Original Article

A questionnaire-based study on the role of environmental factors in allergic bronchopulmonary aspergillosis

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ABSTRACT

Background and Aims: Allergic bronchopulmonary aspergillosis (ABPA) is an immunological disorder caused by hypersensitivity against *Aspergillus fumigatus*. The pathogenesis of ABPA remains unknown. Few studies have investigated the role of environmental factors in pathogenesis of ABPA. Herein, we investigate the role of environmental factors in ABPA. **Materials and Methods:** In this prospective case-control study, consecutive patients with asthma (*Aspergillus* sensitized and unsensitized) and ABPA were investigated using a standardized questionnaire to enquire into their demographic characteristics, clinical details, exposure to organic matter and living conditions (home environment, presence of moisture in the walls, and others). Asthma severity and control was assessed using the 2002 The Global Initiative for Asthma (GINA) recommendations and asthma control test, respectively. **Results:** During the study period, 202 subjects of asthma (103 and 99 *Aspergillus* unsensitized and sensitized asthma, respectively) and 101 ABPA with a mean (SD) age of 35.3 (14.7) years were included. The baseline characteristics were similar in the two groups except for a higher prevalence of severe persistent asthma in the ABPA group (79% *vs*. 44%, $P = 0.0001$). No significant differences in environmental factors were noted in the ABPA population compared to asthmatic patients except for a higher rural residence in ABPA (47% *vs*. 66%, $P = 0.007$). **Conclusions:** The study found no significant environmental differences in ABPA compared to asthmatic patients. It is likely that environmental factors are not the primary pathogenetic factors in causation of ABPA.

KEY WORDS: Allergic bronchopulmonary aspergillosis, allergic bronchopulmonary mycosis, aspergillus, asthma

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INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological disorder caused by hypersensitivity against *Aspergillus fumigatus* colonizing the tracheobronchial tree of asthmatic patients.[1] The disorder was first described by Hinson *et al.*, in 1952 from the U.K.,[2] whereas the first report from India was published almost two decades later.[3] Despite, six decades of research, the disease remains elusive, and is often misdiagnosed as pulmonary tuberculosis, in India.[4] Allergic aspergillosis clinically presents with poorly controlled asthma, fleeting pulmonary opacities and bronchiectasis.[5] The diagnosis is made on a combination of clinical, radiological and immunological findings. Recently, the 'ABPA complicating asthmatics' working group formed by the International Society of Human and Animal Mycology has laid down new criteria for diagnosis and staging so as to simplify the recognition of this disorder.[6]

The pathogenesis of ABPA remains unknown. Familial occurrence of the disease suggests a possible genetic contribution to the development of ABPA,[7] and several genetic polymorphisms have been identified with increased frequency in ABPA compared to asthmatic patients.[6,8] The identification of cases of a relatively uncommon disorder within a family may also suggest environmental factors in the causation of the disease apart from genetic predisposition. Allergic aspergillosis has been described in cane sugar mill workers and in those working in small workshops of soybean products.[9]

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.135762

We have observed patients with ABPA both from rural and urban backgrounds. Based on these observations, we hypothesized that certain environmental factors such as moisture in the walls and others, which predispose to moldy homes, may be associated in causation of ABPA. In this questionnaire-based study, we investigate the role of environmental factors in ABPA.

MATERIALS AND METHODS

This was a prospective case-control study conducted between July 2008 and June 2009 in the Chest Clinic of this Institute. An informed consent was obtained from all patients and the study was approved by the Ethics Review Committee. Bronchial asthma was defined on the presence of both the following: (a) History of recurrent or episodic attacks of chest tightness, breathlessness and cough and/or wheeze on examination of the chest; (b) obstructive defect on spirometry with the presence of bronchodilator reversibility.[10] Patients without bronchodilator reversibility at the time of entry into the study were included only if there was a documented bronchodilator reversibility at some point in their illness. Patients of asthma were divided into two subgroups based on the presence of a positive or negative *Aspergillus* skin test as *Aspergillus* sensitized and *Aspergillus* unsensitized asthma, respectively.

