

Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis among asthma patients in eastern India

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To find out the clinico-radiomycopathological profile of allergic bronchopulmonary Aspergillosis (ABPA) and incidences of aspergillus hypersensitivity (AH) among asthma patients, 215 consecutive extrinsic asthma patients were screened with aspergillus intradermal test and those found positive for AH were investigated further for ABPA. Out of 215 asthma patients (124 males and 91 females), 54 were hypersensitive to AH and 15 of them fulfilled criteria for ABPA. On repeated culture of sputum and/or broncho-alveolar lavage fluid, *A. flavus* was the most common isolate (40%), followed by *A. fumigatus* (26.67%). No species was isolated in 4 cases (26.6%). AH/ABPA is not very uncommon in this part of the country. Diseases similar to ABPA caused by other fungus might be diagnosed if allergen tests for other fungal antigens are made widely available. A strong clinical suspicion and proper laboratory backup is essential for diagnosing ABPA and related diseases. [J Indian Med Assoc 2010; 108: 863-5]

Key words : Allergic bronchopulmonary aspergillosis, aspergillus spp, asthma hypersensitivity.

Allergic bronchopulmonary aspergillosis (ABPA) is an immunologically mediated pulmonary disorder caused by hypersensitivity to aspergillus antigen. Only a minority of patients with aspergillus hypersensitivity (AH) actually develop the clinical features of ABPA. The first description of the condition was by Hinson *et al*¹ and the diagnostic criterion of classical ABPA was led by Rosenberg *et al*².

Since then various authors³⁻⁷ have considered different sets of major and minor criteria to establish the diagnosis of ABPA. The prevalence of ABPA in bronchial asthma (2-32%) and ABPA in asthma patients with AH (6-68%) as reported in previous literatures vary widely due to non-uniformity in the diagnostic criteria adapted, lack of standardization of antigen used (commercial *versus* local made) and difference in the disease specific cut-off values^{2,4}. The main objective of this study is to find out the prevalence of AH/ABPA among asthma patients and study of the clinico-radiomycopathological profile of ABPA as diagnosed in a chest clinic in a tertiary hospital of eastern

India.

MATERIAL AND METHOD

A total of 215 asthma patients attending the chest clinic over a period of one year were screened with intradermal skin test for aspergillin antigen after adequate counselling and obtaining informed consent at RG Kar Medical College.

Patients who received oral glucocorticoids for more than 2 weeks in preceding 6 months were not included in the study. Those with clinical diagnosis of allergic rhinitis and chronic sinusitis excluded from the study population.

The aspergillin antigen (indigenously developed in PGIMER, Chandigarh) used for intradermal skin test was prepared from isolates of stock culture and properly sterilised and standardised. The inoculation site was observed for wheal and flare reaction every 15 minutes for first one hour test (type I hypersensitivity reaction); then for subcutaneous oedema at the end of 6 hours (Type III reaction); and indurations more than 5mm after 48hours/72hours (type IV reaction) subcutaneous oedema. Patients with immediate type hypersensitivity reaction to aspergillus were investigated further to rule out ABPA. All of the patients with AH were investigated with complete blood count (reveals eosinophilia), chest radiograph, microscopic studies, culture preparations, chest radiography, high resolution computed tomography (HRCT) of the chest, immunodiffusion test for aspergillus by Oudin and Ouchaterlony method and immunoglobulin assay (total IgE and aspergillus specific IgE/IgG).

Those who were found to have peripheral eosinophilia

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(absolute eosinophil count $>500/\text{cmm}$) with or without transient or fixed pulmonary shadow were further investigated for detailed radiological evaluation with high resolution CT thorax, sputum / BAL fluid microscopy and slide culture in potato dextrose agar and SDCA, immunodiffusion test for aspergillus (culture filtrate of *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*) by Oudin and Ouchaterlony method. Wet mount from sputum/BAL were prepared using of 10-20% KOH. Smears were examined by light microscopy as well as fluorescent microscopy (using Calcofluor white) later was found 15% more sensitive than the previous one. Aspergillus specific IgG/IgE titre was measured by ELISA and was considered to be positive if the test value was more than twice the average value as measured in non-ABPA but AH asthma patients. All patients underwent spirometry with bronchodilator reversibility and were categorised as mild, moderate and severe obstructions as per standardised practice.

The diagnosis of ABPA was made if they met a minimum of five major and one minor criterion in the original description by Rosenberg *et al*². Major criteria include: (1) History of asthma, (2) peripheral blood eosinophilia, (3) type I cutaneous hypersensitivity reaction to aspergillus spp, (4) precipitating antibody against aspergillus spp, (5) fleeting or fixed radiological opacities in chest x-ray, (6) raised specific serum IgG against aspergillus spp, (7) raised specific serum IgE against aspergillus spp, (8) HRCT-thorax showing proximal bronchiectasis.

