with diagnosed tuberculosis patients admitted in our hospital during the study period were included in this study. The exclusion criteria being parents not giving consent.

Study tools

Relevant history and clinical examination. Clinical history regarding current complaints of fever, cough, sputum production, haemoptysis, and weight loss was taken. All patients were evaluated for headache, seizures, chest pain, breathlessness and neck swelling or any other evidence of extrapulmonary tuberculosis. Case definition of TB suspect- children with persistent fever and/or cough for more than 2 weeks, loss of weight/no weight gain (History of unexplained weight loss or no weight gain in past 3 months; loss of weight is defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months) and/or history of contact with infectious TB cases (In a symptomatic child, contact with a person with any form of active TB within last 2 years maybe significant).[1]

Presumptive extrapulmonary TB- presence of organ specific symptoms and signs like swelling of lymph node, pain and swelling in joints, neck stiffness, disorientation, etc and/or constitutional symptoms like significant weight loss, persistent fever for more than 2 weeks, night sweats.

Laboratory investigations- complete hemograms, erythrocyte sedimentation rate (ESR), Mantoux test, Zeihl- Neelsen (ZN) smear, fine needle aspiration cytology (FNAC), histopathology (HPE) of samples, and culture.

Instruments for radiological studies eg. Chest radiograph ultrasonography (USG), computed tomography (CT) scan magnetic resonance imaging (MRI) scan, magnetic resonance spectroscopy (MRS) if indicated.

CBNAAT of samples sputum/induced sputum, gastric aspirate/lavage, cerebrospinal fluid (CSF), pleural fluid, ascitic fluid, bronchoalveolar lavage (BAL), FNAC material.

Indication of performing BAL- To get adequate samples for testing in patients with a low bacterial load or in those who do not expectorate with a clinical and radiological

Suspicion of pulmonary tuberculosis.[18]

Patients were selected as per the inclusion criteria and recruited in the study. Detailed history taking, physical examination and relevant laboratory investigations were done. A pre designed semi structured proforma was used to obtain data based on socio-economic profile, clinical profile and investigations after explaining the purpose of the study and obtaining informed consent from the parent/guardian of the child in writing.

Methodology

All the samples were collected in well labelled falcon tubes. In pulmonary cases two sputum/induced sputum (Sputum induction was done in a well-ventilated room with an ultrasonic nebuliser and nebulisation done with 10-20mL of 3% hypertonic saline until patient coughed up at least 2mL of sputum or a maximum of 15 minutes.) samples were collected: one early morning and other supervised spot specimen. Smears of both the sputum samples were made, stained by ZN procedure, examined under light microscope. Thereafter, if the samples were positive for acid fast bacilli (AFB), then the positive sample otherwise good quality or early morning sample was used for CBNAAT. So, only one sample was further processed for CBNAAT. In infants and small children gastric lavage was collected in place of sputum. Where invasive techniques like BAL were required, only one sample was collected. Bronchoscopy was done with Pentax fibre optic bronchoscope (FOB) under local anaesthesia with 4% lignocaine jelly and mouth spray. Bronchial washing and lavage was performed by instilling 20mL aliquots of normal saline at room temperature upto 100-120mL and collected into a sterile suction trap by aspiration. In extrapulmonary cases the samples collected were CSF by lumbar puncture (LP), lymph node fluid by FNAC, pleural fluid by pleural tap and ascitic fluid by ascitic tap.

Statistical Analysis

The data was analyzed using SPSS 19 (SPSS Inc. Chicago, IL, USA) Windows software program. Descriptive frequencies were expressed using mean and standard deviation. Sensitivity and specificity were calculated with 95% confidence interval (CI) where relevant.

