

Prevalence and Risk Factors for Allergic Bronchopulmonary Aspergillosis in Indian Children with Cystic Fibrosis

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Objectives: Allergic bronchopulmonary aspergillosis (ABPA) is a common complication in patients with cystic fibrosis. This cross-sectional study was planned to determine the prevalence and risk factors for ABPA in Indian children with cystic fibrosis.

Methods: Clinical evaluation, spirometry, chest radiograph, sputum, total IgE, specific IgE for *Aspergillus fumigatus*, IgG precipitins and skin prick tests were done in 33 CF patients.

Results: Prevalence of allergic bronchopulmonary aspergillosis was 18.2% (95% CI 6.9% - 35.4%); allergic bronchopulmonary aspergillosis was higher in patients with low cystic fibrosis score, age >12 years, atopy, and eosinophilia.

Conclusion: Prevalence of ABPA is higher in Indian children with cystic fibrosis.

Keywords: *Aspergillus*, *Bronchiectasis*, *Epidemiology*.

Aspergillus colonization increases with age in children with cystic fibrosis [1]. Prevalence of allergic bronchopulmonary aspergillosis (ABPA) ranges from 2% to 15%. Older age, poor nutritional status, atopy, use of inhaled antibiotics, inhaled corticosteroid, long-term azithromycin therapy, RhDNase therapy, and *Pseudomonas* infection are some risk factors [2]. Cystic fibrosis is increasingly being diagnosed in Indian sub-continent and there is paucity of data from the region.

METHODS

This cross-sectional study was conducted in Pediatric chest clinic of All India Institute of Medical Sciences, New Delhi, India. The study was approved by the Institutional ethics committee. Informed written consent was taken. Clinical evaluation, spirometry, chest radiograph, sputum, total IgE, specific IgE for *Aspergillus fumigatus*, IgG precipitins and skin prick test (SPT) were done. ImmunoCAP test was used for estimation of total IgE, *A. fumigatus* specific IgE and common aeroallergen [3]. IgG precipitins were assayed by agar gel double diffusion method [4]. SPT was done using *A. fumigatus* extracts (All Cure Pharma Pvt. Ltd. Bahadurgarh, Haryana) [5].

We assessed the following risk factors: age, gender, body mass index (BMI), CF score, atopy, airway reversibility, inhaled or systemic antibiotics, inhaled corticosteroid (ICS), azithromycin, *Pseudomonas* and

aspergillus colonization. CF score was estimated using Shwachman-Kulczycki score [6]. The diagnosis of ABPA was based on the criteria suggested by the Cystic Fibrosis Foundation [7]. Aspergillus colonization was defined as the presence of *Aspergillus* species in sputum from two samples collected on two consecutive days [8]. Aspergillus sensitization was defined as positive specific IgE (>3.5 KU) in serum against *A. fumigatus* or immediate cutaneous reactivity [7]. Eosinophilia was defined as absolute eosinophil count (AEC) > 500/mm³. Atopy was defined as >1 IU/mL IgE antibody to more than one aeroallergen [9]. Analyses were done using Stata 9.0 software (Stata Corp., College Station, TX, USA). Continuous and categorical variables were analyzed by Student-t-test and Odds ratio (95% CI), respectively.

RESULTS

Out of 41 children with CF, 33 (24 boys) were enrolled. The mean (SD) age was 141.5 (58.5) months. The mean (range) age at diagnosis of CF was 46.2 (2-138) months. The mean (SD) BMI was 14.38 (2.41) kg/m². Chest radiographs were abnormal in 26 (78.7%) patients, with bronchiectasis seen in 15 (45%).

Colonization with *Aspergillus* species was present in six (18.2%) patients. Fifteen (45.5%) patients were sensitized to *A. fumigatus*. Six patients were diagnosed as ABPA by minimal diagnostic criteria giving prevalence of 18.2% (95% CI 6.9% - 35.4%). Out of six ABPA diagnosed patients, 3 were in acute stage, 2 in exacerbation and 1 in remission [10].

