Original Article

DOI: 10.7860/JCDR/2020/43385.13698

Allergic Bronchopulmonary Aspergillosis in Acute Severe Asthma- A Cross-sectional Study

Others Section

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ABSTRACT

Introduction: The prevalence of Allergic Bronchopulmonary Aspergillosis (ABPA) is sparingly studied among asthmatics in Southern India.

Aim: To assess the occurrence of ABPA in patients with Acute Severe Asthma and to describe the clinical spectrum of ABPA among them.

Materials and Methods: This was a cross-sectional analytical study performed on 150 patients of acute severe asthma, who attended Pulmonary Medicine Department and Emergency Medical Services department in a government tertiary care institute in Southern India; from January 2016 to December 2017 over a period of two years. Patients were evaluated for ABPA using Rosenberg-Patterson criteria.

The distribution of data for the categorical variables such as gender of patients, signs and symptoms, radiological parameters etc., was expressed as frequencies and percentages. The comparison of these variables between the groups was carried out by using Chi-square or Fishers-Exact test. The comparison of these variables between the groups was carried out by using independent Students t-test or Mann-Whitney U test whichever was appropriate. All statistical analysis was carried out at 5% level of significance and p-value <0.05 was considered significant.

Results: There were 49 males and 101 females (mean age 40.25±12.8 years). As per Rosenberg Paterson criteria, 31.3% had ABPA-Central Bronchiectasis and 10% ABPA-Seropositive. The occurrence of *Aspergillus* Hypersensitivity (AH) was 54% (81/150) and occurrence of ABPA was 41.3% (62/150) in acute severe asthma.

Conclusion: The study reflects high occurrence of AH and ABPA in severe asthmatics. Such alarming values calls for the use of Skin prick test as a screening tool for evaluation of patients with severe asthma. There is a pressing need for early diagnosis and timely treatment to protect the patients from irreversible lung damage.

Keywords: ABPA, Aspergillus hypersensitivity, Rosenberg patterson criteria

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is recognised as a group of immunologically mediated pulmonary disease, first described by Hinson KFW et al., in 1952 [1]. ABPA occurs due to airway hypersensitivity to *Aspergillus* species and the most common fungus implicated in the pathogenesis of ABPA is *Aspergillus fumigatus*. This ubiquitous fungus possesses immune-evasive properties which predispose susceptible individuals to develop an allergic or invasive disease [2].

Patients with bronchial asthma and cystic fibrosis have a high risk of developing ABPA. Studies show that 1-2% of asthmatics and 2-15% of cystic fibrosis patients develop complications related to hypersensitivity to *Aspergillus fumigatus* [3]. Asthma-related hospital admissions and deaths are significantly higher in patients with skin test reactivity to *Aspergillus*.

Despite the well-known fact that Asthmatics with ABPA are at high risk of repeated asthma exacerbation; hospitalisation and mortality, majority of the studies are hospital based and describes the prevalence of ABPA. Only a few studies have assessed the outcome of patients with ABPA [4].

Because of the indolent nature of the disease, clinician has to maintain a high index of suspicion in cases with poor asthma control [5]. It is in this perspective; this study was conducted to measure the occurrence of ABPA in patients with acute severe asthma.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pulmonary Medicine and Clinical Immunology in a tertiary care institute in Southern India, during the period of January 2016 to December 2017. Study protocol was approved by Institute Ethics Committee vide letter dated 06.02.2016, JIP/IEC/SC/2015/25/287. A detailed informed and written consent from the patient was obtained in Tamil language.

The primary objective was to assess the occurrence of ABPA in patients with Acute Severe Asthma. The secondary objective was to describe the clinical spectrum of ABPA among the patients presenting as Acute Severe Asthma.

Inclusion Criteria

1. Patients of acute severe asthma-Pulse Rate >120/min, Respiratory Rate >30/min, spO_2 <90% in room air, Peak Expiratory Flow Rate <50%, who attended the Emergency Medical Services Department and Department of Pulmonary Medicine, during the study period.
2. Aged more than 18 years.

Exclusion Criteria

Patients previously diagnosed as ABPA, patients on systemic glucocorticoids over past 1 week, Patients treated with systemic glucocorticoids for more than three weeks within last six months and pregnant patients.

