DOI: 10.7860/JCDR/2022/53715.16164

Original Article

Internal Medicine Section

Efficacy of CBNAAT versus Adenosine Deaminase in Fluids in Extrapulmonary Tuberculosis

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ABSTRACT

Introduction: Tuberculosis though primarily, is a pulmonary disease, it may manifest as Extrapulmonary Tuberculosis (EPTB). The gold standard method for the diagnosis of extrapulmonary tuberculosis is blood culture. Increased activity of Adenosine Deaminase (ADA) is observed in tuberculosis. Cartridge-based Nucleic Acid Amplification Test (CBNAAT) or Gene Xpert Mycobacterium tuberculosis/Rifampicin (MTB/RIF) is based on Real Time-Polymerase Chain Reaction (RT-PCR). Extrapulmonary tuberculosis may present with varied features, may mimic malignancy, and pose a diagnostic challenge.

Aim: To assess and compare the efficacy of Cartridge-based Nucleic Acid Amplification Test (CBNAAT) and Adenosine Deaminase (ADA) in cases with extrapulmonary tuberculosis.

Materials and Methods: This cross-sectional study was conducted on presumptive cases of extrapulmonary tuberculosis presenting in Department of Medicine at People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India, from November 2019 to August 2021. All the patients were subjected to detailed history and clinical examination including series of blood and radiological investigations. Apart from this, ADA analysis and CBNAAT was done in all the cases and were treated accordingly. The two tests were compared using Chi-square test. The p-value <0.05 were considered statistically significant.

Results: Male predominance was observed and with no statistical difference in age (p-value=0.09) and gender (p-value=0.21). Out of 19 cases of Tubercular Meningitis (TBM) from total 125, ADA was raised in 10 (52.6%) cases, whereas out of 42 Tubercular Pleural Effusion (TBPE) and 24 Tubercular Peritonitis (TBP) cases, ADA was raised in 26 (61.9%) and 4 (16.7%) cases, respectively. Out of 19 cases of TBM, CBNAAT was positive in 4 (21.1%) cases, whereas out of 42 TBPE and 24 TBP cases, CBNAAT positivity was documented in 8 (19%) and 2 (8.3%) cases, respectively. Overall, the sensitivity of ADA was higher for detection of TBM and TBPE as compared to CBNAAT but the specificity of CBNAAT was higher for all the extrapulmonary tuberculosis. Overall diagnostic accuracy of ADA was higher (61.6%) as compared to CBNAAT (43.2%) for detection of extrapulmonary tuberculosis.

Conclusion: Extrapulmonary tuberculosis poses diagnostic challenge and thus for diagnosis, evaluation of each component i.e., history, physical examination, blood investigations, fluid analysis, ADA estimation, and CBNAAT is important. Relying solely on single diagnostic modality may be associated with low diagnostic yield, and thus each step of patient assessment must be given equal preference so as to improve the diagnostic yield.

Keywords: Cartridge-based nucleic acid amplification test, Tubercular meningitis, Tubercular peritoneal effusion, Tubercular pleural effusion

INTRODUCTION

Tuberculosis (TB) is one of the oldest known infectious diseases which is still the single leading cause of mortality all over the globe [1]. Though primarily, it is a pulmonary disease, the disease may manifest as Extrapulmonary Tuberculosis (EPTB) [2]. World Health Organisation (WHO) (2020) estimates approximately, 10 million cases of tuberculosis worldwide. Of them, 1/4th of the cases are reported from India accounting for approximately 2.6 million cases. The burden of EPTB may range from 15-20% [3,4]. The most common sites affected in extrapulmonary tuberculosis include lymph nodes, bone, and joints, pleura, urogenital tract, and meninges [5]. WHO recommends that EPTB must be suspected based upon relevant clinical manifestation, culture, histological features of the granulomatous lesion [6,7]. The gold standard method for the diagnosis of EPTB is blood culture. But it has been associated with certain disadvantages which include its high cost, non availability in resource-poor settings, and delay in getting the results i.e., 4 to 8 weeks [2].