WHAT THIS STUDY ADDS?

- Prevalence of allergic bronchopulmonary aspergillosis in Indian children with cystic fibrosis is 18%.
- ABPA is more common in those with low CF score, age >12y, airway reversibility, atopy, and eosinophilia.

Table I compares the clinical and investigational profile of children diagnosed to be having ABPA with those not having it. ABPA was more often seen in patients with low CF score, age >12 years, reversibility after bronchodilator, atopy, and eosinophilia. Patient with ABPA had a trend towards lower FEV1 and FVC. Immediate skin reactivity to *A. fumigatus* was seen in 14 patients. Measures of correlation between IgE specific for *A. fumigatus* and skin prick test showed no discordance. There was 87.5% agreement between the two tests with a kappa value of 0.74. A similar agreement (85.4%; kappa 0.68) was seen between total serum IgE level (>500) and IgE specific for *Aspergillus fumigatus* (>3.5 KU). IgG precipitins were negative in all patients.

DISCUSSION

Aspergillus species causing illness in children with CF has a wide spectrum ranging from ABPA, colonization, IgE sensitization and chronic bronchitis [7]. IgE sensitization of *aspergillus* is associated with a more rapid decline of pulmonary function [8]. Colonization of *A. fumigatus* is frequent with reported prevalence of 40% but only 1% to 11% may develop ABPA [1]. Though there is increasing recognition of CF in India, there is paucity of information about *Aspergillus* in children with CF [11].

We observed prevalence of colonization and ABPA in 6 (18.2%) patients each in CF. ABPA was more often seen in patients with low CF score, age >12 years, airway reversibility, atopy, and high eosinophil count.

Various studies from Europe and United States have reported prevalence of ABPA ranging from 2%-15% [12-14]. The high prevalence of ABPA in our study may be due to low BMI, regular use of azithromycin and ICS or frequent requirement of antibiotics for pulmonary infections. Lower colonization rate (18%) with *aspergillus* in present study could be because of stringent criteria of two sputum samples collected on two consecutive days were positive instead of two positive cultures over a period of one year used in other studies [8].

There was statistically significant correlation between SPT and IgE specific *A. fumigatus* indicating that SPT can be reliably done in screening for ABPA in resource limited countries.

In our study, none of the patients had positive test for precipitins. Such negative results were seen in two previous studies [7,14], which can be due to less potent antigens or poor IgG response.

Limitations of present study include: diagnosis of

TABLE I COMPARISON OF RISK FACTORS BETWEEN ABPA AND NON-ABPA GROUP

Variable	ABPA (n=6)	Non ABPA (n=27)	P/ Odds ratio(CI)
Age, mo	181.3 (71.2)	133.0 (55.3)	0.07
Males	3 (50)	21 (77)	0.28 (0.04-1.73)
*CF score	58.3 (10.8)	75.2 (17.5)	0.03
*Antibiotic use in last 1y	14.5 (5.5)	15.6 (20.8)	0.90
Reversibility on PFT	3 (50)	6 (31)	3.5 (0.57-21.2)
Pseudomonas present	1 (16.7)	12 (44.4)	0.25 (0.01-2.79)
Presence of AC	1 (16.7)	5 (18.5)	0.88 (0.01-11.0)
Inhaled antibiotics	2 (33)	8 (29.6)	1.18 (0.08-10.39)
Inhaled corticosteroids	6 (100)	26 (96)	—
Azithromycin use	5 (83)	23 (85)	0.86
AEC >500	4 (66)	#4 (16)	10.5 (1.59-68.3)
Atopy	6 (100)	\$4 (15)	<0.001

Categorical values are mentioned as n (%); *Mean(SD); #25 and \$26 children.

bronchiectasis by X-ray rather than high resolution CT scans, and use of IgG precipitins rather than IgG anti-Af ELISAs [15] Present study provides data on different aspects of *Aspergillus* infection in children with CF from India.

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