

REGULAR ARTICLE

The diagnostic criteria for allergic bronchopulmonary aspergillosis in children with poorly controlled asthma need to be re-evaluated

Meenu Singh (meenusingh4@gmail.com)¹, Subhamoy Das¹, Anil Chauhan¹, Nandini Paul¹, Kushaljit Singh Sodhi², Joseph Mathew¹, Arunaloake Chakrabarti³

1.Advanced Pediatric Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

2.Department of Radiodiagnosis, Post Graduate Institute of Medical Education and Research, Chandigarh, India

3.Department of Medical Microbiology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Keywords

Airway inflammation, Allergy, Asthma

Correspondence

Meenu Singh, MD, Advanced Pediatric Centre, Post Graduate Institute of Medical Education and Research, Sector-12, Chandigarh, India 160012.

Tel: +91-172-2755306 |

Fax: +91-172-2744401 |

Email: meenusingh4@gmail.com

Received

26 June 2014; accepted 13 January 2015.

DOI:10.1111/apa.12930

ABSTRACT

Aim: The aim of this study was to examine the association between allergic bronchopulmonary aspergillosis (ABPA) and poorly controlled asthma in children and appraise the diagnostic criteria.

Methods: The study included 100 children with poorly controlled asthma. We diagnosed ABPA using the *Aspergillus* skin test, pulmonary function test, total and specific immunoglobulin E (IgE) to *Aspergillus fumigatus*, chest radiograph and high-resolution computed tomography. Patients were diagnosed and classified according to the Rosenberg–Patterson criteria for ABPA. The cut-off value for total serum IgE was calculated by receiver operating characteristics curve analysis.

Results: Of 100 children with poorly controlled asthma, 26 patients were ABPA positive. There was a significant difference in the forced expiratory volume in 1-sec/forced vital capacity ratio between ABPA positive (0.78 ± 0.14) and negative (0.87 ± 0.15) children ($p = 0.008$). ABPA positive children were categorised as seropositive, central bronchiectasis and other radiological findings. The receiver operating characteristics curve was constructed, and a value of 1200 IU/mL of total IgE was observed, with 88.5% sensitivity and 70.5% specificity.

Conclusion: This study showed an association between ABPA and poorly controlled asthma in children and suggests a higher cut-off value of total IgE for the diagnosis of ABPA.

BACKGROUND

There is overwhelming evidence for the presence of fungal sensitisation in patients with asthma. A large number of *Aspergillus* species have been found to be associated with asthma, the most prevalent being *Aspergillus fumigatus*. This is thought to be the strongest candidate responsible for two extreme immunologic phenomena, *Aspergillus*-sensitive asthma and allergic bronchopulmonary aspergillosis (ABPA). ABPA is an inflammatory pulmonary disorder that is characterised by immunological hypersensitivity to the allergens of *Aspergillus fumigatus* (1). The immunoglobulin E (IgE) level is a marker of immunologic response in ABPA, with a fall in the level representing remission and a rise indicating exacerbation (1). The disorder was first reported in 1890 and was later described by Hinson et al. in 1952 (2). Although *Aspergillus fumigatus* is most frequently

associated with ABPA, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus oryzae* and *Aspergillus glaucus* are also responsible for ABPA (2). There are few studies on ABPA in children with bronchial asthma, although it could be suspected that poorly controlled asthma might be associated with fungal sensitisation (3,4). Studies on fungal sensitisation in asthmatics have shown that it is associated with a reduced postbronchodilator forced expiratory volume (FEV1) (5). There is a lack of consensus on the

Abbreviations

ABPA, Allergic bronchopulmonary aspergillosis; BMI, Body mass index; FEV1, Forced expiratory volume; FVC, Forced vital capacity; IgE, Immunoglobulin E.

Key notes

- This study examined the association between allergic bronchopulmonary aspergillosis (ABPA) and poorly controlled asthma.
- Just over a quarter (26/100) of the children were ABPA positive with a significant difference in the forced expiratory volume in 1-sec/forced vital capacity ratio between ABPA positive and negative children.
- We found an association between ABPA and poorly controlled asthma and suggest a higher cut-off value of total immunoglobulin E for diagnosis.

diagnostic criteria for ABPA in children, as high levels of total IgE and IgE specifically related to *Aspergillus fumigatus* are commonly seen in children with asthma. The existing diagnostic criteria are based on studies conducted in the adult population, as very few studies have been carried out in the paediatric population. This study re-examined the diagnostic criteria, especially total IgE levels in children with ABPA and poorly controlled asthma.

