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Original Research Article

Pattern of tuberculosis among tribal population of Central India with special reference to cartridge based nucleic acid amplification test as diagnostic tool: a descriptive study at tertiary care hospital

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ABSTRACT

Background: Tuberculosis (TB) kills close to half a million Indians every year. Lack of reliable rapid diagnostic techniques for TB hampers timely diagnosis and leads to continued disease transmission, causing significant morbidity and mortality. The potential of newly recommended CBNAAT in TB and MDR-TB detection has been underutilized in our area due to lack of awareness regarding the same. Hence we utilized this rapid, logistically simplified test to study the pattern of tuberculosis among tribal population of Central India.
Methods: Descriptive study of suspected TB patients in tertiary care centre from March 2016 to March 2019. Appropriate specimens from suspected TB patients were collected and subjected to CBNAAT and AFB smear to study the pattern of TB and Rifampicin- Resistant(RR) TB in our area.
Results: CBNAAT detected overall 27% MTB cases; 27.72 % Pulmonary-TB cases as against smear positivity rate of 20.73% whereas 12.74% Extra-pulmonary-TB (EPTB) cases as against smear positivity rate of 1.59%.Overall 94.91% were RiF Sensitive(RS-TB) and 4.58% were RR-TB. Of the 57 (4.16%) HIV-TB coinfected cases; 96.49% were RS-TB and 5.26% were RR-TB. Co-infected patients have high incidence of EPTB(21.05%) involvement with RR-TB 3.50%. Among EPTB cases; lymph node aspirate and pus provided highest CBNAAT positive cases and almost 90.62% EPTB specimens were RS-TB .
Conclusions: Availability of new diagnostic services has increased early identification of TB and RR-TB. Awareness among physicians regarding diagnostic utility of CBNAAT should be further increased as early identification of possible MDR cases is key to reducing community transmission and treatment initiation, particularly in high-burden, resource-limited settings.

Keywords: Cartridge Based Nucleic Acid Amplification Test, Extra-pulmonary tuberculosis, Pulmonary tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a major global health problem. It causes ill-health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease.[1] It accounts for 9.6 million cases globally as per the WHO Global TB Report 2015. Among these cases, India contributes to 2.2 million incidence cases and has not only high morbidity but also the mortality is high with 0.22 million deaths in 2015.[2] In India alone 1.8 million new cases of TB arise annually.[3] Additionally, a million 'missing' undiagnosed or inadequately diagnosed cases

go unnotified annually.[4] Not surprisingly, drug-resistant tuberculosis (DR-TB) is a significant problem, and India now has the most number of cases of multidrug- resistant tuberculosis (MDR)-TB in the world, contributing one-fourth of the global burden.[4] In India in 2015,there were an estimated 79,000 new cases of MDR-TB/ Rifampicin Resistant (RR)-TB cases were notified and drug resistance shows that 3.5% of new and 16% of previously treated TB cases were estimated to have MDR/RR-TB.[5] Lack of reliable rapid diagnostic techniques for MDR TB hampers timely diagnosis and leads to continued disease transmission, causing significant morbidity and mortality. Thus, making a rapid diagnosis of MDR TB is of utmost importance.

Sputum smear microscopy is inefficient due to its variable sensitivity particularly in patients with sputum smear-negative and/or extra-pulmonary disease, and drug-resistant TB.[6] The conventional culture DST methods are time-consuming and require trained laboratory personnel, which are a practical hurdle in resource-limited developing countries. The Catridge Based Nucleic Acid Amplification Test (CBNAAT) is a semi-quantitative nested nucleic acid amplification test based on molecular detection of a mutated gene. It can be carried out in automated manner including bacterial lysis, nucleic acid extraction, and amplification and amplicon detection. It is cost-effective and does not require technical expertise. It enables diagnosis of DR TB within 2 hours and also has minimal false positive rates due to use of disposable closed cartridges preventing cross-contamination.[7] Thus, in resource-limited settings where facilities for culture DST are not available, CNBAAT/ Xpert MTB/RIF Assay is extremely useful for rapid diagnosis of MDR TB. It was developed as a rapid test to diagnose pulmonary TB and to detect rifampicin (RIF) resistance.[8] Revised National TB Control Programme is also currently using Xpert MTB/RIF to diagnose pulmonary TB (PTB), paediatric TB, extra-pulmonary TB(EPTB) and rifampicin resistance and MDR-TB in high risk populations like HIV positive as recommended by WHO under 2013 policy recommendations.[9] Prior to application of this assay, patients at high risk for MDR TB would have to be referred to a tertiary setting and wait 6-8 weeks for results of phenotypic drug susceptibility testing resulting in high loss to follow up and delays in treatment initiation. The line probe assays for MDR diagnosis have also largely been limited to reference tertiary centres in low and middle income countries. However, early identification of possible MDR cases is key to reducing community transmission and reducing the incidence of MDR TB.[10]