Results

Total 457 patients were included in the study, youngest patient being 3 months and oldest being 11 years 5 month old. This Table 1 shows that majority of patients were males (68.68%). Majority of patients belonged to the age group <5 years (46.75%). Only 20.80% of patients had history of contact with TB patient and

16.10% of patients showed positive Mantoux test (Table 2-4)

Table 1: Demographic profile of cases

Parameters	Number of cases	Percentage (%)
Gender		
Male	307	68.68
Female	140	31.31
Age group		
< 5 years	209	46.75
5-9 years	191	42.72
10-12 years	47	10.51
y of contact with TB patient		
Yes	93	20.80
No	354	79.19
Mantoux test		
Positive	72	16.10
Negative	375	93.90

Table 2: Type and number of samples used

Variables	Type of sample	Total samples	MTB detected by CBNAAT
Pulmonary (n=361)	Sputum/Induced sputum	108	23 (21.29
	Gastric lavage/ aspirate	248	89 (35.88)
	Bronchoalveolar lavage	5	0 (0)
Extra pulmonary (n=86)	CSF	63	9 (14.28)
	Pleural fluid	13	1 (7.69)
	Ascitic fluid	6	0 (0)
	FNAC material from lymph node	4	3 (75)
		447	125

Table 3: Performance of CBNAAT versus culture

Variables	Culture positive	Culture negative	Total
CBNAAT positive	119	6	125
CBNAAT negative	13	309	322
Total	132	315	447

CBNAAT detected MTB in 119 of the 125 culture positive cases (95.2%) and in 6 of the culture negative cases (4.8%).

Table 4: Performance of ZN smear versus culture

Variables	Culture positive	Culture negative	Total
ZN smear positive	53	42	95
ZN smear negative	79	273	325
Total	132	315	447

ZN smear detected MTB in 53 of the 132 culture positive cases (40.15%) and in 42 of the culture negative cases.

Table 5: Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT and ZN smear in reference to culture

Variables	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CBNAAT versus culture	90.15%	98.09%	95.2%	95.2%
ZN smear versus culture	40.15%	86.66%	55.78%	84%

Table 6: CBNAAT Performance in ZN smears positive and negative cases.

Variables	ZN smear positive for AFB	ZN smear negative for AFB	Total
MTB positive by CBNAAT	95	30	125
MTB negative by CBNAAT	0	322	322
Total	75	352	447

CBNAAT detected MTB in 95 of the ZN smear positive cases and also in 30 of the ZN smear negative cases

Table 7: Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT in reference to ZN smear.

Variables	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CBNAAT versus ZN smear	100%	91.47	76%	100%

Discussion

The recent introduction of the CBNAAT assay has significantly revolutionized the diagnostics of tuberculosis in adults, but its application for the diagnosis of pediatric TB is under evaluation. To date, there are only a few studies on the application of CBNAAT for the diagnosis of pediatric tuberculosis in India, more so in eastern India. The Gene Xpert MTB/Rif test is a cartridge-based fully automated NAAT (nucleic acid amplification test) for TB case detection and rifampicin resistance testing, suitable for use in disease-endemic countries. It purifies concentrates, amplifies (by rapid, real-time PCR) and identifies targeted nucleic acid sequences in the TB genome, and provides results from unprocessed sputum samples in less than 2 hours, with minimal hands-on technical time.

In the present study, 447 patients were included, youngest patient being 3 months and oldest being 11 years 5 month old, with male: female ratio 2;1.Majority of patients belonged to the age group <5 years (46.75%). Only 20.80% of patients had history of contact with TB patient and 16.10% of patients showed positive Mantoux test. Samples were taken from 361 pulmonary and 86 extrapulmonary TB patients. Among the pulmonary samples, CBNAAT detected MTB in 23 of the 108 sputum/induced sputum samples (21.29%), 89 of the 248 gastric lavage/aspirate samples (35.88%) and 0 of the 5 bronchoalveolar lavage samples (0%). Among the extrapulmonary samples, CBNAAT detected MTB in 9 of the 63 CSF samples (14.28%), 1 of the 13 pleural fluid samples (9.6%), 0 of the 6 ascitic fluid samples (0%) and 3 of the 4 lymph node aspirate samples obtained by

FNAC (75%). CBNAAT was positive in 125 (27.96%) and was negative in 322 of the 447 cases (73.03%). ZN smear detected AFB in 95 (21.25%) and failed to detect AFB in 352 of the 447 cases (78.75%). Culture was positive in 125 (27.96%) and was negative in 322 of the 447 cases (72.4%).

