

Original Research Article

Allergic bronchopulmonary aspergillosis in resistant asthmatics

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ABSTRACT

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an immune mediated lung disease caused due to hypersensitivity reaction of antigen *Aspergillus fumigates*. ABPA is more prevalent in patients with asthma and cystic fibrosis. Thus, the current investigation was done to estimate the prevalence and association of ABPA with resistant asthma, to identify the clinical and laboratory pointers of ABPA and to identify the effect of ABPA and its treatment on the course of resistant asthma.

Methods: Current investigation was a prospective and non-blinded study conducted on patients of Rajiv Gandhi government general hospital, Chennai with bronchial asthma, having frequent exacerbation related problems. Demographic, clinical (hematological) and radiological investigations were performed for staging and treatment of all the enrolled patients. Follow up of patients was done periodically to investigate re-admission of respiratory events or other illnesses. All the collected data was statistically analyzed.

Results: Prevalence of ABPA in treatment resistant bronchial asthma patients was 19%. Positive family history, history of atopy and recurrent exacerbations were identified as significant risk factors among ABPA patients. Whereas duration and severity of asthma had no significant association with ABPA patients, bronchiectasis and parenchymal damage were significantly observed in patients of ABPA. Skin prick test serum eosinophils and IgE antibody levels were observed as good screening test parameters to identify ABPA. Prednisolone and itraconazole are considered as highly reliable and effective treatment strategies in ABPA.

Conclusions: Current investigation revealed that ABPA must be considered as a possible prevailing disease in treatment refractory cases of asthma on conventional steroids.

Keywords: ABPA, *Aspergillus fumigates*, Resistant asthma, Prevalence, Clinical and radiological pointers, Immunocompromised patients

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a common fungal infection predominantly affecting the human lungs considered as an immunologically mediated lung disease.¹ ABPA is a consequence of hypersensitivity reaction to repeated inhalation of antigen *Aspergillus* spores, specifically *Aspergillus fumigatus* which has the ability to colonize in lungs.^{1,2} ABPA is observed to be more prevalent in asthmatics, patients of cystic fibrosis, and immuno-compromised patients who are on steroid therapy.³ ABPA is observed predominantly in adults of age

group between 30 to 50 years of age, but it is also observed in children.¹⁻³ It is reported that approximately 4 million people worldwide are affected and incidence of ABPA are observed to be highest in winter season worldwide.⁴ Published literature and reports states that prevalence of ABPA patients of asthma and cystic fibrosis is approximately 13% and 9% respectively.⁵ Common symptoms of ABPA include wheezing, weight loss, cough, fatigue, coughing up blood, shortness of breath and in rare cases fever and it characteristically presents with eosinophilia, bronchospasm and pulmonary infiltrates.⁶ Although the mortality rate due to ABPA is low and

observed only in extreme conditions like, resistant secondary bacterial infections in the preexisting dilated airways, progressive desaturation and respiratory failure and cor pulmonale but significant morbidity due to ABPA can result due to poor asthma control, difficulty in tapering off corticosteroids and other drugs, bronchiectasis and parenchymal scarring.⁷

ABPA is classified into three different classes based on symptomatology immunological values.⁸ In ABPA-S class patients correlates with the clinical, immunological and blood values fitting into recommended criteria without proximal bronchiectasis.⁹ In ABPA-CB class patients express additional clinical parameters and serum values together with the proximal bronchiectasis and in ABPA-CB-ORF class ABPA patients together with all the above said features exhibits proximal bronchiectasis in X-ray findings. Patients also exhibits roentgenographic features such as lung fibrosis, scars, bullous changes, cavity formation, and other pleural involvement like effusions and thickening.⁸⁻¹⁰ A clinical system has been developed in order define different stages of ABPA; according to the system stage I is acute, stage II is remission, stage III is recurrent exacerbation, stage IV is steroid-dependent asthma and stage V is pulmonary fibrosis.¹¹ Stage I patients are known asthmatic and exhibit positive diagnostic features of ABPA like raised serum Immunoglobulin E levels and raised eosinophil counts with a positive intradermal skin prick test. X-ray indicates upper and middle lobes opacity such as consolidation.¹² Prednisolone is the preferred line of treatment in stage I for symptomatic relief and limiting exacerbations. In Stage II, reduction of symptoms due to prednisolone therapy is observed; immunoglobulins remain at basal values without any rise or fall in titre and complete clearance of opacity is observed in X-ray, this stage of individuals may remain static or proceed to next step at any point of time.¹¹⁻¹³ In stage III recurrence of asthma with rising immunoglobulin E titre and new roentgenographic shadows on chest X-ray is observed. In stage IV persistence of cough and sputum, with audible rhonchi and infiltrates in chest X-ray are observed. Symptoms and blood values of absolute eosinophil counts and levels of immunoglobulins remains elevated. Despite of prednisolone treatment the patients in this stage deteriorate continuously. In stage V ABPA patients who are undiagnosed and simply treated with reliever and controller treatment protocols for asthma end up in parenchymal and airway destruction bronchiectasis, cavity and fibrosis.¹¹⁻¹⁵

