

Prevalence of Allergic Broncho Pulmonary Aspergillosis in patients with Asthma attending allergy clinic in a North West Indian Tertiary Care Institute

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Abstract

Context: Allergic Broncho Pulmonary Aspergillosis (ABPA) is an allergic disorder. *Aspergillus fumigatus* is the most common pathogen responsible for occurrence of ABPA. There can be serious consequences of ABPA including worsening of symptoms of asthma and more sinister complications like extensive fibrosis and bronchiectasis.

Aims: To find out the prevalence of ABPA among asthma patients and association of former with factors like age, sex, occupation, family history of bronchial asthma, socioeconomic status and other relevant factors. Settings and Design: This study was a descriptive type of observational study conducted at our tertiary care institute.

Methods and Material: Three hundred severe asthmatic patients underwent skin prick test (SPT) for five *Aspergillus* species. Four tests were applied to all SPT positive patients -Total serum IgE, spirometry, chest x-ray and High-resolution Computed Tomography (HRCT) scan of thorax. The diagnosis of ABPA was made when the patient fulfilled at least three out of four criteria.

Results: Out of 300 severe asthmatic patients 27 (9%) patients were found SPT positive. Out of these 27 SPT positive patients, four patients refused for further investigations, and 23 were investigated further. Out of 23 SPT positive patients, eight patients (2.7%) were diagnosed as ABPA. It was also found that two out of eight patients with ABPA were misdiagnosed and treated earlier as pulmonary tuberculosis.

Conclusions: All patients with bronchial asthma should be screened for ABPA by skin test for *Aspergillus*. There is need to implement screening programme and meticulous approach by physicians to diagnose and treat such patients.

Key Messages: A diagnosis of allergic bronchopulmonary aspergillosis should be considered in patients coming with asthma. Skin prick test can be used to screen such patients. A further workup of the skin test positive patients leads to a high diagnostic yield.

Keywords: Asthma, Skin tests, Allergic Broncho Pulmonary Aspergillosis.

1. Introduction

Allergic Broncho Pulmonary Aspergillosis (ABPA), as the name signifies, is an allergic disorder that most commonly involves respiratory system. The most common allergen responsible for its causation is *Aspergillus* fungi. Patients having bronchial asthma and cystic fibrosis are typically predisposed to ABPA. In due course of time, ABPA can worsen the course of pre-existing asthma or cystic fibrosis and can lead to irreversible lung damage. Steroids and antifungal drugs, mainly itraconazole are the main line of treatment for this disease. Early diagnosis and treatment can prevent a variety of complications.

Therefore, it is very important to know about the exact burden and other factors associated with the disease.

Knowledge about the disease can prevent misdiagnosis and ensure better quality of life to many.

It has been difficult to estimate the exact burden of disease based on studies conducted on ABPA so far. As far as frequency of ABPA in asthmatic patients is concerned it ranges from less than one to about 30%. [1-3] There seems to be marked local variations as studies from different regions of India report a difference of many folds in the results. [3-8] Fungi are more prone to grow in wet and humid environment. Based on availability of water, the state of Rajasthan is considered dry as compared to the rest of India. It would be important to know if the frequency of ABPA is same or differs significantly from other parts of India. Not much work has been done in this regard in the state of Rajasthan;

therefore, it was planned to undertake this study to understand the disease.

2. Methodology

2.1 Study design:

This study was a descriptive type of observational study.

2.2 Study duration:

Study was conducted for one year of duration.

2.3 Sampling and study participants:

All patients of previously diagnosed asthma attending the outpatient department of Allergy and Pulmonary Medicine at the institute, over one-year period from June 2012 to May 2013 were selected for the study.

2.4 Inclusion and exclusion criteria:

Patients of all age groups, with previous positive history of asthma, who gave consent for the study, were included. Patients with pregnancy, alpha-1 antitrypsin deficiency or any other major medical illness were excluded from the study.

2.5 Study strategy:

After approval from Institute Ethics Committee, study was conducted on selected subjects after obtaining written informed consent. All selected asthma patients (as defined by Global Initiative for Asthma [9]) underwent skin prick test (SPT) for five common fungal antigens namely *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus tamari*, and *Aspergillus versicolor*. The patients were not allowed to use antihistamines and steroids by oral or parenteral route in the preceding 72 hours. Credisil *Aspergillus* antigens manufactured by Creative Diagnostic Medicare Pvt. Ltd, Mumbai was used. Histamine 0.1% w/v, and normal saline 0.9% w/v were used as a control for SPT. The mean wheal diameter was measured after 20 minutes. The result of the test was measured according to Shivpuri's criteria of grading positive skin-prick reactions.[10] A wheal >2 mm than the size of the negative control was considered as positive result for SPT.