Patients were diagnosed as ABPA, if they met all the following criteria: (a) Bronchial asthma; (b) total IgE values >1000 IU/mL; (c) *A. fumigatus* specific IgE levels >0.35 kUA/L; and, three of the following criteria: (a) type 1 *Aspergillus* skin test positivity; (b) presence of serum *A. fumigatus* precipitins; (c) fixed or transient chest radiographic opacities; (d) peripheral blood eosinophil count >1000 cells/μL; (e) bronchiectasis on high-resolution computed tomography (HRCT) of the chest.[4,11-13] Patients with chronic obstructive airway disease and those not willing to provide informed consent were excluded.

All study subjects were investigated using a standardized questionnaire to enquire into their demographic characteristics (occupation, residence), clinical details regarding the duration and severity of asthma, current treatment, exposure to organic matter, family history of asthma and exposure to tobacco smoke. Living conditions like home environment, presence of moisture in the walls, details of house type, presence of separate kitchen, use of exhaust fan, coolers, air conditioners, type of fuel used, and contact with farms, cattle and pets were also enquired. Assessment of severity of asthma was carried according the 2002 Global Initiative for Asthma (GINA) recommendations, which include the effect of treatment on the disease severity.[14] Asthma control was assessed using the asthma control test (ACT), a validated, self-administered questionnaire with five items to assess symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning.[15] A score of ≥20 defines "well-controlled" asthma, 15-19 "not controlled" asthma, and ≤14 "very poorly controlled" asthma.[16]

Aspergillus skin test (AST) was performed by injecting 0.2 mL of 100 PNU/mL (1 PNU = 0.00001 mg/mL) *Aspergillus* antigen intradermally in the forearm with phosphate buffer saline (0.2 mL) serving as the control. A positive type 1 reaction was defined if a wheal and erythema developed within one minute, reached a maximum after 10 to 20 minutes, and resolved within one hour, with the antigen arm skin reaction diameter at least 8 mm greater than the control.[17] Total IgE levels were assessed using quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany), whereas the *A. fumigatus* specific IgE levels were assayed using fluorescent enzyme immunoassay (UniCap Systems; Phadia, Stockholm, Sweden).

Aspergillus precipitins were detected using the Ouchterlony gel diffusion technique according to the method described by Longbottom and Pepys.[18] Total eosinophil count was assessed multiplying the total leucocyte count (determined using an auto-analyzer) with the percentage of differential leucocyte count (counting and classifying 100 WBCs on a peripheral blood smear). Pulmonary function test was performed on a dry rolling seal spirometer to determine the lung function measurements and bronchodilator reversibility. Age, gender, height and spirometry data were recorded for all patients using computer software previously developed by us.[19] High-resolution computed tomography of the chest was performed using a 16-row, multiple-detector CT scanner (LightSpeed Plus; GE Medical Systems; Slough, UK) with a matrix size of 512 × 512. Image acquisition was contiguous, and the images (1.25 mm at 10-mm intervals) were reconstructed using a high-spatial-frequency algorithm. The diagnosis of bronchiectasis on HRCT chest was made according to previously described criteria.[20]

Statistical analysis

Data was analyzed using the commercial statistical package StatsDirect for MS-Windows (Version 2.7.2, StatsDirect Ltd., UK). Data are expressed in a descriptive fashion as mean (SD) or number (percentage). The difference between continuous and categorical variables was analyzed using Mann-Whitney U and Chi-square test, respectively.

RESULTS

During the study period, 202 consecutive subjects of bronchial asthma (103 and 99 *Aspergillus* unsensitized and sensitized asthma respectively) and 101 consecutive subjects of ABPA with a mean (SD) age of 35.3 (14.7) years were included. The baseline characteristics of the study population are shown in Table 1. Majority of the subjects were women with minimal exposure to tobacco smoke either active or passive. The lung function was similar in the three groups. A family history of asthma and the duration of asthma prior to the presentation at the Chest

Clinic was higher in the ABPA group compared to the asthma group but was similar in *Aspergillus* sensitized and unsensitized asthma [Table 1]. The vast majority of patients in the study had persistent asthma and the number of patients with severe persistent asthma were significantly higher in the ABPA group compared to the asthma population. The asthma was well controlled in 65% of the study population, and the asthma control was similar in the three groups. Asthmatic patients required mild to moderate dose of inhaled steroids for asthma control while those with ABPA required significantly higher doses of inhaled corticosteroids.