Our institution in central India serves a population of tribal and rural poor who often travel great distances to be seen in clinics .There is an emphasis on same day diagnostics and treatment wherever possible. Moreover, the potential of CBNAAT in TB detection has been underutilized in our area due to lack of awareness regarding the same. Hence, we conducted the study to use this rapid and logistically simplified test in the diagnosis of TB to study the pattern of tuberculosis among tribal population of Central India.

METHODS

The study is a descriptive study conducted at Department of Microbiology, and in laboratory accredited by RNTCP for CBNAAT testing, Government Medical College, Gondia after obtaining permission from the Institutional ethical committee.

Inclusion criteria

- All the suspected inpatient and outpatient pulmonary tuberculosis cases
- All the suspected inpatient and outpatient extra-pulmonary tuberculosis cases
- All the suspected HIV-TB (pulmonary, extra-pulmonary) co-infection cases
- All the suspected pulmonary and extra-pulmonary paediatric (less than 15 years) cases

Exclusion criteria

Cases not satisfying the inclusion criteria were excluded from study.

The study is descriptive study conducted from March 2016 to March 2019. A total of 5170 specimens were collected from all the suspected pulmonary and extra-pulmonary tuberculosis either inpatient or outpatient RNTCP registered cases.

A total of 5170 appropriate specimens were collected from all the suspected pulmonary and extra-pulmonary tuberculosis patients. Samples collected included sputum, lymph node aspirates, pus, pleural fluid, CSF, gastric lavage, cystic fluid, peritoneal fluid, ascitic fluid, synovial fluid, urine. All the specimens were subjected to acid fast staining and CBNAAT as per the standard procedure. The specimens for CBNAAT assay were collected in pre-sterilized falcon tubes with three layer packing system. Specimens were processed in laboratory accredited by RNTCP for CBNAAT testing according to the GeneXpert Dx system operator manual provided by manufacturer. The assay is designed for extraction, amplification and identification of rpoB gene of M. tuberculosis as it accounts for more than 95% of mutations associated with rifampicin resistance, ensuring high degree of specificity by use of three specific primers and 5 unique molecular probes 9. Xpert MTB/RIF cartridge is a disposable, single self-enclosed test unit in which all steps of NAAT i.e. Sample processing, PCR amplification and detection are automated and integrated. The manual steps involved in the assay are adding reagent to liquefy specimen and sample loading .The test procedure is made biosafe by tuberculocidal property of the assay's sample reagent 11The data obtained was then analyzed using appropriate statistical methods.

Statistical analysis: All the data were entered in Microsoft excel and the statistical analysis was performed using Epi- data analysis software (versionV2.2.2.178) .Summary statistics for all the categorical clinical parameters were presented as frequency and percentage.

RESULTS

The study was done to evaluate the pattern of Tuberculosis in our tribal region over a period of 3 years. The number of patients diagnosed from March 2016 reveals steady increase in numbers till 2019 as depicted in Table 1. A total of 5170 specimens were included in the study out of which 4919 (95.14 %) were pulmonary and 251(4.85%) were extra-pulmonary specimens. (Figure 1); 1320 i.e.25.53% were from HIV positive patients and 364 i.e. 7.04% were from paediatric patients.

In our study, all the5170 specimens subjected AFB smear and CBNAAT assay. Overall 27% i.e. 1396 patients were reported MTB positive on CBNAAT.

