Original Article

DOI: 10.7860/JCDR/2022/50922.15909

Bronchial Hyper-responsiveness in Post-tubercular Patients: A Case-control Study

Internal Medicine Section

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ABSTRACT

Introduction: Bronchial hyper-responsiveness is the manifestation of excessive bronchoconstriction in response to diverse types of stimuli both physical and chemical. It is the most characteristic feature of bronchial asthma; it also occurs in a spectrum of other diseases like Chronic Obstructive Pulmonary Disorders (COPD) and reactive airway syndrome and may be provoked by a variety of stimuli like histamine and methacholine. Patients of healed pulmonary Tuberculosis (TB) show varying extent of lung impairment such as fibrosis, collapse, emphysema and broncho alveolar destruction.

Aim: To assess the incidence and severity of obstructive airway diseases in previously treated TB patients.

Materials and Methods: This was a prospective case control study, carried out in the Department of Tuberculosis and Respiratory Diseases, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India, from September 2017 to September 2019, this study included 120 patients of previously treated TB, who were divided into two groups. The case group (71) included patients who completed treatment for TB and had dyspnoea. The control group (49) consisted of patients who completed the treatment but did not have dyspnoea. The patients were subjected to spirometry, histamine bronchial challenge test and computed chest tomogram along with routine investigations including sputum for Acid Fast Bacilli (AFB).

Results: The present study showed significant histamine hypersensitivity among post TB patients. In the case group, 34 (56%) patients showed positive response to bronchial challenge test with histamine; while in control group only 7 (14%) showed a positive response (p-value=0.004). Pulmonary function test (spirometry) showed an obstructive pattern in 35 (49%) case group patients, while normal pattern was the most common finding seen in 23 (47%) in the control group followed by obstruction in 10 (21%) patients. Among the cases, the mean Forced Expiratory Volume in the first second (FEV1) was 65.77±15.98, while among the controls, it was 80.02±8.81. The case group had a mean Forced Expiratory Volume in the first second/Forced Vital Capacity (FEV1/FVC) of 78.09±15.75, as against 81.33±16.79 in the control group.

Conclusion: Airway bronchial hyper-reactivity is a prominent feature in previously treated tubercular patients. This underlines the need for proper attention towards post-tubercular lung function impairment and proper treatment of such patients so as to lessen the impact of bronchial hyper-reactivity on patient symptoms and their quality of life.

Keywords: Histamine challenge test, Pulmonary function tests, Reactive airway dysfunction syndrome

INTRODUCTION

Post-tubercular lung impairment is a distinct entity, marked by involvement of both small and large airways in the form of bronchial asthma, bronchiectasis, obstructive lung disease. The most frequently seen lung damage occurring after pulmonary Tuberculosis (TB) are bronchiectasis, Chronic Obstructive Pulmonary Disorders (COPD), emphysema [1] but not much recommendations are available for management of post TB lung impairment, which is one of the contributing factor for global burden of COPD [2]. This can be linked to the host-pathogen interaction and various immunological events that follow afterwards. The post-tubercular lung diseases have varied presentation in the form of fibrosis cavitation or collapse. Chronic lung disease is the fourth leading cause of mortality worldwide hence, an important health concern [3].

Pulmonary TB is found to result in chronic lung impairment in the form of fibrosis cavity or granuloma formation which causes mucosal oedema, hypertrophy and hyperplasia of mucous glands and decreases airflow [4] due to mechanism of cicatricial fibrosis, there is also a decrease of total lung capacity. Post TB patients may have restricted exercise tolerance and significant debility which may affect routine activities. Pulmonary function in persons with pulmonary TB showed variable patterns and severity of impairment [2]. Pulmonary function studies can demonstrate restrictive, obstructive, or mixed patterns and range from normal to severe impairment. Bronchial Hyper-Responsiveness (BHR), sometimes mentioned as airway hyper-responsiveness, is the manifestation of excessive bronchoconstriction in response to a number of inhaled stimuli, both chemical and physical [1,5,6].