Only those asthma patients showing positive response to the SPT with fungal antigens were investigated further for the diagnosis of ABPA. For this purpose, spirometry, total serum IgE levels, chest x-ray and HRCT scan of thorax were done in all the SPT positive asthmatic patients. The diagnosis of ABPA was made when the patient fulfilled either all or three of the following four criteria:

1) Spirometry:

All patients underwent spirometry along with bronchodilator reversibility test. Reversibility was defined according to the American Thoracic Society (ATS) guidelines as 12% and 200 ml increase in the FEV1 following bronchodilator (200 µg of inhaled Salbutamol) as compared to the pre-bronchodilator value. EasyOne NDD spirometer was used for spirometry.

2) The total serum IgE:

It was assessed by the ELISA method. Total IgE levels >1000 ng/ml was taken as positive result.

3) Chest x-ray:

All recent and previous chest radiographs were reviewed for the presence of fleeting opacities, tooth-paste and gloved-finger shadows, ring shadows, tramline or for evidence of fibrosis.

4) HRCT thorax:

High-resolution CT (HRCT) scan of the chest was done in all SPT positive patients to look for any bronchiectasis (central if confined to the inner 2/3 of the lung field on either side), parenchymal fibrosis and mucous plug. 128-Slice Phillips imaging CT scan machine was used with a slice thickness of 1.25 mm.

For statistical analysis, the data were presented in a descriptive fashion as the mean (\pm SD) or the median (range). Statistical significance was assumed at a p-value of < 0.05 or a significant Odds ratio along with confidence interval.

3. Results

Total of 300 severe asthmatic patients underwent SPT for *Aspergillus* species and 27 (9%) of them were found to be SPT positive. Out of 27 SPT positive patients, 23 patients were evaluated further after excluding four dropouts due to reason mentioned above. ABPA was diagnosed in eight patients (34.78% of 23 SPT positive patients) and among them one was seropositive ABPA (ABPA-S) and seven were ABPA with central bronchiectasis (ABPA -CB). Mean age of ABPA positive patients was 28.75 (SD \pm 13.83) years with median age 32.5 years (range 4-45 years) (Table-1).

Among 300 severe asthmatic study patients, 152 were male and 148 were female. Out of 152 severe asthmatic male patients, 15 were SPT positive and out of 148 severe asthmatic female patients, 12 were SPT positive. A gender predilection toward male was found for SPT positivity in our study which was not statistically significant with an odds ratio of 1.24 (95% CI: 0.56-2.75). Similarly, in 23 SPT positive patients, fifteen were male and eight were female. Out of fifteen SPT positive males, four were ABPA positive and out of eight SPT positive females, four were ABPA positive. No significant gender predilection was found for ABPA in our study with an odds ratio of 0.36 (95% CI: 0.06-2.19).

We also looked for any relation of socioeconomic status with SPT positivity and ABPA. Out of 300 severe asthmatic patients 12 patients were BPL (below poverty line) patients and 288 patients were non-BPL patients. Among 12 BPL patients, three were SPT positive for *Aspergillus* species. Among 288 non-BPL patients 24 were SPT positive for *Aspergillus* species. We found higher SPT positivity for *Aspergillus sp.* in BPL patients in comparison to non-BPL

patients with an odds ratio of 3.67 with slightly less favourable 95% CI of 0.93-14.45.

Similarly, no significant relation was found between low socioeconomic status (BPL patients) and ABPA. Out of 23 patients with SPT positivity for *Aspergillus* species, two were BPL patients and 21 were non-BPL patients. Among two SPT positive BPL patients no one was ABPA positive and all eight ABPA patients were from non-BPL.

Among 23 patients with SPT positivity for *Aspergillus* species, seven had positive family history of bronchial asthma and sixteen had negative family history of bronchial asthma. Out of seven patients with positive family history of bronchial asthma, one patient was ABPA positive. Out of sixteen patients with negative family history of bronchial asthma, seven were ABPA positive. No significant relationship was found between family history of asthma and ABPA in our study with an odds ratio of 0.21 (95%CI: 0.02-2.22)

No occupational relationship could be found with ABPA in our study. Two of them were housewife, two

younger patients were student and one each was a farmer, an ANM (Auxiliary Nurse Midwife) in medical department, a private shop worker and in transport business.