Table 1: Year- wise distribution of specimens tested on CBNAAT from March 2016 to March 2019.

Year	No. of specimens tested by CBNAAT	MTB Detected (New + Retested)	MTB Not Detected
March 2016- Dec. 2016	744	202(27.1%)	542
2017	1166	324(27.7%)	842
2018	2668	745(27.9%)	1923
Jan 2019-March 2019	592	125(21.1%)	467
Total	5170	1396(27.0%)	3774

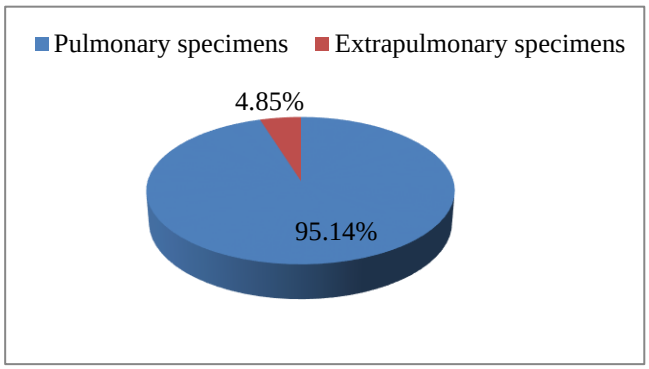

Figure 1: Distribution of specimens.

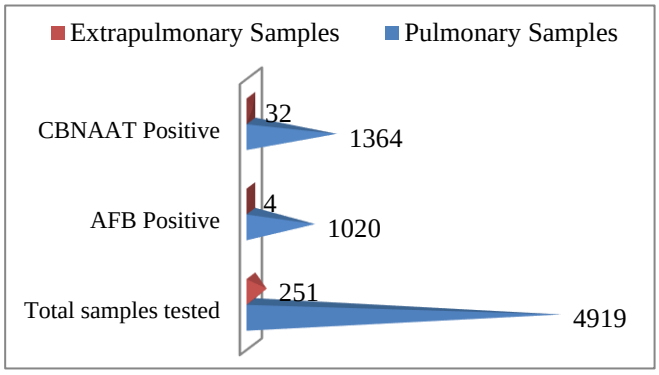

Figure 2: Comparision between MTB detection by CBNAAT and AFB smear in pulmonary and extra-pulmonary specimens.

Among 4919 suspected PTB cases, CBNAAT detected MTB in 1364 i.e. 27.72% cases as against the smear positivity rate of 20.73% (1020 cases) whereas among 251suspected EPTB cases, CBNAAT detected MTB in 32 i.e. 12.74% cases as against the smear positivity rate of 1.59% (4 cases) (Figure 2). None of the CBNAAT negative specimens were found to be positive on AFB smear.

Overall 1396 patients were reported MTB positive in CBNAAT; 1325 (94.91%) were RiF Sensitive TB (RS-TB) and 64 (4.58%) were RiF Resistant TB (RR-TB). Among RR-TB cases, more than 2/3rd of patients were male and the mean age was 32 years.

Out of the total 1396 CBNAAT MTB positive cases, 57 i.e. 4.16% were found to be HIV-TB coinfected. Of these, 55 (96.49%) were RS-TB and 2(3.50%) were RR-TB. (Table 2). As depicted in table 2; HIV TB coinfected patients have high incidence of EPTB involvement (21.05%) with RR-TB 3.50% as compared to EPTB involvement (1.49%) without any RR-TB (0%) in isolated MTB cases without HIV. Sex wise- distribution showed that of the 57 co- infected cases 38(66.66%) were male and 19 (33.33%) were female and all were in the age group of more than 20 years.

Among 251 suspected extra-pulmonary tuberculosis cases, CBNAAT detected MTB in 32 i.e. 12.74% cases as against the smear positivity rate of 1.59% (4 cases). Almost 90.62% (29) EPTB specimens were RIF sensitive and 9.37% were RIF resistant on (3) CBNAAT. Among the EPTB cases male constituted 54.6% compared to 45.6% females. The major site of predilection was in the following sequence: lymph node (249, 52.9%) followed by pleura (122, 24.9%), abdomen (40, 8.5%), spine (24,

5.2%), bone (18, 3.9%) as depicted in Fig. 4. Pleural fluid was the most common sample for which CBNAAT performed (38.1%) was followed by lymph node aspirate (23.8%). Lymph node aspirate and pus provided the highest CBNAAT positive cases.