Sample size was estimated using the statistical formula for estimating a proportion with 5% level of significance and 5% absolute precision. For the expected proportion of 27% of patients with ABPA [6], the estimated sample size was 150 with 20% relative precision.

A detailed clinical history was taken for all patients with respect to presenting complaints, and clinical examination was done. The peripheral blood eosinophil count was carried out by Neubauer counting chamber. The *Aspergillus* Skin Prick Test (SPT) was performed using *Aspergillus fumigatus* antigen (Aspergillin; Merck

Allergopharma, Germany).

Levels of serum total IgE, specific IgE and specific IgG for *Aspergillus fumigatus* were assayed with commercially available kits using the fluorescent enzyme immunoassay (UniCap Systems; PharmaciaUpjohn, Stockholm, Sweden). All recent and previous chest radiographs were reviewed for the presence of fleeting opacities, toothpaste or gloved finger shadows, ring shadows or tramline shadows indicative of bronchiectasis, or for evidence of fibrosis. High-resolution CT of the thorax was performed.

For the diagnosis of ABPA, Rosenberg-Patterson criteria (1977) were used [Table/Fig-1] [7]. The presence of six out of eight major criteria makes the diagnosis of ABPA and was further classified as seropositive ABPA (ABPA-S) or ABPA with central bronchiectasis (ABPA-CB) based on the absence or presence of central bronchiectasis [8].

1. Asthma
2. Roentgenographic fleeting pulmonary opacities
3. Skin test positive for *Aspergillus* (type I reaction, immediate cutaneous hyper-reactivity)
4. Eosinophilia
5. Precipitating antibodies (IgG) in serum
6. IgE in serum elevated (>1,000 IU/mL)
7. Central bronchiectasis
8. Serum *Aspergillus fumigatus*-specific IgG and IgE

[Table/Fig-1]: Rosenberg-Patterson criteria [7] (1977).

STATISTICAL ANALYSIS

The distribution of data for the categorical variables such as gender of patients, signs and symptoms, radiological parameters etc., was expressed as frequencies and percentages. The comparison of these variables between the groups was carried out by using Chi-square or Fishers-Exact test. The data for the continuous variables such as age, haematological parameters, pulmonary function parameters etc were expressed as mean with SD or median with range. The comparison of these variables between the groups was carried out by using independent Students t-test or Mann-Whitney U test whichever was appropriate. All statistical analysis was carried out at 5% level of significance and p-value <0.05 was considered significant. The statistical software package IBM PASW Statistics Version 19.0 was used.

RESULTS

One hundred and fifty patients, who fulfilled the inclusion criteria, were enrolled in the study; 49 patients were males and 101 patients were females. Mean age of the patients was 40.25±12.8 years, with minimum age 18 and a maximum of 71 years. Median duration of symptoms was 12 years with interquartile range of 10 years.

Sixty-two (41.3%) patients were found to have Allergic Broncho-Pulmonary Aspergillosis; 47 patients were categorised as ABPA-CB and 15 patients were Seropositive ABPA (ABPA-S) based on Rosenberg Patterson criteria [Table/Fig-2].

Criteria	ABPA-S N=15(%)	ABPA-CB N=47(%)
Uncontrolled asthma	15 (100)	47(100)
Skin prick test	15 (100)	47 (100)
Median absolute eosinophil count	1310	1437
Median serum total IgE	1280	1320
Specific IgE	12	38
Specific IgG	5	25
Fleeting infiltrates	1	6
HRCT-CB	0 (0)	47 (100)

[Table/Fig-2]: Table showing ABPA-S and ABPA-CB patients as per Rosenberg Patterson criteria.
ABPA-S: Seropositive ABPA; ABPA-CB: ABPA with Central Bronchiectasis; HRCT: High resolution computed tomography

SPT was performed for all patients using *Aspergillus fumigatus* antigen. Immediate cutaneous reactivity was observed in 54% (n=81) of study subjects whereas, 46% (n=69) showed negative response.

Median Absolute Eosinophil Count (AEC) of ABPA-CB study subjects was 1437 cells/microLitre with interquartile range of 750. Median AEC for ABPA-S study subjects was found to be 1310 cells/microLitre. Median total IgE of ABPA –CB patients was 1320 IU/mL with interquartile range 1103 IU/mL and for ABPA-S, median total IgE was 1280 IU/mL with interquartile range 945 IU/mL [Table/Fig-3].