Body fluids such as pleural, pericardial, and peritoneal fluids can be accessed easily and may be an important diagnostic clue for extrapulmonary tuberculosis. Increased activity of Adenosine Deaminase (ADA), an enzyme involved in purine metabolism, predominantly found in lymphocytes is observed in tuberculosis. ADA measurements in pleural, pericardial, and peritoneal fluids are widely used as a surrogate marker of EPTB [8-10]. Different cut-off values have been proposed for ADA activity in various fluids. In pleural fluid, the cut-off value is suggested as 40 IU/L with a sensitivity of 92% and specificity of 89% [9]. For Cerebrospinal Fluid (CSF) in meningitis, sensitivity and specificity of 59% and 96%, respectively have been documented at ADA cut-off of 8 IU/L [10]. For peritoneal fluid, ADA estimation at 36 to 40 IU/L is 100% sensitive and 97% specific [11]. However, for TB pericarditis, at a cut of 40 IU/L, EPTB can be diagnosed with 88% sensitivity and 83% specificity [12]. The National Tuberculosis Elimination Program has promoted public-private partnerships and has certified private sector and Non Governmental Organisation (NGO) laboratories to provide quality assured services to all patients [13]. For promoting the early diagnosis of EPTB, Cartridge-based Nucleic Acid Amplification Test (CBNAAT) or Gene Xpert Mycobacterium tuberculosis/Rifampicin (MTB/RIF) was introduced as a new technique by WHO in 2010 and Revised National TB Control Programme (RNTCP) in 2012 in central tuberculosis laboratories [14].

CBNAAT is based on Real Time-Polymerase Chain Reaction (RT-PCR). Its introduction was considered as a boon for the diagnosis of tuberculosis in developing countries like India, due to its high diagnostic yield and rapidity of results (within 2 hours). Also, it is helpful in detecting rifampicin resistance with minimum expertise [15]. Extrapulmonary tuberculosis may present with varied features,

may mimic malignancy, and pose a diagnostic challenge. The present study was therefore conducted to determine CBNAAT assay and ADA levels in pleural fluid, ascitic fluid and CSF in presumptive cases of extrapulmonary tuberculosis.

MATERIALS AND METHODS

This cross-sectional study was conducted on presumptive cases of extrapulmonary tuberculosis {Tubercular Meningitis (TBM), Tubercular Pleural Effusion (TBPE) and Tubercular Peritonitis (TBPE)} reported in Department of Medicine at People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India, from November 2019 to August 2021. Ethical clearance from Institutional Ethical Committee (IEC No.-PCMS/OD/2019/1439/23) was obtained.

Inclusion and Exclusion criteria: All presumptive cases of extrapulmonary TB (pleural, peritoneal and meningeal) admitted in Department of Medicine and Pulmonary Ward and patient with informed consent were included in study. Patients <18 years of age and already receiving antitubercular medication were excluded from the study.

Procedure

Detailed data pertaining to socio-demographic variables and clinical history was obtained from all the study participants. Further, all the participants were subjected to detailed general, local and systemic examination and data was documented. Patients were subjected to a series of blood and radiological investigations. Further, ADA analysis and CBNAAT was done and patients were treated accordingly.

Adenosine deaminase analysis: ADA is an enzyme involved in purine metabolism that is found in many tissues, particularly in T-lymphocytes from the lymphoid tissue [7]. A 20 mL each pleural fluid, ascitic fluid and 1mL CSF sample were taken and collected in a sterile vessel and ADA levels were estimated in cases of presumptive extrapulmonary tuberculosis. The cut-off limit of ADA levels for TBM was more than 10 IU/L, whereas that for TBPE and TBP was above 40 IU/L and 40 IU/ML, respectively. Technique used was Diazyme autoanalyser method [16].

Cartridge-based nucleic acid amplification test: CBNAAT is based upon the principle of Polymerase Chain Reaction (PCR) which helps in rapid detection of *Mycobacterium tuberculosis*. For CBNAAT, 1mL sputum sample was taken from the patients. It targets rpoB gene and helps in identification of rifampicin resistance as well. This method is highly specific as this method uses 3 primers and 5 molecular probes which specifically target rpoB gene of *Mycobacterium tuberculosis* [17].

As patients with suspected tuberculosis were enrolled, all the patients underwent complete diagnostic workup and were categorised into 4 groups:

- Extrapulmonary tuberculosis patients
  - Tuberculous Pleural Effusion (TBPE)
  - Tubercular Meningitis (TBM)
  - Tubercular Peritonitis (TBP)
- Patients without tuberculosis

STATISTICAL ANALYSIS

The data was compiled using Microsoft Excel and analysed using IBM Statistical Package for the Social Sciences (SPSS) software version 20.0. Categorical variables were expressed as frequency and percentage whereas continuous variables were expressed as mean±Standard Deviation. The two tests were compared using Chi-square test. The p-value <0.05 was considered statistically significant. Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of ADA and CBNAAT was calculated for diagnosis of EPTB and expressed as percentage.

