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DIAGNOSTIC ACCURACY OF CBNAAT FOR DETECTION OF MYCOBACTERIUM TUBERCULOSIS IN PULMONARY TUBERCULOSIS PATIENTS

Medical Science

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ABSTRACT

Background: Mycobacterium tuberculosis remains to be one of the most significant causes of death from an infectious agent. CBNAAT (Cartridge Based Nucliec Acid Amplification Test) also known as Gene Xpert MTB/RIF assay is a novel integrated diagnostic device for the diagnosis of tuberculosis and rapid detection of RIF resistance in clinical specimens.

Material and Methods: A cross sectional study was conducted at CHC Katra, a block level Hospital of District Reasi, Jammu from January 2018 to December 2018. The study included the entire population above ten years of age who were presumptive pulmonary tuberculosis patients as per Revised National Tuberculosis Control Programme (RNTCP) guidelines. Patients with history of receiving antituberculous drugs within 3 months before enrollment were excluded. Sputum smear for acid-fast bacilli was performed on fresh specimen at the designated microscopy centre of CHC Katra Hospital. The positive smears were sent for CBNAAT.Sputum specimens of the smear negative patients who were strongly suspected for PTB were also sent for CBNAAT.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Xpert was assessed in relation with sputum smear microscopy.

Results: Out of 305 presumptive cases of pulmonary TB who were tested for sputum by smear microscopy, acid fast bacilli were detected in 17 cases only giving a sensitivity of 5.6%. A total of 55 sputum specimens were sent for Xpert MTB/RIF inclusive of 17 patients positive on sputum smear microscopy. It yielded positive result in 24 specimens (with sensitivity of 43.63%).

Senstivity and Specificity of CBNAAT was 100% and 81.6% respectively. Positive and Negative Predictive Value of CBNAAT was 70.8% and 100% respectively.

Conclusion: Xpert MTB/RIF is highly sensitive and good specificity in detecting M. tuberculosis from respiratory specimens and very valuable in making a rapid diagnosis

KEYWORDS

CBNAAT, Pulmonary Tuberculosis, Sputum Smear Microscopy, Senstivity ,Specificity, Xpert MTB/RIF

Introduction

Tuberculosis (TB) is an age old disease – studies on skeletons of mummies show that it has affected humans for thousands of years dating back to 2400-3400 B.C [(1)] On 24 March 1882, Dr Robert Koch discovered the bacillus Mycobacterium tuberculosis as the causative organism of TB, an event that is now commemorated every year as World TB Day. [(2)] WHO declared TB a global health emergency in 1993. [(3)] TB typically affects the lungs (pulmonary TB), but can also affect any other organ of human body (extrapulmonary TB). The disease spreads by droplet aerosol transmission from infected patient to healthy person. TB affects all countries and all age groups. In many developed countries, the national case rates (per 100 000 population) are falling by up to 10% per year and mortality rates falling even faster. For many developing countries like India, however, the "end" of TB as an epidemic and major public health problem is still a distant reality. It is because of the fact that detection of Mycobacterium tuberculosis by acid-fast sputum smear remains the main diagnostic method in most of these resource limited countries [(4).] It is less sensitive and only 50 to 60% of new cases of PTB can be diagnosed. [(5, 6)] Sputum culture has a higher diagnostic yield, but it is an expensive, more time consuming, (2 to 4 weeks) and non-easy availability test that is done at few reference laboratories. [(7)] Smear negative pulmonary TB (SNPT) constitutes nearly half of the PTB patients. Ten to twenty percent of TB transmission in the community is attributable to SNPT patients. [(8)]

In the above two situations, Cartridge Based Nuclear Acid Amplification Test (CBNAAT) of sputum also called Xpert MTB/RIF looks convincing as a good diagnostic method for the purpose of diagnosing or ruling out pulmonary tuberculosis. Endorsed by WHO in 2011, it is a fully automated, closed system that performs real-time PCR and can be used by operators with minimal technical expertise, enabling diagnosis of TB and simultaneous assessment of rifampicin resistance to be completed within 2 hours. World Health Organization currently recommends that CBNAAT *may* replace smear in this way in any patient and *should* do so for those with suspected multidrug resistant MDR TB or HIV associated TB[(9)] Therefore, Xpert assay is strongly recommended as the initial diagnostic test in individuals suspected of having multidrug resistant (MDR) TB and in those with HIV/TB co infection. It is also recommended as a follow-on test in TB-suspected patients with acid-fast negative sputum smear. This study, therefore, was conducted to evaluate diagnostic performance of Xpert MTB/RIF assay in northern India on patients with clinically suspected pulmonary tuberculosis.

MATERIAL AND METHODS

Study Design: We conducted a cross sectional study at CHC Katra, a block level Hospital of District Reasi, Jammu and Kashmir between January 2018 to December 2018. The study included the entire population above ten years of age who were presumptive pulmonary tuberculosis, which was defined as having 2 or more of the following symptoms: fever and/or cough for more than 2 weeks, significant weight loss defined as loss of more than 5% weight as compared to the highest weight recorded in last three months, pleuritic chest pain, hemoptysis, and with or without abnormal chest radiograph compatible with pulmonary tuberculosis (cavitary lesion, infiltration, and miliary pattern). Patients with history of receiving antituberculous drugs within 3 months before enrollment were excluded.