Broadly used as an objective measure of variable airflow, BHR is observed as a 'hallmark' or 'defining feature' of asthma. Though, BHR also occurs in other lung diseases like (COPD, cystic fibrosis), it is frequently noticed in atopic persons, in patients with rhinitis but without pulmonary symptoms, in smokers and ex-smokers, after respiratory infections and following acute inhalation exposure to toxic chemicals [7]. It is also seen in asymptomatic non smoking members of the general population [8]. The BHR testing has played an important part in the diagnosis of airway diseases such as asthma, Reactive Airway Dysfunction Syndrome (RADS) and COPD.

Post-tubercular patients present with obstructive airway diseases like asthma, reactive airways syndrome, COPD like illness. Mycobacterial infection may be the cause of increased bronchial reactivity in such patient groups. The BHR provides useful insight into pathology of airway diseases. Airway hyper-responsiveness to non specific stimuli may arise from bronchial inflammation [9]. The BHR in bronchial asthma is diffuse and characterised by epithelial detachment while bronchial inflammation is mostly limited in post TB patients [1]. Studies have shown an increased incidence of BHR in patients of endobronchial TB [1,10] but not exactly bronchial

hyper-respnsiveness. The mechanism is not known but it may be due to exposure of irritant receptors, the main inflammatory cells are mast cells and eosinophils in bronchial asthma while lymphocytes are the predominant cells in endobronchial TB (type 1 helper cells) [11]. The present study aimed to assess the incidence and severity of obstructive airway diseases in previously treated TB patients.

MATERIALS AND METHODS

This was a prospective case-control study, carried out in the Department of Tuberculosis and Respiratory Diseases, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India, from September 2017 to September 2019. Ethical clearance was taken vide letter number 1024/FM dated 13/07/18. All patients signed an informed voluntary consent. All patients who fulfilled the inclusion criteria during the study period were taken as case groups, this way 120 patients were enrolled for the study.

Inclusion criteria: All patients above 18 years or more, previously treated for pulmonary TB were taken as case group, assessed from their treatment history, chest X-ray changes in the form of calcification, collapse or fibrosis, along with two consecutive smear negative sputum samples to ensure that no active case of TB was recruited for study.

Exclusion criteria: The patients with history of current or previous smoking, history of occupational exposure control group, history of asthma and Chronic Obstructive Pulmonary Disease (COPD), before receiving antitubercular treatment. Ischaemic heart disease, interstitial lung disease, active pulmonary TB, family history of atopy or bronchial asthma, severe airflow obstruction baseline Forced Expiratory Volume in the first second (FEV1) <50% predicted, uncontrolled hypertension, systolic Blood Pressure (BP) >200, and diastolic BP >120 mmHg, known aortic aneurysm were excluded from the study.

All patients who fulfilled the inclusion criteria during the study period were taken as case groups, this way 120 patients were enrolled for the study. The patients were divided into two groups-those who had dyspnoea (symptomatic case group) and others who did not have dyspnoea (asymptomatic, control group), as assessed by their pulmonary function tests. There were 71 patients in case group and 49 patients in the control group. Of these 120 patients bronchial challenge test with histamine was performed in 110 patients, as 10 patients (eight patients of severe obstruction and two patients of very severe obstruction) had baseline FEV1 <50% of predicted value which is a contraindication for histamine challenge.