Rapid diagnosis, implementation and execution of proper treatment and management strategy are critical to prevent complications and disease progression in ABPA.¹⁶ Clinical investigations, radiographic and immunological findings would assist in describing the etiology, for evaluation, and effective management of ABPA.¹⁷ Lack of standardized diagnostic criteria and management protocols even till date makes ABPA a challenge to the pulmonologist.¹⁸ Some of the widely followed diagnostic strategies for ABPA includes known asthmatic, positive

skin prick test, raised serum IgE concentration (>1000 ng/ml), serum precipitin levels, absolute eosinophil count, chest X-ray and proximal bronchiectasis.¹⁶⁻¹⁹ Diagnostic and treatment strategies in ABPA are aimed towards identifying and classifying the disease, to prevent worsening of asthma and retard the relentless progression of ABPA, to identify and treat the cases at a early stage to prevent recurrent attack, to sterilize the airways and mucosal secretion against this monomorphic fungus to prevent further attacks and relapse, to get relief from the recurrent attacks of ABPA like cough, breathlessness, wheezing, to arrest the stage wise progression of disease and prevent permanent structural and functional damage like central bronchiectasis and for controlling episodes of acute inflammation and limit progression of lung injury.²⁰⁻²² It is imperative to consider ABPA in patients who are resistant and refractory to standard protocol based treatment for bronchial asthma.²³ The importance thus lies on the fact that, on correct identification and with appropriate treatment, patients can be relieved of their ordeal. Thereby the patient's quality of life can be improved with increased disease-free interval and reduced workplace absenteeism. Anti-inflammatory drugs like corticosteroids, steroid therapy, antifungal therapy, Anti IgE therapy, omalizumab and bronchodilators are some of the preferred therapies in ABPA.^{23,24} Since ABPA being recognized as a disease that predominantly affects asthmatics the aim of the current investigation was to diagnose and stage ABPA and to estimate its prevalence and association with bronchial asthma. The current investigation was also carried out to study the impact of ABPA on asthmatics that were refractory to protocol-based treatment.

Aim and objectives

Aim of the current investigation was to study the prevalence's and clinical impact of ABPA in patients with resistant asthmatics with frequent exacerbation. Primary objectives of the current study were to determine the prevalence of ABPA in patients with resistant asthma, to identify the clinical and laboratory pointers of ABPA and to identify the effect of ABPA and its treatment on the course of resistant asthma. Secondary objectives of current study were; to assess the disease severity and treatment modification for control in asthmatics due to the coexistence of ABPA and to periodically assess the prognosis after the modification of treatment.

METHODS

Study design, location, population and duration

Current investigation was a prospective, uncontrolled non-blinded study conducted on patients visiting both out-patients and in-patients departments of Rajiv Gandhi government general hospital for asthma related problems, atopy and allergic rhinitis with frequent exacerbation. The study was conducted on total 100 patients, visiting medical OPD, emergency wards and asthma department

of Rajiv Gandhi government general hospital; a tertiary care centre for the urban and rural population in an around Chennai and neighboring states. Current investigation was done for duration of six months with a periodic follow up at time intervals of 15 days initially for first month and then monthly up to 6 months.

