CLINICAL STUDY

Diagnostic Utility of GeneXpert (CB-NAAT) and BACTEC (960) and Socio-clinical Profile of Children with Tuberculous Meningitis

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ABSTRACT

Introduction: Tuberculosis has always remained puzzling to diagnose. Many children with tuberculous meningitis are diagnosed late due to non-availability of rapid and sensitive diagnostic tests. This study examines the diagnostic utility of GeneXpert test and BACTEC (960) and compares of the sensitivity and specificity of these newer tests. **Material and methods:** This hospital-based prospective study was conducted in the Dept. of Pediatrics, Sir Padampat Mother and Child Health Institute, SMS Medical College, Jaipur, Rajasthan. Seventy children of >6 month and <18 years age, presenting with fever of >2 weeks duration, headache, signs of meningeal irritation, altered consciousness level and focal neurological deficits were included in the study. **Results:** Out of 14 patients detected positive by GeneXpert, BACTEC (960) was detected positive in only 4 patients. Out of 56 negative patients detected by GeneXpert, 2 patients were detected positive by BACTEC (960). The sensitivity was 66.67%, specificity was 84.38%, positive predictive value was 28.57%, negative predictive value was 96.63% and accuracy was 82.86%. **Conclusions:** The GeneXpert has higher sensitivity compared to other currently available diagnostic modalities including liquid culture BACTEC.

Keywords: Tuberculosis, tuberculous meningitis, GeneXpert, BACTEC (960), sensitivity, specificity

Tuberculous meningitis (TBM) due to *Mycobacterium tuberculosis* is a dreaded consequence. Early diagnosis and treatment for TBM is the best predictor of survival.[1-4] However, many children are diagnosed late because of vague initial signs, paucibacillary nature and lack of rapid and sensitive diagnostic tests. Various laboratory tests such as microscopy and culture of cerebrospinal fluid (CSF) have poor yield. Ziehl-Neelsen (ZN) microscopy staining of CSF is the most widely applied rapid diagnostic technique; however, sensitivity for TBM rarely exceeds 20%.[5] Liquid culture techniques, including the mycobacterial growth indicator tube (mycobacterial growth indicator tube [MGIT]; BACTEC) and the mycobacterial observation drug susceptibility assay (MODS) culture, offer improved sensitivity over solid culture, to a sensitivity of almost 60%.[5]

The present study was conducted to assess the diagnostic utility of GeneXpert test and BACTEC (960) in detection of *M. tuberculosis* in TBM and to assess and compare the sensitivity and specificity of GeneXpert (Catridge-based nucleic acid amplification test [CB-NAAT]) and BACTEC (960) molecular diagnostic test.

MATERIAL AND METHODS

This hospital-based prospective study was conducted in the Dept. of Pediatrics, Sir Padampat Mother and Child Health Institute, SMS Medical College, Jaipur, Rajasthan, after getting requisite clearance from the research review board of the institute. All children >6 month and <18 years age, presenting with fever of >2 weeks duration, headache, signs of meningeal irritation, altered consciousness level and focal neurological deficits were considered for study and were diagnosed on the basis of Indian Academy of Pediatrics (IAP) 2015 guidelines. Sample size was calculated at 95%

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confidence level (-error of 0.05) assuming 38.2% sensitivity of GeneXpert in suspected TBM cases. At the prevalence of 61% of suspected TBM among clinically suspected TBM, the required sample size will be 68 clinically suspected TBM cases, which were further rounded of to 70 cases. Patients already on antituberculosis drugs and patients having comorbid disease and patients with negative consent were excluded from the study. The Xpert MTB/RIF (resistance to rifampicin) is a CB-NAAT, an automated diagnostic test that can indentify *M. tuberculosis* DNA and RIF by nucleic acid amplification test (NAAT). BACTEC MGIT (960) produced by Becton Dickinson (BD) is specially designed to accommodate MGIT and incubate them at 37°C. Results are obtained within 2 hours. The instrument scans the MGIT every 60 minutes for increased fluorescence. Analysis of the fluorescence is used to determine if the tube is instrument positive; i.e., the test sample contains viable organisms. Culture tubes which remain negative for a minimum of 42 days (up to 56 days) and which show no visible signs of positivity are removed from the instrument as negative and discarded.[6]

OBSERVATIONS AND RESULTS

Demographic Patterns of Study Population

In our study, maximum patients (64.29%) were in the 6 months to 6 years age group followed by 24.29% patients aged 6-12 years and 11.43% patients aged 12-18 years (Fig. 1). Nearly 58.57% patients were male and 41.43% patients were female.

