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A STUDY ON SENSITIVITY AND SPECIFICITY OF BAL CBNAAT WITH RESPECT TO DURATION OF SYMPTOMS IN PRESUMPTIVE PULMONARY TB.

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ABSTRACT Diagnosis of paucibacillary pulmonary tuberculosis poses significant clinical challenge. There is paucity of the literature regarding the relationship between sensitivity of a diagnostic tool like CBNAAT (Catridge based nucleic acid amplification test) in relation to duration of the disease. In our study we found progressively increasing sensitivity of CBNAAT with increasing duration of the symptoms.

KEYWORDS :

INTRODUCTION:

Tuberculosis (TB) is a global health problem. India has the highest burden of TB constituting one fourth of world's TB cases. It is estimated that 40% of Indian population is infected with TB bacilli.[1] Smear positive patients expectorate 10^8 -10^{10} bacilli per mililitre (ml) and a smear negative patient expectorate less than 10^3 bacilli per ml of the sputum. Diagnosis in the later poses clinical challenge. The diagnosis of pulmonary TB often delayed in these smear negative cases and if left untreated, 70% progress to active disease in 12 months.[2] Early diagnosis of smear negative pulmonary TB and initiation of Anti tubercular therapy (ATT) ensures cure, reduces morbidity and prevents transmission of the disease.

Sensitivity and specificity of Catridge based nucleic acid amplification test (CBNAAT) on sputum samples in detecting smear negative pulmonary TB for is 67% and 98% respectively.[3] When compared to the smear microscopy it is more sensitive and also has added benefit of detecting drug resistance. Sensitivity and specificity of CBNAAT on broncho alveolar lavage (BAL) of patients on smear negative patients is 65% to 80% in different studies[4,5]. Hence CBNAAT is a crucial tool in the early diagnosis of pulmonary TB.

However there is a paucity of the literature regarding the relationship between sensitivity of a diagnostic tool like CBNAAT in relation to duration of the disease. This relationship might give a possible "window period" phenomenon for this diagnostic tool. This will help the clinician to recommend the the best diagnostic tool in relation to the time frame of presentation. In this study an attempt is made to find the sensitivity , specificity of BAL CBNAAT with respect to duration of the disease in smear negative presumptive pulmonary TB patients.

MATERIALS AND METHODS:

After obtaining institutional ethical clearance, we retrospectively analysed the data of 99 presumptive pulmonary TB patients who had TB symptoms whose sputum smear was negative. This study included patients presented over a period of 2 years. Patients with any of the signs and symptoms suggestive of TB including cough more than 2 weeks, significant weight loss ,hemoptysis and any abnormality in chest radiograph was considered as presumptive pulmonary TB case. Based on the duration of the presentation, patients were divided into three groups . Group A: Symptoms duration less than 15 days , Group B: Symptom duration between 15 and 30 days, Group C: symptom duration more than 30 days. All patients had undergone flexible video bronchoscopy, and BAL was collected from the affected site. BAL was subjected to CBNAAT and liquid blood culture with mycobacteria growth indicator tube (MGIT BACTEC). The primary objective was to estimate the sensitivity and specificity of the CBNAAT in smear negative presumptive pulmonary TB patients in relation to duration of symptoms.

The statistical analysis was performed on STATA 11.2 (College station TX USA) and SPSS version 20. Validation of CBNAAT was based upon sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) in comparison to the gold MGIT BACTEC.

RESULTS

A total of 99 subjects data was analyzed retrospectively. 72 patients were males , 27 were females with mean age of 44.02 yrs . Past history of pulmonary TB was present in 3 patients. Co morbidity like diabetes, alcoholic liver disease, bronchial asthma was present in 9 patients.

Group wise distribution of subjects is shown in Figure 1. Sensitivity, Specificity, PPV and NPV of CBNAAT compared to the gold standard BACTEC was calculated. Sensitivity of the CBNAAT was 50%, 62.5% and 72% in Group A, B and C respectively. Specificity of CBNAAT was 100%, 88.89% and 88.89% in Group A, B and C respectively. (Table 1). Sensitivity and specificity trends across various groups shown in Figure 2. Sensitivity, specificity , PPV and NPV across various groups shown in Figure 3.

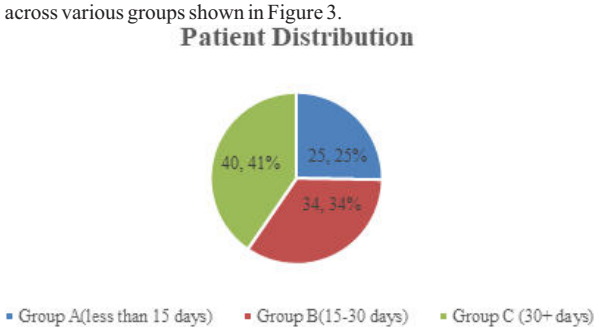

Figure 1. Showing Distribution Of Group Wise Subjects

Table 1. Showing Sensitivity And Specificity Of CBNAAT In Comparison To BACTEC

	Group A (less than 15 days)	Group B (15-30 days)	Group C (30+ days)	Overall
Sensitivity	50.0%	62.50%	72.00%	67.50%
Specificity	100.0%	88.89%	88.89%	93.22%
PPV	100.00%	83.33%	88.89%	87.10%
NPV	95.83%	71.43%	72.73%	80.88%