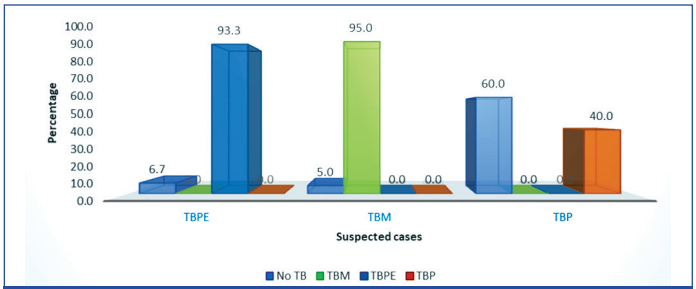
RESULTS

A total sample size of 125 was taken with presumptive diagnosis of TBP (n=60), TBPE (n=45) and TBM (n=20). These suspected cases were further categorised based upon final diagnosis as no tuberculosis (n=40), TBM (n=19), TBPE (n=42) and TBP (n=24). Mean age of the patients with TBM, TBPE and TBP was 38.26±17.94, 41.24±20.33 and 46±14.62 years, respectively. Male predominance was observed and with no statistical difference in age (p-value=0.09) and gender (p-value=0.21) [Table/Fig-1].

Baseline variables	Non TB (n=40)	TBM (n=19)	TBPE (n=42)	TBP (n=24)	p-value
Age (years)					
≤ 20	1 (2.5)	4 (21.1)	5 (11.9)	1 (4.2)	0.09
21-30	5 (12.5)	5 (26.3)	15 (35.7)	3 (12.5)	
31-40	5 (12.5)	1 (5.3)	1 (2.4)	5 (20.8)	
41-50	9 (22.5)	3 (15.8)	7 (16.7)	6 (25)	
51-60	12 (30)	4 (21.0)	6 (14.3)	6 (25)	
>60	8 (20)	2 (10.5)	8 (19)	3 (12.5)	
Mean±SD	49.48±15.40	38.26±17.94	41.24±20.33	46±14.62	
Gender					
Male	22 (55)	11 (57.9)	32 (76.2)	16 (66.7)	0.21
Female	18 (45)	8 (42.1)	10 (23.8)	8 (33.3)	
Body mass index (kg/m²)					
<18.5	3 (7.5)	6 (31.6)	15 (35.7)	2 (8.3)	0.01
18.5-22.9	17 (42.5)	8 (42.1)	17 (40.5)	14 (58.3)	
23-24.9	6 (15)	4 (21.1)	4 (9.5)	2 (8.3)	
≥25	14 (35)	1 (5.3)	6 (14.3)	6 (25)	
Mean±SD	23.42±3.07	20.33±3.25	20.64±4.25	23.07±4.95	

[Table/Fig-1]: Association of site of extrapulmonary tuberculosis with baseline variables. p-value less than 0.05 were considered statistically significant

Out of 45 suspected TBPE cases, 93.3% (42) cases actually had TBPE, whereas out of 20 TBM and 60 TBP cases, 95% (19) and 40% (24) cases had respective tuberculosis. Majority of suspected TBP cases had no tuberculosis [Table/Fig-2].



[Table/Fig-2]: Association of provisional diagnosis with final diagnosis.

Out of 19 cases of TBM, ADA was raised in 52.6% cases, whereas out of 42 TBPE and 24 TBP cases, ADA was raised in 61.9% and 16.7% cases, respectively [Table/Fig-3].

Out of 19 cases of TBM, CBNAAT was positive in 21.1% cases, whereas out of 42 TBPE and 24 TBP cases, CBNAAT positivity was documented in 19% and 8.3% cases, respectively [Table/Fig-4].

Overall, the sensitivity of ADA was higher for detection of TBM and TBPE as compared to CBNAAT but the specificity of CBNAAT was higher for all the extrapulmonary tuberculosis. Overall diagnostic accuracy of ADA was higher (61.6%) as compared to CBNAAT (43.2%) for detection of extrapulmonary tuberculosis [Table/Fig-5].