Approximately 68.57% patients belonged to rural area and 31.43% patients were from urban area. Nearly 92.86% patients were Hindu and 7.14% patients were Muslim. Most of the patients (38.57%) were from lower socioeconomic strata and 28.57% patients were from upper lower socioeconomic strata, 15.71% patients were from lower middle socioeconomic strata. About 8.57% patients were from lower middle and upper socioeconomic strata. In our study, all patients presented with fever, 54 patients presented in altered sensorium, 34 patients presented with headache, 22 patients presented with vomiting and 21 patients presented with seizure (Fig. 2).

We observed that 41.43% patients presented with positive family history of tuberculosis and 47.14% patients presented positive history of bacillus Calmette-Guérin (BCG) vaccination. Out of 42 confirmed cases of TBM, BCG scar was positive in 2 cases; so other factors like malnutrition may be attributable for depressed immunity in BCG vaccinated children.

Nutritional Status Indicators of Affected Children

In our study, 30% patients had weight-for-age between -3 and -2 SD followed by 28.57% patients with weight-for-age -2 to -1 SD, 8.57% patients weight-for-age was below -3 SD and 22.85% patients weight-for-age normal (Table 1).

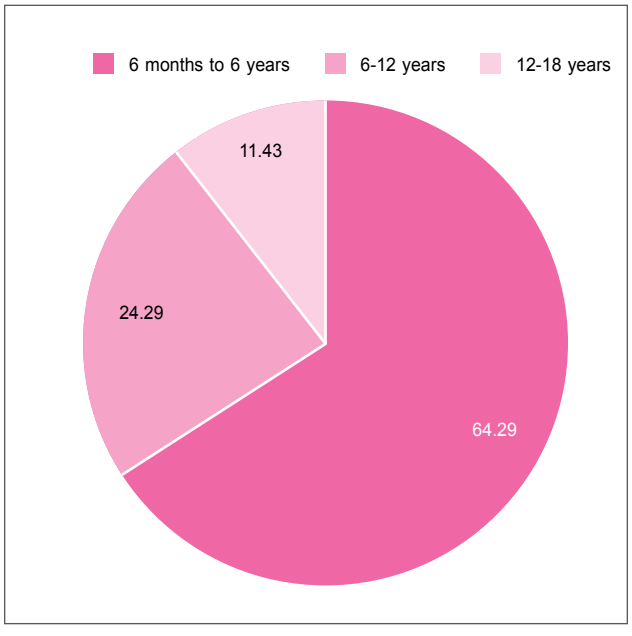

Figure 1. Age distribution of study population.

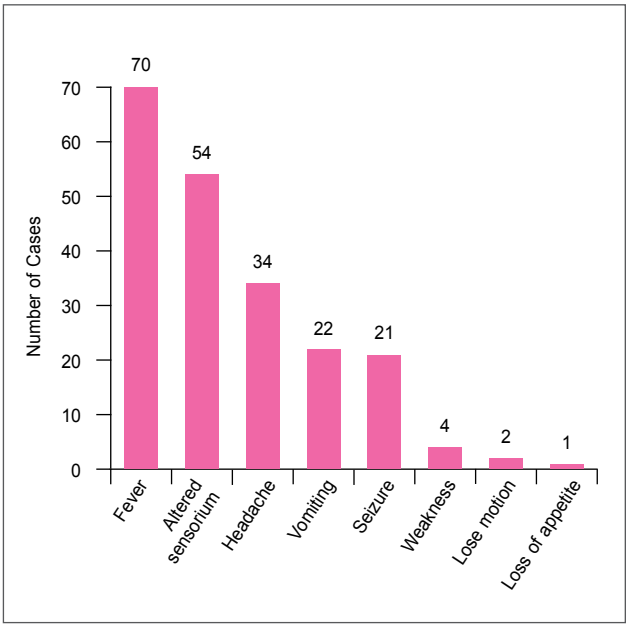

Figure 2. Clinical profile of study population.

