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Original Research Article

Diagnosis of paediatric tuberculosis by cartridge based nucleic acid amplification test and its effectiveness as compared to the other conventional diagnostic methods

Jyotiranjan Champatiray[1], G. Dharmaraj Patra[2]*

[1]Department of Pediatrics, SCB Medical College, Cuttack, Odisha, India,
[2]Department of Pediatrics, Dr. Ram Manohar Lohia Hospital, New Delhi, India

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***Correspondence:**
Dr. G. Dharmaraj Patra,
E-mail: rajdrdharma@gmail.com

ABSTRACT

Background: Childhood TB constitutes 10-20% of all TB cases in high burden countries like India and accounting for 8-20% of TB related deaths. Diagnosis of TB in children is difficult. One test, CBNAAT which was recently endorsed by WHO has the potential to lead a revolution in diagnosis of active TB disease.
Methods: A cross sectional study in SCB MCH and SVPPGIP, Cuttack in all the suspected TB patients admitted during the period from January 2016 to October 2017.
Results: A total of 100 suspicious patients admitted to the Department of Pediatrics in SCB MCH and SVPPGIP during the study period. Of these 45 were diagnosed TB and rest others were diagnosed otherwise than TB. Diagnosis of TB was established on basis of Microscopy, CBNAAT, culture, biochemistry, cytology, clinical findings, neuroimaging, FNAC/biopsy, USG abdomen. Out of 45 TB patients 30 were CBNAAT positive taking the body fluid samples other than blood, urine and stool with a sensitivity of 66.7% and specificity of 100%. Out of 45 TB patients 14 were having ZN Smear positive taking the same fluid sample with a sensitivity of 31.1% and specificity of 100%. Whereas out of these 45 TB patients 32 were MGIT culture positive taking the same sample with a sensitivity of 71.1% and specificity of 100%. When diagnostic performances of CBNAAT and MGIT culture were compared, it was found to be statistically insignificant with a P value 0.54.
Conclusions: The CBNAAT is able to confirm a diagnosis of TB with 66.7% sensitivity and 100% specificity within 2 hours. We can use CBNAAT as a diagnostic method as it provides rapid result and simultaneous better sensitive result, it can be helpful in starting ATT in sick patients and also in outdoor patients.

Keywords: Antitubercular therapy, Cartridge based nucleic acid amplification test, Mycobacteria growth indicator tube

INTRODUCTION

Tuberculosis is one of the most infectious diseases affecting almost one third of the world's population. The disease is an important cause of morbidity and mortality among adults and children mainly in developing countries.[1] The epidemiology of TB in young children (<5year old), a vulnerable population where diagnosis and treatment are most challenging, is not well understood, especially in countries with limited public health resources. Diagnosis of TB in children however is difficult because: Routine sputum smear microscopy rarely identifies TB in children, mantoux test may be negative if the child is malnourished, since cavitary lesions due to pulmonary TB is rare in childhood, chest x rays are not always helpful except in adolescents.[2]

Approximately 95% of children of less than 12 years old with TB are smear negative.[3] Gastric aspirates also have a low specificity.

This leads to an underdiagnosis of TB in children. TB in children is also a sentinel marker for active transmission of TB within communities.[4] The need is for accurate, feasible, rapid, affordable and if possible, near-point-of-case TB diagnostic tests for use in resource limited settings. One test, gene Xpert MTB/RIF (CBNAAT), which was recently endorsed by the WHO, has the potential to lead a revolution in the diagnosis of active TB disease and multidrug resistance TB. It is a semiquantitative test with two uses. The detection of mycobacterium tuberculosis complex DNA in any body fluid sample except blood, urine and stool. Detection of rifampicin resistance.[5]

METHODS

A cross sectional study in a tertiary care hospital. Patient were admitted to Department of Pediatrics in SCB Medical college and SVPPGIP, Cuttack, Indoor patients admitted to Department of Pediatrics who were suspected of Tuberculosis were included in the study group. Study duration were for a period from January 2016 to October 2017.

Inclusion Criteria

- Age: from birth to 14 years of age.
- Clinical features suggestive of tuberculosis anywhere in the body.

