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Prevalence and Risk Factors of Allergic Bronchopulmonary Aspergillosis and Aspergillus Sensitization in Children with Poorly Controlled Asthma

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ABSTRACT

Background: Allergic bronchopulmonary aspergillosis (ABPA) may be a risk factor for poorly controlled asthma in children. The studies regarding prevalence and risk factors of ABPA in children with poorly controlled asthma are limited in number.

Objectives: To determine prevalence and risk factors of ABPA and aspergillus sensitization (AS) in children with poorly controlled asthma.

Methods: In this prospective cross-sectional study from a tertiary care center in India, we enrolled asthmatic children 5–15 years of age with poorly controlled asthma. We did the following investigations: spirometry, skin prick test, serum total immunoglobulin E (IgE), aspergillus-specific IgE and immunoglobulin G, serum precipitin for Aspergillus, absolute eosinophil count, chest X-ray and high-resolution computed tomography of the chest. ABPA and AS were diagnosed as per the recently proposed criteria.

Results: We enrolled 106 children [boys 72 (67.9%); mean age of 10.2 ± 2.6 years] with poorly controlled asthma. The prevalence of ABPA and AS were 11.3% (95% CI, 5.2–17.5%) and 61.3% (95% CI, 52.0–70.7%), respectively. The presence of brownish sputum was significantly more in ABPA compared with non-ABPA patients (33.3 vs. 4.2%, $p = 0.002$). The age, gender, allergic rhinitis and gastroesophageal reflux were not significantly different in ABPA compared with non-ABPA patients.

Conclusion: The prevalence of ABPA and AS was 11.3 and 61.3%, respectively in children with poorly controlled asthma. We could not find any risk factors for ABPA except that the presence of brownish sputum was more in children with ABPA. Spirometry parameters were not significantly different in ABPA compared with non-ABPA patients.

KEYWORDS: asthma, children, allergic bronchopulmonary aspergillosis, aspergillus sensitization

INTRODUCTION

Asthma is a chronic inflammatory condition of the airways associated with bronchial hyperresponsiveness, variable airflow obstruction and chronic structural changes [1]. Although asthma is usually well controlled with medications, 10–20% of patients may have poorly controlled asthma [2]. Common reasons for poorly control of asthma include inappropriate usage of medications (improper technique, inadequate dosage, empty canister, poor compliance), persistence of triggers, presence of comorbid conditions like allergic rhinitis, adenoids, nasal polyps etc. However, in a few patients the symptoms persist even after the above conditions are reasonably ruled out/taken care of. One of the important cause in such children may be hypersensitivity to aspergillus, most commonly *Aspergillus fumigatus*. Other causes of poorly controlled asthma may be true steroid therapy resistant asthma and neutrophilic asthma.

Allergic bronchopulmonary Aspergillosis (ABPA) is a hypersensitivity reaction to aspergillus with predominant Th2 CD4+ response occurring mainly in immunocompetent hosts with asthma or cystic fibrosis (CF) [3]. It is characterized pathologically by mucoid impaction of the bronchi, eosinophilic pneumonia and bronchocentric granulomatosis in addition to histological features of asthma [4]. Children with ABPA usually presents with poorly controlled asthma. ABPA should be considered in poorly controlled asthma if it is associated with expectoration of mucus plugs, hemoptysis, constitutional symptoms, fleeting radiological opacities or bronchiectasis [5]. ABPA is relatively well studied in adults. However, information about prevalence and risk factors of ABPA in asthmatic children is scanty. Knowledge of prevalence and risk factors for ABPA in asthmatic children will help in early identification and management. If clinicians suspect ABPA early and treat it appropriately, long-term sequelae of ABPA such as fibrosis may be prevented. Therefore, we did the study to evaluate prevalence and risk factors of ABPA in children with poorly controlled asthma.

