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Original Article

The Diagnostic Yield of CBNAAT for Microbiological Diagnosis of Pulmonary Tuberculosis in Children: An Observational Study at a Tertiary Care Centre

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ABSTRACT

Background: The microbiological confirmation of diagnosis of pulmonary tuberculosis is difficult because paucibacillary nature of disease and younger children are unable to do expectorate. Cartridge based nucleic acid amplification test (CBNAAT) is newer test for diagnosis of tuberculosis. However, its role in the diagnosis of pulmonary tuberculosis in children is yet to need more evidence to establish.
Objective: To determine the effectiveness of CBNAAT for microbiological diagnosis of pulmonary tuberculosis in children.
Methods: This was a cross sectional observation study conducted on 132 children, aged 6 months to 18 years with presumptive pulmonary tuberculosis (PPTB) were enrolled in study. After obtaining informed parental consent, gastric aspirate and sputum/induced sputum from all enrolled patients were sent for direct smear, CBNAAT (Xpert MTB/RIF* assay) and MGIT culture. Chest skiagrams, tuberculin sensitivity test (TST) and CECT thorax (in selected cases) were also done. The diagnosis of PPTB was made as per the revised national tuberculosis control program (RNTCP). The sensitivity, specificity, positive predictive value and negative predictive value were calculated using MGIT culture as gold standard.
Results: The mean age (months) of enrolled patients was 77.87 ± 64.39 months. Out of 132 children with PPTB, 60 had microbiologically confirmed pulmonary tuberculosis. Overall, 39.4% enrolled children were positive for CBNAAT. GA and sputum/induced sputum CBNAAT had sensitivity and specificity of 86.67% (95% CI: 75.83-93.09%) and 100% (95% CI: 94.93-100%) respectively as compared culture gold standard.
Conclusion: CBNAAT can be used for definitive diagnosis of pulmonary tuberculosis in children as this is highly sensitive and specific test in gastric aspirate and sputum/induced sputum.

Keywords: *CBNAAT, Presumptive Pulmonary Tuberculosis, PPTB, Diagnostic Yield, Gastric Aspirate, Sputum.*

INTRODUCTION

Tuberculosis is one of most common chronic communicable endemic disease caused by mycobacterium tuberculosis complex. Pediatric tuberculosis is representing 12% of the global burden of TB.[1] Pediatric tuberculosis has been relatively neglected, because mainly challenges in the availability of effective diagnostic tools.[2]

The microbiological confirmation of diagnosis of pulmonary tuberculosis is difficult because paucibacillary nature of disease and younger children are unable to do expectorate. Cartridge based nucleic acid amplification test (CBNAAT) is newer test for diagnosis of tuberculosis. However, its role in the diagnosis of pulmonary tuberculosis in children is yet to need more evidence to establish its utility in pediatric tuberculosis.[3]

The present study was conducted to determine the effectiveness of CBNAAT for microbiological diagnosis of pulmonary tuberculosis in children.

METHODOLOGY

This was a cross sectional observation study conducted at SMS Medical College, Jaipur from September 2017 to August 2018. Hospitalized 132 children, aged 6 months to 18 years with **presumptive pulmonary tuberculosis** (PPTB) were enrolled into the study. After ruling out the all possible differential diagnosis of pulmonary tuberculosis, the diagnosis of PPTB was made on the basis of recommendation of RNTCP and Indian academy of pediatrics. PPTB was diagnosed when any patient had fever(documented) and cough (non remitting) for more than two weeks with/without documented weight loss more than 5% in preceding 3 months with/without contact with TB patient in 2 years.

After obtaining informed parental consent, the demographic and clinical details of all enrolled children were filled in predesigned proforma and excel sheet. All children with PPTB were subjected for Chest x- ray, tuberculin sensitivity test (TST). CECT thorax was also done in selected patients. As per RNCTP and IAP recommendations the radiological finding in chest x- ray is considered highly suggestive of pulmonary tuberculosis if any one or more of following is/ are present: Mediastinal lymph node enlargement/Mediastinal widening, fibro-cavitatory lesion and miliary shadows those were not explained by other diseases.

All enrolled patients with PPTB were underwent gastric aspirate (GA) and sputum/induced sputum samples collection for two consecutive days.[4] The standard protocol was followed during collection of these samples. After proper labeling and packing, immediately these samples were sent to central TB laboratory of SMS Medical College for testing of AFB smear microscopy, CBNAAT (Xpert MTB/RIF* assay) and BACTEC-MGIT culture.[5] Result of CBNNAT are generated after 2 h and reported as M. tuberculosis - negative or positive with semi-quantified bacillary load as high, medium, intermediate or low and if the pathogen is RIF sensitive or resistant.[6] After obtaining of result of these tests, results entered in excel sheet.

The diagnosis of microbiologically confirmed pulmonary tuberculosis was made if any test including AFB smear microscopy, CBNAAT and MGIT culture result is positive for mycobacterium tuberculosis and rest all PPTB patients were diagnosed as non microbiologically confirmed pulmonary tuberculosis/clinico- radiologically diagnosed pulmonary tuberculosis.