Provisional diagnosis	ADA	Tuberculosis	Non tuberculosis	Total	p-value
Tubercular meningitis	Normal	9 (47.4)	1 (100)	10	0.31
	Raised	10 (52.6)	0 (0)	10	
	Total	19	1	20	
Tubercular pleural effusion	Normal	16 (38.1)	1 (33.3)	17	0.87
	Raised	26 (61.9)	2 (66.7)	28	
	Total	42	3	45	
Tubercular peritonitis	Normal	20 (83.3)	35 (97.2)	55	0.06
	Raised	4 (16.7)	1 (2.8)	5	
	Total	24	36	60	
Total	Normal	45 (52.9)	37 (92.5)	62	0.01
	Raised	40 (47.1)	3 (7.5)	43	
	Total	85	40	125	

[Table/Fig-3]: Role of Adenosine Deaminase Analysis (ADA) in detection of extrapulmonary tuberculosis.
p-value less than 0.05 were considered statistically significant

Provisional diagnosis	CBNAAT	Tuberculosis	Non tuberculosis	Total	p-value
Tubercular meningitis	Negative	15 (78.9)	1 (100)	16	0.61
	Positive	4 (21.1)	0 (0)	4	
	Total	19	1	20	
Tubercular pleural effusion	Negative	34 (81)	3 (100)	37	0.41
	Positive	8 (19)	0 (0)	8	
	Total	42	3	45	
Tubercular peritonitis	Negative	22 (91.7)	36 (100)	58	0.08
	Positive	2 (8.3)	0 (0)	2	
	Total	24	36	60	
Total	Negative	71 (83.5)	40 (100)	111	0.01
	Positive	14 (16.5)	0 (0)	14	
	Total	85	40	125	

[Table/Fig-4]: Role of Cartridge-based Nucleic Acid Amplification Test (CBNAAT) in detection of extrapulmonary tuberculosis.
p-value less than 0.05 were considered statistically significant

as well as extrapulmonary tuberculosis. Apart from this, availability of immediate results i.e., within 2 hours and simultaneous assessment of rifampicin resistance is the two major advantages of CBNAAT. Its introduction revolutionised the field of infectious disease [15].

The present study was conducted on a total of 125 suspected cases of extrapulmonary tuberculosis with the aim to find out utility of CBNAAT and ADA as laboratory tests for diagnosis of presumptive extrapulmonary tuberculosis cases of pleural effusion, meningitis and peritonitis. Out of 125 cases of suspected extrapulmonary tuberculosis, 60, 45 and 20 cases were suspected TBP, TBPE and TBM cases, respectively. Out of them, 40 cases were non tubercular cases which were wrongly suspected as TBPE (n=3), TBM (n=1) and TBP (n=36). The final diagnosis was established based upon clinical examination, fluid analysis and ADA and CBNAAT levels.

ADA levels and CBNAAT are two modern diagnostic tests which are valuable tool for diagnosis of tuberculosis. Though exact physiological role of ADA is not known, ADA activity in extrapulmonary tuberculosis is sensitive and specific method for diagnosis of EPTB [10-12]. Different cut-off values have been proposed for ADA activity in various fluids. In our study, ADA cut-off of 10, 40 and 40 IU/L was considered for CSF, pleural and peritoneal fluid respectively. CBNAAT has no such cut-off values; it can give results either as positive or negative. Its introduction was considered as a boon and this method is based on RT-PCR. It has high diagnostic yield, give results rapidly (within 2 hours) and helps in detecting the rifampicin resistance [18].

For diagnosis of TBM, at the cut-off of 10 IU/L, the specificity and PPV of ADA was 100%, which is similar to CBNAAT, but sensitivity of ADA for diagnosis of TBM was much higher (52.6%) than CBNAAT (21.1%). Overall diagnostic accuracy of ADA was 55% whereas that of CBNAAT was 25% for diagnosis of TBM. Chotmongkol V et al., using the ROC curve identified the cut-off of 15.5 U/l for CSF ADA with a sensitivity of 75%, specificity of 93% [19]. Barua R and Hossain MA at a cut-off point of 8.5 IU/l of ADA documented the sensitivity and specificity of 57% and 87%, respectively. They observed decline in sensitivity when the cut-off of ADA was raised to 10 IU/l (specificity-90%, sensitivity-36%) [20]. Kohli M et al., however reported much higher sensitivity of CBNAAT for estimation of TBM i.e., 89% [21].