PATIENT AND METHODS

We recruited 100 children with poorly controlled asthma after obtaining informed consent, in compliance with the Institute's ethical committee guidelines. Children aged from 5 to 15 years of age were enrolled over a period of 18 months during 2011 and 2012 from the Paediatric Allergy and Asthma Clinic of Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. The study was approved by the Institute's Ethics committee, PGIMER, Chandigarh (Memo No. 8543/PG/2Trg/10/15144).

The patients with bronchial asthma had to have two of the three following criteria: (i) a history of recurrent or episodic attacks of chest tightness, breathlessness and a cough that was worse at night, (ii) presence of wheeze on auscultation and (iii) evidence of obstructive defect on spirometry, defined as the ratio of forced expiratory volume in the first second forced expiratory volume (FEV₁) to forced vital capacity (FVC) of less than 70%, with or without significant bronchodilator reversibility (an increment of FEV₁ and/or FVC, of more than 12% and 200 mL after 400 µg of inhaled salbutamol). Poorly controlled asthma was defined according to Expert Panel Report III guidelines (6). Children were excluded if their families were not willing to give consent, if they were infected with HIV, diagnosed with congenital malformation or above 15 years of age or under five.

Criteria for Diagnosing ABPA in Asthma

Patients with bronchial asthma were screened for ABPA using the *Aspergillus* skin test and total serum IgE levels. If the *Aspergillus* skin test (Type 1) was positive and the IgE level was greater than 417 IU/mL, then further investigations for ABPA were carried out by determining their specific IgE levels to *Aspergillus fumigatus* and radio imaging. The *Aspergillus* skin test was performed by an intradermal prick of 0.2 mL of 1:1000 *Aspergillus fumigatus* antigen (Department of Medical Microbiology, PGIMER, Chandigarh) on the surface of skin of the forearm. At the same time, 0.2 mL of phosphate buffered saline at a pH of 7.2 was injected in the other forearm as a negative control. The reactions were classified as Type I, if a wheal and erythema developed within a minute, reached a maximum after 10–20 min and went away within 1–2 h. The reactions were classified as type III if any amount of subcutaneous oedema was present after 6 h (7). Levels of serum total IgE and specific IgE to *Aspergillus fumigatus* were assayed with commercially available kits using the fluorescent enzyme

immunoassay (UniCap Systems; Pharmacia Upjohn, Stockholm Sweden). *Aspergillus fumigatus* precipitins were detected using ouchterlony gel diffusion techniques, according to the method devised by Longbottom and Pepys (8). The Rosenberg and Patterson criteria were used to diagnose children with ABPA (Table S1) (9). The disease was further classified as seropositive or central bronchiectasis, based on the absence or presence of central bronchiectasis on radiological investigations. High-resolution computed tomography of the chest was carried out on patients who showed a radiological abnormality on plain chest radiology. Spirometry was carried out according to American Thoracic Society guidelines (10). The FEV₁ (%), FVC (%) and FEV₁/FVC ratio of all the enrolled patients were noted and compared.

Statistical analysis

Descriptive statistics and analytic statistics were carried out using the statistical package SPSS (SPSS version 17, for Windows; Chicago, IL, USA). The data were equally distributed, and parametric testing was carried out. The association with ABPA was presented as a percentage. The difference between categorical variables was analysed using Fisher's exact test, where a p-value of <0.05 was considered statistically significant.

RESULTS

Of the 100 enrolled children with poorly controlled asthma, 29 reacted positively to the *Aspergillus* skin test. Of these, 26 fulfilled the criteria for the diagnosis of ABPA. There was no difference in the age, weight or body mass index (BMI) of the children. However, there was a difference in the sex ratio distribution of the children meeting the criteria for a diagnosis of ABPA. In the ABPA positive group, the male female ratio was 4:1 and in the rest of the children, who had poorly controlled asthma but were ABPA negative, the male female ratio was 3:1 (Table S2). The mean age at presentation was 9.56 ± 2.23 years, and the youngest age at presentation was 5.5 years. More patients in the ABPA positive group lived in rural areas. Vital parameters, such as pulse, blood pressure and respiratory rate were similar in both groups, but FEV₁% was lower in the ABPA positive group. Of the 26 children who fulfilled the criteria of ABPA, three (11.5%) presented with central bronchiectasis on high-resolution computed tomography, 18 (69.2%) had some abnormal findings using this technique or other radiological findings and five (19.2%) were diagnosed as ABPA seropositive. There was no statistically significant difference in the age of onset, duration of cough, wheeze, duration of wheeze, mean number of exacerbations in the last 1 year and inhaled corticosteroids dose between the ABPA positive and negative groups (Table 1). But there was a significant difference in FEV₁/FVC between patients with ABPA (0.78 ± 0.14) and those without ABPA (0.87 ± 0.15) (p = 0.008).