Exclusion Criteria

- Patients having comorbidities like underlying heart diseases

After obtaining clearance from institutional ethics committee, necessary number of patients fulfilling the inclusion criteria were taken into the study. All pt. with above inclusion criteria taken in to considerations. All body fluids except blood, urine and stool were taken for smear, CBNAAT and culture along with TST, Chest Xray, CSF Study, FNAC/biopsy, USG abdomen, neuroimaging and all routine tests were done to rule out other diseases. Approximately 5 ml of sample were collected when possible in order to improve microbiological confirmation rate.[6] Approximately 2 ml sample was sent to microbiology and biochemistry laboratories. And the remainder where be sent to TB laboratory.

Upon receipt in the TB laboratory, samples were centrifuged for 15 min. Supernatant was removed to leave a 0.5-ml deposit, which was then used for Ziehl-Neelsen smear preparation (100 µl), inoculation of MGIT culture (100 µl), and Xpert testing (200 µl). The remaining deposit was stored at -20°C. All tests were performed by one of three technicians highly experienced in microbiological tests for TBM diagnosis. Clinical data and results of biochemical investigations were not available to the technicians at the time of the test; technicians were aware of smear results.

Ziehl-Neelsen smear

Ziehl-Neelsen smears were prepared using standard methods with two modifications. First, the smear was layered, with two drops of sample deposit applied. The layered smear was then stained according to standard procedures. Second, the ZN smear was meticulously examined for up to 30 min under a ×1,000 magnification before being recorded as negative. Observation of a single acid-fast bacillus was considered a positive result.

Xpert MTB/RIF

A 200 µl portion of the deposit was resuspended in phosphate-buffered saline to a 500 µl volume. The sample reagent supplied with the test (1.5 ml) was then added. The mixture was vortexed for 30 s to ensure all bacteria were resuspended. The sample was left to stand for 15 min, as per the manufacturer's instructions, with intermittent manual shaking. The solution was then transferred to the Xpert cartridge using a Pasteur pipette, and the cartridge was loaded onto the Xpert machine for analysis. Results were reported as positive or negative for M. tuberculosis. Positive results were placed in one of four categories; very low, low, medium, or high. Rifampicin resistance results were reported as susceptible or resistant.

MGIT culture

A 100 µl portion of the deposit was used to inoculate a MGIT tube containing 0.8 ml MGIT supplement (PANTA antibiotics (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, andazlocillin) and growth supplements). MGIT tubes were incubated in a MGIT 960 machine until they were automatically identified as positive or for 42 days. All positive cultures were tested for susceptibility to rifampicin using a Bactec MGIT SIRE kit (Becton, Dickinson) according to the manufacturer's instructions.

Diagnostic classification

For this study, patients were taken into study using Keith Edwards scoring system (Narayan S et al, Indian journal of Pediatrics, 2003) and WHO TB chart for children (1996) as having TB if no other diagnosis was made and the attending physician made the decision to treat for TB based on the clinical algorithm.[7,8]

All these cases were treated as a case of suspected case of TB and body fluid samples were sent for examination and treatment were started in the line of TB.

The diagnosis of TB was established on the basis of ZN stain, CBNAAT, culture, biochemistry and cytology, clinical findings, neuroimaging, findings from CT/MRI scan, FNAC/biopsy, USG Abdomen. Neuroimaging will be performed only in selected subjects under clinical suspicion of TBM. Rest others were categorized as NONTB.

Keith Edward scoring for diagnosis of tuberculosis in children[7] (Table 1)

Table 1: Score chart for the diagnosis of TB in children.

Score chart for the diagnosis of tb in children						
	Score if present					
Feature	**0**	**1**	**2**	**3**	**4**	**score**
General						
Duration of illness (weeks)	<2week	2-4 week		>4week		
Nutrition (%weight for age)	>80	60-80		<60		
Family history of TB	None	Reported by family		Proved sputum positive		
Tuberculin skin test				Positive		
Malnutrition				Not improving after 4 weeks		
Unexplained fever and night sweat			No response to malaria treatment			
Local						
				Lymph nodes		
				Joint or bone swelling		
				Abdominal mass or ascitis		
				CNS sign & usually abnormal CSF findings		
					Angle deformity of spine	
Total score						

A score of 7 or more than 7 is indicative of tuberculosis

Clinical entry criteria

Symptoms and signs of TB including one or more of the following

- Persistent fever,
- Persistent cough >2 weeks,
- Loss of weight or no weight gain,
- Any patient in contact with TB case,
- Progressive enlargement of lymph node>2weeks, size>2cm or sinus formation,
- Patient having HIV infection,
- Headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy,
- Patients having ascitis with hepatosplenomegaly,
- Baby having mother suffering from active tuberculosis,

Statistical evaluation

Sensitivity, specificity, positive predictive value, and negative predictive value with p value were calculated. The proportion of positive results for each test (smear, MGIT culture, and X pert MTB/RIF) was compared using Z test. The sensitivity of X pert MTB/RIF stratified by body fluid volume was also analyzed. All statistical analyses were done using SPSS 21 version.

