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Original Article

Internal Medicine Section

Proportion of Allergic Bronchopulmonary Aspergillosis Presenting as Difficult-to-control Asthma in Patients Attending a Tertiary Care Centre using the Modified ISHAM Criteria: A Cross-sectional Study

PILLAI NEETU SOMAN[1], PAULO VARGHESE AKKARA[2], SUNNY GEORGE[3], TP RAJAGOPAL[4]

ABSTRACT

Introduction: Difficult-to-control asthmatics, as defined by the Global Initiative for Management of Asthma (GINA), belong to a subset of patients whose symptoms remain uncontrolled despite adhering to maximal optimised therapy. Complex hypersensitivity reactions in response to airway colonisation with Aspergillus fumigatus, which occurs in patients with asthma or cystic fibrosis, are established factors for a poor response to treatment and frequent exacerbations. Only limited data related to Allergic Bronchopulmonary Aspergillosis (ABPA) is available from India, particularly from Kerala.

Aim: To assess the occurrence of ABPA in patients with difficult-to-control asthma using the modified ISHAM criteria.

Materials and Methods: This cross-sectional analysis was conducted in the Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India from February 2019 to July 2020. The study population comprised asthmatics attending the Pulmonary Medicine Outpatient Services who were on regular medications, including optimal doses of inhaled corticosteroid and long-acting beta-agonist combinations. Patients with two or more exacerbations per year requiring systemic steroids for symptom control and a positive skin test for Aspergillus fumigatus antigen were further analysed using the modified International Society for Human and Animal Mycology (IHAM) criteria to determine the proportion of difficult-to-control asthmatics with ABPA. A total of 185 subjects were enrolled. Twelve patients opted out of the study, and the remaining 173 patients were screened using the modified ISHAM criteria. Statistical analysis was performed using Stastistical Packages of Social Sciences (SPSS) software version 21.0. Continuous parameters were expressed as mean and median, while categorical parameters were measured as frequency and percentages.

Results: It was observed that 104 (60.1%) patients belonged to the age group between 41-60 years, while approximately 60 patients (34.7%) were below 40 years of age. Among the 173 patients, 86 (49.7%) tested positive for Aspergillus fumigatus antigen. Applying the ISHAM criteria, it was found that only 17 (9.8%) of these patients satisfied the criteria for co-existent ABPA. A total of 101 patients (58.4%) required at least one hospital admission, while 4 (2.3%) patients required more than three hospital admissions per year. Total 21 (12.1%) patients had IgE specific to Aspergillus fumigatus, while total IgE levels were elevated in 46 (26.6%) cases. Thirty-six cases (20.8%) had a high peripheral eosinophil count

Conclusion: This study suggests the possibility of the treating physician overlooking 10% of asthmatics in this region who are being managed as difficult-to-control asthma, but who have co-existent ABPA. This subset should be identified early in the course and managed separately for better treatment response.

Keywords: Aspergillus fumigatus, Asthma, International society for human and animal mycology

INTRODUCTION

Exacerbations of asthma are episodes characterised by a progressive decrease in lung function, warranting a change in treatment [1,2]. Aspergillus fumigatus is a ubiquitous saprophytic mould that thrives on decaying organic matter [3]. It induces a cascade of hypersensitivity reactions, propagating inflammation and resulting in pneumonia, mucoid impactions, bronchial obstructions, and resultant bronchiectasis. It may mimic slowly resolving pneumonia, tuberculosis, pulmonary thromboembolism, bronchogenic carcinoma, or even pleural effusion [4-7]. Clinically, it presents as difficult-to-control asthma despite frequent use of steroids. It may also be associated with fever, malaise, blood in sputum, or may present predominantly as allergic rhinosinusitis [8,9]. The condition is being increasingly recognised, and recent publications have reported prevalence rates ranging from 5.9% to 20.5% for ABPA and 38-43% for Aspergillus Hypersensitivity (AH) [10-13]. After conducting an exhaustive search in PubMed and National Centre for Biotechnology Information (NCBI), two studies were found that evidently were prevalence studies done in North India. In one study done by Singla N et al., a high prevalence of 70% was found among a series of 50 patients [14]. It was completely based on serology. In the second study done among severe asthmatics by Nath A et al., in a North Indian tertiary care center, it was observed that out of 350 patients, 21.7% were found to have ABPA [15]. Prasad R et al., reported a prevalence of 30.3% for AH and 7.4% for ABPA [16]. They performed screening through Aspergillus skin tests and serology. If clinical suspicion for ABPA exists, laboratory and imaging studies should be obtained to establish the diagnosis.