X-ray chest, sputum Acid Fast Bacilli (AFB) and pulmonary function testing was done in all patients. Interpretive algorithms were used in defining restrictive or obstructive patterns and spirometry results were analysed and classified in four groups as follows [20]:

1. **Normal:** Forced Expiratory Volume in the first second/Forced Vital Capacity (FEV1/FVC) ratio of >70% and an Forced Vital Capacity (FVC) of >80% predicted.
2. **Obstructive:** Airway obstruction was defined as an FEV1/FVC ratio of <70% and an FVC of >80% predicted.
   - **Mild obstruction:** FEV1 ≥80% of predicted; FEV1/FVC <70%
   - **Moderate:** FEV1 ≥50% - ≤80% predicted; FEV1/FVC <70%
   - **Severe:** FEVI <50% predicted; FEV1/FVC <70%
3. **Mixed:** Combined defects were FVC of <80% predicted and an FEV1/FVC ratio of <70%.
4. **Restrictive:** Defects as FEV1/FVC ratio of >70% with an FVC of <80% predicted.

Bronchial challenge test is usually performed either to confirm or exclude airway hyper-responsiveness. The test implies administering a substance in increasing dosages (usually methacholine or histamine) to evoke a response that is measured after each new concentration. Certain medications were avoided before bronchial challenge testing, as stated in [Table/Fig-1].

Medications	Time interval prior to test procedure
Short acting inhaled bronchodilators (e.g., albuterol, terbutaline)	8 hours
Medium acting inhaled bronchodilators (e.g., ipratropium)	24 hours
Long acting inhaled bronchodilators (e.g., formoterol, tiotropium)	48 hours
Long acting theophylline	48 hours
Hydroxyzine and cetirizine	72 hours
Leukotriene modifiers	24 hours
Coffee, tea, cola	Day of procedure

[Table/Fig-1]: Instructions before test.

Procedure

Two alternative dosing protocols have been recommended by ATS [8] and the European Respiratory Society (ERS) [12], one using a two minute tidal breathing exposure from a nebuliser and the other five deep (i.e., total lung capacity) breaths from an inhalation dosimeter with a five seconds breath hold. The tidal breathing approach elicits greater bronchial responsiveness and yields higher rates of positive tests. In the present study, the two minute tidal breathing exposure of histamine from a nebuliser machine was given. All patients included in the study underwent baseline spirometry on a spirolab-3 spirometer. Patients having baseline FEV1 >50% predicted value were subjected to bronchial challenge testing. The dose of histamine ranged from 2 to 8 mg/mL. The two minute tidal breathing exposure method was used with serial doubling concentrations of histamine (2, 4, 8 mg/mL) that were freshly prepared prior to each test and delivered through a nebuliser machine to the patients. Pulmonary Function Tests (PFT) was performed 30 seconds and 90 seconds after each histamine dose, drop in FEV1 was observed. After each inhalation, the patient was questioned about symptoms such as chest tightness and wheezing. The test was stopped when atleast 20% fall or more in FEV1 from baseline was observed or the patient developed symptomatic bronchospasm. The later was reversed using salbutamol inhaler. If a 20% fall in FEV1 was not recorded even with 8 mg/mL histamine, a higher concentration was not given. Patients who showed a 20% or more fall in FEV1, from baseline were classified as positive for bronchial challenge test and those who did not show 20% or more were classified negative for bronchial challenge test [12].

STATISTICAL ANALYSIS

Differences in categorical data were compared using R and Excel software. The results were presented as mean±SD or percentage. Differences in categorical data were compared using chi-square test and a p-value <0.05 was considered as statistically significant.

RESULTS

A total of 120 patients of previously treated pulmonary TB were included in the present study. There were 71 symptomatic patients in the case group and 49 asymptomatic patients in the control group.

The patient's age ranged from 19 years to 53 years, with the mean being 38.27 years. Among the cases, the mean FEV1 was 65.77±15.98 while among the controls it was 80.02±8.81. The case group had a mean FEV1/FVC of 78.09±15.75 as against 81.33±16.79 in the control group [Table/Fig-2].

