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Original Research Article

Role of CB-NAAT in diagnosing extra pulmonary tuberculosis in correlation with FNA in a tertiary care center

Sunil Kumar Komanapalli[1], Uma Prasad[1], Bhagyalakshmi Atla[1]*, Nammi Vasundhara[2], Divya Yendluri[3]

[1]Department of Pathology, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India
[2]DTCO (District Tuberculosis Control Officer), RNTCP, Government of Andhra Pradesh, Visakhapatnam, Andhra Pradesh, India
[3]Medical Officer, RNTCP, KGH, Visakhapatnam, Andhra Pradesh, India

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***Correspondence:**
Dr. Bhagyalakshmi Atla,
E-mail: dr.a.bhagyalaxmi@gmail.com

ABSTRACT

Background: The diagnosis of extra-pulmonary tuberculosis (EPTB) is challenging due to the pauci-bacillary nature of disease. Recently, WHO recommends GeneXpert/CBNAAT to be used as the initial diagnostic test in patients suspected extra-pulmonary tuberculosis (EPTB). The study was done to assess the role of Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) in the diagnosis of EPTB. Aims and objectives was to study the role of FNAC, CBNAAT and Fluorescent LED in diagnosing extra-pulmonary tuberculosis (EPTB).
Methods: This is a descriptive observational study carried out over a period of 12 months (April 2017 to March 2018) at department of Pathology, Andhra Medical College. All presumptive cases of extrapulmonary tuberculosis and purulent aspirates from the various sites between the age group of <10yrs to 60 years of age were included in the study. FNA was done and material sent to CBNAAT and fluorescent LED (Light-emitting Diode) microscopy in all the cases and results tabulated.
Results: The total number of cases with presumptive extra pulmonary Tb were 289. Majority of the aspirates are from lymph nodal and cervical swellings 94.1% (272/289). CBNAAT has detected 6.5 % of cases (19/289) which were not detected by FNA and 9.3% of cases (27/289) LED negative cases. Resistant to rifampicin was identified in 2.1% (3/142 cases) of CBNAAT positive cases.
Conclusions: FNA still remains the cheapest test to diagnose TB. In cases with *Granulomatous lymphadenitis* and purulent aspirates CBNAAT has an important role in diagnosing EPTB. In addition it offered rapid detection of rifampicin-resistant *M. tuberculosis* strains which is an added advantage.

Keywords: CB-NAAT, EPTB, Fine needle aspiration cytology

INTRODUCTION

India is the home of world's largest tuberculosis (TB) burden, accounting for around 21% of the TB incidence globally. Although pulmonary involvement is the most common presentation, it can potentially affect any organ or system of the body. Extra pulmonary tuberculosis is defined according to WHO classification criteria as an infection by *M. tuberculosis* which affects tissues and organs outside the pulmonary parenchyma.[1] In India, EPTB constitutes 10-15% of total TB cases which primarily involve the pleura, lymph nodes, gastrointestinal tract and other organs with a significant case mortalityrate (25 to 50%).[2]

As the number of Mycobacterium Tuberculosis Bacilli (MTB) in extra pulmonarysites is often low, diagnosis of EPTB still remains challenging.[3] In such situation, not only early diagnosis and treatment is very crucial but also may save many lives. Cytology and conventional smear microscopy have been used as the initial diagnostic tools in the extra pulmonary tuberculosis in resource poor settings.

Fine needle aspiration cytology (FNAC) is a simple and rapid diagnostic technique, but with low specificity.[4] Conventional smear microscopy lacks sensitivity due to the paucibacillary nature of fine needle aspirates (FNA).[5] So, both FNAC and smear microscopy have limitations by the absence of species confirmation and or lack of drug resistance guidance. Mycobacteriological culture and drug susceptibility testing are not always available in resource poor settings or their results may take 4 to 8 weeks orlonger.[6]

In line with these limitations more rapid and reliable methods are needed. In December 2010, WHO endorsed CBNAAT/GeneXpert MTB/RIF1(Cepheid, USA) for use in TB laboratories. CBNAAT was adopted in India by RNTCP in 2012. It first started as a pilot project in Maharashtra state, India.[7] The CBNAAT assay consists of a closed system that is based on real-time polymerase chain reaction (PCR). Which requires minimal technical expertise in the diagnosis of TB and rifampicin resistance within 2hours.[8] However, the Xpert assay has been validated and optimized for sputum samples to diagnose HIVassociated TB and multidrug-resistant TB. WHO strongly recommends widespread use of CBNAAT for these groups of patients.[9]

More recently a number of studies were done to evaluate this assay using non-respiratory clinical samples from patients suspected of having EPTB.[10,11] In 2014, WHO has recommended CBNAAT over the conventional tests (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having EPTB.[12] However, this was a conditional recommendation due to very low-quality evidence available. More studies are therefore needed particularly in settings with high EPTB prevalence.