Statistical analysis

The statistical analysis was performed using STATA 11.0 (college station, Texas, USA). Sensitivity and specificity of CBNAAT were determined by considering MGIT culture as gold standard. The Positive predictive values (PPV), negative predictive value (NPV) for CBNAAT were calculated with 95 % CI (confidence intervals). A p-value of <0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value and negative predictive value were calculated using MGIT culture as gold standard.

RESULTS

In this study 132 children (59.8% female), aged 6 months to 18 years (mean age in months: 77.87 ± 64.39) with presumptive pulmonary tuberculosis were enrolled. Out of 132 study subjects 60(45.5%) children had microbiologically confirmed pulmonary tuberculosis (PTB) and 72(54.5%) were diagnosed as microbiologically negative (clinico-radiological) pulmonary tuberculosis (Table 1).

80 (60.6%) children with PPTB were vaccinated with BCG. Among microbiologically confirmed PTB 38(63.3%) children were vaccinated with BCG and 42(58.3%) children with microbiologically negative PTB received BCG vaccination (P Value: 0.684). TST was reactive in reactive in56.7% of microbiologically confirmed PTB and also reactive in 58.3% of microbiologically negative PTB (P= 0.987). Family history of TB contact was found in 68.3% of microbiologically confirmed PTB and in 69.5% of microbiologically negative PTB. The radiological finding of chest x-ray highly suggestive of PTB was found in 91.7% of microbiologically confirmed PTB and in 61.1% of microbiologically negative PTB (P Value=<0.001). Overall 99 (75%) children with PPTB had highly suggestive radiological finding in chest x-ray (Table 2)

Out of 60 children with microbiologically confirmed PTB, 52 (86.7%) children had CBNAAT positive and rest 8 children were diagnosed as microbiologically confirmed PTB by either positive AFB smear microscopy or MGIT culture (P value: <0.001).Out of 132 children with PPTB, 52(39.4%) children had positive CBNAAT result (Table 3).

The sensitivity of CBNAAT in sputum/induced sputum and gastric aspirate sample was 86.67% %(95% CI: 75.83-93.09%). The specificity of CBNAAT in sputum/induced sputum and gastric aspirate samples was 100 %(95% CI: 94.93-100%). Overall positive predictive values in sputum/induced sputum and gastric aspirate sample in reference to Bactec-MGIT960 culture was100 %(95% CI: 93.12-100%) (Table 4).

Table 1. Demographic profile of study subjects

Total no of study subject(presumptive pulmonary TB)			132
Microbiological diagnosis of the study subjects		Microbiologically confirmed pulmonary TB	60(45.5%)
		Microbiologically non confirmed pulmonary TB	72(54.5%)
Age		**Mean ± SD (Months)**	77.87 ± 64.39
Sex	Male		53(40.2%)
	Female		79(59.8%)
Clinical presentation	Persistent non remitting cough>2 weeks		132(100%
	Documented fever >2 weeks		132(100%)
	Documented weight loss>5% in last 3 month		105(79.5%)

Table 2. The clinico radiological characteristics of study subjects

Characteristics		Microbiologically confirmed pulmonary TB	Microbiologically non confirmed pulmonary TB	Total	P Value
Radiological findings in chest skiagram highly suggestive of tuberculosis	Present	55(91.7%)	44(61.1%)	99(75%)	<0.001
	Absent	5(8.3%)	28(38.9%)	33(25%)	
BCG vaccinated		38(63.3%)	42(58.3%)	80(60.6%)	0.684
Mantoux Test (positive)	Reactive	34(56.7%)	42(58.3%)	76(56.6%)	0.987
	Non reactive	26(43.3%)	30(41.7%)	56(42.4%)	
Family history of TB	Present	41(68.3%)	50(69.5%)	91(68.9%)	0.959
	absent	19(31.7)	22(30.5%)	41(31.1%)	

Table 3. The status of CBNAAT result among study subjects

Status of CBNAAT in sputum/gastric aspirate		Microbiologically confirmed pulmonary TB	Microbiologically non confirmed pulmonary TB	Total	P Value
Any sample for CBNAAT	Positive	52(86.7%)	0	52(39.4%)	<0.001
	Negative	8(13.3%)	72(100%)	80(60.6%)	

Table 4. Sensitivity, specificity and predictive values of CBNAAT in sputum/induced sputum and gastric aspirate sample in reference to Bactec-MGIT960 culture.