METHODS

This prospective cross-sectional study was performed at a tertiary care referral institute in Northern India from March 2016 to January 2018. The study was approved by the Institute Ethics Committee. Based on 26% prevalence of ABPA in children with poorly controlled asthma in a study by Singh *et al.* [6] in 2015 and assuming precision of 10%, the sample size required was 77 children. We enrolled 100 children to compensate for incomplete work-up or any sample loss.

Consecutive children between 5 and 15 years of age with asthma attending Pediatric Chest Clinic, Pediatric outpatient or admitted in pediatric ward were assessed for asthma control. We chose to study children 5–15 years of age as diagnosis of asthma below 5 years of age is difficult and ABPA is very uncommon below 5 years of age. Asthma was diagnosed clinically based on recurrent episodes of airway obstruction and reversibility by history or by bronchodilator test. Control of asthma was assessed as per GINA 2016 guidelines [7]. Children with 'partly controlled' or 'uncontrolled' asthma were considered as 'poorly controlled asthma' for the study. Children with poorly controlled asthma were eligible for inclusion in the study. Children already diagnosed with ABPA and having co-morbidities like tuberculosis or CF were excluded from study.

Children were enrolled after obtaining written informed consent from the parents/caretaker and additionally, assent from children of 7 years or older. Detailed clinical history related to asthma control, clinical features of ABPA and risk factors for ABPA were taken. Clinical features assessed for ABPA were wet cough, fever, anorexia, weight loss, dyspnea, hemoptysis and production of brown mucus plugs. Risk factors assessed for ABPA were: age of child, gender, duration of asthma, dosage of inhaled steroids, technique of inhalation, any exacerbation requiring oral steroids or hospitalization or emergency visits in the past 12 months, exposure to smoke and presence of any co-morbid condition like obesity, adenoid hypertrophy, sinusitis, allergic rhinitis and gastroesophageal reflux (GER). Obesity was defined as body mass index of more than 95th centile for age and gender. Adenoid hypertrophy was diagnosed clinically by presence of mouth breathing, adenoid facies and snoring OR by enlarged adenoids in X-ray of neck if available. Sinusitis was considered if there was chronic nasal discharge, chronic nasal

obstruction and/or pain on pressure over cheek, OR presence of sinusitis in X-ray of paranasal sinuses if available. Allergic rhinitis was considered in presence of recurrent rhinorrhoea, sneezing, itching in nose with or without allergy markers (allergic shiner, Dennie's lines, allergic crease, allergic salute and allergic gape). GER was considered clinically in presence of recurrent vomiting, nausea, retrosternal pain/burning, epigastric pain or sour taste in mouth OR presence of reflux in GER scintigraphy if available.

The general living condition of the patient was asked including rural vs. urban residence, socioeconomic status as per Kuppuswamy's scale [8] and presence of dampness at residence (by history). Detailed general and systemic physical examination of the child (including anthropometry-height and weight, ear-nose-throat evaluation and chest auscultation) was done.

The following investigations were performed on enrolled children: spirometry, skin prick test using *A. fumigatus* antigen, total immunoglobulin E (IgE) and *A. fumigatus*-specific IgE, serum precipitins against *A. fumigatus,* serum immunoglobulin G (IgG) against *A. fumigatus,* haemogram including eosinophil count and chest X-ray. High-resolution computed tomography (HRCT) was considered only if chest X-ray was abnormal or there was high index of suspicion for ABPA (serologically positive ABPA).

Spirometry was performed using Spirolab III spirometer (MIR, Italy) as per standard procedure [9] and following parameters were assessed: forced expiratory volume in 1st second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow (PEF), forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75}$). We used Knudson references for North Indian population for predicted values of spirometry parameters. Skin prick test was done using commercially available kit containing *A. fumigatus* antigen (Allergo Skin Prick Test from Merck Specialities Private Limited, India) along with positive control (histamine) and negative control (normal saline). The wheal diameter of 3 mm or more was considered positive. Serum total IgE and *A. fumigatus*-specific IgE levels were done using the enzyme-linked immune sorbent assay (ELISA)-based ImmunoCAP method (Phadia). Serum precipitin test for precipitating IgG antibody was done using double immunodiffusion technique (Immy ID fungal antibody system, from USA). The Serum precipitin test was reported as positive or negative. Serum IgG against *A. fumigatus* was done in all enrolled patients using ELISA based ImmunoCAP method (Phadia). Complete hemogram was done with emphasis on absolute eosinophil count.