CBNAAT detected MTB in 119 of the 125 culture positive cases (95.2%) and in 6 of the culture negative cases (4.8%). So, there were 3 false positives that were CBNAAT positive but culture negative in our study. This was probably because 2 among these 3 patients had taken anti tubercular treatment for 4 months and then stopped treatment and 1 had stopped treatment after 3 months. CBNAAT can detect nucleic acids from dead and live organisms, so may remain positive long after treatment is completed and the culture is negative in these cases.[10] ZN smear detected MTB in 53 of the 125 culture positive cases (42.4%) and in 42 of the culture negative. Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT in reference to culture are 90.15%, 98.09%, 95.2% and 95.2% respectively. Specificity was 98.9% with 8 false negatives who were CBNAAT negative but culture positive because 1 culture sample was positive for MOTT and CBNAAT only detects MTB. In other 12 samples, although MTB growth is in culture but it is possible that the bacterial load may have been too low for the CBNAAT to detect the DNA from MTB- complex. It shows that a patient with a negative CBNAAT can still have TB with MTB or MOTT.[11] Also, the negative predictive value is high as liquid culture method was used in our study in comparison to LJ media used in most of the earlier studies.[11] Sensitivity, specificity, positive predictive value and negative predictive value of ZN smear in reference to culture are 40.15%, 86.66%, 55.78% and 84% respectively. It is evident that sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT are far better than ZN smear for diagnosing pediatric tuberculosis. CBNAAT detected MTB in 95 of the ZN smear positive cases and also in 30 of the ZN smear negative cases. Sensitivity, specificity, positive predictive value and negative predictive value of CBNAAT in reference to ZN smear are 100%, 91.47,76 and 100% respectively. CBNAAT also detected 6 cases of rifampicin resistance among the 125 cases detected by CBNAAT.

In the study of Sowjanya (Andhra Pradesh, India) (June 2012- December 2013), CBNAAT detected MTB in 144 out of 205 pulmonary specimens (70.24 % detection rate) whereas sputum for AFB was able to detect only 108 cases (52.68% detection rate). CBNAAT detected 108 out of the 109 sputum smear positive cases, and 36 out of the 96 sputum smear negative cases.[12] In the study of Singh (Delhi, India), with culture as gold standard, sensitivity of CBNAAT was 84.6% and specificity was 86.4%.[13] Raizada tested 8,370 paediatric presumptive TB & presumptive DR-TB cases between April–November 2014and showed that TB detection rates were two fold higher with CBNAAT as compared to smear microscopy.[14] The meta-analysis by Maynard-Smith showed that median sensitivity and specificity of Xpert assay with a culture based reference standard were 0.83 (IQR, 0.68–0.94) and 0.98 (IQR, 0.89–1.00) respectively.[15]

