The prevalence Aspergillus Skin Hypersensitivity in Patients of COPD versus healthy controls

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ABSTRACT

The prevalence of aspergillus skin hypersensitivity (AH) has been well studied in patients of bronchial asthma. However not many studies have evaluated the rate of AH in patients of COPD. The aim of this study is to assess rate of AH to common aspergillus antigens in patients of COPD normal healthy volunteers. The study was conducted on 100 patients of COPD and 100 normal healthy volunteers. 11% of the patients COPD showed AH positivity to aspergillus fumigatus and none of the controls were positive. Whenever suspected patients of COPD should be investigated for AH and Allergic bronchopulmonary aspergillosis (ABPA).

Introduction:

COPD is the leading cause of mortality and morbidity worldwide and results in economic burden that is both substantial and increasing. COPD is a result of cumulative exposure over decades. Often, the prevalence is directly related to the prevalence of tobacco smoking although, in many countries outdoor, occupational and indoor air pollution, latter resulting from burning of wood and other biomass fuels- are major COPD risk factors[1]. Prevalence of COPD in India is 5 percent in male and 2.7 percent in female population with a male to female ratio of 1.6:1[2].

Aspergillus is a ubiquitous mold representing between 0.1% and 22% of the total air spores sampled. There are approximately 250 species of Aspergillus, but only a few are human pathogens[3]. The most common human pathogens are A. fumigatus, A. flavus, and A. niger with A. fumigatus causes more than 80% of cases of ABPA. Other two commercially available antigens in India are Aspergillus versicolor (AV) and tamari (AT).

Allergic bronchopulmonary aspergillosis (ABPA) is the most frequently recognised manifestation of allergic aspergillosis. It is an immunologically mediated lung damage caused by hypersensitivity to the antigens of the fungus. This disease is generally believed to complicate the course of patients with bronchial asthma and cystic fibrosis[4].

Aspergillus hypersensitivity (AH) is generally defined as the presence of an immediate cutaneous hypersensitivity to commercial extracts of species of Aspergillus especially A.fumigatus. AH is generally regarded as the first step in the development of ABPA[5]. The prevalence of AH and ABPA in chronic asthma is well studied and as per recent study the prevalence of AH in asthma varies from 15 – 48% whereas that of ABPA varies from 8-19%[6].

There have been case reports on ABPA complicating the course of COPD[7,8]. One study have also been conducted to evaluate the prevalence of AH and ABPA in patients with COPD in which Aspergillus hypersensitivity was demonstrated in 8.5% patients of COPD[5]. However the rate of AH to the various other Aspergillus species including A Fumigatus (AF), A Flavus (AFl) and A Niger (AN) have not been studied. The aim of present study was to evaluate the rate of AH to these antigens in patients of COPD.

Material and methods

Design

This was a prospective case-control study conducted in the Department of Chest and Tuberculosis, Government Medical College, Patiala. The cases involved 100 consecutive patients with COPD and the controls were 100 healthy volunteers who had no respiratory symptoms. Written informed consent was obtained from all cases and controls.

Patients

For inclusion in the study, the patients were diagnosed to have COPD as per symptoms, progressive breathlessness and cough with minimal mucoid expectoration for at least three months in a year for two successive years, history of smoking and evidence of obstructive defect on spirometry defined as a ratio of forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) less than 70% with no bronchodilator reversibility (increment of FEV1 and/or FVC less than 12% and 200 ml after 400 g of inhaled salbutamol)[3].

Patients who were HIV positive or receiving steroids were excluded from the study. The controls were healthy volunteers and were recruited from among the attendants accompanying the patients attending the OPD. Cases and Controls were subjected to a clinical history, physical examination followed by an Aspergillus skin test. The socioeconomic status of the patients was derived as per modified Kuppuswami scale[9].

Site and method of testing

All the anti-histaminics were stopped 48 hours before testing. The flexor aspect of forearm was cleaned with soap and water and was air dried.

0.2 ml of phosphate buffer saline was injected intra-dermally taking aseptic precautions, raising a bleb of 2mm. Care should be taken that the solution is injected intra-dermally and not beneath it. In the same way 0.2 ml of Aspergillus antigens (A.fumigatus, A.flavus and A.versicolor) were injected intra-dermally in the other forearm at 4cm intervals. The injection site was examined after 15 min. The reactions were labelled as immediate reaction if wheal and erythema developed within 1 min, reached a maximum after 15 min. A wheal of 3mm or more was considered positive[10].