Variables	Case (n=71)	Control (n=49)	Total (N=120)	p-value (Chi-square)
Age (years) Mean±SD	40.58±8.25	34.92±10.15	38.27±9.45	<0.001
FEV1% Mean±SD	65.77±15.98	80.02±8.81	71.59±15.2	<0.001
FEV1/FVC Mean±SD	78.09±15.75	81.33±16.79	79.42±16.19	<0.001

[Table/Fig-2]: Age and baseline spirometry of case and control groups.
p-value <0.05 was considered statistically significant

The most common finding on spirometry in case group was obstructive pattern, seen in 37 (52%) patients. In the control group, normal pattern was the most common finding, seen in 23 (47%) patient [Table/Fig-3].

Pattern	Case n (%)	Control n (%)	Chi-square	p-value
Normal	20 (28.16)	23 (46.93)	12.517	0.005
Obstruction	37 (52.12)	8 (16.33)		
Mixed	9 (12.68)	7 (14.29)		
Restriction	5 (7.04)	11 (22.45)		
Total	71 (100%)	49 (100%)		

[Table/Fig-3]: Spirometry pattern of case and control groups.
p-value <0.05 was considered statistically significant

Out of 45 patients with obstructive pattern on spirometry, nine had mild obstruction. In the case group, 34 (56%) patients showed a positive response to bronchial challenge test with histamine whereas in the control group, only 7 (14%) patients showed a positive response to the bronchial challenge test. Total 26 had moderate obstruction, eight had severe obstruction and two had very severe obstruction [Table/Fig-4,5].

Severity of obstruction	Case n (%)	Control n (%)	Chi-square	p-value
Mild	4 (10.81)	5 (62.5)	11.642	**0.008**
Moderate	23 (62.16)	3 (37.5)		
Severe	8 (21.62)	0		
Very severe	2 (5.41)	0		
Total	37 (100)	8 (100)		

[Table/Fig-4]: Degree of airflow obstruction between case vs control groups.
p-value <0.05 was considered statistically significant

Bronchial challenge test	Case	Control	Chi-square	p-value
Positive	34 (55.7%)	7(14%)	21.77	**0.004**
Negative	27 (43.8%)	42 (86%)		
Total	61* (100%)	49 (100%)		

[Table/Fig-5]: Outcome of bronchial challenge test with histamine.
p-value <0.05 was considered statistically significant; *10 patients (severe and very severe obstruction) were not included

As shown in [Table/Fig-6], in case group baseline FEV1 predicted value was in the range of 55-87%, while in control group it was 62-95%. In case group, out of 61 patients, 34 showed equal to or more than 20% decline in FEV1 value from baseline whereas in control group out of 49 patients, sevene showed equal to or greater than 20% decline in FEV1 value from baseline after giving successive doubling concentration of histamine during bronchial challenge.

Bronchial hyper-responsiveness sometimes referred to as airway hyper-responsiveness is the occurrence of excessive bronchoconstriction in response to a variety of inhaled stimuli, both chemical and physical. Other than asthma, BHR is also found in COPD, cystic fibrosis, in atopic individuals, in patients with rhinitis (without pulmonary symptoms), in smokers and ex-smokers, after respiratory infections, after acute inhalation exposure to chemicals [7-9].

The present study revealed statistically significant bronchial hyper-responsiveness in those patients who were previously treated and have recovered from pulmonary TB. Out of the 71 cases, 34 patients (55.7%) showed positive response to the bronchial challenge test with histamine. Among the control group, 7 patients (14%) had bronchial hyper-responsiveness. The study findings are consistent with the study conducted by Park CS et al., [13]. Their study showed that 12 out of 15 patients who were previously treated for TB had bronchial responsiveness, which in turn was the reason for dyspnoea [13].