Accordingly, management strategies and screening algorithms could be incorporated, or modifications could be suggested to standard accepted management guidelines. The diagnostic criteria for ABPA have been a subject of debate, and the method of screening patients with asthma has also undergone considerable change with the proactive intention of identifying the various phenotypes. This is the reason for the variable prevalence rates of AH and ABPA reported in the literature. Aspergillus skin tests have been used

for screening patients with bronchial asthma for AH and ABPA. If specific IgE is used, there is a possibility that patients colonised with other Aspergillus species might be overlooked, leading to underdiagnosis. Furthermore, it is important to note that 40% of patients with uncontrolled asthma can have AH without ABPA [17]. Patients who do not meet the diagnostic criteria for ABPA are classified as having Severe Asthma with Fungal Sensitisation (SAFS) [18,19]. ISHAM criteria have been widely used to diagnose ABPA, and several modifications have been suggested to the original criteria [20].

However, prevalence data from southern India is sparse. In resource-limited settings, the search for easier ways to make a proper diagnosis of ABPA in patients labeled and referred to as refractory asthmatics from elsewhere has been the major intention behind the present study. Thus, the aim of the study was to assess the occurrence of ABPA in patients with difficult-to-control asthma using modified ISHAM criteria.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Pulmonary Medicine, Government Medical College, Kozhikode, Kerala, India among asthmatics attending the Outpatient Department at the Institute of Chest Diseases. The study included patients who were on regular medications and had experienced two or more exacerbations per year, requiring systemic steroids for symptom control, over a period of 18 months from February 2019 to July 2020. The study obtained approval from the Institutional Ethics Committee (IEC approval number: GMCKKD/RP 2019/IEC/73).

Sample size: The sampling method used was consecutive sampling, and the sample size was determined based on a prevalence of ABPA as 16% from a previous study [12]. The minimum sample size calculated was 185.

Inclusion criteria: Patients diagnosed with asthma who were on optimal inhaled medications with or without oral corticosteroids, and had a history of at least one acute episode in a three-month period within the last year.

Exclusion criteria: Patients previously diagnosed with ABPA, patients on systemic glucocorticoids for more than one week or for more than three weeks within the last six months, patients with asthma-COPD overlap, diagnosed cases of Chronic Obstructive Pulmonary Disease (COPD), Cystic fibrosis, Pulmonary Tuberculosis, Post-Tuberculosis sequelae, People Living With HIV-AIDS (PLWHA) and patients on long-term immunomodulators, patients with bilateral bronchiectasis of established alternate aetiology, and pregnant patients.

Study Procedure

In this study, the authors utilised the modification proposed by the ISHAM working group in 2013 for making a diagnosis in target group [Table/Fig-1] [20]. Chest X-ray (CXR) was the only imaging tool used in the present study. A total of 185 subjects were included in the study, and 12 patients who were not willing to participate were excluded. High Resolution Computed Tomography (HRCT) was a component of the criteria, but due to ease and cost-effectiveness, CXR was considered an alternative in this study.

Predisposing conditions:
1. Bronchial asthma
2. Cystic fibrosis

Obligatory criteria (Both should be present):
1. Type I aspergillus skin test positive (immediate cutaneous hypersensitivity to Aspergillus antigen) or elevated IgE levels against A.fumigatus
2. *Elevated total IgE levels (>1000 IU/mL)

Other criteria (at least two of three):
1. Presence of IgG antibodies against A.fumigatus in serum
2. Radiographic pulmonary opacities consistent with ABPA
3. Total eosinophil count >500 cells/µL in steroid naïve patients (may be historical)

(*If the patient meets all other criteria an IgE value <1000 IU/mL may be acceptable)