The environmental differences in the three groups are tabulated in Table 2. Almost half the study population resided (53%) in the rural area in the cemented houses. There was a significantly higher rural residence in the ABPA group compared to asthmatic patients. The use of biomass fuel was higher in the asthmatic group compared to the ABPA, but there was no difference between the *Aspergillus* sensitized and unsensitized asthma group. The use of water-based air cooler was higher in the *Aspergillus* sensitized group compared to *Aspergillus* unsensitized or ABPA group. History of contact with pets or cattle and exacerbation of symptoms with organic matter did not differ much in the three groups. There was no relationship between IgE (total and *A. fumigatus* specific) and any of the environmental factors. There were only seven patients with serological ABPA and the difference in exposure was not different between ABPA patients with and without bronchiectasis.

DISCUSSION

Few studies have investigated the role of environmental factors in pathogenesis of ABPA despite the fact that *Aspergillus* species represent between 0.1% and 22% of total air spores sampled.[21] The current study represents the largest study investigating the role of environmental factors in causation of ABPA. We found no significant environmental factors associated with ABPA with the exception of higher rural background. Although, *Aspergillus* is a ubiquitous organism, compost, hay or grain support heavy growths of *A. fumigatus*.[22] It has been suggested that exposure to large concentrations of *A. fumigatus* conidia may be related to the disease,[23] and that ABPA is more common in agricultural conditions.[2,24] We found no increased prevalence of farming in ABPA compared to asthmatic patiens. Exposure to high concentrations of *A. fumigatus* spores from garbage dump sites, bird droppings, and smoking moldy marijuana have all been reported to cause ABPA.[25-27] Other investigators have found a correlation between worsening of airway obstruction in patients with ABPA with an increase in *A. fumigatus* spores in the immediate external environment,[28] whereas others did not find such an association.[29,30]

The study found that patients with ABPA were more likely to hail from rural areas compared to asthmatic patients. In contrast, McCarthy *et al*., reported that majority of their patients were urban dwellers.[31] The current study also observed a higher prevalence of water-based air coolers in *Aspergillus* sensitized patients (asthma

Table 1: Baseline characteristics of the study population

	Aspergillus unsensitized asthma (*n*=103)	*Aspergillus* sensitized asthma (*n*=99)	Allergic broncho-pulmonary aspergillosis (*n*=101)	*P* value
Age (years)	36 (15.9)	35.8 (14.8)	34 (13.3)	0.69
Male gender, no. (%)	39 (37.9)	42 (42.4)	51 (50.5)	0.18
Height (meters)	1.58 (0.09)	1.59 (0.09)	1.6 (0.1)	0.18
Weight (kg)	57.6 (13.7)	57.8 (11.9)	56.6 (11.6)	0.51
Family history of asthma, no. (%)	21 (20.4)	29 (29.3)	39 (38.6)	0.02
Duration of asthma (years)	6 (2-10)	8 (3-15)	15 (5-20)	0.0001
Tobacco smoking, no. (%)	4 (3.9)	4 (4.0)	2 (1.9)	0.66
ETS exposure	8 (7.8)	6 (6.1)	14 (13.9)	0.13
Dose of inhaled steroids, median (IQR)	625 (500-100)	800 (313-1250)	1000 (650-1250)	0.008
FEV1 (in liters)	1.9 (0.83)	1.78 (0.79)	1.98 (0.82)	0.23
FVC (in liters)	2.62 (0.93)	2.63 (0.87)	2.8 (0.95)	0.29
FEV1/FVC	71.9 (16.1)	66.1 (14.8)	69.4 (11.7)	0.01
Severity of asthma, no. (%)				
Mild intermittent	15 (14.6)	12 (12.1)	5 (5)	0.0001
Mild persistent	7 (6.8)	4 (4)	3 (3)	
Moderate persistent	40 (38.8)	36 (36.4)	13 (12.9)	
Severe persistent	41 (39.8)	47 (47.5)	80 (79.2)	
Asthma control test, no. (%)				
Well-controlled	63 (61.2)	64 (64.6)	69 (68.3)	0.49
Not controlled	24 (23.3)	15 (15.2)	17 (16.8)	
Very poorly controlled	16 (15.5)	20 (20.2)	15 (14.9)	