Inclusion criteria

Patients with uncontrolled bronchial asthma, patients with frequent asthma exacerbation and patients having difficulty in tapering inhalational steroids were included in the study.

Exclusion criteria

Severely ill patients, patients with coexistence of other respiratory diseases, patients with disorientation and patients who were unwilling or unable to participate in the investigation were excluded from the study.

Procedure

In current investigation, patients were screened initially as per the inclusion and exclusion criteria. Those patients who got admitted for asthma exacerbation and steroid dependent asthma were enrolled in current study and were assessed for the risk factors of ABPA. Staging, treatment and follow up of ABPA among the patients who were found to have resistant to conventional treatment was done after taking a written informed consent from the patients or their legal representatives. In current investigation a semi structured questionnaire was filled after interviewing the patients or their attendees. Stratification of bronchial asthma and ABPA patients was done according to guidelines. Laboratory investigations like complete blood count, total serum IgE concentration, chest X-ray, absolute eosinophil count, pulmonary function test, KOH mount, and skin prick test were performed on all the enrolled patients. The patients were then consulted to investigate any re-admission for respiratory events or other illnesses. All the collected data was statistically analyzed.

Statistical analysis

Study data were analyzed using statistical package for social sciences (SPSS) and Epi Info software's. Data was analyzed using ANOVA and Chi-square statistical tests, p<0.05 was considered as level of significance.

RESULTS

Population characteristics

Results and observations of current investigation revealed that out of total 100 patients who were enrolled in current study after fulfilling inclusion criteria 40 were male asthmatics and 60 were female asthmatics. ABPA was diagnosed in total 19 patients out of 100 refractory asthmatics. Out of 19 patients with ABPA, 11 (57.9%) were females and 8 (42.1%) were males (Figure 1). The

mean age of ABPA positive patients was observed to be 34.421±10.90 years (Table 1). ABPA positive patients were observed to be suffering from asthma from on an average of 15 years (Figure 2). Statistically significant number of (17 out of 19) ABPA positive patients had family history and positive to skin prick test (Figure 3).

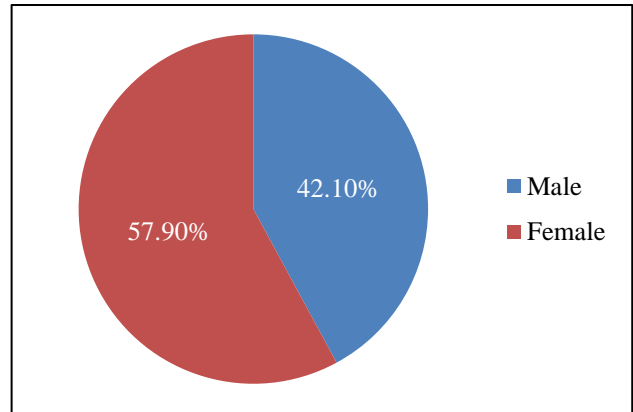


Figure 1: Gender based distribution of patients.

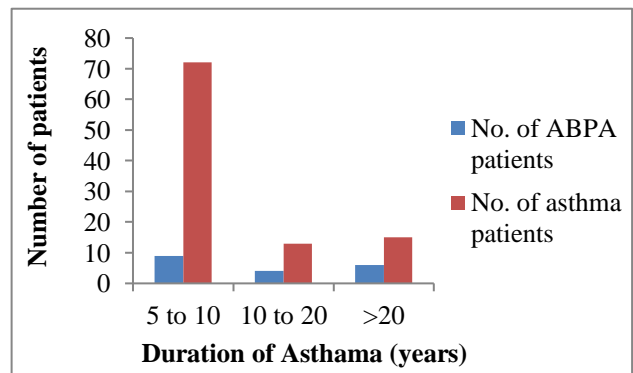


Figure 2: Distribution of patients according to duration of disease.

P=0.39 statistically insignificant difference.