RESULTS

A total of 100 suspicious patients presented to the Department of Pediatrics 0f SCB Medical College and SVPPGIP, Cuttack, Orissa, India with suspected TB during the study period January 2016 to October 2017. Of these 45 were diagnosed TB patients and 55 patients were not having TB. These non-TB patients are diagnosed otherwise than TB.

Table 2: Results of smear, MGIT culture, and XPERT MTB/Rif testing by final diagnosis.

Test result	No of Patients			Total
		TB	Not TB	
Xpert MTB/RIF	Positive	30	0	30
	Negative	15	55	70
	Total	45	55	100
Ziehl-Neelsen smear	Positive	14	0	14
	Negative	31	55	86
	Total	45	55	100
MGIT culture	Positive	32	0	32
	Negative	13	55	68
	Total	45	55	100

As seen in Table 2, out of 45 cases in TB group xpert MTB show positive result in 30 cases, whereas ZN stain and MGIT show positive result in 14 and 32cases respectively. All the result of Xpert MTB, ZN stain and MGIT among 55 non-TB group was negative.

Table 3: Diagnostic accuracy of XPERT MTB in TB and non-TB group.

Test	TB	Non-TB
Xpert MTB $^{+}$ve	30 (66.7%)	0 (0%)
Xpert MTB $^{-}$ve	15 (33.3%)	55 (100%)

Sensitivity= 66.7%; Specificity =100%; PV=100%. NPV=78.57%.

As seen from Table 3, the sensitivity of Xpert was 66.7% compared to clinical diagnosis of TB. Specificity was 100%. Positive predictive value and negative predictive value was 100% and 78.57% respectively.

Table 4: Diagnostic accuracy of ZN stain in TB and non-TB group taking same body fluids.

Test	TB	Non-TB
Z N stain+ve	14 (31.1%)	0 (0%)
Z N stain -ve	31 (68.9%)	55 (100%)

The above Table 4 shows the sensitivity and specificity of smear relative to final clinical diagnosis was 31.1% and 100%. The PPV and NPV relative to final clinical diagnosis was 100% and 63.95% respectively.

Table 5: Diagnostic accuracy of MGIT in TB and non-TB group taking same body fluids.

Test	TB	Non -TB
MGIT culture +ve	32 (71.1%)	0 (0%)
MGIT culture-ve	13 (28.9%)	55 (100%)

The above Table 5 shows sensitivity of MGIT culture compared to clinical diagnosis of TB was 71.1%. specificity was 100%. The PPV and NPV relative to final clinical diagnosis was 100% and 80.88% respectively.

Table 6: Comparison of diagnostic accuracy among XPERT MTB, ZN stain and MGIT in detecting TB taking same body fluid sample.

Test	Sensitivity	Specificity	PPV	NPV
XPERT MTB	66.7%	100%	100%	78.57%
ZN stain	31.1%	100%	100%	63.95%
MGIT	71.1%	100%	100%	80.88%

Table 7: Comparison between XPERTMTB and ZN Stain in TB group.

Test	Sensitivity	Specificity	Z value P value
XPERT MTB	66.7%	100%	Z=4.72 p=0.001
Zn stain	31.1 %	100%	

This Table 6 compares the diagnostic performance of gene XPER TMTB, ZN stain and MGIT culture. The sensitivity of XPERTMTB, ZN stain and MGIT culture was 66.7%,31.1%and 71.1% respectively. The PPV among all test was 100% and NPV of XPERTMTB, ZN stain and MGIT culture was 78.57%, 63.95% and 80.88% respectively.

This Table 7 compares the diagnostic performance of gene XPERT MTB as compared to ZN stain. it shows that 66.7% of sample +ve for XPERT MTB, whereas 31.1% of sample +ve for ZN stain. The difference was statistically significant. P =0.001

Table 8: Comparison between MGIT culture and ZN stain in TB group.