Chest X-ray was taken in all enrolled patients. A radiologist, who did not know the patient's clinical and laboratory information, reported all chest X-rays. Chest X-rays were assessed for the presence of radiological features compatible with ABPA as per the diagnostic criteria proposed by Agarwal *et al.* [10]. HRCT chest was done only if chest X-ray was abnormal or if there was high index of suspicion such as serologically positive ABPA. HRCT of the chest was done to look for any bronchiectasis, parenchymal fibrosis, consolidation, atelectasis and mucous plug.

The diagnosis of ABPA was based on recent criteria proposed by Agarwal *et al.* [10] in 2013. A child was diagnosed with ABPA if there was (i) increased total IgE levels (>1000 IU/ml), (ii) positive skin prick test or increased aspergillus-specific IgE levels (>0.35 kUA/l) and (iii) two out of three criteria [(a) radiological abnormality of ABPA, (b) positive serum precipitants or increased aspergillus-specific IgG levels of >27 mgA/l and (c) total eosinophil counts >500/mm^3] were fulfilled [10]. Aspergillus sensitization (AS) was defined as increased aspergillus-specific IgE (>0.35 kUA/l) or positive skin prick test for aspergillosis without fulfilling the criteria for ABPA. We compared the clinical and laboratory variables between children with ABPA and without ABPA to identify risk factors for ABPA.

Data management and statistical analysis

Data were collected on predesigned case record form and entered in MS Excel spreadsheet. Data were analysed using STATA 12.0 software (Stata Corp, College Station, TX). The prevalence of ABPA and AS was calculated as percentage and its 95% confidence interval (CI). Dichotomous data were presented as percentage and continuous data as mean ± SD if normally distributed and as median with interquartile range (IQR) if not normally

distributed. The risk factors for ABPA were compared between children with ABPA and without ABPA. To compare continuous data with normal distribution and skewed distribution, student '*t*'-test and Mann-Whitney test, respectively were used. To compare dichotomous data, chi-square test or fisher exact test (if a value was <5 in 2×2 table) was used. We considered for regression analysis if many risk factors for ABPA were identified. A p-value of < 0.05 was considered significant.

RESULTS

A total of 235 asthmatic children were assessed for asthma control and 106 [Boys 72 (67.9%), Girls 34 (32.1%)] children with poorly controlled asthma were enrolled in this study. The mean (SD) age of children was 10.2 (2.6) years.

Of 106 children, 12 (11.3%; 95% CI 5.2–17.5%) children had ABPA. A total of 65 children (61.3%; 95% CI 52.0–70.7%) had AS. Overall, total IgE levels were more than 1000 IU/ml in 44 (41.5%) children. Out of these, 12 children fulfilled criteria for ABPA, and remaining 32 did not fulfilled criteria for ABPA.

Only one (0.9%) child was positive for serum precipitants for aspergillus, whereas 13 (12.3%) children had serum IgG against aspergillus more than 27 mg/dl. Almost half (51, 48.6%) children had absolute eosinophil counts more than 500/mm^3. A total of 43 (40.6%) included children had abnormal X-ray findings and commonest finding was bilateral hyperinflation (Fig. 1A) in 13 (12.3%) patients. A total of 29 (28.7%) children had imaging findings suggestive of ABPA [consolidation 17, nodules 6, bronchiectasis 5 (central bronchiectasis 2), fibrosis 1]. X-ray findings of two children with ABPA are shown in Fig. 1B and C and HRCT chest of another child with ABPA is shown in Fig. 2. Five (4.7%) children had bronchiectasis (two had central bronchiectasis, two had non-central bronchiectasis and one had bronchiectasis on right side), out of them three (two central bronchiectasis and one non-central bronchiectasis) patients fulfilled the criteria for ABPA.