Thus, we want to evaluate the role of CBNAAT for the diagnosis of EPTB using routinely collected FNA samples and compared it against cytology and fluorescent LED microscopy.

Aims and objectives was to compare the FNAC findings of extra pulmonary tuberculosis with CBNAAT and to assess the difference in results of extra pulmonary tuberculosis with CBNAAT and fluorescent LED microscopy in comparison with FNAC findings. Also, to know the diagnostic performance of CBNAAT in diagnosing EPTB.

METHODS

It's an observational study done in the Department of Pathology, Andhra Medical College, Visakhapatnam over a period of 12 months (April 2017 to March 2018) With a Sample size of 289 cases.We have included all presumptive cases (clinically suspicious) of extra pulmonary tuberculosis, Purulent aspirates on FNA from the various sites between the age group of <1yr to 60 years and excluded cases that were already diagnosed, recurrent, follow up cases of extra pulmonary tuberculosis.

Procedure

All patients or guardians in case of children were requested for written consent prior to enrolment to the study. FNAC specimens were collected from 289 patients by aspirating two to three passes of a 23- or 25-gauge needle attached to a 5ml syringe. Clinical features of the case and Gross specimen appearance (caseous, purulent, and/or blood stained) was recorded at the time of specimen collection. Three smears were prepared from each aspirate, two fixed with commercial cytology fixative for H and E staining and were evaluated for adequacy and examined for the presence of epithelioid cells with or without necrosis (Figure 1) and third smear evaluated by fluorescence LED microscopy for direct detection of mycobacterium in all cases.

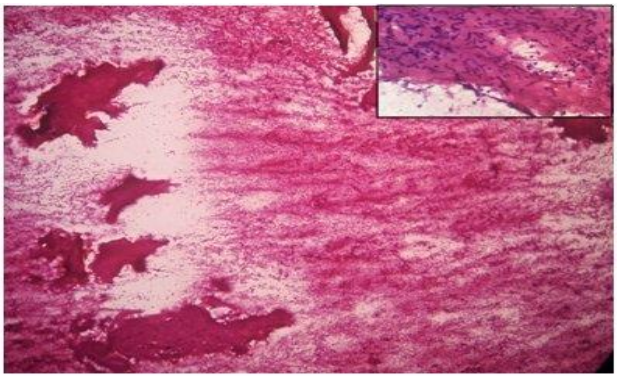

Figure 1: Caseous necrosis (inset showing epitheloid cells). H and E stain (400X).

Smears for LED fluorescent microscopy were prepared with Auramine O stain which appears bright yellow fluorescent curved bacilli (Figure 2) and reported as negative (zero AFB/1length),"scanty" (1-19), 1+, (20-199)2+, (5-50/1 field) 3+ (>50/1 field) acid-fast bacilli (AFB) according to standard IUATLD/WHO scale. (IUATLD -The International Union Against Tuberculosis and Lung Diseases). The material from the remaining aspirate was added with buffer in 1:2 ratio, collected in to pre-sterilized falcon tubes and incubated at room temperature for 25 to 30min. Two ml of the reagent sample mix was then transferred to an Xpert cartridge using a pasteur pipette and the cartridge was loaded onto Xpert (Cepheid, Dx System Version 4.0c) machine.

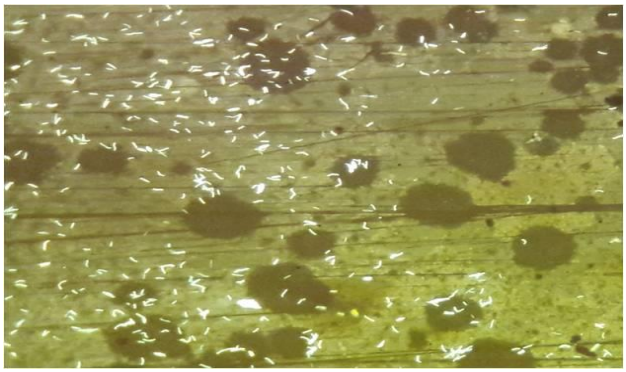

Figure 2: Bright yellow fluorescent *Mycobacterium bacilli* under LED microscopy (20x).