Minor criteria include: (1) Type III cutaneous reactivity to aspergillus antigen, (2) sputum culture positive for aspergillus spp, (3) passage of mucus plugs in sputum.

They were further classified as ABPA-S (seropositive)

with no obvious radiological findings, ABPA-CB and ABPA-CB-ORF (central bronchiectasis with other radiological finding) based on HRCT findings, depending on the presence or absence of central bronchiectasis.

OBSERVATIONS

A total of 215 asthma patients including 124 males and 91 females, age ranging from 21 years to 72 years (mean age 35.6 years) has been enrolled in the study. Out of 215 asthma patients,

only 54 patients (25.12%) showed immediate type hypersensitivity reaction (type I reaction) to aspergillus antigen. Complete blood count for absolute eosinophil count and chest radiograph was done in all 54 patients (29 males and 25 females). Absolute eosinophil count was found to be more than 1000/cmm in 14 out of 54, more than 500 but less than 1000 per cmm in 8 out of 54. The chest radiograph was found to be abnormal in 20 out of 54. Finally ABPA was diagnosed in 15 (27.78%) of these 54 fulfilling a minimum six major criteria. The clinical details of 15 patients (9 males and 6 females) diagnosed with ABPA were reviewed and presented in Table 1. Thus the overall prevalence of ABPA among asthma patients in this study group was 15 (6.97%) out of 215. Average duration of illness before diagnosis of ABPA was made and was 3.7 years. History of atopy was present in all of these patients. The most common presentation was frequent exacerbations of asthma (85%), haemoptysis 20%, fever (42%) and fleeting pneumonia 15%.

The most common radiological finding was central bronchiectasis (93%) followed by early bronchiectatic changes (35%), areas of consolidation (27.5%), fleeting shadow (40%) and lobar collapse in one probably due to mucus impaction. Total IgE level is above 1000 IU/ml in all 14 cases. Aspergillus specific IgG was borderline positive in 2 (cases 10 and 12) according to local laboratory reference value. By repeated culture of sputum and/or BAL fluid, *A. flavus* was isolated in 6 out of 15 (48%), *A. fumigatus* in 4 (26.67%), *A. niger* in one of the *A. flavus* cases and no growth in 4 (26.67%). According to minimum diagnostic criteria, ABPA-CB was diagnosed in 13 (86.67%) and ABPA-S in 2 (13.33%). Serum precipitin test was done in

Table 1 — Clinical Profile and Serological Results as Observed in Patients Diagnosed with ABPA

Sl No	Age in years/sex	Extrinsic	Fleeting pneumonitis	Eosinophilia (absolute)	Intradermal test	Immunodiffusion test	Serum IgE (IU/ml)	Central/proximal bronchiectasis	Aspergillus sp IgG/IgE (U/ml)	Repeated culture of sputum/BAL	Minimal diagnostic criteria for ABPA	No of major criteria fulfilled
1	22M	+	-	1260	+	+	2500	+	38	<i>A. flavus</i>	ABPA-CB	7/8
2	31M	+	-	800	+	+	5260	+	42	<i>A. flavus</i> , <i>A. niger</i>	ABPA-CB	6/8
3	50M	+	-	560	+	+	1440	+	24	<i>A. flavus</i>	ABPA-CB	6/8
4	40M	+	+	600	+	+	1800	-	40	<i>A. fumigatus</i>	ABPA-S	6/8
5	35F	+	+	2300	+	+	3800	+	26	<i>A. flavus</i>	ABPA-CB	8/8
6	54F	+	-	1800	+	+	2800	+	32	<i>A. flavus</i>	ABPA-CB	7/8
7	72F	+	-	1620	+	+	3600	+	40	<i>A. flavus</i>	ABPA-CB	7/8
8	67F	+	-	1020	+	-	1360	+	32	No growth	ABPA-CB	6/8
9	55F	+	-	1145	+	-	1680	+	14	No growth	ABPA-CB	6/8
10	49M	+	+	1220	+	-	1440	+	18	No growth	ABPA-CB	7/8
11	52M	+	+	625	+	-	1852	+	12	No growth	ABPA-CB	6/7
12	45M	+	+	1144	+	+	1799	+	20	<i>A. fumigatus</i>	ABPA-CB	8/8
13	52 F	+	+	1680	+	+	>2500	+	>200	<i>A. fumigatus</i>	ABPA-CB	8/8
14	148M	+	-	2400	+	+	1760	+	>200	<i>Aspergillus spp</i>	ABPA-CB	7/8
15	45M	+	+	620	+	+	1450	-	28	<i>Aspergillus spp</i>	ABPA-s	7/8

M-Male; F-Female

all but one and was positive in 10 out of 14 (71.43%).