Aspergillus hypersensitivity (AH) was defined as the presence of
immediate cutaneous hyperreactivity to the *Aspergillus* antigen. The standardized antigens were procured from Alcit India.

**Results:**

The 100 COPD patients consisted of 95 males and 5 females with a mean (95% CI) age 51.34 years (49.19-53.59). The majority of the COPD patients were smokers (95%). All the non-smokers were females and gave significant history of exposure to biomass fuel. The mean absolute eosinophil count of COPD patients was 298.21 as compared to 204.77 in the control group. Majority of the COPD patients (67%) and normal control (56%) belonged to upper lower class. Mean smoking index of the COPD patients was 525.64 with standard deviation of 240.96.

*Aspergillus* hypersensitivity to *A. fumigatus* and *A. niger* was demonstrated in 11% and 4% COPD patients respectively. 6% COPD patients demonstrated *Aspergillus* hypersensitivity each to *A. flavus, A. versicolor* and *A. tamarii*. None of the members in the control population demonstrated hypersensitivity to any of the tested *Aspergillus* antigens. None of the COPD patients were positive for all the five *Aspergillus* antigens. 2% and 4% COPD patients showed hypersensitivity to four and three *Aspergillus* antigens respectively.

*Aspergillus* hypersensitivity to only one *Aspergillus* antigen was observed 5% COPD patients. 15% of the COPD patients were positive to at least one of the five *Aspergillus* antigens tested (table 1).

Table 1:

<table>
<thead>
<tr>
<th>Skin Positivity</th>
<th>COPD (n=100)</th>
<th>Normal (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus Fumigatus</td>
<td>11 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillus Flavus</td>
<td>6 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillus Niger</td>
<td>4 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillus Tamarii</td>
<td>6 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillus Versicolor</td>
<td>6 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>At least one antigen</td>
<td>15 (15%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Discussion:**

COPD is a composite term that is used to describe a variety of diseases including chronic bronchitis and emphysema. Like asthma, COPD is characterized by a variable airflow obstruction that manifests as episodic shortness of breath, dyspnea, and wheezing. In contrast to asthma, however, the airways obstruction in COPD is classically irreversible or incompletely reversible, and the mucous metaplasia of chronic bronchitis and the alveolar destruction of emphysema cause a chronic, progressive loss of lung function.

The differences between asthma and COPD in inflammation, airway re-modelling, alveolar re-modelling, and cytokine production are not as disease-specific as they once were thought to be. Atoxy, increased IgE levels, AHR, eosinophilia, and asthma, all have been shown to be risk factors for developing COPD in smokers. Rapid rates of lung function loss have been seen in asthmatic patients who smoke. The latter observations highlight an important, but poorly understood, relationship between atopy, and Th2-like responses and susceptibility to the adverse effects of cigarette exposure [11].

Longitudinal studies have shown that only a minority of cigarette smokers develop progressive deterioration of lung function sufficient to lead to appreciable disability. More than 20 years ago Dutch workers proposed that susceptible smokers might be those individuals who showed non-specific bronchial hyperresponsiveness and subsequent studies have shown that smokers with an accelerated decline in lung function show bronchial hyperresponsiveness to methacholine and histamine.

According to study done by Lim et al there is increased prevalence of positive skin responses in ex-smokers. Alternative interpretation of study shows that some of them had a subclinical form of asthma: in these men bronchial hyper-responsiveness might have been "endogenous," preceeding the onset of smoking, and stopping smoking might have been preferentially induced by symptoms related to the hyper-responsiveness [12].

What has remained enigmatic is the observation that not all smokers demonstrate a similar susceptibility to the decline in lung function and that broncho-reversibility in COPD patients is demonstrable only in a subgroup of patients. However, it is important to identify this subgroup of patients for making treatment decisions. It has been proposed that smokers with an allergic diathesis have a greater predisposition to develop severe and chronic airflow obstruction, what was popularly known as the "Dutch hypothesis" [13].

Even in the scarcity of studies showing direct evidence of aspergillus skin hypersensitivity in patients of COPD there are enough studies in the literature pointing towards the possibility. This study shows that AH and later on ARPA can occur in patients of COPD and high index of suspicion should be kept in mind to find this entity early so as to prevent the occurrence of ABPA. This study is just a step forwards to explore this possibility and differentiate patients of COPD with element of aspergillus skin hypersensitivity so that they can be treated in a better way.

**References:**