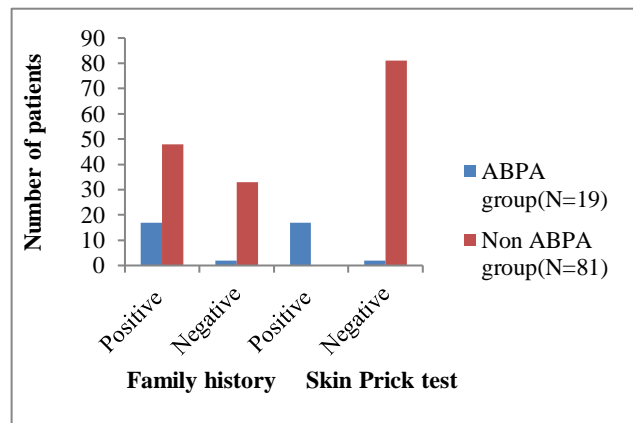


Figure 3: Distribution of patients according to family history and skin prick test parameters.

P<0.01 for family history and p<0.0001 for skin prick test indicated that difference in both the parameters was statistically significant.

Laboratory investigations

Laboratory investigations revealed that in ABPA positive patients mean absolute eosinophil count was observed to be 1322.73 ± 458.99 against 288.13 ± 338 in ABPA negative patients (Figure 4). Results of IgE level determination studies revealed that in ABPA positive patients the average IgE level was 2245 ± 458.99 whereas for ABPA negative patients the average IgE level was 694.41 ± 567.07 (Figure 4). In majority of the ABPA positive patients (63.15%); chest X-ray and HRCT chest were observed to be normal (Figure 5). Sputum of significant number of ABPA positive patients (10 out of 19) was observed to be spore positive in KOH mount study (Figure 5). Current study investigational results also indicated that significant number of ABPA positive patients (14 out of 19) were atopic (Figure 5). It was observed through current study findings that ABPA positive patients had significantly higher pre-treatment exacerbations with mean value of 3.52 ± 1.17 in comparison to ABPA negative patients with a mean pre-treatment exacerbations value of 0.90 ± 0.63 (Figure 6). It was also observed through current study results that there was a significant reduction in the average post-treatment exacerbations value of ABPA positive patients (0.94 ± 0.70) in comparison to ABPA negative patients (0.85 ± 0.03) (Figure 6). Results revealed that mean saturated oxygen levels (SpO₂) in ABPA positive patients was observed to be $95 \pm 3\%$ which was significantly lower than ABPA negative patients with average SpO₂ level of $98 \pm 1\%$ (Table 1). Mean ratio of forced expiratory volume (FEV1)/forced vital capacity (FVC) value in ABPA negative patients was observed to be 0.73 ± 0.06 which was significantly lower than the mean value in ABPA positive patients (0.85 ± 0.03) (Figure 7).

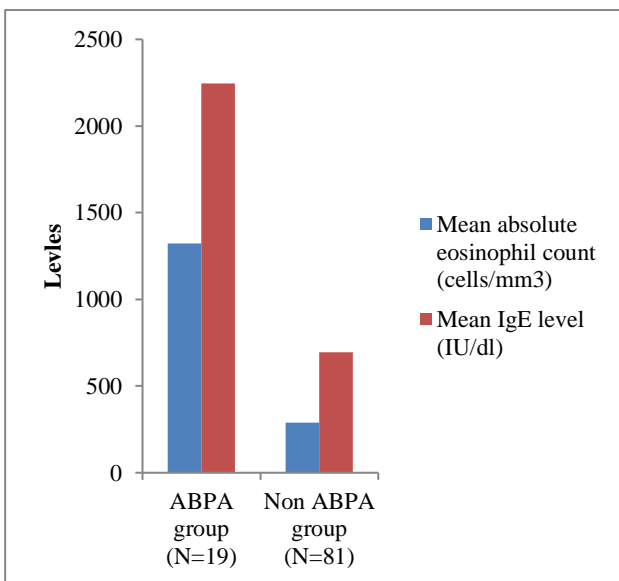


Figure 4: Comparison between mean absolute eosinophil count and IgE level values between ABPA positive and negative groups.

P<0.0001 for both the parameters indicated that difference in both the parameters was statistically significant.