Out of 23 SPT positive patients twelve cases were of SPT positive for *A. fumigatus* and among them eight cases (66.67%) were found to be ABPA positive. *A. fumigatus* was found to be the most common pathogen for ABPA as all eight ABPA patients were SPT positive for *A. fumigatus*. Three out of eight ABPA patients were also SPT positive for *A. flavus*.

Among eight ABPA patients, all (100%) had infiltrates on chest x-ray, seven (87.5%) patients has HRCT thorax changes, seven (87.5%) patients had serum total IgE >1000ng/ml (87.5%) and four (50%) patients fulfilled the spirometry criteria. In our study, HRCT thorax with central bronchiectasis was the most specific feature for the diagnosis of ABPA with 100% specificity and a good sensitivity (87.5%). On the other hand, infiltrates on chest x-ray was the most sensitive test for diagnosis of ABPA with 100% sensitivity but a lower specificity (40%).

Table No. 1: Demographic and clinical profile of ABPA patients

Variables	Values
Mean age in years ± (S.D.)	28.75 ± 13.83
Sex ratio (M:F)	1:1
Frequency in asthmatic patients (%)	2.70
Frequency in asthmatics with SPT positivity for <i>Aspergillus</i> species (%)	34.78
Frequency in asthmatic patients with SPT positivity for <i>A. fumigatus</i> (%)	66.67
Family history of bronchial asthma (odds ratio with confidence interval)	0.21 (95% CI: 0.02- 2.22)
HRCT Thorax (changes suggestive of ABPA)	
Sensitivity (%)	87.5
Specificity (%)	100
Serum total IgE >1000ng/ml	
Sensitivity (%)	87.5
Specificity (%)	93.33
Mean serum total IgE levels ng/ml	>2000
Spirometry (postbronchodilator increase of >12% and >200ml in FEV1)	
Sensitivity (%)	50
Specificity (%)	73.33
Chest x-ray Infiltrates	
Sensitivity (%)	100
Specificity (%)	40
Cases misdiagnosed as tuberculosis (%)	25 (2 /8)

Table 1 showing relationship of various factors with ABPA like frequency (2.7% in asthmatics), age (mean age 28.75 ± 13.83 years), sex (male female ratio 1:1), family history of bronchial asthma (not significant), mean total serum IgE level (>2000ng/ml) and also sensitivity and specificity of tests found in our study (HRCT thorax most specific and chest X ray most sensitive).

4. Discussion

This study conducted at allergy clinic of S.M.S. Hospital (Jaipur, Rajasthan) reported the prevalence of ABPA in asthmatic patients as 2.7% in contrast to the prime studies conducted so far in India like by Kumar and Gaur, Maurya *et al*, Agarwal *et al*, and Agarwal *et al* with a higher prevalence of ABPA of 16%, 7.5%, 27.2%, and 20.5% respectively.[3-6] Our study found lower prevalence (2.7%) in north western part of India which may due to drier environmental IJBAR (2016) 07 (05)

conditions as compared to rest of the sub continent. As it has been known that dryness in environment does not favour fungal allergen habitant, which may contribute to lower prevalence. Other reasons for such diversity of results may be due to difference in duration of studies and sample size along with referral and selection bias of the subjects to the tertiary level institutes in other studies.[8,11] Never the less earlier no prime study has been conducted over this part of India and more studies are required for comparison and for better

understanding of environmental and other factors responsible for low prevalence of the disease in this part of India.

This study also signifies that substantial work is still needed over ABPA in different geographical areas of Indian sub continent to assess the actual disease burden because that may have diversity of results.

The prevalence of SPT positivity for *Aspergillus* species in our study population was 9% (27/300). The study having nearest result is Ma *et al*, [12] reporting a prevalence of 5.5%. Various other studies have reported different results of SPT positivity in asthmatic patients, ranging from 16% to 43.3% like Hendrick *et al* (16%), Schwartz and Citron (28%), Malo and Paguin (21.5%), Benatar *et al* (22%), Attapattu (43.3%), Eaton *et al* (18.4%), Kumar and Gaur (23.5%), Al-Mobeireek *et al* (23%), Maurya *et al* (28.5%), Agarwal *et al* (39.5%), Agarwal *et al* (38.5%), Prasad *et al* (30.3%), and Sarkar *et al* (31.7%). [3-8,13-19]

Different results in these studies may be due to lack of uniform diagnostic criteria for interpretation of positive skin test. Some of the studies took only *A. fumigatus* antigen for skin testing, while others included other fungal allergens too. [4,5,7,13-18]

Similarly, type I, type III and type IV skin test reactivity was considered in some studies and only type I in others. [3,4,7, 13,17] There was also a difference in the type of skin test used in various studies like some studies used prick test while others used intradermal test. [4-7,13-15] All these factors may contribute to diversity of the results.