Table 1. Nutritional Status Indication of Affected Children

	Weight-for-age according to WHO growth chart	
	Yes	%
Below -3 SD	6	8.57
-3 to -2 SD	21	30.00
-2 to -1 SD	27	38.57
Normal	16	22.85
Total	**70**	**100.00**

Table 2. Sputum - AFB (ZN-staining)

GA/Sputum-AFB (ZN-staining)	Number of patients (n = 70)	Percentage (%)
Present	4	5.71
Absent	66	94.29
Total	**70**	**100.00**

Mantoux test: In the study, 31.43% patients tested tuberculin positive with Mantoux test (MT) >10 mm. MT >10 mm was considered positive and presence of BCG scar did not affect interpretation. Most of the unvaccinated children (without BCG scar) developed invasive tuberculosis.

GA/Sputum for AFB (ZN-staining): Sputum for acid-fast bacilli (AFB) test was positive in only 5.71% patients (Table 2).

Sputum CB-NAAT (GeneXpert): Sputum CB-NAAT was positive in 4.29% (3) patients.

CSF for AFB (ZN-staining): CSF for AFB was positive in 15.71% (11) patients.

CSF for BACTEC (960): CSF for BACTEC (960) was positive 8.57% patients.

CSF for GeneXpert (CB-NAAT): CSF for GeneXpert (CB-NAAT) was positive in 20% (14) patients.

Comparison b/w GeneXpert and CSF AFB: Comparison of results between GeneXpert and CSF AFB suggested that out of 14 positive patients detected by GeneXpert, CSF for AFB was positive only in 6 patients. Out of 56 negative patients detected by GeneXpert, 3 patients were positive by CSF for AFB (Table 3). When comparing GeneXpert and CSF AFB, the sensitivity was 72.73%, specificity was 89.83%, positive predictive value was 57.14%, negative predictive value was 93.64% and accuracy was 87.14% with Chi-square P value = 0.001.

Table 3. Comparison b/w GeneXpert and CSF AFB

GeneXpert	Total	CSF AFB	
		Yes	No
Yes	14	6	8
No	56	3	53

Table 4. Comparison b/w GeneXpert and BACTEC (960)

GeneXpert	Total	BACTEC (960)	
		Yes	No
Yes	14	4	10
No	56	2	54

Comparison b/w GeneXpert and BACTEC (960): Out of 14 patients detected positive by GeneXpert, BACTEC (960) was detected positive in only 4 patients. Out of 56 negative patients detected by GeneXpert, 2 patients detected positive by BACTEC (960) (Table 4). The sensitivity was 66.67%, specificity was 84.38%, positive predictive value was 28.57%, negative predictive value was 96.63% and accuracy was 82.86% with Chi-square = P value = 0.0124.

SUMMARY AND CONCLUSIONS

Maximum patients (64.29%) were in 6 months to 6 years age group followed by 24.29% patients of 6-12 years of age and 11.43% patients aged 12-18 years. Approximately 47.14% patients presented positive history of BCG vaccination and only 7.14% patients presented with history of measles and pertusis. In 30% patients, weight-for-age was -3 to -2 SD, followed by 28.57% patients with weight for age -2 to -1 SD. In 8.57% patients, weight-for-age was below -3 SD and 22.85% patients' weight-for-age was normal. Nearly 31.43% patients' tuberculin test was positive and 5.71% patients' sputum for AFB test was positive.

Additionally, 4.29% patients' sputum CB-NAAT was positive; 15.71% patients' CSF for AFB was positive; 8.57% patients' CSF for BACTEC (960) was positive. In 20% patients, CSF for GeneXpert (CB-NAAT) was positive. The sensitivity was 72.73%, specificity was 89.83%, positive predictive value was 57.14%, negative predictive value was 93.64% and accuracy was 87.14% observed while comparing GeneXpert and CSF AFB. The sensitivity was 66.67%, specificity was

84.38%, positive predictive value was 28.57%, negative predictive value was 96.63% and accuracy was 82.86% observed while comparing GeneXpert and BACTEC (960). The GeneXpert has higher sensitivity compared to other currently available diagnostic modalities[7] including liquid culture BACTEC. In 2015, the World Health Organization (WHO) also endorsed the Xpert MTB/RIF for use in TB endemic countries.[8]

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