Specimen Collection and Processing: Two specimens of expectorated sputum were collected from the eligible patients. Sputum smear for acid-fast bacilli was performed on fresh specimen at the designated microscopy centre of CHC Katra Hospital. The positive smears were sent for CBNAAT, the centre for which is located at Udhampur District. Sputum specimens of the smear negative patients

who were strongly suspected for PTB based on history, clinical examination, chest radiography and/or history of close contact with microscopically confirmed case of PTB were also sent for CBNAAT. The method was performed according to manufacturer's instruction of Xpert MTB/RIF. Sputum acid-fast smear results were categorized into positive (reported AFB found per field as 1+, 2+, 3+, and 4+) or negative. Sputum Xpert MTB/RIF results were also categorized as positive or negative.

The age, sex, past medical history of lung diseases and HIV serostatus of all the patients were recorded. Clinical data including fever, days of fever, chest pain, dyspnea, hemoptysis, weight loss, cough, and the extrapulmonary sites of tuberculosis were collected.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Xpert were compared to sputum smear positive tuberculosis.

RESULTS:

Out of 305 presumptive cases of pulmonary TB who were tested for sputum by smear microscopy, acid fast bacilli were detected in 17 cases only giving a sensitivity of 5.6%. The sputum specimen of these positive patients was subjected to Xpert MTB/RIF to detect rifampicin resistance. So, remaining 288 sputum smear negative patients, the sputum specimens of 38 patients were also sent for CBNAAT. So a total of 55 sputum specimens were sent for Xpert MTB/RIF which yielded positive result in 24 specimens (with sensitivity of 43.63%). All smear positive patients were also found positive on CBNAAT.

Regarding age and sex distribution of 55 cases whose sputum specimens were sent for CBNAAT examination, males were more in no. as comapared to females.There were 36 males(65.4%) and 19 females (34.6%)with M:F ratio of 1:1.9.Maximum patients belonged to age group of more than 40 years(49%).(Table 1)

Senstivity of CBNAAT in detecting true positive Tuberculosis cases was 100% and specificity i.e ability to exclude true negative cases was around 81.6% in comparison to sputum smear examination. Positive Predictive Value of CBNAAT was 70.8% where as Negative Predictive Valuewas 100%. (Table 2)

Nine patients had underlying lung disease while none of the patient was HIV positive. The median time to get results from Xpert assay was 4 days. Four patients were found multi drug resistant out of which 1 patient died, 1 patient was lost to follow up and remaining two were responding to the treatment.

DISCUSSION

The most important factor in decreasing the burden of TB is early diagnosis and early management in order to prevent the further spread of this disease. But even today, the diagnosis of TB remains elusive. Smear microscopy is the cornerstone for the diagnosis of TB in resource-limited settings but it has only modest (35-80%) sensitivity and a poor positive predictive value (PPV)[10] Culture is the "gold standard" for final determination, and also permits drug susceptibility testing. However, it remains largely inaccessible in resource limited settings as a result of infrastructure and financial limitations. Even where accessible, culture results are typically not available for 2-6 weeks. Diagnosis through either smear or culture requires multiple steps that significantly impede program effectiveness.

A meta-analysis from 27 studies showed that Xpert assay of respiratory specimens had a pooled sensitivity of 89% and specificity of 99% in diagnosing PTB [11] Data from several studies in culture-proven TB patients with acid-fast positive sputum specimens showed that Xpert assay had a pooled sensitivity of 98% (95% CI 97%, 99%) in the detection of *M. tuberculosis* [12]. In the present study the sensitivity of Xpert assay to detect *M. tuberculosis* was 100% in acid-fast positive sputum specimens. This finding confirmed that it is unlikely for Xpert MTB/RIF to miss the diagnosis of TB in patients with positive sputum acid-fast smear. In another study done in Bihar, the use of CBNAAT for the rapid detection of TB has increased by 21%.[13]

The difference in sensitivity of Xpert assay in detecting M.tuberculosis can be attributed to the variations in the inclusion criteria of different studies. Patients with minimal symptoms or normal chest X-ray may have low bacillary load and can result in higher rates of negative results from Xpert assay.

In the present study,Majority of cases were from rural areas. Most common symptom in our study was cough (82.2%) followed by fever (73.4 %). In a similar study from France Le Palud et al. in 2014 found cough (51.9%) as the main symptom followed by general symptoms (45.1%). [14]

DRAWBACKS

Sample size was much less as compared to other studies. Sputum culture was not routinely done in all cases.

CONCLUSION:

This study showed that Xpert MTB/RIF is highly sensitive in detecting M. tuberculosis from respiratory specimens and very valuable in making a rapid diagnosis and initiating early treatment of tuberculosis in sputum smear negative cases. It has an added advantage of detection of multi-drug resistant cases

Table 1 Age and Sex wise distribution of cases

Age(years)	Males n(%)	Females n(%)	Total n(%)
10-20 years	7(58.3%)	5(41.7%)	12(21.8%)
20-40 years	9(56.3%)	7(43.7%)	16(29.0%)
>40 years	20(74.1%)	7(25.9%)	27(49.5%)
Total	36(65.5%)	19(34.5%)	55(100%)

Table 2 Sensitivity and Specificity of CBNAAT in relation to Sputum Smear Examination

	Sputum Smear Examination			
CBNAAT		TB Positive	TB Negative	Total
	TB Positive	17	7	24
	TB Negative	0	31	31
	Total	17	38	55

Senstivity of CBNAAT= 17/17× 100= 100%
Specificity of CBNAAT= 31/38× 100= 81.6%
Positive Predictive Value of CBNAAT= 17/24× 100=70.8%
Negative Predictive Value of CBNAAT= 31/31× 100=100%

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