Sensitivity	86.67 %(95% CI: 75.83-93.09%)
Specificity	100 %(95% CI: 94.93-100%)
Positive predictive value	100 %(95% CI: 93.12-100%)
Negative predictive value	90 %(95% CI: 81.49-94.85%)
Diagnostic accuracy	93.94 %(95% CI: 88.5-96.9%)

DISCUSSION

This was enrolled 132 children with presumptive PTB. All these children were subjected for tuberculin skin test (TST. It reflects cell-mediated immunity to mycobacterium tuberculosis through a delayed-type hypersensitivity reaction using a protein precipitate of heat-inactivated tubercle bacilli (purified protein derivative [PPD]–tuberculin). The TST is one of useful method to diagnose the LTBI. The TST is administered by the intradermal injection of 0.1 ml of PPD (5 TU) into the volar surface of the forearm (Mantoux method) to produce a transient wheal. The test is interpreted at 48–72 hours by measuring the transverse diameter of the palpable induration. A reaction of ≥10 mm is considered positive TST.[7]

In our study, Overall 76(56.6%) children with PPTB had positive TST. Out of 60 children with microbiologically confirmed pulmonary tuberculosis,34(56.7%) children had positive TST and 42(58.3%) children with microbiologically

negative PTB had positive TST(P value: 0.987). Heather J. Zar et al. performed the TST in 196 children of presumptive PTB. They were found TST positive in 99(57.2%) children. which is consistent with our study.[8]

The main route of mycobacterium tuberculosis infection is via inhalation. The initiation of infection occurs when infected droplets are deposited in the terminal airway or alveoli. This leads to localized parenchymal inflammation known as Ghon focus. Then there is spread through lymphatic vessels to the ipsilateral regional lymph nodes. The upper lobes drain to ipsilateral paratracheal lymph nodes while the remaining lung drains to the perihilar lymph nodes. These parenchymal focus and enlarged lymph nodes collectively are known as Ghon complex.[9]

As the disease progresses, adjacent enlarge lymph node can compress the airways that can result in obstructive atelectasis or over inflation. This is commonly found on the right side at the level of the right lobar bronchus or bronchus intermedius. Destruction and fibrosis of lung parenchyma leads to traction bronchiectasis and cavity formation. This is called progressive pulmonary tuberculosis (progressive Ghon focus).[10] Chest x ray is still a crucial tool for diagnosis of pulmonary tuberculosis in children.[11] The radiological findings in chest x ray suggestive of pulmonary tuberculosis are perihilar or mediatinal lymphadenopathy, fibro cavitatory lesion and miliary shadows. The fibro-cavitatory lesions are rare in pediatric pulmonary tuberculosis as this is paucibacillary tuberculosis.[12]

We found that 55(91.7%) children with microbiologically confirmed pulmonary TB had highly suggestive radiological finding in chest x ray whereas only 5 children did not show specific radiological finding suggestive of tuberculosis among microbiologically confirmed TB (P value: <0.001). 44(61.1%) children with microbiologically non confirmed pulmonary TB demonstrated highly suggestive chest x ray findings for pulmonary tuberculosis. In our study the commonest chest x ray finding suggestive of tuberculosis was enlarged hilar lymph nodes. 75% children had hilar lymphadenopathy on the chest x ray. Right sided lung (68%) involvement was more than left sided lung (21%) involvement.

Boloursaz et al were done retrospective study on 70 children with clinical, radiological and microbiologically diagnosed pulmonary tuberculosis. They did found that right lung involvement was observed in 65% whereas left lung was involved in only 23% children and hilar lymph nodes enlargement was seen in 70% children on chest x-ray.[13]

The WHO End TB strategy endorsed the early diagnosis of TB, highlighting the need for accessible, accurate, and rapid diagnostic tests in resource-limited settings. CB-NAAT is presently recommended by WHO to be used for diagnosis of TB in children.[14]

In the present study CBNAAT was positive in 86.7% children with microbiologically confirmed pulmonary tuberculosis among any sample of sputum/induced sputum or Gastric aspirate. Only among eight patients with microbiologically confirmed pulmonary tuberculosis, it was negative (P value: <0.001).The overall positivity of CBNAAT among any sample of gastric aspirate or sputum was 39.4%. Similar study was done by dayal et al among 114 children with presumptive PTB. The overall, positivity of CBNAAT in their study was 57.9%.[15] In our study the overall sensitivity of CBNAAT in any sample (gastric aspirate + sputum/induced sputum) was 86.67% but it was 71.2 % in gastric aspirate alone. The findings of present study are concordant with study performed by singh et al.[16] The sensitivity of CBNAAT is increased by testing gastric aspirate along with sputum/IS for pulmonary tuberculosis in children. The overall specificity of CBNAAT in gastric aspirate with sputum was 100%. Almost similar results have reported in other study conducted by Habeenzu C et al and they found that CB-NAAT to have sensitivity and specificity of 88.4% and 93.9%, respectively, with reference to culture.[17] Sekadde MP et al. did similar study as valuation of the Xpert MTB/RIF test for the diagnosis of childhood pulmonary tuberculosis in Uganda. They were found that the Xpert MTB/RIF test had a sensitivity of 79.4% (95% CI 63.2 - 89.7) and a specificity of 96.5% (95% CI 93 – 98.3) in sputum. [18] Finding of study conducted by Reither et al . Were showing the sensitivity of 68% (95% CI, 50%e82%) and specificity of 100% (95% CI, 97%e100%) in respiratory specimens.[19]

CONCLUSION

The findings of our study suggest that CBNAAT can play an important role in diagnosis of pulmonary TB in children. The CBNAAT is one of the most rapid molecular test for diagnosis of pulmonary tuberculosis. This test is highly sensitive and specific in gastric aspirate and sputum as well to diagnose pulmonary tuberculosis in children.

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