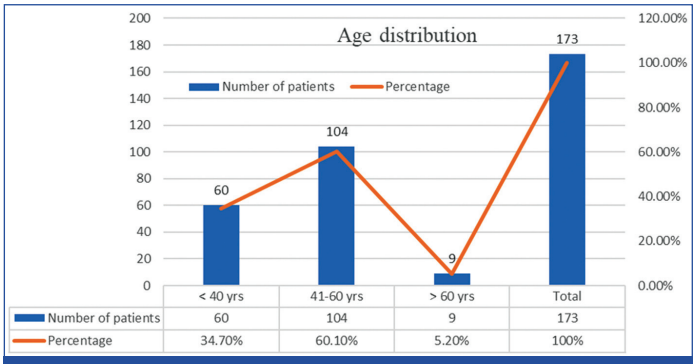
[Table/Fig-1]: ISHAM working group (modified criteria) 2013.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software version 21.0. Continuous parameters were expressed as mean and median, while categorical parameters were measured as frequency and percentages.

RESULTS

A total of 173 patients who satisfied the inclusion criteria were included in the study. Among the 173 patients, 86 (49.7%) tested positive for Aspergillus fumigatus antigen. Out of this, 100 (57.8%) were males and 73 (42.2%) were females. It was observed that 104 (60.1%) patients belonged to the age group between 41-60 years, while approximately 60 patients (34.7%) were below 40 years of age [Table/Fig-2].



[Table/Fig-2]: Age distribution of difficult-to-control asthmatics.

When the modified ISHAM criteria were applied to the study group, a total of 17 out of 173 patients met the criteria for ABPA, accounting for 9.83%, which is a significant proportion. The number of exacerbations in the previous year for these patients is as per the data shown in [Table/Fig-3]. A large majority of these patients, 101 (58.4%), required at least one hospital admission per year [Table/Fig-3].

Number of exacerbations	Number of patients	Percentage (%)
Two	93	53.9
Three	69	39.9
Four	4	2.3
Hospitalisation episodes		
Zero	18	10.4
One	101	58.4
Two	50	28.9
Three	4	2.3
Total	173	100.0

[Table/Fig-3]: Asthma exacerbations and hospitalisation episodes in last one year (N=173).

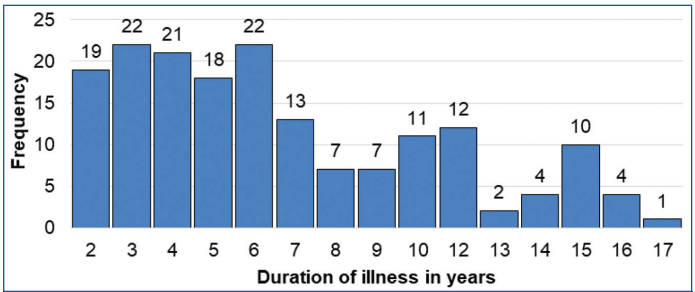
It was observed that 59 (34%) patients were smokers, and they tended to have more exacerbations compared to others. Most of them also reported a history of dust exposure as part of their occupation, which could be a reason for confounding bias. Among asthmatics who were smokers, 36 (59.3%) had 2 or 3 episodes of exacerbations [Table/Fig-4].

Number of exacerbations	Smoker asthmatics	Percentage (%)
One	Twenty four	40.7
Two	Thirty one	52.5
Three or more	Four	6.8

[Table/Fig-4]: Smokers amongst asthmatics and their exacerbations frequency (n=59).

Most of the patients selected for the study had a duration of illness of more than three years, but a duration of illness as high as 15 years was also noticed [Table/Fig-5]. Approximately 98 (56.6%) patients had a family history of asthma in either of their parents. Spirometry

results showed that 107 (61.8%) patients had an obstructive pattern, while approximately 57 (32.9%) had a mixed pattern, and 9 (5.2%) had restrictive abnormalities.



[Table/Fig-5]: Duration of asthma in the study group from first diagnosis.

When analysing the treatment history, it was observed that a large proportion, 160 (92.5%) of patients, were already on the appropriate inhaler comprising inhaled corticost frequency table. The cut-off value used eroids in the appropriate dosage with a long-acting beta agonist combination, as per GINA guidelines, and proper inhaler technique was monitored by the investigator during each visit [Table/Fig-6] [1,21].