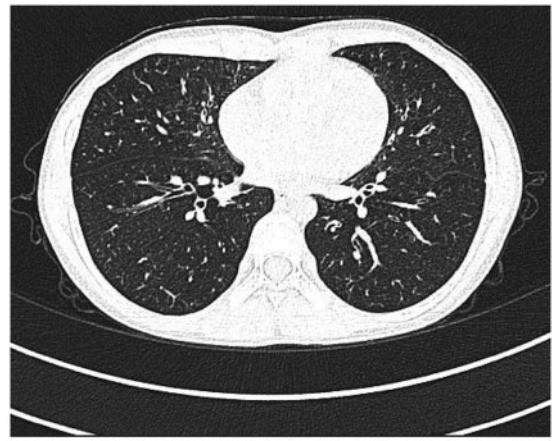

Fig. 2. HRCT chest of a child with ABPA showing early central bronchiectasis.

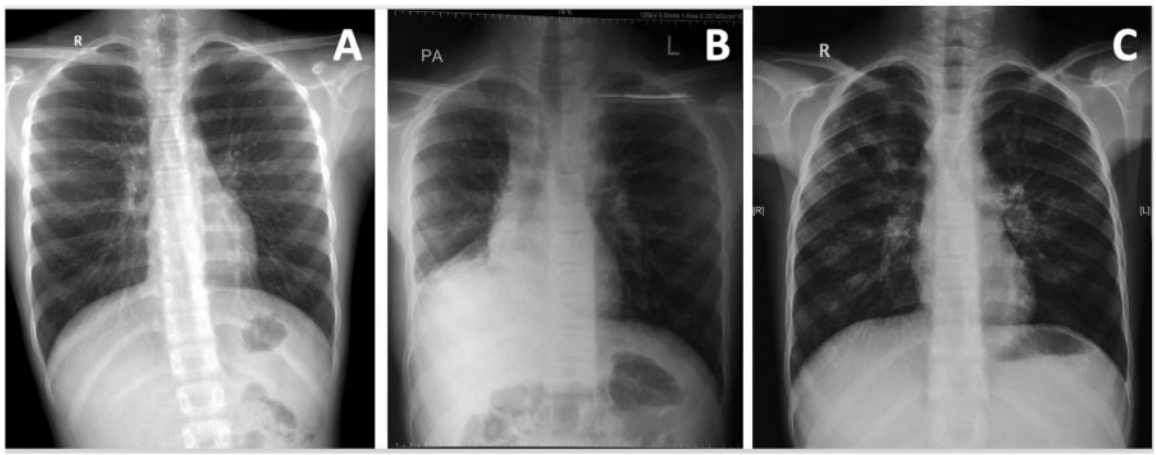

Fig. 1. Chest X-rays of three different asthmatic children with ABPA; (**A**) hyperinflation, (**B**) collapse of right lower lobe and (**C**) Bronchiectasis with mucus impaction.

Table 1. Factors associated with ABPA among asthmatic children

Risk factor	ABPA ($N = 12$)	No ABPA ($N = 94$)	*p*-value
Age, years (mean ± SD)	10.3 ± 2.7	10.1 ± 2.6	0.831
Boys: girls	9: 3	63: 31	0.577
Duration of asthma in years, median (IQR)	3.5 (2, 4.5)	4.5 (2, 6)	0.229
Number of courses of oral steroids in last 1 year, median (IQR)	1 (0.5, 2)	1 (0, 2)	0.328
Number of emergency visits in last 1 year, median (IQR)	1 (0, 2)	1 (0, 2)	0.696
Poor compliance to therapy	4/11 (36.4)	32/95 (33.7)	0.932
Brownish sputum	3/9	3/71	**0.002**
Smoking at home	3/12	18/93	0.645
GER	3/12	8/94	0.084
Obesity	0/9	2/71	0.766
Allergic rhinitis	11/12	63/93	0.087
Sinusitis	2/12	10/93	0.545
Adenoid hypertrophy	5/12	30/93	0.515
Presence of dampness at home	4/12	27/93	0.795
Residence, urban: rural	7: 3	61: 20	0.716

SD, standard deviation; IQR, interquartile range; GER, gastroesophageal reflux. *p*-values in bold suggest statistical significant.