Results were reported as positive or negative for M. tuberculosis as CBNAAT gives semiquantitative estimate of the concentration of bacilli as defined by the Ct (cycle threshold) range (high, <16; medium, 16-22; low, 22-28; very low, >28). Assays that are negative for M. tuberculosis and for the internal control are reported as invalid assays. Rifampicin resistance results were reported as susceptible, resistant. Performance calculations, including test sensitivity, specificity, positive and negative likely hood ratio done using SPSS software to compare the diagnostic performance of the CBNAAT test to the Composite Reference Standard (CRS).[13] It includes if either positive for cytology (cytomorphology consistent with TB) or direct visualization of the organism on fluorescence LED microscopy we considered the case is TB.

RESULTS

All 289 cases were subjected to FNAC, LED and CBNAAT. Out of 289 cases, cytomorphological features consistent with Tb (FNAC) were 51.04%, CBNAAT diagnosed 49.1% cases and LED detected 39.7% cases only. Majority of the cases are in between 11-30 years age group with female preponderance (Table 1) and in the present study Majority of the CBNAAT cases are also seen in between 11-30 years age group with female preponderance (Table 2).

Table 1: Age and sex distribution of total cases (n=289).

Age group	No. of cases	Male	Female
2months -10	35	27	8
11-20	76	25	51
21-30	85	37	48
31-40	51	23	28
41-50	26	18	8
51-60	16	10	6
Total	289	140 (48%)	149 (51%)

Table 2: Age and sex wise distribution of CBNAAT positive cases (n=289).

	CBNAAT positive			
Age group	No of cases	Total	Male	Female
2months -10	35	5	4	1
11-20	76	38	10	28
21-30	85	50	22	28
31-40	51	35	19	16
41-50	26	9	7	2
51-60	16	5	4	1
Total	289	142	66 (23%)	76 (26.2 %)

Table 3: Site wise distribution of total cases along with CBNAAT positivity (n=289).

Site	Total	%	CBNAAT positive
Lymph node and cervical swellings	272	94.1%	138/272 (50.7%)
Breast swelling	6	2.07%	1/6(0.16%)
Chest wall	4	1.38%	2/4(0.5%)
Hypochondrium	1	0.35%	1/1
Leg swelling	2	0.7%	
Fore arm swelling	2	0.7%	
Nape of the neck swellings	2	0.7%	
Total	289		142

Majority of the (94.1 %) of cases were aspirated from cervical and lymphnodal swellings in which 50.7% of cases were positive for CBNAAT followed by breast and chest wall swellings (Table 3). Majority of the cases 55% (161/289) were purulent aspirates out of which 62.1% (100/161) of cases were CBNAAT positive (Table 4).

In 50.5% cases of Tuberculous lymphadenitis on cytology, 84.34% of cases were CBNAAT positive. CBNAAT result of total 42 cases were not correlated with FNA (Table 5).

Table 4: Distribution of type of FNA aspirates along with CBNAAT results (n=289).

Type of aspirate	Total	CBNAAT positive	CBNAAT negative
Purulent	161 (55%)	100 (62.1%)	61
Thick grey white (cheesy)	12 (4.0%)	5 (41.6%)	7
Blood mixed	116 (41%)	37 (31.8%)	79
Total	289	142 (49.1%)	147

Table 5: Comparison of cytomorphological diagnosis with CBNAAT (n=289).

Cytomorphological (FNA) diagnosis	Total	CBNAAT +	Not correlated with FNA CBNAAT -/+
Tuberculosis	146 (50.5%)	123 (84.34%)	23 (7.9%)
Abscess	49 (17%)	16 (32.6%)	16 (5.6%)
Acute lymphadenitis	23 (7.9%)	2 (8.69%)	2 (0.7%)
Acute sailadenitis with suspicious granuloma	1 (0.3%)	1 (100%)	1 (0.3%)
Squamous cell carcinoma/deposits	6		
Reactive lymphadenitis	53		
Hodgkins lymphoma	1		
Fungal infection (aspergillus)	1		
Neurofibroma	1		
Infected epidermal cyst	7		
Branchial cyst	1		
Total	289	142	42

Table 6: Distribution of non correlated cases with FNA in comparison to CBNAAT Results (n=42).