Test	Sensitivity	Specificity	Z value P value
MGIT culture	71.1%	100%	Z =4.576 p=0.0001
Zn stain	31.1%	100%	

Table 8 compares the diagnostic performance of gene MGIT culture as compared to Zn stain. It shows that 71.1% of sample +ve for MGIT culture, whereas 31.1% of body fluid sample +ve for Zn stain. The difference was statistically significant. P =0.0001.

Table 9: Comparison between XPERT MTB and MGIT culture in TB group.

Test	Sensitivity	Specificity	Z value P value
XPERT MTB	66.7%	100%	Z=0.621 p=0.54
MGIT culture	71.1 %	100%	

The above Table 9 compares the diagnostic performance of gene XPERT MTB as compared to MGIT culture. It

shows that 66.7% of sample +ve for XPERT MTB, whereas 71.1% of body fluid sample +ve for MGIT culture. The difference was statistically insignificant. P =0.54.

DISCUSSION

A total of 100 patients presented to the Department of Pediatrics, SCB medical college and SVPPGIP, Cuttack, Orissa, India, with suspected TB during the study period. Of these,45 were finally classified as having definite TB and 55 as not having TB. Patients in the "non -TB" group were diagnosed with other diseases other than TB.

In present study the result of smear microscopy was 31.1%. This low sensitivity of TB diagnosis using believe that high sensitivity depends upon the meticulous examination of individual slides for 30 min by a highly skilled and experienced technician.

This may be difficult to replicate outside a dedicated research setting due to the work burden in public health laboratories of resource-limited countries. In other studies, like Zhang et al, shown sensitivity of 33% and 57% in gastric lavage and sputum samples respectively with specificity of 100% while Bates M et at, shown sensitivity of 30% and specificity of 97%.[9,10]

In our studies the sensitivity of MGIT culture was 71.1%. MTB culture studies in several case series established body fluid culture sensitivities of 25 to 70%. In present studies the sensitivity of XPERT MTB was 66.7%, which was nearly similar to other studies.

Table 10: Comparison of sensitivity of XPERT with the sensitivity of other studies.

Authors	Reported year	Sensitivity (%)	Specificity (%)
Zhang et al[10]	2016	28.60	87.50
Detjen et al[11]	2015	62	98
Bunyasi EW et al[12]	2015	26.70	100
Giang et al[13]	2015	20.60	94.70
Bholla Met al[14]	2016	58	93
Wang XW et al[15]	2015	65	99
Togun TO et al[16]	2015	42.90	98.70
Christi MJ et al[17]	2014	67	92
Bates M et al[9]	2013	68.80	90
Zar HJ et al[18]	2013	57.10	98.90
Sekadde MP et al[19]	2013	79.40	96.50
Nicole MP et al[20]	2011	75.90	98.90
Present study	2017	66.7	100

From the above Table 10, The sensitivity of Xpert reported here was nearly similar to the sensitivity of other studies mentioned above for diagnosis of TB taking different body fluid samples.

An explanation for the lower sensitivity of PCR in present study could be the sometimes-small volume of CSF available for testing (after using for smear and culture) so that the sample could not be concentrated. The volume of sample is of great significance in PCR, especially in tuberculous meningitis, due to frequent low number of bacteria in the CSF. Culture of CSF also requires larger volume and when both culture and PCR have to be done, the minimum volume of CSF should be 2 ml. Another reason for low sensitivity of PCR may be presence of PCR inhibitors in the CSF as well as poor lysis of mycobacteria unlike non automated PCR tests, the Xpert MTB/RIF depends upon capture of intact bacilli from the sample within the cartridge, and it is probable given the reported limits of detection that not all bacilli are captured and lysed during the process. Therefore, in high-volume laboratories with low sensitivity for smear microscopy, Xpert MTB/RIF is likely to substantially improve the diagnostic confirmation of TB, since it is less dependent on the skill and time of individual technicians.

MGIT culture is not directly useful in making a decision to treat for TB due to the time required for a positive result; TB is a medical emergency, and delayed treatment is strongly associated with mortality in every case series. Further comparative study of the optimal sampling processing and inoculation volumes for each test to maximize early diagnosis while also obtaining M. Tuberculosis isolates for drug susceptibility testing (DST) is required.

