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A Study on Prevalence of Allergic Bronchopulmonary Aspergillosis in Patients of Bronchial Asthma

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Citation: R. Prasad, R. Garg, Sanjay & R. P. Dixit : A Study on Prevalence of Allergic

Bronchopulmonary Aspergillosis in Patients of Bronchial Asthma . *The Internet*

Journal of Pulmonary Medicine. 2008 Volume 9 Number 2

Keywords: Allergic | Bronchopulmonary Aspergillosis | Prevalence

Abstract

Objective: To determine the prevalence of allergic bronchopulmonary aspergillosis (ABPA) in patients of bronchial asthma.

Methods: Two hundred and forty four patients of bronchial asthma, recruited consecutively over a period of three years were analyzed prospectively by clinical evaluation, chest radiography, skin test, sputum culture for fungus and serum precipitin test. Those patients with suspicion of ABPA were further investigated by serum titers of specific IgG and IgE against *A. fumigatus*. Diagnosis of ABPA was made on pre determined major and minor criteria, where at least five major criteria had to be present.

Results: During the study period, 244 patients (150 males; 94 females) with bronchial asthma diagnosed on basis of clinical features and spirometric findings were recruited in the study, with mean age of 27.1 years (9 to 60 years). Mean duration of illness of these patients was 11.2 years (1.5 to 32 years). Immediate cutaneous reactivity to *A. fumigatus* (Type I) revealed hypersensitivity to the fungus in 30.3% of the patients. On basis of clinical, radiological and immunological criteria, 18 (7.4%) patients (13 males and 5 females) were diagnosed to have ABPA. Their mean age was 33.5 years (17 to 48 years) and mean duration of illness was 11.8 years (1.5 to 28 years). Family history suggestive of atopy was present in 61.5% and history of passage of mucus plugs was present in 66.6% patients. All these patients with ABPA were misdiagnosed as cases of pulmonary tuberculosis, and were given anti tuberculosis treatment.

Conclusion: Allergic bronchopulmonary aspergillosis is seen in 7.4% patients with bronchial asthma. Efforts should be made to improve the awareness level about this disease, among general physicians who frequently confuse it with pulmonary tuberculosis, for timely diagnosis and institution of appropriate treatment so as to avoid misuse of antitubercular drugs and prevention of end stage irreversible lung damage.

Introduction

Pulmonary aspergillosis is a clinical spectrum of lung disease caused by the fungus *Aspergillus species*. The classification of pulmonary aspergillosis includes saprophytic aspergillosis in the form of pulmonary aspergilloma, immune disease in the form of allergic bronchopulmonary aspergillosis (ABPA) and hypersensitivity pneumonitis, and infectious disease in the form of invasive and semi-invasive necrotizing aspergillosis¹. ABPA is the best recognized manifestation of *Aspergillus*-associated hypersensitivity to *Aspergillus* antigens in patients with long standing atopic asthma and characterized by the presence of asthma, pulmonary infiltrates, peripheral blood eosinophilia, type I skin reactivity and serum precipitin antibodies to *aspergillus fumigatus*, elevated total serum IgE, increased levels of *aspergillus* specific IgE and IgG and central bronchiectasis.

The true prevalence of ABPA among asthmatics is not known. This may be attributed to the lack of a uniform diagnostic criterion and standard tests². Various other Western studies suggest that ABPA complicates 1-6% of all chronic cases of asthma³. This disorder is not uncommon in India⁴. In a recent study from India, prevalence of ABPA was found to be 27% in patients of asthma⁵. However, the disease is still underdiagnosed in India, and almost half of the cases are initially misdiagnosed as pulmonary tuberculosis⁵. The present study was conducted to determine the prevalence of ABPA in asthmatics patients in India.

Material And Methods

Two hundred and forty four patients (150 males and 94 females) with bronchial asthma, diagnosed on basis of clinical history, physical findings and spirometry (reversible airway obstruction to 200 µg of inhaled salbutamol) were recruited for the present study over a period of 3 years (ie, from January 2002 to December 2004).

Patients recruited in the study underwent preliminary evaluation by detailed clinical history, family history of atopic disorder, past treatment, physical examination, routine blood test, spirometry and chest radiograph. All 244 patients also underwent skin test for Type I and Type III cutaneous reactivity to *Aspergillus* antigen, sputum culture for *A. fumigatus* on Sabouraud chloromycetin agar and serum

precipitin test by immunodiffusion technique for *A. fumigatus*. Patients with clinical and immunological suspicion were further subjected to serum titers of specific IgG and IgE to *A. fumigatus* by ELISA technique and value more than two times the control was taken as positive.

