ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIAGNOSTIC ROLE OF CBNAAT IN SPUTUM SMEAR NEGETIVE/NON-PRODUCTIVE SPUTUM PATIENTS WITH CLINICO-RADIOLOGICAL SUSPICION OF PULMONARY TUBERCULOSIS.

Pulmonary Medicine

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ABSTRACT

Background:- Mycobacterium tuberculosis remains leading cause of death from an infectious agent. Rapid diagnosis of tuberculosis and detection of Rifampicin (RIF) resistance are essential for effective disease control and management. CBNAAT (Cartridge Based Nucleic Acid Amplification Test) also known as Gene Xpert MTB/RIF assay is the new cutting edge integrated diagnostic modality for diagnosis of tuberculosis and rapid detection of RIF resistance if any in clinical specimens. Also has role in patients who are sputum smear negetive or have non-productive sputum but are clinico-radiologically suspicious of pulmonary tuberculosis.

Materials and Methods:- A total of 100 patients were retrospectively assessed who had sputum for AFB negetive and or were non-productive of sputum and were clinico-radiologically suspected of pulmonary tuberculosis. All patients who do not have contraindications to bronchoscopy were subjected to procedure and bronchial aspirate was obtained. Smear and CBNAAT examination of aspirate was done.

Results:-Out of total 100 patients 57% were males and 43 were females,70% patients came from rural areas ,Cough 82% was most common presenting symptom, Most common radiological abnormality was consolidation 35%, 52% patients were labelled as microbiologically confirmed cases of pulmonary tuberculosis of which BAL smear positives were 7% and BAL smear negetive but CBNAAT positive cases were 45%.

Conclusion:- CBNAAT done on broncho-alveolar lavage fluid obtained via bronchoscopy can be an important adjunct to bacteriological confirmation of suspected cases who were otherwise sputum negative or not productive of adequate sputum sample. Also resistance to rifampicin can be detected prior to the treatment.

KEYWORDS

Cartridge based nucleic acid amplification test, Acid fast bacili, Bronchoscopy

Introduction:-

Tuberculosis is a major health problem worldwide .Almost 50% of patients are negative in smear microscopy. For several decades, smear microscopy and conventional culture techniques have been mainstay of diagnostic testing. While smear microscopy has poor sensitivity and issues related to quality control, conventional cultures have a long turnaround time of 6-8 weeks. GeneXpert/CBNAAT/MTB/RIF is an automated, real time PCR that detects MTB and also test for rifampicin sensitivity using molecular beacons. Both results are available in 90 minutes. Various methods have been used in smear negative cases to obtain material for other modalities of investigation to diagnose PTB.

In developed countries, FOB (fibreoptic bronchoscopy) is considered a good option for cases that pose a diagnostic challenge, although smear exhibits a low sensitivity on FOB samples, i.e. 5.35% on aspirates and 10-30% on BAL (Pierre, et al)[1].

Since December 2010, WHO has recommended the GeneXpert MTB/RIF assay for sputum samples, but no specific recommendation is there for FOB samples. FOB sampling with Xpert outperforms smear with a sensitivity around 80% (Pierrre, et al)[1]. BAL Xpert when compared to culture as a reference standard has a sensitivity, specificity, PPV and NPV as 91.86%, 71.42%, 97.53% and 41.66% (Kanwal, et al)[2].

Materials and Methods:-

This is a retrospective study conducted in 100 patients who were clinicoradiological suspects of pulmonary tuberculosis with atleast two initial sputum smear negative samples with prior history of ATT were studied during the period from March 2017 to March 2018 in the Department of Respiratory medicine, Mahatma Gandhi Medical College and Hospital, Jaipur, .

Inclusion Criteria

Patients with clinical suspicion of PTB based on symptoms (e.g., cough more than two weeks, hemoptysis, fever, asthenia, loss of weight and night sweats) or radiological features (e.g., nodule, consolidation, cavation and other opacities) who either have a negative sputum AFB smear microscopy or were unable to produce sputum were included in the study.

Exclusion Criteria

Sputum positive cases, isolated extra-pulmonary tuberculosis, HIV positive patients and patients not fit for bronchoscopy procedure, e.g. those having refractive hypoxemia, bleeding disorders, cardiovascular instability, status asthmaticus and marked hypercapnia were excluded from the study.