Tuberculosis	Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Diagnostic accuracy (%)
Tubercular meningitis	ADA	52.6	100	100	10	55
	CBNAAT	21.1	100	100	6.25	25
Tubercular pleural effusion	ADA	61.9	33.3	92.9	5.9	60
	CBNAAT	19.1	100	100	8.1	24.4
Tubercular peritonitis	ADA	16.7	97.2	80	63.6	65
	CBNAAT	8.3	100	100	62.1	63.3
Overall	ADA	47.1	92.5	23.02	59.7	61.6
	CBNAAT	16.5	100	100	36.04	43.2

[Table/Fig-5]: Diagnostic accuracy of Adenosine Deaminase Analysis (ADA) and Cartridge-based Nucleic Acid Amplification Test (CBNAAT) for types of TB.

DISCUSSION

For improving the diagnosis of EPTB, various methods have been suggested, depending upon the site of tuberculosis; e.g., for peritoneal tuberculosis, laparoscopic guided peritoneal biopsy is the investigation of choice. To increase the diagnostic yield, PCR assays have been suggested along with biopsy and culture. Assessment of various body fluids, depending upon the site of EPTB was identified as an important tool for predicting EPTB. The body fluid may show atypical features but the absence of these features does not rule out extrapulmonary tuberculosis [15]. The role of ADA (an enzyme involved in purine metabolism) was suggested in the body fluids for detection of EPTB [15]. Apart from ADA, the estimation of Interferon-gamma (IFN-γ) in pleural or pericardial fluid has been suggested as an important tool for early detection of EPTB cases. The introduction of CBNAAT was considered as a boon due to its high diagnostic value in pulmonary

For diagnosis of TBPE, the cut-off level of ADA was 40 IU/L At this cut-off, the sensitivity of ADA was 61.9% whereas that of CBNAAT was 19.1%. However, PPV and specificity of CBNAAT was 100% i.e., much higher as compared to ADA. Overall, the diagnostic accuracy of ADA was better (60%) for diagnosis of TBPE as compared to CBNAAT (24.4%). Our study findings were concordant with the findings of Naik M et al., in which, ADA >40 units/liter was observed in 72% cases and the sensitivity, specificity, PPV and NPV of CBNAAT was 95.24%, 36.70%, 28.57%, and 96.67%, respectively [22]. Modi SD et al documented the sensitivity of ADA for diagnosis of TBPE as 89.47%, whereas specificity was 48.28%, PPV was 81.9% and NPV was 63.65% [23]. Similar to our study, Jain J et al., reported much lower sensitivity (16.7%) but 100% specificity with diagnostic accuracy of 52.5% of CBNAAT for diagnosis of TBPE [24]. However, Phuljhele S et al., documented the sensitivity and specificity of CBNAAT for diagnosis of TBPE and TBM as 100% [25].

In present study, the cut-off of ADA for detection of TBP was 40 IU/L. At this cut-off value, the specificity and PPV of ADA was 97.2% and 80%, respectively but sensitivity and NPV was low. Similarly, the specificity and PPV of CBNAAT for TBP was 100% whereas sensitivity was much lower. Enas H et al., documented the sensitivity and specificity of 10% and 92.6% for ADA at the cut-off level of 35 IU/L [26]. Lawn SD and Zumla AI observed the sensitivity of CBNAAT for estimation of TBP as 78.7% [27]. However, Kohli M et al., documented the specificity of more than 98% for peritoneal fluid assessment in PTB [20]. In third world countries, where newer and fancy investigations are not available, comparison between conventional and new investigations help us in determining EPTB.

Limitation(s)

Current study had certain limitations, firstly, the sample size was small and secondly, as sensitivity obtained for ADA was found to be low. A gold standard method like Acid-Fast Stain in pleural tissue or a growth of MTB on culture medium should have been employed in the study. The findings could not be generalised as it was a cross-sectional single centre based study.

CONCLUSION(S)

Extrapulmonary tuberculosis cases pose diagnostic challenge and its diagnosis cannot be relied on single test. Each component i.e., history, physical examination, blood investigations, fluid analysis, ADA estimation, and CBNAAT are important in evaluation of such cases and provide some diagnostic clues. Relying solely on single diagnostic modality may be associated with low diagnostic yield, and thus each step of patient assessment must be given equal preference so as to improve the diagnostic yield. However, our study documented ADA as better tool as compared to CBNAAT for diagnosis of extrapulmonary tuberculosis.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jan 05, 2022
- Manual Googling: Jan 25, 2022
- iThenticate Software: Feb 14, 2022 (8%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 04, 2022**
Date of Peer Review: **Jan 28, 2022**
Date of Acceptance: **Feb 19, 2022**
Date of Publishing: **Mar 01, 2022**