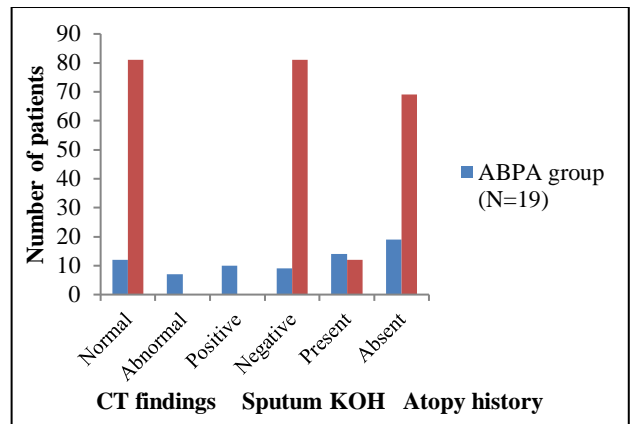


Figure 5: Comparison of CT findings, sputum KOH mount and history of atopy parameters between mean between ABPA positive and negative groups.

P<0.0001 for all the parameters indicated that difference in all the parameters was statistically significant.

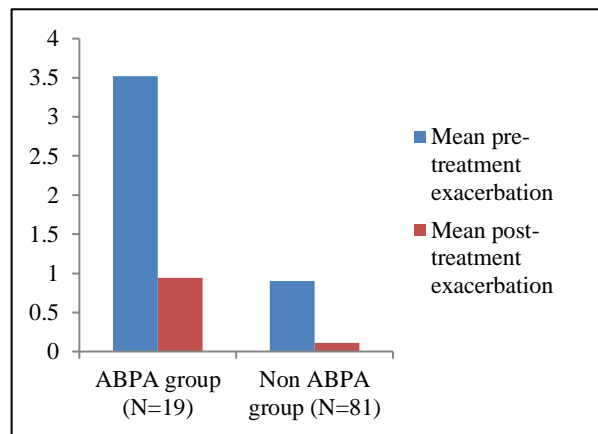


Figure 6: Comparison of mean pre-treatment and post-treatment exacerbation values between mean between ABPA positive and negative groups.

P<0.0001 for both the parameters, indicated that difference was statistically significant.

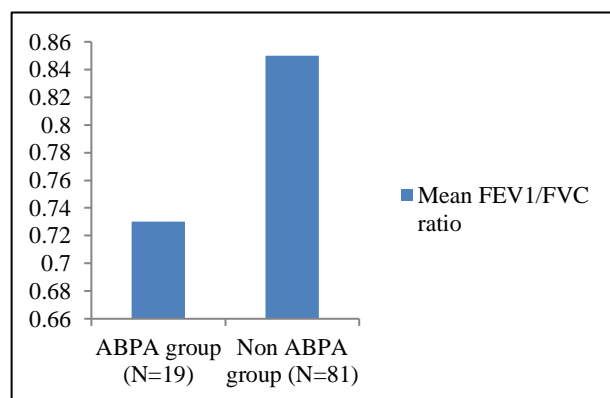


Figure 7: Comparison of mean FEV1 to FVC ratio between mean between ABPA positive and negative groups.

P<0.0001 indicated that difference was statistically significant.

Type of ABPA

Among the total 19 ABPA positive patients' majority (63%) were categorized under ABPA-serological (ABPA-S) stage, while 26% of the ABPA positive patients were categorized under ABPA-other radiological feature (ABPA-ORF) stage and 11% under ABPA-central bronchiectasis (ABPA-CB) stage (Table 2).

Comparative characterization parameters amongst different types of ABPA patients

Results of current study revealed that maximum number of

ABPA positive patients (12 out of 19) were categorized as ABPA-S type. The average age of ABPA-S type of patients was observed to be 35.33±11.06 years and females (58.33%) outnumbered males (41.66%) in ABPA-S type of patients. It was observed that ten out of twelve ABPA-S patients had positive family history, whereas all twelve ABPA-S patients exhibited positive results in skin prick test. Comparative results of laboratory investigational parameters among patients of different types of ABPA are depicted in (Table 2). Results of statistical comparison of patients of different ABPA types based on various parameters is depicted in (Table 3).

Table 1: Comparative study of various demographic and clinical variables amongst ABPA positive and negative patients.