Xpert has two significant advantages: the closed-cartridge-based format and the ability to simultaneously detect M. tuberculosis and RIF resistance. The cartridge-based format removes the need for manual DNA extraction processing, and the closed system dramatically reduces any potential for cross-contamination of samples with PCR amplicons. The addition of a brief vortexing step after addition of the sample reagent improved sensitivity of Xpert in these paucibacillary samples, and further optimization of sample processing for extra pulmonary samples may be required to improve detection rates. The overall increase in sensitivity for TB was 10%, with a 20% increase for definite TB cases (P =0.04).

The Xpert test system depends upon capture and lysis of whole bacilli, and therefore, as for other microbiological tests for TB, high volumes (5ml) of body fluid are crucial to achieve high sensitivity.

The cost of smear microscopy is substantially lower than the cost of an Xpert MTB/RIF test (consumable and reagent cost) but the hands-on time required to achieve high sensitivity in smear testing is greater (approximately

40min for smear versus 20min for Xpert). Additionally, in two cases Xpert detected rifampicin resistance within 2 hours.

Rapid detection of drug resistance in the paucibacillary body fluid has been a major challenge to improving outcome for patients with MDR TB. Without rapid diagnosis and administration of second-line regimens, mortality100%. However, rare false-positive results for rifampicin resistance have been reported with Xpert and the consequences of mistakenly treating a patient with rifampicin-susceptible TB with weak second-line regimens would be grave. It will be extremely difficult to accumulate sufficient data on MDR TB diagnosis to demonstrate robustly the accuracy of the test for this condition due to its rarity, and accuracy must be inferred from other paucibacillary forms of TB.

Therefore, a rifampicin-resistant TB diagnosis by Xpert should be evaluated in the context of the clinical information and response to treatment and wherever should be confirmed by a second rapid test, such as a line probe assay. An M. tuberculosis isolate remains necessary to confirm susceptibility patterns for all drugs, including rifampicin since Xpert detects rpoB mutations, which are present in only 95% of phenotypically rifampicin-resistant M. tuberculosis isolates. Liquid culture methods where available, have the highest sensitivity and speed for M. tuberculosis isolation. However, for patients with rifampicin resistance detected by Xpert MTB/RIF and a clinical suspicion of MDR TB, second-line drugs with should not be withheld until the results from conventional DST become available.

Authors have shown that Xpert MTB/RIF is a rapid and specific test for the diagnosis of TB. As with other tests for TB, a negative result cannot exclude a diagnosis of TB.

CONCLUSION

From all the observations, authors can summarize that out of 100 cases 45% were TB,55% were not TB. In diagnosis of tubercular diseases the sensitivity of ZN stain was 31.1%,sensitivity of MGIT culture was 71.1%,and sensitivity of Xpert MTB was 66.7% and the specificities of all of the methods were 100%.Compared with microscopy, Xpert offered better sensitivity for the diagnosis of Tuberculosis in children though remained suboptimum to culture results. Although the sensitivities for medium- and high-volume samples were greater than those for low-volume samples, this difference did not reach statistical significance (P = 0.341).

The Xpert MTB/RIF test is able to confirm a diagnosis of childhood TB with 66.7%sensitivity and 100% specificity, along with rifampicin resistance within 2 hours. Confirmatory diagnosis of TB particularly in children is a medical challenge. No laboratory or radiological test can reach to a satisfactory level of diagnostic sensitivity. However, in this study authors found that combination of multiple diagnostic test can give much better yield, though not optimum.

Although culture is considered as a gold standard method but as it takes weeks to come positive and simultaneous detection of Rifampicin resistance is not possible with it. On other side geneXpert can be a useful diagnostic method in patients of suspected TB either AFB smear negative or positive due to its rapidity and simultaneous detection of Rifampicin resistance especially beneficial in patient with MDR and HIV associated tuberculosis. Cost effectiveness of GeneXpert in low income countries like India with high prevalence of tuberculosis need to be done.

Positive geneXpert, but culture negative results need to be read cautiously and should be well correlated with clinical and treatment history of the patient. Hence good clinical acumen is still needed to decide when to start Anti Tubercular Therapy. A long-term prospective study is needed to find out the association of body fluid volume and outcome of Gene Xpert test.

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