Denkinger (USA) performed a systematic review and meta-analysis to assess the accuracy of Xpert for the detection of extrapulmonary TB. They determined the accuracy of Xpert compared with culture and a composite reference standard (CRS). They identified 18 studies involving 4461 samples. In lymph node tissues or aspirates, Xpert pooled sensitivity was 83.1% (95% CI 71.4-90.7%) versus culture and 81.2% (95% CI 72.4-87.7%) versus CRS. In cerebrospinal fluid, Xpert pooled sensitivity was 80.5% (95% CI 59.0-92.2%) against culture and62.8% (95% CI 47.7–75.8%) against CRS. In pleural fluid, pooled sensitivity was 46.4% (95% CI26.3- 67.8%) against culture and 21.4% (95% CI 8.8–33.9%) against CRS. Xpert pooled specificity was consistently >98.7% against CRS across different sample types. Based on this systematic review, the World Health Organization now recommends Xpert over conventional tests for diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis.[16] Dewan (New Delhi, India) demonstrated that 10(25%) out of the 40 CBNAAT positive patients had rifampicin resistance. Among them 9 hadmulti- drug resistant tuberculosis (MDR-TB) as detected by LPA.[17] Shah (Maharashtra, India) demonstrated that the sensitivity and specificity of Xpert MTB/RIF for bacteriologically (either AFB or culture positive) confirmed cases of tuberculosis were 80% and 71.4%.[18] An in-vitro study demonstrated a limit of detection as low as 131 CFU/ml of MTB by Xpert Assay. Xpert will divert treatment away from “false cases” to “true” smear-negative TB cases, thereby increasing the accuracy of treatment and cost-effectiveness, while reducing the burdens of toxicity and cost of treatment in patients who do not in fact have TB. Sharma (New Delhi, India) described that Xpert has 77.7% sensitivity for smear negative and culture positive TB in comparison to 99.2% for smear and culture positive TB.[20] In the study of Mohanty (Cuttack, India) (April 2016 to March 2017), with culture as gold standard, sensitivity, specificity, positive predictive value(PPV) and negative predictive value(NPV) of sputum induction CBNAAT were 61.9%, 96.5%, 96.3%, 63.6%, respectively and of BAL CBNAAT were 88.09%,

%, 97.36%, 84.84%, respectively.[21] Agrawal (Delhi, India,

Jan 2015 to Nov 2015) demonstrated that using culture as reference, sensitivity, specificity, PPV and NPV of CBNAAT were 86.8%, 93.1%, 78.5% and 96% respectively.[19]

Thus, our study adds data from TB endemic third world country that CBNAAT can help in rapid diagnosis of pediatric tuberculosis with high sensitivity, specificity, positive predictive value and negative predictive value. Also it simultaneously detects rifampicin resistance, so correct treatment can be started at an early stage of the disease.

It also detects true TB negative patients, thus, contributes to cost saving by avoiding unnecessary treatment. However the assay has severaldisadvantages:

1. Xpert cannot be used for assessing the emergence of rifampicin resistance during treatment. Also it is not suitable to detect isoniazid monoresistance.

2. Inability to differentiate extensively drug resistant (XDR-TB) from multi-drug resistant (MDR-TB) as it can detect only rifampicin resistance. It can detect rifampicin resistance only if rpoB allele is present in at least 65% of DNA present i n sample.

3. It is not suitable for monitoring patients' response to treatment and so conventional microscopy and culture are required for monitoring MDR-TB patients during treatment.

4. Xpert Assay also have several technical problems, including requirement for stable electricity supply, limited temperature range, availability of maintenance, and bulky consumables.

Multicentre studies with larger sample size can be carried out to further validate the results, finding the positive and negative likelihood ratio, the cost effectiveness and patient acceptability. Likewise, studies on diagnostic usefulness of CBNAAT in diagnosing TB in patients infected with HIV will be useful because of the atypical clinical presentation of TB disease and the paucibacillary nature of pulmonary disease in patients with HIV. Also studies to compare rifampicin resistance found on Xpert MTB/RIF with that of drug susceptibility tests (DST) can be done.

Conclusion

CBNAAT assay is a rapid test which identifies both the presence of Mycobacterium tuberculosis (with high sensitivity, specificity, positive predictive value and negative predictive value) and resistance to rifampicin associated with mutation of rpoB gene in a single test. This can enable early and appropriate treatment initiation, as well as accelerating the implementation of MDR-TB control measures, and ultimately reducing TB case incidence. It also helps to avoid injudicious use of anti-tuberculosis drugs. Revised National TB Control Programme (RNTCP) is also currently using Xpert MTB/RIF to diagnose pulmonary TB, paediatric TB, extrapulmonary TB and rifampicin resistance and Multi Drug Resistance Tuberculosis in high risk populations like HIV positive as recommended by WHO under 2013 policy recommendations.

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