Serum total immunoglobulin E (IU/mL)	No. of patients with central bronchiectasis (n=47)
Less than 1000	8
1000<2000	28
2000<3000	5
3000 and above	6

[Table/Fig-3]: Distribution of serum IgE values among ABPA-CB class.

The median serum total IgE for ABPA (ABPA-S+ABPA-CB) patients was 1380 IU/mL. The difference in the measurement of AEC between ABPA-CB and ABPA-S was statistically significant. (Mann-Whitney test p-value<0.05) [Table/Fig-4,5].

Group	Median AEC (cells/mL)	p-value
ABPA-CB (N=47)	1437	**<0.05**
ABPA-S (N=15)	1310	

[Table/Fig-4]: Median Absolute Eosinophil Count in different groups of ABPA. The difference in the measurement of AEC between ABPA-CB and ABPA-S is statistically significant (Mann-Whitney test).

Group	Median total IgE (IU/mL)	p-value
ABPA-CB (N=47)	1320	**<0.05**
ABPA-S (N=15)	1280	

[Table/Fig-5]: Median total IgE in different groups of ABPA (Mann-Whitney test).

Chest radiograph was done for all 150 patients and findings were analysed as per ABPA class. Among 47 study subjects with ABPA-CB, cystic shadows with hyperinflation were the most common chest radiographic finding which was seen in 13 (27.7%) patients. Among 15 Seropositive ABPA patients, chest radiograph showed fleeting opacities in one patient.

Among subjects with ABPA-CB, HRCT thorax showed peripheral bronchiectasis with central bronchiectasis in 22 (46.8%) subjects. Out of 15 seropositive ABPA patients, 6 patients (40%) showed normal findings in HRCT thorax.

On analysing the serum specific IgE, out of 62 study subjects with ABPA, 80.6% of patients were positive for specific IgE and 48.3% were positive for specific IgG [Table/Fig-6,7].

Serum specific Immunoglobulin parameters		ABPA-CB (N=47)	
		Frequency	Percentage
Specific IgE	Positive	38	80.9
	Negative	9	19.1
Specific IgG	Positive	25	53.2
	Negative	22	46.8

[Table/Fig-6]: Serum specific Immunoglobulin estimation among study subjects with ABPA-CB.

Association of specific IgE positivity to *Aspergillus fumigatus* with central bronchiectasis in the ABPA-CB class was evaluated. There was an association between specific IgE positivity and central bronchiectasis in the ABPA-CB class [Table/Fig-8]. The association between specific IgG positivity and central

bronchiectasis in ABPA-CB class was not statistically significant [Table/Fig-9].

Serum specific immunoglobulin parameters		ABPA-S (N=15)	
		Frequency	Percentage
Specific IgE	Positive	12	80
	Negative	3	20
Specific IgG	Positive	5	33.3
	Negative	10	66.6

[Table/Fig-7]: Serum specific Immunoglobulin estimation among study subjects with ABPA S.

Serum specific immunoglobulin parameters		ABPA-CB (N=47)		p-value
		Frequency	Percentage	
Specific IgE	Positive	38	80.9	p<0.001
	Negative	9	19.1	

[Table/Fig-8]: Serum specific IgE estimation among study subjects with ABPA-CB (Fisher's-exact test).

Serum specific immunoglobulin parameters		ABPA-CB (N=47)		p-value
		Frequency	Percentage	
Specific IgG	Positive	25	53.2	p=0.10
	Negative	22	46.8	

[Table/Fig-9]: Serum specific IgG estimation among study subjects with ABPA-CB (Fisher's-exact test).

DISCUSSION

Being a ubiquitous fungus, it is highly unlikely to avoid exposure. It should be remembered that establishing a cause and effect between fungi and asthma is still a challenge. A number of patients develop sensitisation before development of lung changes. Patients with severe and persistent asthma are more prone to fungal colonisation and sensitisation.