Preventive inhalers	Number of patients (n)	Percentage (%)
Not properly using	13	7.5
Properly using	160	92.5
Total	173	100.0

[Table/Fig-6]: Inhaler use and adequacy of proper technique.

A total of 173 patients who satisfied the eligibility criteria were subjected to an intradermal aspergillus skin test, and 86 (49.7%) showed positivity. Serum total IgE levels above 1000 IU/mL were considered positive, and 46 (26.6%) patients tested positive. The cut-off value used for IgE specific to Aspergillus fumigatus, as per ISHAM group criteria, was >35 kuA, and the results were plotted in a frequency table. The cut-off value used for Absolute Eosinophil Count (AEC) was >500 cells/UL, as per the ISHAM criteria, determined through peripheral blood investigation. Total 36 (20.8%) patients in the study group satisfied this criterion [Table/Fig-7].

Test for ABPA screening	Number of patients (N=173)	Percentage (%)
Skin test for A. fumigatus	86	49.7
Serum IgE >1000 IU/mL	46	26.6
A. fumigatus specific IgE	21	12.1
AEC >500 cells/mm^3	36	20.8

[Table/Fig-7]: Screening tests for ABPA as per modified ISHAM criteria.
A.fumigatus: Aspergillus fumigatus

Radiological evaluation for the 21 patients who satisfied the remaining three criteria in the ISHAM criteria revealed normal CXR in 12 patients (57.1%), while the rest presented with fleeting infiltrates, ring shadows, and pneumonic patch consolidation. Only 9 (42.9%) patients had chest radiographic abnormalities, and the rest had normal X-rays [Table/Fig-8].

Radiological findings consistent with ABPA	Frequency	Percentage (%)
Present	9	42.9
Absent	12	57.1
Total	21	100

[Table/Fig-8]: Radiological findings fulfilling modified ISHAM criteria.

DISCUSSION

Refractory asthma, also known as difficult-to-control asthma, is a global cause of morbidity and mortality. It is estimated that there are approximately five million cases of ABPA globally, with India alone accounting for about 1.4 million cases [10]. The occurrence of ABPA among asthmatic patients in specialised clinics can be as high as 13% [11]. Studies investigating the causes of exacerbations and recurrent flare-ups have been conducted in various parts of the world [22-25]. However, one of the commonly overlooked causes is ABPA, which remains underdiagnosed due to factors such as complexity in diagnostic criteria and the lack of a gold standard treatment [26,27].

In a study involving 155 patients with ABPA complicating asthma, nearly 19% of the patients were classified as having well-controlled asthma with the use of inhaled corticosteroids and long-acting β2 agonists [28]. In the current study, approximately 93% of the patients were also using the appropriate inhaler with proper inhaler technique, which was confirmed as acceptable. Early detection and initiation of treatment can potentially prevent the progression of the disease to bronchiectasis and end-stage pleuro-parenchymal fibrosis, which are commonly associated with increased morbidity and mortality in ABPA. The use of systemic steroids, which is the current standard treatment strategy for ABPA, is not acceptable to a significant number of patients labeled as asthmatics. Convincing patients to accept this treatment is a major obstacle, and some may consider the exacerbation stage as an ineffective response to long-term steroid use. Unfortunately, there is insufficient scientific evidence to support firm conclusions for alternative treatment options, and randomised clinical trials are required to investigate the efficacy and safety of biologics for ABPA. Therefore, early identification of these cases can have a significant impact on their outcomes, rather than labeling them as refractory asthma.