We compared various clinical (Table 1) and laboratory (Table 2) parameters between children with ABPA and without ABPA.

Allergic rhinitis, GER and brownish sputum were more in ABPA compared with non-ABPA patients, though allergic rhinitis and GER did not have statistically significant difference (Table 1).

The absolute eosinophil counts, total IgE levels and aspergillus-specific IgE levels were significantly higher in ABPA group (Table 2). But, median value of aspergillus-specific IgG was not different between the groups. The percentage of children with positive skin prick test for aspergillus, and percentage of children with aspergillus IgG > 27 mgA/l were not different between children with ABPA and without ABPA (Table 2). Percentage predicted values of FEV1 and $FEF_{25–75}$ were lower in asthmatic children with ABPA, though it did not reach statistically significant difference (Table 2). We also compared clinical and laboratory parameters among children with or without AS and are shown in Supplementary Tables S1 and S2. Among clinical parameters, allergic rhinitis and residence in mud house were seen more often in children with AS (Supplementary Table S1). As expected, aspergillus-specific IgE levels and positive skin prick test was more in AS as these were defining criteria. But, median value of aspergillus-specific IgG, and percentage of children with aspergillus IgG >27 mgA/l were not different among children with or without AS (Supplementary Table S2). Spirometry parameters were not different among children with or without AS except PEF that was high in children with AS compared with without AS (Supplementary Table S2).

DISCUSSION

We observed prevalence of ABPA in poorly controlled asthmatic children as 11.3% (95% CI 5.2–17.5%). ABPA is well recognized in adult asthmatics, but there are mainly case reports and small case series in asthmatic children (Table 3).

Shah *et al.* [29] reported 42 cases of ABPA among asthmatic children over 31 years of period, though they did not report denominator to evaluate prevalence of ABPA. Shah *et al.* [29] screened for ABPA in children with asthma having eosinophilia and abnormal chest X-ray. The first prevalence study of ABPA in asthmatic children by Chetty *et al.* [30] reported prevalence of ABPA as 15% in children with perennial asthma and prevalence of 6.5% in all children with asthma [30]. It is difficult to compare the prevalence directly as inclusion criteria by Chetty *et al.* [30] was not children with poorly controlled

Table 2. Laboratory parameters among asthmatic children with ABPA and without ABPA

Parameter	ABPA criteria fulfilled ($N = 12$)	ABPA criteria not fulfilled ($N = 94$)	*p*-value
FEV1[a], mean ± SD	76.1 ± 21.2 ($n = 10$)	85.3 ± 19.7 ($n = 77$)	0.172
FVC[a], mean ± SD	76.4 ± 18.6 ($n = 10$)	85.8 ± 21.3 ($n = 77$)	0.183
FEV1/FVC[a], mean ± SD	97.7 ± 10.4 ($n = 10$)	96.9 ± 12.4 ($n = 77$)	0.847
PEF[a], mean ± SD	87.5 ± 33.6 ($n = 10$)	83.6 ± 29.5 ($n = 77$)	0.712
FEF_{25-75}[a], mean ± SD	76.1 ± 35.2 ($n = 10$)	83.1 ± 34.0 ($n = 77$)	0.544
Hemoglobin (g/dl), mean ± SD	12.9 ± 1.1	13.0 ± 1.1	0.671
% of eosinophils, median (IQR)	10 (5.7, 14.1) ($n = 12$)	3 (1.15, 8.3) ($n = 93$)	**0.0016**
AEC (/mm^3), Median (IQR)	956 (793, 1278) ($n = 12$)	276 (95, 786) ($n = 93$)	**0.0009**
AEC >500/mm^3, *n/N* (%)	11/12 (91.7%)	40/93 (43.0%)	**0.002**
Aspergillus-specific IgE levels (kUA/l), Median (IQR)	2.24 (0.38, 16.34)	0.07 (0.03, 0.20)	**<0.0001**
Total IgE (kU/l), Median (IQR)	2517.5 (1470.5, 3752.5)	658.5 (273, 1689)	**0.0003**
Aspergillus-specific IgG (mgA/l), Median (IQR)	18.5 (6.05, 28.2) ($n = 12$)	8.98 (5.64, 19.65) ($n = 90$)	0.208
Positive skin prick test, *n/N* (%)	9/12 (75.0%)	44/94 (46.8%)	0.066
Aspergillus-specific IgG > 27 mgA/l, *n/N* (%)	3/12 (25.0%)	11/90 (12.2%)	0.225
Chest imaging suggestive of ABPA	12/12 (100.0%)	17/89 (19.1%)	**<0.0001**