As per the study conducted by Riffo-Vasquez Y et al., Mycobacterium TB chaperonins like cpn60.1 and cpn10 can be potent Th1 inducers and may be responsible for bronchial hyper-responsiveness in patients with endobronchial TB [14]. Airway responsiveness to non specific stimuli may arise from bronchial inflammation [15,16]. In bronchial asthma, the airway inflammation was diffuse and characterised by epithelial detachment resulting in exposure of epithelial nerves [17]. In contrast, airway inflammation was rather focal and limited in EBTB patients when compared with bronchial asthma patients. The major inflammatory cells involved in bronchial asthma and EBTB are very different: mast cells and eosinophils in bronchial asthma and lymphocytes in EBTB. Of course, lymphocytes also participate in airway inflammation of the asthmatic airway, but their subtypes are different: type-2 helper cells in bronchial asthma [17] and type-I helper cells in EBTB [18].

According to the study conducted by Yuan YR et al., in 24 patients with confirmed diagnosis of endobronchial TB, as many as 41.7% of the patients were found to have BHR, which had never been recognised before. The patients with EBTB usually had severe cough (100%, 24/24), shortness of breath (54%, 13/24), and wheezing, but bloody sputum was found in only 21% (5/24), and so the patients tended to be misdiagnosed as having asthma, especially cough variant asthma. FEV(1%) in the group of EBTB with BHR was significantly higher than that in the group of EBTB without BHR (t=2.345, p-value <0.05). But there was no significant difference of FEV(1)/FVC%, MMEF%, V (75%) and Raw between the two groups. In the group of EBTB with BHR, FEV(1%) showed a negative correlation with BHR (r=-0.61, p-value <0.05), but there was no remarkable correlation between the other pulmonary function parameters with BHR [19].

Groups	Baseline FEV1(%) range value	Baseline FEV1/FVC range value	% decline in FEV1 after 2 mg/mL histamine		% decline in FEV1 after 4 mg/mL histamine		% decline in FEV1 after 8 mg/mL histamine		Number of patients showing equal to or >20% decline in FEV1 from baseline
			1-3%	4-7%	2-5%	6-9%	3-6%	7-10%	
Case (n=61)*	55-87	63-102	22%	39%	26%	35%	19 %	42 %	34
Control (n=49)	62-95	68-108	37 %	12%	39%	10 %	32 %	17 %	7

[Table/Fig-6]: Percentage decline in FEV1, from baseline predicted values after giving successive doubling doses of histamine during bronchial challenge in two groups.
*10 patients (severe and very severe obstruction) were not included

DISCUSSION

Even though bronchial hyper-reactivity is a characteristic feature associated with bronchial asthma, it can also be seen in post endobronchial TB patients. Hence, many patients with healed pulmonary TB present with asthma like symptoms. The present study aimed to assess incidence of bronchial hyper-responsiveness in previously treated pulmonary TB patients. It also aimed to detect the incidence of obstructive airway diseases in these patients and also to assess the severity of obstructive airway diseases in post TB patients.

Bronchial hyper-responsiveness is present in a considerable number of patients with EBTB, and therefore attention should be paid to the differential diagnosis of EBTB and cough variant asthma.

Limitation(s)

The sample size was relatively small as it is a single centre study, not all patients were easily convinced to undergo bronchial challenge test, and pulmonary function tests, when they completed anti TB treatment, similar studies on large number of patients are needed to properly assess influence of old pulmonary

TB and occurrence of airway hyper-responsiveness and its effect on patient conditions.

CONCLUSION(S)

The present study identified presence of bronchial hyper-responsiveness in post TB patients. The pulmonary impairment and clinical symptoms in follow-up patients of TB might be due to this bronchial hyper-responsiveness. The present study reveals significant prevalence of obstructive airway diseases in patients previously treated for pulmonary TB. Most of these patients have moderate to severe disease and they would get benefit from its early identification and appropriate treatment. This underlines the importance of follow-up in previously treated TB patients for long term assessment of obstructive airway disease.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 18, 2021
- Manual Googling: Nov 23, 2021
- iThenticate Software: Dec 28, 2021 (19%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 17, 2021**
Date of Peer Review: **Jul 26, 2021**
Date of Acceptance: **Dec 01, 2021**
Date of Publishing: **Jan 01, 2022**