Table 2: CBNAAT in HIV positive and HIV negative patients.

Variables	HIV +ve	HIV –ve	Total
Total No of specimens tested	1320 (25.53%)	3850(74.46%)	5170
TB +ve	57 (4.31%)	1339 (34.77%)	1396 (27%)
Rif. Sensitive MTB (Total)	55 (96.49%)	1277 (95.36 %)	1332
Pulmonary TB	43(75.43%)	1250(93.35%)	
Extra-pulmonary TB	12(21.05%)	20(01.49%)	
Rif. Resistant MTB (Total)	03 (5.26%)	61 (4.55 %)	64
Pulmonary TB	01 (1.75 %)	61(4.55 %)	
Extra-pulmonary TB	02 (3.50%)	0 (0%)	

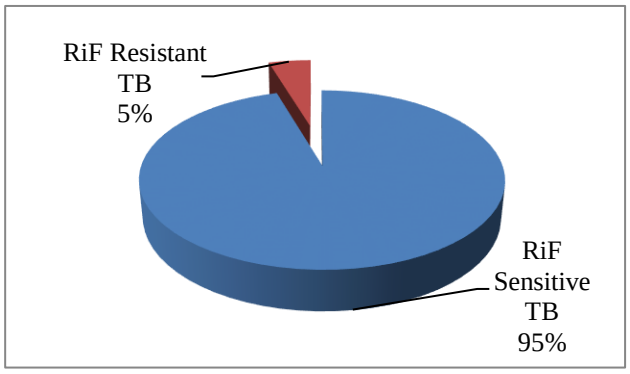

Figure 3: Percentage of rifampicin sensitive and resistant TB.

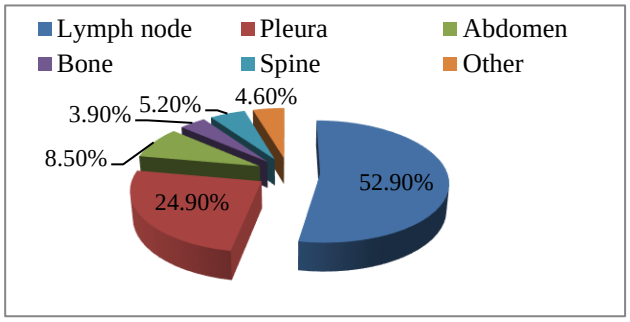

Figure 4: Distribution of site of predilection of extra-pulmonary specimens.

DISCUSSION

India contributes to one-fourth of the global burden of multidrug-resistant tuberculosis (MDR-TB) with inadequate diagnostic infrastructure for drug susceptibility testing (DST).The Xpert MTB /RiF test or CBNAAT exhibits high sensitivity and specificity for detecting pulmonary TB disease. An in vitro study demonstrated a limit of detection of as few as 131 colony forming units /ml of MTB compared with approximately 10,000 colony forming units /ml with conventional smear microscopy.[12] Studies from different part of world have reported high sensitivity and specificity by using Xpert MTB/RIF test based on this assay. Steingart et al. performed an updated Cochrane Review as part of a WHO process to develop updated guidelines on the use Xpert® MTB/RIF assay and reported test to be sensitive and specific. In adults thought to have TB, with or without HIV infection, compared with smear microscopy, Xpert® MTB/RIF substantially increases TB detection among culture-confirmed cases. For rifampicin resistance detection, Xpert® MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment.[13] CBNAAT is also a useful surrogate test for screening for MDR-TB as past studies on drug resistance have shown that rifampicin resistance seldom occurs alone and around 90% of rifampicin resistant patients are diagnosed to have MDR-TB.[12] CBNAAT is having unmatched significance in TB endemic areas like India where there is high prevalence of MDR TB, around 3% in new cases and 12 to 18% in previously treated cases.[12] Hence we utilsed this newly started test in our area to study the burden and pattern of pulmonary, extra-pulmonary and drug resistant TB.