In this study, the occurrence of *Aspergillus* hypersensitivity among patients with acute severe asthma was 54% and occurrence of ABPA was found to be 41.3%. In a recent meta-analysis (20 studies, 5092 asthmatics), conducted by Agarwal R et al., it was found that *Aspergillus* Hypersensitivity was prevalent among 28% of outpatient asthmatics and ABPA was prevalent among 12.9% of outpatient asthmatic population [6]. The index study in which outpatients and inpatients were included, higher prevalence of ABPA was observed.

In this study, skin prick test positivity to *Aspergillus fumigatus* antigen was found in 54% of patients with acute severe asthma. Among asthmatics, Skin prick test positivity to *Aspergillus fumigatus* as per various studies, ranged from 14% to 46% [6,9,10]. Indian studies done by Maurya V et al., reported SPT positivity of 28.5% and Agarwal R et al., reported 38.5% SPT positivity among outpatient asthmatics [6,9]. Another study by Agarwal R et al., among acute severe asthma patients reported SPT positivity of 50.9% [11]. The occurrence of Skin prick test positivity for *Aspergillus fumigatus* is slightly higher in the present study population.

Absolute Eosinophil Count (AEC)

Median Absolute Eosinophil Count of study subjects with ABPA-CB was higher than for those study subjects with ABPA-S. This notifies the importance of peripheral eosinophilia in evaluation of patients with severe asthma. When there is a patient with poor asthma control and frequent exacerbations with Absolute Eosinophil Count above 1000 cells/microLitre further evaluation for ABPA has to be done. However, various studies show conflicting evidence in this regard [11-13]. According to the study by Agarwal R et al., 53% of patients with ABPA had AEC less than 1000/ microliter [11]. In another study done by Sarkar A et al., the mean AEC for patients with ABPA was 2048 cells/microlitre which was higher than the cut-off value of 1000 cells/microlitre as per Rosenberg-Patterson criteria [12].

Serum Immunoglobulin

In this study, the median serum total IgE for ABPA (ABPA-S+ABPA-CB) patients was 1380 IU/mL. In a study by Agarwal R et al., the mean serum total IgE was 3237 IU/mL (ABPA-S+ABPA-CB) [10]. This difference could be explained by the lower concentration of antigen in this geographical region as proposed by Nath A et al., [13].

Among 47 patients with Central bronchiectasis, eight patients with central bronchiectasis had serum total IgE less than 1000 IU/mL who were positive for ABPA-CB by other 6 criteria. The difference in serum total IgE among patients with ABPA-CB and ABPA-S was statistically significant (p-value <0.05). Patients with higher values of serum total IgE may be more likely to belong to ABPA-CB class. A study by Natarajan S and Subramanian P, found that patients of ABPA-CB and ABPA-CB with other radiological features had a mean serum IgE values of 5,588 IU/ml and 11,740 IU/ mL, respectively [14].

There were 80.6% patients who were positive for specific IgE. In a study done by Prasad R et al., out of 13 patients with ABPA, all 13 had elevated serum specific IgE ad specific IgG [15].

Among 62 patients with ABPA-CB, chest radiograph showed bronchiectasis in 47 patients and it was confirmed by HRCT. Chest radiograph remains a valuable and cost-effective tool in diagnosis of ABPA in resource limited settings, where HRCT is not available. Twenty two subjects with central bronchiectasis had associated peripheral bronchiectasis also. Agarwal R et al., reported peripheral bronchiectasis in 33-43% depending on the criteria used for defining central bronchiectasis [16].

Limitation(s)

All patients who had received glucocorticoid were excluded from the study. This would have lead to an underestimation of the actual prevalence of ABPA. This was a hospital based study and the results cannot be directly extrapolated to the population. Follow-up of the study participants was not done.

CONCLUSION(S)

The high prevalence of Allergic Bronchopulmonary Aspergillosis calls for early evaluation of ABPA in patients with severe asthma.

Acknowledgement

The authors would like to acknowledge the help of Dr. R. Manju head of Pulmonary Medicine for her support and Mr. D. Kalaiarasan, BCG technician for the help in spirometry.

Disclaimer: This study was presented by the author in American Thoracic Society International Conference in 2019.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Dec 16, 2019
- Manual Googling: Feb 13, 2020
- iThenticate Software: Apr 18, 2020 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Dec 10, 2019**
Date of Peer Review: **Dec 30, 2019**
Date of Acceptance: **Mar 13, 2020**
Date of Publishing: **May 01, 2020**