[a]% of expected.

SD, standard deviation; IQR, interquartile range; GER, gastroesophageal reflux; AEC, absolute eosinophil count; FEV1, forced expiratory volume in 1st second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF_{25-75}, forced expiratory flow between 25 and 75% of FVC. *p*-values in bold suggest statistical significant.

asthma. Singh *et al.* [6] reported prevalence of ABPA as 26% in poorly controlled (defined as Expert Panel Report 3) asthmatic children from Northern India using Rosenberg-Patterson criteria, but used total IgE cut offs as > 1000 IU/ml rather than 417 IU/ml. The prevalence studies and large case series are mainly from India. There is hardly any large case series or prevalence study from developed countries. The reason for this regional difference may be environmental factor or some genetic predisposition. The regional difference in ABPA prevalence needs further research. India, being a tropical country, may be more aspergillus spores in environment, especially in overcrowded houses with poor ventilation.

The variable prevalence of ABPA in asthmatic children may be due to different diagnostic criteria for ABPA and different study inclusion criteria for asthmatic children. Singh *et al.* [6] used Rosenberg-Patterson criteria but total IgE cut offs was same as we used (>1000 IU/ml). In our study, only 1 (8.3%) out of 12 ABPA children had positive precipitin antibody. Similarly, Singh *et al.* [6] found positive precipitin antibody in four (15.4%) ABPA patients.

Rosenberg-Patterson *et al.* [31] proposed diagnostic criteria in 1977. Since then, the ABPA criteria are evolving over time [32]. The precipitating antibody criteria were removed from ABPA criteria recently. The second significant change in ABPA diagnosis criteria over time is increased cut off for total IgE from 417 to 1000 IU/ml [32].

In our study, out of 12 ABPA patients, 8 (72.7%) had abnormality in chest X-ray and 3 (27.3%) had bronchiectasis (2 had central bronchiectasis) on CT chest. Singh *et al.* [6] reported X-ray abnormality and central bronchiectasis in 69.2 and 11.5% ABPA cases, respectively. Shah *et al.* [29] reported central bronchiectasis in 76.2% (32/42) asthmatic children with ABPA. Lower prevalence of bronchiectasis in our study