Results:-

Out of total 100 patients who were sputum smear negative and clinico-radiological suspects of PTB ,maximum 57 % of patients were males, most patients 67% belonged to rural areas ,Cough 72% was most common presenting symptom followed by fever 52%,weight loss 40%, night sweats 22% and lastly hemoptysis 10%. Most common radiological abnormality in our study was Consolidation which was seen in 35% of patients, nodules 15%,cavity 12%, fibrosis 8%,interstitial shadows 5%,mass 3%,non-specific/mixed findings 20% of patients. Out of total 100 patients 52 patients were diagnosed and labelled as microbiologically confirmed cases of pulmonary tuberculosis of which BAL smear positives were 7% and BAL smear negetive but CBNAAT positive cases were 45%.Lastly because of dual diagnostic advantage of CBNAAT rifampicin resistance was detected in 5 % of cases. Rest 48 patients were kept in follow-up on antibiotic therapy, on the basis of BAL culture and sensitivity report and majority of them improved

Demographic features (N-100)

Characteristic	Frequency (N)	Percentage (%)
Males	57	57
Females	43	43
Rural	67	67
Urban	33	33

Clinical Profile of patients

Symptoms	Percentage (%)
Cough	72
Fever	52
Weight loss	40
Night sweats	22
Hemoptysis	10

Profile of Radiological abnormality of patients

Abnormality	Frequency (N)	Percentage (%)
Consolidation	35	35
Mixed/Non-specific Findings	20	20
Nodules	15	15
Cavity	12	12
Fibrosis	8	8
Interstitial Shadows	5	5

Final yield of diagnostic tests

Test	Frequency(N)	Percentage (%)
Total Bacteriologically confirmed cases of PTB	52	52
BAL Smear Positive	7	7
BAL Smear negetive but CBNAAT Positives	45	45
R-Resistant Cases	5	5
Total	52	52

CBNAAT VS Smear Microscopy

Total Suspected cases	Sputum Smear Positive	BAL Smear Positive	CBNAAT Positive	Total Bacteriological Yield
100	0	7	45	52

Discussion :-

Early diagnosis of PTB by smear microscopy is the approved method.

Smear negative and culture positive state is observed in 22-61% (J.Balakrishna ,et al)[3]. Mycobacterial culture is gold standard which requires good quality sputum and a turnaround time of 6-8 weeks.

Causes of SSNPTB (sputum smear negative PTB) include poor quality sputum and low bacterial load. Smear negativity is also seen in the immunosuppressed and paediatric population. Because mortality rate for smear negative and culture positive cases is around 14% and 50% need chemotherapy by 12 months, it is very important to diagnose SSN-PTB cases and to break the chain of transmission. The various methods used in SSNPTB cases include Sputum Induction (SI), gastric lavage, TTNA (transthoracic needle aspiration), bronchoscopy (bronchial aspirate, washing, BAL) and samples so collected to be subjected to smear, culture, histopathological study and molecular methods. Sputum smear negative pulmonary tuberculosis constitutes about 50% of all new cases of pulmonary tuberculosis. Although the relative transmission rate of smear negative tuberculosis is lower than that of smear positive cases, it is still responsible for 17% of tuberculosis transmission[4].

Conventional laboratory techniques like direct microscopy are less sensitive and going for culture is a time consuming process for the diagnosis of tuberculosis. Therefore it is the need of time to develop new techniques for rapid identification of the Mycobacterium tuberculosis in pauci-bacillary samples. Recently, attention has been devoted to latest nucleic acid amplification diagnostic processes due to their speed and accuracy.

In our study out of total cases, 57% were male while 43% population were of female. Majority of patients belonged to rural (67%) as compared to urban (33%). Most common symptom in our study was cough (72%) followed by fever (52 %). 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%)[5].

Most common radiological abnormaily was consolidation (35%) and mixed findings (20%),Nodules 15%. whereas in study by Le Palud et al. nodules (53.7) were the most common radiological finding[5] .

Out of 100 clinico-radiologically suspected patients, only 7 were BAL smear positive while another 45 were further detected by CBNAAT giving a total bacteriological yield of 52. Out of 45 CBNAAT positive samples, 5 were resistant to Rifampicin. Raquel Moure et al. in their research in 2012 concluded that out of 108 smear-negative extrapulmonary samples 58.3% were positive with the Xpert MTB/RIF assay (GX) for Mycobacterium tuberculosis[6]. In a similar study by Vadwai in 2011, the sensitivity of the Xpert assay was 64% for smear-negative cases[7]. Our results are little lower than these two study likely because we did not perform CBNAAT on BAL smear AFB positive samples and our sample size was much less as compared to other studies. Out of total 100 patients 52 patients were diagnosed and labelled as microbiologically confirmed cases of pulmonary tuberculosis of which BAL smear positives were 7% and BAL smear negetive but CBNAAT positive cases were 45%.Lastly because of dual diagnostic advantage of CBNAAT rifampicin resistance was detected in 5 % of cases.

Conclusion:-

Our study confirmes diagnostic utility of Xpert® MTB/RIF assay (CBNAAT), compared to Smear Microscopy, for early diagnosis of suspected pulmonary TB requiring fibre-optic bronchoscopy, performed on per procedure samples. Gene Xpert MTB/RIF assay is efficient and reliable technique for detection of rapid smear negative cases. Its simplicity, sensitivity, speed and automation, makes this technique a very efficient tool for diagnosis of Mycobacterium tuberculosis from smear negative cases of TB suspects with a added advantage of detection of multi-drug resistant cases.

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