Non correlated cases	Purulent	Blood mixed	Caseous material
23 (FNA+CBNAAT -)	5	11 (47.8%)	7
19(FNA-CBNAAT +)	16(84.2%)	3	0
Total =42	21	14	7
	FNA + CBNAAT-	**FNA-CBNAAT +**	**Total**
Children	16(69.5%)	3	17
Adults	7	15(78.9%)	20
Total	23	19	42

Table 7: Diagnostic performance of CBNAAT with Composite Reference Standard (CRS) (n=289).

	CRS +	CRS -	Total
CBNAAT +	138	4	142
CBNAAT -	23	124	147
Total	161	128	289

Table 8: Diagnostic performance of the CBNAAT and LED versus FNAC was done (n=146).

Reference standard	Total cases	Sensitivity	Specificity	Positive likely hood ratio	Negative likely hood ratio
CBNAAT vs FNA	123/146	84.25%	86.71%	6.34	0.018
LED vs FNA	100/146	68.49%	89.51%	6.53	0.35

Table 9: Diagnostic accuracy of the CBNAAT and LED versus FNAC in HIV (n=21).

Reference standard	Total cases	Sensitivity	Specificity	Positive likely hood ratio	Negative likely hood ratio
CBNAAT vs FNA (HIV)	15/21	78.95%	50%	1.58	0.42
LED vs FNA (HIV)	12/21	63.16%	100%	-	0.37

Table 10: Xpert /CBNAAT result (Ct range) (n=142).

Ct values	CBNAAT
Very low	87 (61.26%)
low	40 (28.1%)
medium	11(7.8%)
High	4 (2.8%)
Total	142

Table 11: Comparison of Xpert semi-quantitative result (Ct-value) and LED smear grade (n=115).

Fluorescent LED microscopy		CBNAAT ct values			
IUATLD/WHO scale	**Total**	**Very low**	**Low**	**Medium**	**High**
Scanty	66 (57.3%)	65	1	0	0
1+	32	2	30	0	0
2+	12	0	2	10	0
3+	5	0	0	1	4
Total	115	67(58.2%)	33 (28.6%)	11 (9.8%)	4 (3.4%)

Out of 142 CBNAAT positive cases on comparison with CRS (composite reference standard) ,138 (FNA, LED +/) were positive for Tb, 4 were both negative (FNA/LED -). Out of 147 CBNAAT negative cases, 23 were positive according to CRS (FNA+/LED-) 124 cases all were negative (FNA/LED/CBNAAT) which constitutes reactive and acute lymphadenitis, abscess, squamous cell carcinoma deposits, Hodgkins lymphoma, fungal infection, neurofibroma, infected epidermal cyst and branchial cyst.

Out of 42 cases, aspirates of majority of FNA+ CBNAAT- cases were blood mixed and 69.5% of such cases aspirated from children. Whereas majority of CBNAAT+ FNA-cases aspirates were purulent and majority of them (78.9%) aspirated from adults (Table 6).

Diagnostic performance of CBNAAT with Composite Reference Standard (CRS)(n=289) was done. Sensitivity, specificity, positive likely hood ratio and negative likely hood ratio of CBNAAT were 85.71%, 96.87%, 21.21, 0.15 respectively (Table 7).

Diagnostic performance of the CBNAAT and LED versus FNAC was done. (n=146) sensitivity of CBNAAT is more when compared with LED against FNAC (Table 8). Diagnostic accuracy of the CBNAAT and LED versus FNAC in HIV (n=21) was done. Sensitivity of CBNAAT is more but specificity is less when compared with LED against FNA (Table 9).

Out of 142 CBNAAT positive cases majority of them have 61.26 % (87/142) have very low Ct values confirming paucibacillary nature of extra pulmonary Tb cases. (Table 10). In the present study comparison of Xpert semi-quantitative result (Ct-value) and LED smear grade was done; (n=115) showed well correlation with CBNAAT results (Table 11). Only 2.1% (3/142) cases were rifampicin resistance out of total 142 CBNAAT positive cases in the present study.