The study was done to evaluate the pattern of Tuberculosis in our tribal region over a 3 years period. The number of patients diagnosed from March 2016 reveals steady increase in numbers till March 2019; this may be due to improved awareness among the clinicians and availability of new diagnostic modalities with time and awareness to register in RNTCP services for availing the services. In our study, overall 27% patients were reported MTB positive on CBNAAT. In a study by Raizada et al, that covered a population of 8.8 million across 18 sub-district level tuberculosis units (TU) in India, Overall 28% TB cases were bacteriologically confirmed, of which 27.6% TB cases were detected on CBNAAT against the smear positivity rate of 12.9%.[14] In a study carried out by Kasat et al. among 166 EPTB

cases, CBNAAT detected MTB in 25 cases as compared to AFB smear which detected MTB in only 16 cases and concluded that CBNAAT is more effective as compared to AFB smear in the diagnosis of EPTB cases and CBNAAT should be routinely utilized for rapid diagnosis of EPTB along with other conventional methods.[15] Similarly in a study carried out at Hydrabad India, for pulmonary samples the sensitivity and specificity of CBNAAT samples were 79.2% and 89.5% respectively while that for sputum smear negative were 41.5% and 98.2% respectively. For extra-pulmonary samples ,the sensitivity and specificity of CBNAAT samples were 85.7% and 93.5% respectively while that for smear negative were 60.7% and 100% respectively.[16]

CBNAAT is a useful surrogate test for screening for MDR-TB as past studies on drug resistance have shown that rifampicin resistance seldom occurs alone and around 90% of rifampicin resistant patients are diagnosed to have MDR –TB.[12] The specificity of CBNAAT in detecting rifampicin resistance is very high (98%), and increasing evidence has shown that the infrequent occurrence of so-called false-positive results may be linked to the detection by Xpert MTB/RIF of strains that are truly resistant to rifampicin, but which are not detected by the phenotypic culture-based DST, the present reference standard.[17] In our study out of 1396 MTB positive cases, 1325 (94.91%) cases found to be RS-TB and 64 (4.58%) were RR-TB. Most 98% of these patients had history of previous treatment for TB. Only 4 patients were naïve to anti tuberculous drugs. Though the data on prevalence of RR-TB/ MDR TB was sparse in our region; various studies carried out earlier in different regions of India reported high MDR TB rates as 54% in Varanasi in 2014 and 38% in Lucknow in 2013.[18,19] Similarly low MDR TB 5.4% was reported by a study carried out by Datta et al, in 2009 in Jammu Kashmir.[20] Among Rif resistant cases, more than 2/3rd of patients were male and the mean age was 32 years. Udwadia also reported prevalence of younger age group among MDR-TB patients with the mean age of their study groups being 29.7 years and 33.25 years, respectively.[21]

In given study 2.6% patients were found to be HIV-TB co-infected, of which 12(63.15%) were males and 7(36.48%) were females. This male predominance may be accounted their migration for employment within and outside the state thereby subjecting them to risk behaviour. Majority of female are illiterate and are house-wives who don't even have easy access to healthcare facilities, and HIV and TB both being social stigma often go unreported.

Of the 57 Co-infected cases 54 (94.7%) cases were RiF sensitive and 3(5.26 %) cases were RiF resistant. Though there are extensive data on HIV prevalence in TB as a whole, there have been only a few studies on prevalence of HIV among MDR-TB patients from India. In 2014, Nguyen T et al found Rifampicin resistance in 3.7% of HIV positive patients with Tuberculosis.[22] In a study conducted in Chennai, HIV seropositivity among MDRTB patients was 4.42 per cent, which is comparable to rates of HIV observed among ordinary TB patients.[23] It is possible that HIV co-infected patients with MDRTB succumbed to the illness before they could be diagnosed.[24]