Diagnosis of ABPA was made on major and minor criteria laid down by Rosenberg et al.⁶ Major criteria used for diagnosis of ABPA were (1) history of asthma; (2) peripheral blood eosinophilia; (3) Type I cutaneous reactivity to *A. fumigatus* antigen; (4) precipitating antibody against *A. fumigatus*; (5) fleeting or fixed radiological opacities; (6) raised specific serum IgG against *A. fumigatus*; (7) raised specific serum IgE against *A. fumigatus*; (8) HRCT thorax showing proximal bronchiectasis. Other minor criteria included (1) Type III cutaneous reactivity to *A. fumigatus* antigen; (2) sputum culture positive for *A. fumigatus*; (3) passage of mucus plugs in sputum. In present study, at least five major criteria had to be present for diagnosis of ABPA.

Results

Among 244 patients with bronchial asthma recruited in the present study (Table 1), 150 (61.5%) were males and 94 (38.5%) were females. Their mean age was 27.1 years (9 to 60 years) with 155 (63.5%) patients between 20 to 39 years of age. Mean duration of illness was 11.2 years (1.5 to 32 years), with 216 (88.5%) patients having duration less than 19 years. Clinical profile of these patients showed that episodic breathlessness, was predominant symptom in all patients, followed by cough in 155 (63.5%); expectoration in 67 (27.5%); chest pain in 19 (7.8%); haemoptysis in 12 (4.9%); fever in 7 (2.9%) and mucus plugs in 7 (2.9%) patients. Apart from bronchial symptoms, some patients had other disorders like, allergic rhinitis in 123 (50.4%) and atopic dermatitis in 45 (18.4%) patients. Among these patients of bronchial asthma, 50.7% had family history suggestive of atopic disorders. In past treatment they took bronchodilators, with or without oral or inhaled steroids. Those patients with radiological shadows were also prescribed anti tubercular drugs, sometimes in the course of their illness. Absolute eosinophil count (AEC) above 500cells/ μ l was found in 75.3% cases. Chest radiographs were normal in 221 (90.5%) patients of bronchial asthma. Among 23 abnormal radiographs, 15 (6.1%) patients had fleeting shadows, predominantly in upper zone; 5 (2%) had soft infiltrates; 2 (0.8%) had ring shadows; 1 (0.4%) had tram track appearance and 4 (1.6%) had prominent broncho vascular markings. On

skin testing by *A. fumigatus* antigen, 74 (30.3%) patients showed Type I reactivity and 28 (11.5%) patients showed Type III reactivity. Sputum culture with growth of *A. fumigatus* was positive in 71 (29.9%) patients. Other serological tests were done in 144 patients only due to financial constraints, which showed specific IgE to *A. fumigatus* positive in 49 (34.0%) patients, specific IgG to *A. fumigatus* positive in 41 (28.5%) patients and both of them were positive in 26 (18.1%) patients.

Finding	Absolute No. / Total No.	Percentage %
1. Breathlessness	244 / 244	100
2. Cough	155 / 244	63.5
3. Expectoration	67 / 244	27.5
4. Fever	7 / 244	2.9
5. Chest Pain	19 / 244	7.8
6. Haemoptysis	12 / 244	4.9
7. Mucus Plugs	7 / 244	2.9
8. Allergic Rhinitis	123 / 244	50.4
9. Atopic Dermatitis	45 / 244	18.4
10. Other Atopic Illness	12 / 244	4.9
11. Absolute Eosinophil Count (AEC)		
0 - 499	60 / 244	24.6
500 - 999	116 / 244	47.5
1000 - 1499	44 / 244	18.0
1500 - 1999	15 / 244	6.1
> 2000	9 / 244	3.7
12. Radiological Examination		
Normal	221 / 244	90.5
Soft Infiltrates	5 / 244	2.0
Fleeting Shadows	15 / 244	6.1
Ring Shadows	2 / 244	0.8
Tram Track	1 / 244	0.4
Prominent broncho-vascular markings	4 / 244	1.6
13. Specific IgG to Af		
Positive	41 / 144	28.5
Negative	103 / 144	71.5
14. Specific IgE to Af		
Positive	49 / 144	34.0
Negative	95 / 144	66.0
15. Precipitating antibody		
Positive	27 / 244	16.9
Negative	217 / 244	83.1
16. Skin test Type I		
Positive	74 / 244	30.3
Negative	170 / 244	69.7
17. Skin test Type III		
Positive	28 / 244	11.5
Negative	216 / 244	88.5
18. Sputum culture for Af		
Positive	71 / 244	29.9
Negative	173 / 244	71.1