Table 3. Published studies on ABPA in asthmatic children

Sl. No	Author	Country	Number of cases, age	Comments
1.	Slavin *et al.* [11]	USA	1 (9 years)	Probably first case in child with asthma
2.	Chhabra *et al.* [12]	India	2 (4.5 and 12 years)	Both had central bronchiectasis
3.	Ohshima *et al.* [13]	Japan	1 (2 years)	Child had associated IPEX
4.	Meza Brítez *et al.* [14]	Mexico	1 (3 years)	
5.	Ragosta *et al.* [15]	USA	1 (4 years)	Mis-diagnosed as TB initially
6.	Shah A *et al.* [16]	India	1 (9 years)	Presented as middle lobe syndrome
7.	Caballero *et al.* [17]	Spain	2 (6 and 3 years)	
8.	Schwerk *et al.* [18]	Germany	1 (13 years)	ABPA diagnosis delayed by 6 years
9.	Coop *et al.* [19]	USA	1 (13 years)	Masquerading as invasive aspergillosis
10.	Suzuki *et al.* [20]	Japan	1 (9 years)	
11.	Shah *et al.* [21]	India	1 (11 years)	Cavitary lesion
12.	Banerjee *et al.* [22]	India	10 (5–13 years)	
13.	Shah *et al.* [23]	India	2	Both have central bronchiectasis
14.	Bedi [24]	India	1 (10 years)	
15.	Turner *et al.* [25]	USA	2 (below 10 years)	
16.	Imbeau *et al.* [26]	USA	3 (diagnosis 20 months, 10 and 15 years)	First lung shadow at 6 months, 6 and 22 months of age
17.	Shah *et al.* [27]	India	1 (42 months)	Young age at diagnosis
18.	Das *et al.* [28]	India	1 (9 years)	Had associated aspergillus sinusitis
19.	Shah *et al.* [29]	India	42 (mean age 12.9 ± 4 years)	One of the largest series
20.	Chetty *et al.* [30]	India	16/107 perennial asthma (15%)	First prevalence study
21.	Singh *et al.* [6]	India	26/100 poorly controlled asthma	Older diagnostic criteria were used
22.	This study	India	12/106 poorly controlled asthma	We used recent diagnostic criteria

IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

and study by Singh *et al.* may indicate early diagnosis of ABPA before development of bronchiectasis. This is despite using same diagnostic criteria (Rosenberg-Patterson criteria) by Shah *et al.* and Singh *et al.*

The prevalence of AS was high (61.3%; 95% CI 52.0–70.7%) in our study. We could not find any study that reported AS in asthmatic children.

Identification of risk factors will help in conducting screening for ABPA in certain group of children with asthma. It will help in early diagnosis of ABPA and timely treatment. Here, we studied various clinical and laboratory parameters associated with ABPA. Brownish sputum was more in ABPA compared with non-ABPA patients (Table 1). Presence of allergic rhinitis and residing in mud house were risk factors for AS (Supplementary Table S1). Singh *et al.* [6] reported that more patients with ABPA were residing in rural area and FEV1% was lower in ABPA positive group. We didn't find any difference in spirometry parameters in ABPA and non-ABPA group.

There are few concerns for diagnosis of ABPA. There is no gold standard test to diagnose ABPA. The ABPA diagnosis is based on certain cut offs of various parameters that may be affected by steroid therapy. Therefore, a single cut off value of total IgE >1000 IU/ml may not be ideal. Even, in Agarwal 2013 criteria, there is foot note that for diagnosing ABPA, total IgE levels <1000 IU/ml may be accepted if other criteria for ABPA are fulfilled. Further, if ABPA is suspected and total IgE levels are between 200 and 500 IU/ml, the values should be repeated after 1–3 months.

There is ongoing search for biomarkers for ABPA. One such biomarker, the thymus- and activation-regulated chemokine has been evaluated mainly in ABPA in CF patients and it is found to be useful in differentiating ABPA from aspergillus colonization and AS [33]. This biomarker was not available for use in this study.

Evaluating ABPA prevalence in asthmatic children prospectively using recent ABPA diagnostic criteria [10] is strength of the study. Limitations of our study include that we included only poorly controlled asthma, not all asthmatic children, therefore the prevalence of ABPA is for poorly controlled asthmatic children, not for all asthmatic children. Another limitation was that we could not interpret spirometry parameters as per global lung initiative equations. Future studies may be considered to evaluate prevalence of ABPA in all asthmatic children.

CONCLUSION

We observed prevalence of ABPA as 11.3%, but prevalence of AS was high (61.3%) in children with poorly controlled asthma. We could not identify any specific risk factor for ABPA. All children with poorly controlled asthma should be screened for ABPA.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

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