All values are expressed as mean (SD) unless otherwise stated, IQR: Interquartile range, FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity

Table 2: Environmental differences between asthma and allergic bronchopulmonary aspergillosis

	Aspergillus unsensitized asthma (*n*=103)	*Aspergillus* sensitized asthma (*n*=99)	Allergic broncho-pulmonary aspergillosis (*n*=101)	*P* value
Rural residence	50 (48.5)	45 (45.5)	66 (66)*	0.007
Number of people residing in home	5 (4–7)	5 (5.7)	6 (5–7)	0.48
Non-cemented house	17 (16.5)	9 (9.2)	9 (8.9)	0.32
Presence of moisture in walls	22 (21.4)	25 (25.8)	29 (28.7)	0.48
Use of water-based air cooler	43 (41.7)	65 (65.7)*	54 (53.5)	0.003
History of farming	20 (19.4)	18 (18.2)	28 (27.7)	0.20
Biomass fuel	23 (22.4)*	18 (18.1)	11 (10.9)	0.0001
Presence of window in the kitchen	94 (91.3)	88 (88.9)	95 (94.1)	0.43
Presence of exhaust in the kitchen	49 (47.6)	48 (48.5)	58 (57.4)	0.3
Contact with pets	16 (15.5)	8 (8.1)	13 (12.9)	0.56
Contact with cattle	30 (29.2)	25 (25.3)	34 (33.7)	0.43
Exacerbation of symptoms with organic matter	10 (9.7)	9 (9.1)	19 (18.8)	0.07

All values are expressed as number (percentage) unless otherwise stated, *Statistically significant in this group compared to the other two groups

and ABPA) compared to unsensitized patients (60% *vs*. 42%, $P = 0.003$). Whether this finding is because of an exposure to an environment rich in organic matter and *Aspergillus* spores, is not clear from this study, as we did not quantitate the spore counts from air coolers. One study found no difference in the concentrations of *Aspergillus* spores between the homes of mold sensitive and non-mold sensitive individuals.[32] In another study, no high spore concentrations were recorded in the homes of either patients with ABPA or the atopic control patients.[29] We, however, noted an association between exacerbation of symptoms with organic matter that was observed to be higher in patients with ABPA, although was not statistically significant.[29] It has been previously suggested that avoidance of *Aspergillus* spore sources and low overall exposure may play a major role in preventing exacerbations of ABPA.[28]

Environmental factors are probably of less significance than individual host genetic susceptibility in causation of ABPA. Fungal conidia are immunologically inert because of the presence of surface hydrophobin;[33] however, defective clearance of conidia in asthmatic patients allows them to germinate into hyphae. In a genetically predisposed asthmatic patient, defects in innate and adaptive immunity causes persistence of *A. fumigatus*,[8] which releases of a myriad of proteins that activate the innate immune system of the lung leading to production of several inflammatory cytokines.[34-37] Also, the exposure of *A. fumigatus* proteins to pulmonary macrophages primes naïve helper T-lymphocytes to *Aspergillus* specific T-cells. Due to the genetic susceptibility, the host mounts a Th2 $CD4^+$ T cell response with IL-4, IL-5 and IL-13 cytokine secretion instead of the normal Th1 response.[38-42] This causes profound inflammatory reaction with inflow of diverse inflammatory cells (including neutrophils and eosinophils),[43,44] and IgE (total and *A. fumigatus* specific) synthesis.[45]

Finally, our study is not without limitations. The major drawback is the lack of sampling of *A. fumigatus* spores. Other limitations include the conduct of the study at a single center. The strengths include the large sample size (100 patients with ABPA). Future studies should be multicentric and should include quantification of the environmental spore count in the total/representative sample.

In conclusion, the study found no significant environmental differences in ABPA compared to asthma. It is likely that environmental factors are not the primary pathogenetic factors in causation of ABPA.

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How to cite this article: Agarwal R, Devi D, Gupta D, Chakrabarti A. A questionnaire-based study on the role of environmental factors in allergic bronchopulmonary aspergillosis. Lung India 2014;31:232-6.

Source of Support: Nil, **Conflict of Interest:** None declared.