The mean value of total serum IgE was significantly different between children who were ABPA positive (5376 ± 4051 IU/mL) and ABPA negative (1403 ±

Table 1 Clinical profile of enrolled ABPA positive and ABPA negative children

	ABPA positive group (N = 26)		ABPA negative group (N = 74)		p-Value
	Mean	SD	Mean	SD	
Age of onset of cough (years)	5.31	2.79	4.74	2.65	0.35
Duration of cough (years)	4.85	1.99	4.53	2.05	0.49
Age onset of wheeze (years)	5.31	2.79	4.84	2.65	0.45
Duration of wheeze (years)	4.85	1.99	4.40	2.10	0.35
Mean no. of exacerbations in the last 1 year	5.54	2.77	5.47	3.36	0.93
ICS dose ($\mu\text{g}/\text{day}$)*	423.08	153.12	394.26	75.46	0.36
Total serum IgE level (IU/mL)	5376.69	4051.04	1403.34	2052.03	≤ 0.001
Absolute eosinophil count (cell/ μL)	1484.27	2066.13	617.23	1227.92	0.05
FEV1/FVC ratio [#]	0.78	0.14	0.87	0.15	0.008

*ICS - Inhaled corticosteroids.

[#]FEV1/FVC ratio - Forced expiratory volume/Forced vital capacity.

2052 IU/mL) ($p \leq 0.001$) (Table 1). Of the 26 patients, 25 (96.2%) had elevated specific IgE (>0.35 kUA/L) against *Aspergillus fumigatus*, which is used as the cut-off value for diagnosis of ABPA in our laboratory, and 14 patients had lung changes that showed on an high-resolution computed tomography scan. The serum precipitating antibody IgG was positive in five cases in the total study group: in four (15.4%) of the 26 patients with ABPA positive and in one (1.4%) of the 74 patients with ABPA negative. The receiver operating characteristic curve was constructed, and 1200 IU/mL was determined as the cut-off value for the diagnosis of ABPA with 88.5% sensitivity and 70.5% specificity (Fig. 1).

DISCUSSION

In 1985, children with perennial asthma were screened for ABPA by Chetty et al. (11) and the prevalence was reported

to be 15%. The present study found a prevalence of 26% in children with poorly controlled asthma. Various studies from Europe and United States have reported a prevalence of ABPA of between 2% and 15% in patients with cystic fibrosis (12–14). There have not been any studies in India since Banerjee et al. (15) studied the clinical and immunological parameters of 10 children with ABPA. Major findings of this study included clinical features of bilateral infiltration and hilar lymphadenopathy, an elevated eosinophilic count ($300\text{--}2500/\text{mm}^3$) and elevated specific IgE (0.147–0.562) and IgG (0.426–1.8) to *Aspergillus fumigatus*. In our study, cystic fibrosis was only seen in three patients with ABPA positive, which reflects late stage ABPA, underlines the importance of testing these patients to make an early diagnosis. It is important to look for risk factors that may predispose a child with poorly controlled asthma to develop ABPA. Several studies have shown that ABPA affects all age groups, with no age being more predisposed than another to the condition (16). Male children are more susceptible to developing ABPA, and this is supported in our study and previous studies (17).

Allergic bronchopulmonary aspergillosis has been found to affect urban and rural communities with similar frequency (18). But in our study, more males from rural areas were affected than those in urban areas. This could be due to greater exposure to *Aspergillus* spores in northern India, where agricultural farming is the main occupation. Most of the patients came from the Punjab and the surrounding areas. It is very important to carry out a clinical and serological evaluation of all patients with poorly controlled asthma for differential diagnosis of fungal sensitisation and ABPA. Our study diagnosed different forms of ABPA – central bronchiectasis, serologic and other radiological findings – based on serological and radiological findings.

There are no cut-offs for total IgE levels, with many researchers using 1000 IU/mL (19) and others using 1000 ng/mL (equivalent to 417 IU/mL) (20). In our study, even the ABPA negative group had higher levels of total IgE. This could be due to sensitisation to other antigens/

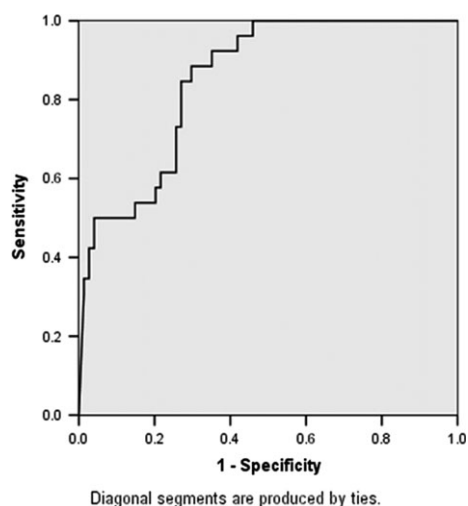


Figure 1 Receiver Operating Characteristic (ROC) Curve showing Total IgE. Diagonal segments are produced by ties.