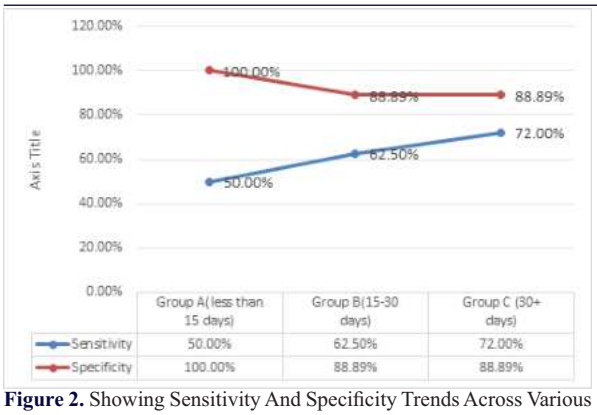

Figure 2. Showing Sensitivity And Specificity Trends Across Various Groups

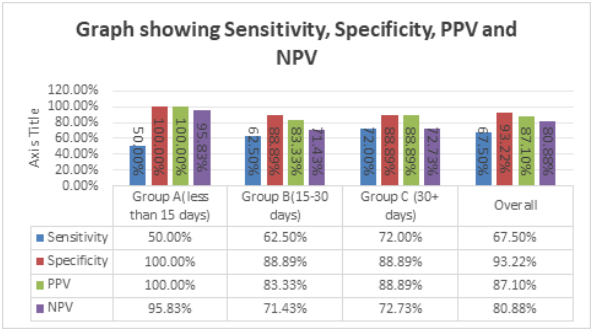

Figure 3. Showing Sensitivity, specificity , PPV and NPV across various groups

DISCUSSION

Sputum smear negativity in patients with pulmonary TB is due to various factors. Patients intrinsic factors like inability to produce sputum, absence of cough as a predominant symptom, good host immune response and extrinsic factors like wrong sampling techniques, errors in processing the lab samples and poor reporting. All these may lead to smear negativity.[6] To increase the yield of TB detection, bronchoscopy and BAL analysis is recommended.

Bacillary load is an important entity in sputum smear microscopy as the number of bacilli in the sputum is vital for diagnosis in smear cytology. Pathogenetically, in the initial phase of the disease, the bacterial multiplication occurs. But late in the disease, bacilli becomes intracellular and gets hidden in preferential locations in the lung. The number of bacilli getting expectorated in the sputum depends on lesion proximity to the air column. Sputum scarce patients and smear negativity has impeded the early identification of the disease. This phenomenon might be explained by the limited amount of sputum production and hidden areas of bacteriological development.

Bacterial load increases with the duration of the disease especially in smear positive pulmonary TB. A study by Heslop et al, showed that in patients with pulmonary TB, there will be more pronounced changes in the immune response in lung during infection which can be measured accurately in sputum samples from the site of infection rather than monitoring the concentration of cytokines in the blood[7]. That indicates sputum/BAL bacterial load would be the surrogate marker for severity of disease.

Literature review shows no correlation between duration of the disease and bacterial load. TB bacilli being predominantly intracellular, host defence might limit its free presence within airway. Host defence further limits the organisms within the cavity or central part of the granulomas.[8]

CBNAAT has been found to be a useful tool in diagnosing smear negative pulmonary TB [9,10,11]. Its utilisation for diagnosis in smear negative and sputum scarce cases has increased the identification of TB cases missed by sputum microscopy alone. Its additional advantage of diagnosing rifampicin sensitivity early in the disease has significant impact in the management of the disease. Its principle in identification of nucleic acid of the bacilli makes it one of the important diagnosing tool. It has been noted in the literature that CBNAAT can detect bacilli as low as 131 colony forming units CFU/ml[12].

In various studies By Patil Shital et al ,Theron et al , Bernard D et al showed sensitivity of CBNAAT on BAL of smear negative presumptive pulmonary TB ranges from 90% to 93% and specificity ranges from 90% to 95%. Though, our study sensitivity was less in comparison to above studies, specificity remained same[9,10,11].

Being a highly sensitive test a negative CBNAAT result in smear negative pulmonary TB raises question on possible existence of a Clinical Window period. The efficacy of CBNAAT in the quantitative assessment of the bacterial load in the diagnostic period, early or late both in smear positive and smear negative cases is not available. In our study we found the sensitivity of the CBNAAT increased with the duration of the disease from 50% in patients with less than 15 days duration of symptoms to 62.5% in patients with duration 15days to 30 days , to 72% in more than 30 days symptom duration. Specificity decreased with the duration of the disease.

Failure of detection of mycobacteria by the CBNAAT early in the disease puts the clinician in a dilemma as to the decision to initiate ATT based only on clinical observations. If CBNAAT test results are negative during evaluation early in the disease, it can be recommended to repeat the test a later again if there is strong clinical suspicion.

Limitations Of The Study:

This was retrospective analysis of previously collected data. CBNAAT sensitivity and specificity was assessed in different patients with reference to the duration of presentation, and not longitudinally in the same patients, which would have been the best way, but clearly not possible for various reasons. Bacteriological load in terms of low, medium or heavy in CBNAAT was not recorded with the results. Only "positive" or "negative" were recorded the case profile.

Scope For Future Research:

Assessment of the CBNAAT in individual smear negative patients at different time frames of the disease might give more insight into the possible window phenomenon. Newer diagnostic modalities like GeneXpert ultra will improve the positivity of diagnostic test in smear neative pulmonary TB cases.

CONCLUSION:

In smear negative presumptive pulmonary TB subjects, progressively increasing sensitivity of CBNAAT was found with increasing duration of the symptoms, with mycobacterial BACTEC culture being considered as the gold standard.

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