Regarding the age of occurrence of ABPA, our study supports the results of previous studies. Five out of eight ABPA patients were in 3rd and 4th decade of life. Mean age (28.75 years) was found a little lower than other studies due to a young ABPA patient in our study who was only 4 years and 9 days of age. Interestingly, so far the youngest case of ABPA in India was reported by Gaur *et al* [20] and that patient was also a four years old female. ABPA can develop at any age but it most commonly develops in the third and fourth decades of life. [6,11,21] In most of the Indian studies mean age of ABPA was found to lie between 30 to 37 years, like Behera *et al* [22] (34.3 years), Kumar and Gaur [4] (34 years), Chakrabarti *et al* [23] (36.4 years), Agarwal *et al* [3] (34.4 years), Agarwal *et al* [6] (33.4 years), Prasad *et al* [7] (33.5 years), and Sarkar *et al* [8] (33.1 years).

No gender predilection was present for ABPA in our study. In most of the studies on ABPA, male-female ratio was either equal or favoured males like Behera *et al* [21] (3:2), Chakrabarti *et al* [22] (1.5:1), Agarwal *et al* [3] (1:1), Agarwal *et al* [6] (1:1), Prasad *et al* [7] (2.6:1), Sarkar *et al* [8] (3:2). While, in study by Ma *et al* [12] the ratio favoured females (2:3). According to contemporary understanding on ABPA, there is no specific gender predilection for ABPA and our study results support the same concept. [24]

Not many studies commented on the relationship between family history of asthma and ABPA in past. No significant correlation was found between family history of asthma and ABPA in our study (Odds ratio = 0.36, 95% CI: 0.06-2.19). According to Kumar *et al* [4] and Prasad *et al* [7], a family history suggestive of asthma/atopy was present in 63% and 61.5% in ABPA patients respectively. More evaluation is needed over this important aspect of ABPA.

A higher but statistically non-significant relationship of SPT positivity for *Aspergillus* was found in BPL patients as compared to non-BPL patients. But, no such relationship was found between ABPA positivity and low socioeconomic (BPL) status. The presence of increased SPT positivity in our BPL as compared to non-BPL patients could not be explained on the basis of the presently available evidence in the scientific literature. According to a study by Cooper *et al* [25], the prevalence of atopy is almost same in rural as well as urban settings. Further studies are required in order to clarify this aspect of atopy and ABPA relationship.

Our study also supports the evidence from recent studies that *A. fumigatus* is the main pathogen responsible for ABPA. [8,11,26] In our study 100% cases of ABPA were having SPT positivity for *A. fumigatus*. Other fungi that can cause ABPA are *A. flavus*, [11,26] *A. niger*, [8,11,14,26] *A. terreus*, [26] *A. nidulans*. [26]

In our study out of eight ABPA patients, three patients had past history of pulmonary tuberculosis and they had taken anti-tubercular treatment for it. When we took detailed history from these three patients, one patient of them was sputum positive for acid fast bacilli (AFB), another two patients were sputum negative for AFB. They consulted doctors for recurrent episode of shortness of breath not associated with productive sputum, fever, night sweats, and weight loss. Probably, these two patients were misdiagnosed and treated as pulmonary tuberculosis. It has been shown in past that almost half of the cases of ABPA are initially misdiagnosed as having pulmonary tuberculosis. ³ This may be due to similarity in radiographic features of both diseases and a tendency of Indian health care providers to over diagnose tuberculosis. As any upper zone abnormalities are usually considered to be tuberculosis unless proven otherwise.

In conclusion, all patients with bronchial asthma should be screened for ABPA by skin test for *Aspergillus* species. If anyone is found SPT positive, special consideration is needed to rule out ABPA as our study revealed a high frequency of ABPA among them. Misuse of anti-tubercular drugs for this disease is an important issue and efforts should be made to improve the awareness about this disease among healthcare providers. Appropriate treatment of the disease entity could prevent further irreversible complications such as lung fibrosis and extensive bronchiectasis.

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