allergens. A recent study proposed a cut-off value of total IgE 1000 IU/mL for the diagnosis of ABPA (17). The receiver operating characteristic curve of total IgE in our study showed a cut-off value of 1200 IU/mL, which may be proposed as a predictive parameter for ABPA in children with asthma. In contrast to the previous study, where 90% patients had visible precipitin (IgG) peaks in the ABPA positive group, our study showed that four of the 26 patients with ABPA positive (15.4%) had the IgG precipitating antibody against *Aspergillus* (21). Further studies are needed to delineate the cut-off value for specific IgE and to find the epidemiological factors that caused a higher prevalence of these conditions in our population.

CONCLUSION

Our study found a higher association with ABPA in children with poorly controlled asthma than earlier studies. Patients with ABPA without central bronchiectasis, but with other radiological features, should be followed up and treated to prevent further lung damage. We suggest a total IgE level of 1200 IU/mL as the diagnostic cut-off value for diagnosing ABPA.

ACKNOWLEDGEMENT

We would like to thank the Department of Medical Microbiology, Post Graduate Institute of Medical Education and Research, Chandigarh.

References

- Agarwal R, Gupta D, Aggarwal AN, Saxena AK, Saikia B, Chakrabarti A, et al. Clinical significance of decline in serum IgE levels in allergic bronchopulmonary aspergillosis. *Respir Med* 2009; 104: 204–10.
- Tillie-Leblond I, Tonnel AB. Allergic bronchopulmonary aspergillosis. *Allergy* 2005; 60: 1004–13.
- Lazarus AA, Thilagar B, McKay SA. Allergic bronchopulmonary aspergillosis. *Dis Mon* 2008; 54: 547–64.
- Chaudhary N, Marr KA. Impact of *Aspergillus fumigatus* in allergic airway diseases. *Clin Transl Allergy* 2011; 1: 4.
- Agbetile J, Fairs A, Desai D, Hargadon B, Bourne M, Mutalithas K, et al. Isolation of filamentous fungi from sputum in asthma is associated with reduced post-bronchodilator FEV1. *Clin Exp Allergy* 2012; 42: 782–91.
- Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007; 120(Suppl.): S94–138.
- Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013; 43: 850–73.
- Longbottom JL, Pepys J. Pulmonary Aspergillosis: diagnostic and immunological significance of antigens and C-substance in *Aspergillus fumigatus*. *J Pathol Bacteriol* 1964; 88: 141–51.
- Knutsen AP, Slavin RG. Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis. *Clin Dev Immunol* 2011; 843763.
- Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J* 2005; 26: 153–61.
- Chetty A, Bhargava S, Jain RK. Allergic bronchopulmonary aspergillosis in Indian children with bronchial asthma. *Ann Allergy* 1985; 54: 46–9.
- Geller DE, Kaplowitz H, Light MJ, Colin AA. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. Scientific Advisory Group, investigators, and coordinators of the epidemiologic study of cystic fibrosis. *Chest* 1999; 116: 639–46.
- Mastella G, Rainisio M, Harms HK, Hodson ME, Koch C, Navarro J, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis. *Eur Respir J* 2001; 17: 1052–3.
- Carneiro AC, Lemos AC, Arruda SM, Santana MA. Prevalence of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis in the state of Bahia. *Brazil. J Bras Pneumol* 2008; 34: 900–6.
- Banerjee B, Joshi AP, Sarma PU, Roy S. Evaluation of clinico-immunological parameters in pediatric ABPA patients. *Indian J Pediatr* 1992; 59: 109–14.
- Hedayati MT, Pasqualotto AC, Warn PA, Bowyer P, Denning DW. *Aspergillus flavus*: human pathogen, allergen and mycotoxin producer. *Microbiology* 2007; 153: 1677–92.
- Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Del Giacco S, et al. Fungal allergy in asthma-state of the art and research needs. *Clin Transl Allergy* 2014; 4: 14.
- Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax* 2009; 64(Suppl. 1): i1–51.
- Patterson R, Greenberger PA, Radin RC, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. *Ann Intern Med* 1982; 96: 286–91.
- Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2002; 110: 685–92.
- Longbottom JL. Allergic bronchopulmonary aspergillosis: reactivity of IgE and IgG antibodies with antigenic components of *Aspergillus fumigatus* (IgE/IgG antigen complexes). *J Allergy Clin Immunol* 1983; 72: 668–75.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Rosenberg – Patterson Diagnostic criteria for ABPA.

Table S2 Demographic profile of enrolled children with poorly controlled asthma.