Five (33.33%) out of 15 cases revealed positive culture for *M. tuberculosis* (BAL fluid-Ziehl-Neelsen stain and AFB culture by BACTEC method) received antituberculosis drug before the diagnosis of ABPA was established. One patient (case 14), along with oral corticosteroids received antituberculosis drugs.

DISCUSSION

The first reported case of ABPA from India was by Shah⁷. Since then various case series have been published from different corners of India^{3,8}. In a study, undertaken by Prasad *et al*⁸ showed 7.4% prevalence of ABPA among patients with bronchial asthma.

According to the criteria led by Rosenberg *et al*¹ only three fulfilled all eight criteria, five fulfilled seven, and six fulfilled six criteria. Thus a total of 15 patients fulfilled a minimum of five major and one minor criterion and diagnosed as a case of ABPA. Sputum and/or BAL fluid culture revealed aspergillus spp in all these 11 cases. However, culture was negative in rest 4 cases. The most common isolate was *Aspergillus flavus* rather than *A. fumigatus* as described classically in ABPA in previous studies^{3,8}. Aspergillus specific IgG was reported to be positive in 12 out of 105 asthma patients, which included 8 patients with ABPA as stated by Maurya *et al*¹. However, none among 26 healthy adults in the control group showed positive reaction. Type I hypersensitivity reaction was positive in 20% of general population as described by Prasad *et al*⁸.

To conclude, this disorder is not uncommon in India but grossly under-reported. The low incidence in the eastern part is partly due to lack of awareness and partly due to poor mycology laboratory facility in this part of the country. Overall a high level of suspicion is needed to make a diagnosis of ABPA.

Table 2 — Various Clinicopathological Parameters in Allergic Bronchopulmonary Aspergillosis in Various Studies

Parameter	Present study	Maurya <i>et al</i> ¹	Prasad <i>et al</i> ⁸	Agarwal <i>et al</i> ³	Chakrabarti <i>et al</i> ⁶
Total no of cases	215	105	42	564	89
AH in asthma	54	30	-	223	74
ABPA in asthma	15	8	42	126	18
ABPA in AH (%)	15/54	8/30	-	126/223	18/89
Mean age of ABPA (years)	48	28	31.2	34.4	32
Mean duration of illness (years)	3.7	-	12.2	8.8	11.0
Family history of atopy (%)	100%	62.5%	52.4	-	88%
History of antituberculous drugs	5	6/8	38/42	59	81
Eosinophilia >1000/cmm	10/15	All	88	-	83
Sputum culture in ABPA	11	3/8	27/39	-	18
CXR :					
Normal	-	-	4.8%	-	-
Fleeting infiltrate	42.9%	100%	66.7%	36.5%	5.5%
Central bronchiectasis	79%	100%	100%	61.2%	83%
Peripheral bronchiectasis	-	-	-	38.8%	-

REFERENCES

- 1 Hinson KFW, Moon AJ, Plumber NS — Broncho-pulmonary aspergillosis: review and report of 8 new cases. *Thorax* 1952; 7: 317-33.
- 2 Rosenberg M, Patterson R, Mintzer R, *et al* — Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; 86: 405-14.
- 3 Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK — Allergic bronchopulmonary aspergillosis lesions from 126 patients attending a chest clinic in North India. *Chest* 2006; 130: 442-8.
- 4 Maurya V, Gugnani HC, Sarma PU, Madan T, Shah A — Sensitization to aspergillus antigens and occurrence of allergic bronchopulmonary aspergillosis in patients with asthma. *Chest* 2005; 127: 1252-9.
- 5 Behera D, Guleria R, Jindal SK, Chakrabarti A, Panigrahi D — Allergic bronchopulmonary aspergillosis: retrospective study of 35 cases. *Indian J Chest Dis Allied Sci* 1994; 36: 173-9.
- 6 Chakrabarti A, Sethi S, Raman DS, Behera D — Eight years study of allergic bronchopulmonary aspergillosis in an Indian teaching hospital. *Mycoses* 2002; 45: 295-9.
- 7 Shah JR — Allergic bronchopulmonary aspergillosis. *J Assoc Physicians India* 1971; 19: 835-41.
- 8 Prasad R, Garg R, Sukla D — Allergic bronchopulmonary aspergillosis: a review of 42 patients from a tertiary care center in India. *Lung India* 2009; 26: 38-40.

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