DISCUSSION

The present study is a hospital based prospective study on the diagnosis of extra pulmonary Tb by CBNAAT and LED microscopy in comparison to FNA.

Table 12: Comparison of age wise distribution of CBNAAT positive cases with other studies (n=289).

Study	Age group	% of cases
Present study	11-30	30.4%
Yassin et al[14]	15-24	30.7%
Aroravk et al[15]	15-24	38%
Brayn et al[16]	15-24	43%
Mulualem et al[17]	16-30	58 %

In the present study, we compared the age and sex wise distribution of CBNAAT positive cases with other studies where Younger age groups were predominantly effected with Tb in all the studies including present study (Table 12) and female preponderance is seen in the present study which is correlated with other studies (Table 13).[14-18] We also compared the distribution of type of FNA aspirate along with CBNAAT result which is not correlated with Mulualem et al study where caseous aspirates (69%) had more CBNAAT positivity compared to present study which has 62.1% cases were purulent aspirates with CBNAAT positivity.[17]

Table 13: Comparison of sex wise distribution of CBNAAT positive cases with other studies (n=289).

Study	Male	Female
Present study	23%	26.2%
Brain et al[16]	46%	54%
Mulualem et al[17]	67%	76%
Poojasingh et al[18]	31%	69%

In the present study non correlated cases of CBNAAT with FNAC were 42, out of which 19 cases were FNA-CBNAAT+ and other 23 cases were FNA +CBNAAT-.

Around 19 FNA-CBNAAT+ patients, 16 were grossly purulent aspirates and cytomorphologically they were abscess, 4 from extra lymphnodal origin includes One breast Tb and 3 cases of musculo skeletal Tb, 12 from nodal origin. Out of 3 blood mixed aspirates, 2 were cytologically acute lymphadenitis cases, 1 was acute sailadenitis with suspicious granuloma. So, in our study the importance of CBNAAT lies in detecting above 19 Tb patients which were cytologically negative for Tb, who were surely benefitted by the CBNAAT.

Out of 23 (FNAC + CBNAAT-cases), majority of the cases were blood mixed (11/42) mostly these aspirates were from the children. It is possible that in these cases representative sample might not be obtained as aspirations from the children is difficult or bacterial load may have been too low for the GeneXpert to detect the DNA from MTB- complex.[19] The possible cause for CBNAAT negativity in seven (7/42) cases of cheesy material might be solid nature of the cheesy material which usually have very low bacillary load in nature compared to liquid caseous material which have high bacillary load.[20] Because of low bacillary load and its detection limit of 131cfu/ml might be the reason for CBNAAT negativity in these patients.[21]

According to WHO Xpert guidelines above 23/42 patients they had received Tb treatment as they were cytologically positive and clinically suspicious.[22] So, CBNAAT negative result can still have Tb or MOTT. On comparison of CBNAAT diagnostic performance of present study (sensitivity 85.71%, specificity 96.8%) (CRS) with Singh KG et al, (sensitivity 91%, specificity 90%) Ligthelm et al (sensitivity-96.7%, specificity 88.9%) showed less sensitivity and more specificity.[23,24] In the present study rifampicin resistance on CBNAAT in cases of EPTB was 2.1% and EPTB cases with HIV, LED showed more specificity than CBNAAT. However, CBNAAT is more sensitive than LED.

CONCLUSION

CBNAAT has detected 6.5 % of cases (19/289) which were not detected by FNA and 9.3% of (27/289) LED negative cases. Musculo skeletal TB and Tb breast were detected by CBNAAT and LED which are cytomorphologically negative for tb. In cases with Granulomatous lymphadenitis and purulent aspirates CBNAAT has an important role in diagnosing EPTB sensitivity of CBNAAT is more compared to fluorescent LED microscopy in the present study. Rifampicin resistance detection by CBNAAT has greater advantage in treatment of the patients with shorter turnaround time (2hours) which is not possible with FNA and LED even though FNA is cost effective in the diagnosis of EPTB, combining with CBNAAT has an advantage of detection of FNA missed cases and it can be integrated into a routine diagnostic protocol.

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Ethical approval: The study was approved by the Institutional Ethics Committee of Andhra Medical College, Visakhapatnam, Andhra Pradesh, India

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