List of variables	ABPA positive, (n=19)	ABPA negative, (n=81)
Number of patients	19	81
Mean age	34.421±10.90	36.67±9.92
Male:female	8:11	32:49
Duration of asthma (Years)	15.2±10.2	17.34±9.60
Family history, (no.)	17	33
Skin prick test positive	17	0
Mean absolute eosinophil count (cells/ mm ³)	1322.73±458.99	288.13
Mean IgE levels (IU/dl)	2245±458.99	694.41±567.07
Chest X-ray	Normal:12, abnormal:7	Normal
HRCT chest	Normal:12 abnormal:7	Normal
Sputum KOH mount	10	0
Atopy history	14	12
Mean pretreatment exacerbation	3.52±1.17	0.90±0.63
Mean SpO ₂ (%)	95±3	98±1
Mean post treatment exacerbation	0.94±0.70	0.85±0.03
Mean FEV ₁ /FVC ratio	0.73±0.06	0.85±0.03

Table 2: Comparative characteristics of patients with different types of ABPA.

Comparative parameters	Types of ABPA			P value
	ABPA-S	ABPA-ORF	ABPA-CB	
Number of patients	12	5	2	-
Age (years)	35.33±11.06	29.8±11.07	40.5±10.6	>0.05
Duration of asthma (years)	13.95±8.6	16.2±13.42	21±18.38	>0.05
Absolute eosinophil count (cells/mm ³)	1365.5±481.3	1105±450.416	1610±93.3	>0.05
Serum IgE level (IU/dl)	2311±502.26	2053.4±539.19	232.5±14.84	<0.0002
Pre-treatment exacerbation	3.3±0.88	3.8±1.2	4±0	>0.04
Post treatment exacerbation	0.833±0.71	1.2±0.83	1±0	0.63
SpO ₂ (%)	96±3	96±2	92±1	0.17
FEV ₁ /FVC	0.761±0.05	0.70±0.05	0.67±0	0.02

Table 3: Statistical comparison of different types of ABPA based on varied parameters.

Variables	Mean difference	Comparison	P value	Significance
Post treatment exacerbation	258.51	Serology vs. ORF	>0.005	No
SpO ₂	2079.4	Serology vs. CB	<0.001	Yes
FEV ₁ /FVC ratio	1820.9	ORF vs. CB	<0.01	Yes

DISCUSSION

Prevalence rate, age and gender

It was observed through current study findings that out of 100 patients of refractory and resistant asthma who exhibited difficulty to treat history, 19 were positive for ABPA thus the prevalence rate observed in current study was 19%. Previous published reports revealed that amongst Indian population the prevalence of ABPA is 3-4% in asthmatics, out of which 15% belonged to the category of steroid sensitive patients.⁷⁻¹² Published literature also revealed that 3-14% patients of other related diseases also exhibited ABPA.⁵⁻⁹ In current study among the 19% of ABPA patients belonging to various stages of ABPA, exhibited definitive radiological evidence like bronchiectasis and related findings. In current study the total number of ABPA-S patients were 12, proximal bronchiectasis patients were 5 and p patients with mucus plugs, fibrosis were 2. The mean age group of ABPA patients was observed to be 36.67 years, which correlated with previous study published by Agarwal et al.¹⁶ In current study it was observed that amongst the 19 ABPA patients 11 were females and 8 were males with a male to female ratio of 0.091. The results of current study depicted that there was no significant correlation of gender difference on prevalence of ABPA but age of the patients significantly affected the prevalence of ABPA, these results were in accordance to previous published literature.¹⁻⁷

Duration of asthma

Current study findings revealed that out of total 19 ABPA patients 9 patients had asthma for 5-10 years, 4 patients for 10-20 years and 6 patients since more than 20 years, thus there was no significant correlation observed between duration of asthma with prevalence of ABPA thereby it was inferred that chronicity and severity were not parallel. These findings were in accordance to the previous published reports which revealed that severity of ABPA was linked with the sensitivity to pathogens and not to chronicity of the asthma.³⁻¹²

Family history

Current study findings revealed that among 100 patients enrolled in current study, 48 had family history of asthma and 17 out of 19 ABPA patients exhibited positive family history. Thus, it can be inferred that familial propensity is present in ABPA, and presence of hereditary causes had significant correlation with prevalence of ABPA, the observation was in accordance with the published literature.²⁵

History of atopy

It was depicted through current study findings that atopy was significantly associated with the predilection of ABPA. 14 out of 19 ABPA patients were atopic

individuals which is coherent with the published study reports.²⁶ It was observed in current study that 2 out of 2 patients with central bronchiectasis were atopic. In the non ABPA asthmatics only 12 out of 81 patients were atopic which exhibited a negative predictive value.