In this study, authors found that the results of CBNAAT were better when compared to AFB smear for EPTB samples. Among 251suspected extra-pulmonary tuberculosis cases, CBNAAT detected MTB in 32 i.e. 12.74% cases as against the smear positivity rate of 1.59%. Lymph node involvement was highest of about 56.3% followed by pleura (31.1%) Similar results were reported by C. Mohan Rao et al, who witnessed 52.9% lymph node involvement followed by 25.9% pleural involvement out of 470 cases with EPTB. EPTB was more witnessed in male (54.6%) than female (45.4%).[25] Similar observations were made in the study by Ramaprakash et al, who documented 51.52% males and Mavila R et al, who reported 112 (59.9%) male as sufferers of extra-pulmonary TB.[26,27] CBNAAT results of EPTB specimen revealed higher diagnostic yield from lymph node aspirate and pus compared to no detection from pleural fluid, CSF and peritoneal fluids. This could be explained by the hypersensitivity phenomenon; because few organisms are present in the pleural space, this is a Cell Mediated Immunity phenomenon.[28]

Epidemiological data suggest that extra-pulmonary TB (EPTB) constitutes about 15-20% of all TB cases, but among HIV-TB co-infection it accounts for 50% of the cases.[29] As depicted in table 1,HIV TB co-infected patients have high incidence of EPTB involvement(21.05%) with RR-TB 3.50% as compared to EPTB involvement (1.49%) without any Rif resistant MTB (0%) strains in isolated MTB cases without HIV. Though the prevalence of pulmonary drug resistant tuberculosis in HIV positive patients was no more than with HIV negative patients; in our study, CBNAAT gave an extra edge over diagnosis of extra-pulmonary TB with MDR strains and pulmonary TB in sputum smear negative HIV patients. Many people with HIV TB co-infection die from TB because these patients are paucibacillary and diagnosis is delayed. Screening of pulmonary and extra-pulmonary samples with CBNAAT in all HIV positive patients has enormous scope in early diagnosis and treatment of TB in terms of active case finding of patients with drug resistant tuberculosis. The results are available in less than 2 hours. This leads to less transmission of disease with reduced morbidity in view of ongoing HIV TB co-infection epidemic.

Although CBNAAT is considered a breakthrough in the diagnosis of PTB and EPTB; there are several limitations of this assay. One of the major limitation is that it cannot distinguish between viable and nonviable microorganisms while detecting mycobacterial DNA. Hence it should not be used to monitor patients or efficacy of treatment. CBNAAT is also sensitive to high

temperature and humid conditions, which are quite prevalent in countries with a high TB burden, like India. Despite these limitations, introduction of this molecular DST technique in the current TB diagnostic algorithm will not only help in early diagnosis of TB but will also provide early information about MDR-TB.

Authors assumed that the specificity of Xpert is high, as every study performed to date and meta-analysis has indicated consistently high specificity of 99%.[15] Therefore, although there is no culture confirmation for comparison, this study was not an evaluation of diagnostic accuracy, which has been comprehensively reported elsewhere in other studies.[13,14] It can be reasonably assumed that the cases studied in our study are genuine, and the rate of false positive diagnosis is unlikely to exceed that of culture. Hence, we conclude that CBNAAT should be routinely used for rapid diagnosis of tuberculosis. The system can be operated under diverse environmental conditions, with minimally trained staff and least biosafety concerns. CBNAAT has high sensitivity, which coupled with its speed and simplicity make it a useful tool in the diagnosis of TB when used in correct clinical context.

CONCLUSION

In the rapidly evolving era of MDRTB an updated knowledge as well as changing research priorities, particularly with respect to new TB diagnostics is the need of the hour. Our findings suggest that use of newer diagnostic modality CBNAAT has significantly increased TB and MDR TB case detection in high risk populations like HIV positive in our area with time from March 2016 to March 2019. Awareness among physicians regarding the diagnostic utility of CBNAAT in PTB, EPTB and MDR should be increased as early identification of possible MDR cases is key to reducing community transmission and treatment initiation, particularly in high-burden and resource-limited settings. It can be a faster alternative to time taking methods like culture DST and at the same time a more efficient alternative to other rapid methods like AFB smear examination in the diagnosis of TB. It could be the best aid for physicians as it has high sensitivity, which coupled with its speed and simplicity make it a useful tool in the diagnosis of TB when used in correct clinical context.

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