Here the researchers utilised the modified ISHAM group criteria from 2013 to diagnose ABPA in refractory patients. This criterion was simple to apply, and since many of our patients lacked medical insurance, couldn't perform the ideal radiological investigation, HRCT. Although consistent radiological opacities are mentioned as an optional criterion, the investigators chose chest x ray as the sole radiological investigation to avoid bias. This decision was made even though newer modifications of the criteria have emerged over time. CXR is the most commonly used imaging technique for diagnosing ABPA, but it is often unreliable, as nearly 50% of individuals may have normal CXRs. This limitation means that subtle lesions, which can only be detected by HRCT, may be missed. However, CXR is still useful as a screening tool. The expert consensus in 2019, on the modified ISHAM criteria, also included post-tuberculous cavitatory disease and COPD as vulnerable groups due to their deranged T-cell mediated immunity. Fleeting shadows, a classic description of ABPA, result from mucus plugs within dilated bronchi and bronchioles. These shadows appear to move to various places as the mucus plugs are expelled through coughing and re-enter different bronchi or bronchioles. Hilar shadows (40%), air-fluid levels (10-20%), diffuse nodular shadows (10-20%), signs of hyperinflation (10-30%), avascular areas (10%), and pleural effusion (though rare, found in about 5% of patients) are other radiological findings. HRCT is considered the best imaging diagnostic modality, and High Attenuation Mucus (HAM) is the hallmark of ABPA on HRCT [29-36].

Elevated levels of Aspergillus-specific IgE are considered the hallmark of ABPA. However, there has been a lot of controversy regarding its normal level or, more specifically, its cut-off level. The current cut-off level, as determined by the ISHAM group, is >0.35 kUA/L, measured using fluorescent enzyme immunoassay. This test has a sensitivity of almost 100% and can be used as a good screening tool but is less reliable for follow-up purposes. Among the patients, 12.1% had IgE specific to Aspergillus fumigatus, while total IgE was elevated in 26.6% of cases. In our setting, an alternate criterion of a skin prick test to assess immediate cutaneous hypersensitivity to Aspergillus antigen was found to be much easier. Although A. fumigatus-specific IgG antibodies in serum are thought to have better sensitivity than serum precipitins, they were not considered in

this study group due to cost constraints and the availability of two other applicable criteria [37]. Absolute eosinophil counts, although easily available, can be elevated in various conditions, making it a nonspecific finding in ABPA. The ISHAM group has determined a cut-off value of AEC >500 cells/microliter for the diagnosis of ABPA. Among the cases, 20.8% had a high absolute eosinophil count. Applying the modified ISHAM criteria, it was found that 9.8% of these patients met the criteria for co-existent ABPA.

The presence of nearly 10% undiagnosed ABPA among difficult-to-control asthmatics highlights the importance of proper identification. Newer treatment strategies that address the pathophysiology of both diseases in this subset require closer observation and randomised trials to assess their efficacy in reducing exacerbation rates, preserving lung function, and halting progression to end-stage fibrotic disease. Currently, corticosteroids are the mainstay of treatment as they control the profound inflammatory process involved in ABPA and asthma, preventing disease progression to end-stage fibrosis [38]. Antifungals are also utilised in ABPA as steroid-sparing agents and to reduce fungal colonisation of the airways. Azoles such as itraconazole,voriconazole, posaconazole, and aerosolised Amphotericin-B agents are used with caution [39,40]. Omalizumab, a humanised monoclonal antibody that targets IgE, as well as newer targeted agents like mepolizumab, benralizumab, and dupilumab, have shown remarkable reduction in the number of exacerbations. Randomised double blind trials are needed to determine whether there are any additional benefits for this subset of patients if monoclonal antibodies could be started, when ABPA is detected earlier in the course of refractory asthmatics [41-45].

Limitation(s)

Asthmatics with frequent exacerbations and difficult-to-control symptoms, attending a tertiary care center, were enrolled in the study. However, it is important to note that this could lead to selection bias due to convenient sampling. Additionally, the lack of HRCT screening for these patients is a major limitation for the study in terms of diagnostic accuracy.

CONCLUSION(S)

This study suggests the possibility that treating physicians may overlook a significant number (10%) of asthmatics who are being managed for difficult-to-control asthma but actually have co-existent ABPA. These patients may require more aggressive management, including the use of systemic steroids, for proper control of their condition. Identifying and diagnosing these individuals early in the course of the disease would open up research opportunities to explore the role of newer biological treatments in this subset of patients.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.
2. Assistant Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.
3. Assistant Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.
4. Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sunny George,
Associate Professor, Department of Pulmonary Medicine, Government Medical College, Ernakulam, HMT Road, North Kalamassery, Kochi-683503, Kerala, India.
E-mail: sunsuna1@gmail.com

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