Smoking history

Current study findings revealed that only 3 persons out of 19 ABPA patients were smokers, thus suggesting that risk of smoking was not a significant factor in the pathobiology of ABPA, but immune dysregulation was still considered to have a role in cause of ABPA.

Skin intradermal test

In present study the study group was analyzed with intradermal screening test. The test results revealed that 17 out of 19 ABPA patients were positive for skin prick test. Whereas in all of the non ABPA patients skin prick test was negative. Thus, significance association of skin prick test in predicting the prevalence of ABPA was inferred.

Absolute eosinophil count

In current study the average absolute eosinophil count value in ABPA patients was observed to be 1322.73 cells/mm³ and for non ABPA patients the average value was 288.135 cells/mm³. It was inferred that number of eosinophils counts plays a pivotal role in diagnosing ABPA cases among the asthmatics. Reports published by Paterson et al also revealed similar findings.²⁷

Serum immunoglobulin E levels

Mean serum IgE level in ABPA patients was observed to be 2245.48 IU/dl in current study whereas non ABPA patients, were found to have lesser levels of serum IgE and the difference was observed to be statistically significant. Group of patients with high IgE levels were found to have no significant correlation with gender. But high IgE levels were significantly correlated with severity of disease and severity of radiological manifestations.

Radiology

Chest X-ray and the CT chest were inferred to have definitive role in diagnosing ABPA in current study. ABPA with proximal bronchiectasis was present in 2 out of 19 patients. Proximal bronchiectasis had more specific value, than the other types of bronchiectasis. No abnormal imaging pattern was present in the non ABPA group (81 patients). Abnormal finding was observed in 7 out of 19 ABPA patients.

Oxygen saturation (SpO₂)

Most of the ABPA patients in current study were observed to maintain good oxygen saturation levels

except in those patients with severe structural lung disease.

Types of ABPA

Out of the prevailing three types of ABPA, in current study ABPA-S was observed as the most commonly identified type.

Exacerbation reduction

Exacerbation is one of the serious clinical manifestations in patients with ABPA. As per current study findings, pretreatment exacerbation was observed to significantly high in ABPA patients compared to non ABPA group. It was also depicted through results of present study that the number of exacerbations reduced significantly, post-treatment in ABPA patients. Hence it was inferred through current study that treatment with prednisolone and itraconazole was effective in reducing the exacerbations. Similar findings were published by Muthu et al who reported a significant correlation of ABPA with the frequency in exacerbation.²⁸

Limitations

Limitation of the current study was the relatively small sample size of the study population, which was not adequate to make concrete recommendations.

CONCLUSION

It was concluded through current study findings that the prevalence of ABPA in the treatment resistant bronchial asthma patients was 19%. Positive family history, history of atopy and history of recurrent exacerbations were identified as risk factors among ABPA patients. Complications like bronchiectasis and parenchymal damage were observed in significant number among the study groups. Duration of asthma and severity of ABPA was observed to have no direct association. Skin prick test was observed as a good screening test to identify ABPA patients among asthmatics. Sputum test for potassium hydroxide mount also showed good number of positive results but cannot be used as a screening test. Blood values of eosinophils and IgE antibody levels significantly correlated with ABPA positivity among asthma patients. Significant differences in lung function were observed between ABPA and non ABPA groups. Exacerbations were reduced after treatment in significant number of ABPA patients thus efficacy of prednisolone and Itraconazole was considered as highly reliable with a good test outcome. Thus, it was overall concluded from current investigation findings that in refractory cases of asthma, ABPA must be considered as possible diagnosis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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