Table 1: Characteristics of patients of Bronchial Asthma

Diagnosed on basis of presence of at least five major criteria described above, 18 (7.4%) patients of bronchial asthma had ABPA (13 males, 5

females) (Table 2). Their mean age was 33.5 years (17 to 48 years) and mean duration of illness was 11.8 years (1.5 to 28 years), with 12 (66.7%) patients having duration between 5 to 15 years. Breathlessness was main complaint in all of them, followed by cough with expectoration in 9 (50%); mucus plugs in 2 (11.1%); fever in 4 (22.2%); chest pain in 2 (11.1%) and haemoptysis in 2 (11.1%) patients. Family history of atopy was present in 11 (61.5%) patients. All these patient were initially misdiagnosed as pulmonary tuberculosis and were prescribed antitubercular treatment. Peripheral blood absolute eosinophil count was more than 1000 cells / μ l in 17 (94.4%) patients. On chest radiographic examination, 1 patient (5.6%) had normal radiograph, while rest of 17 patients with abnormal radiograph had predominantly unilateral, upper zone abnormality, with fleeting pulmonary infiltrates as the most common finding in 15 (88.2%) patients, followed by prominent broncho vascular markings in 4 (22.2%); ring shadows in 2 (11.1%) and tram track appearance in 1 (5.9%) patient. Skin reactivity to *Aspergillus* antigens showed Type I reaction in all patients (100%) and Type III reaction in 16 (88.9%) patients. Sputum culture for *A. fumigatus* and serum precipitin against *A. fumigatus* was positive in all patients. Aspergillus specific IgE and IgG antibodies were positive in all 13 patients of ABPA, who underwent these specific serologic tests.

Finding	Absolute No. / Total No.	Percentage %
1. Male patient	13 / 18	72.2
2. Female patient	5 / 18	27.8
3. Mean Age (years)	33.5	
4. Mean Duration (years)	11.8	
5. Dyspnoea	18 / 18	100
6. Other allergic disorder	15 / 18	83.3
7. Cough	9 / 18	50
8. Mucus Plug	2 / 18	11.1
9. Family history of atopy	8 / 18	61.5
10. Absolute eosinophil count		
500 – 999	1 / 18	5.6
1000- 1999	13/ 18	72.2
> 2000	4 / 18	22.2
11. Radiologic Exam.		
Normal	1 / 18	5.6
Fleeting infiltrates	15 / 18	88.2
Ring shadows	2 / 18	11.1
Tram track	1 / 18	5.6
Prominent broncho-Vascular markings	4 / 18	22.2
11. Specific IgG to Af		
Positive	13 / 13	100
Negative	0 / 13	0
12. Specific IgE to Af		
Positive	13 / 13	100
Negative	0 / 13	0
13. Precipitin test to Af		
Positive	18/ 18	100
Negative	0/ 18	0
14. Type I skin test		
Positive	18/ 18	100
Negative	0 / 18	0
15. Type III skin test		
Positive	16/ 18	88.9
Negative	2/ 18	11.1
16. Sputum Culture (fungus)		
Positive	18/ 18	100
Negative	0/ 18	0

Table 2: Characteristics of patients of Allergic Bronchopulmonary Aspergillosis

Discussion

ABPA is the best recognized manifestation of *Aspergillus* associated hypersensitivity to *Aspergillus* antigens in patients with long standing atopic asthma. The true prevalence of ABPA in patients of bronchial asthma is still not known. This may be due to the lack of a uniform diagnostic criterion and standardized tests⁷. This study, which is carried out to determine the prevalence of ABPA in asthmatic patients, showed a prevalence rate of 7.4%. This is in correlation with the previous

studies in which, the prevalence of ABPA varies from 1 to 11% in patients with asthma^{8,9,10,11,12,13,14,15,16}. Whereas other Indian studies reported the prevalence of ABPA as 27.2% and 16%^{5,17}. This discrepancy may be due to difference in sample size, constitution of study population and local prevalence of the disease. Several Western studies showed that ABPA affects people of all age groups without any sex predilection^{18,19}. In our study, it was predominantly found in people with age less than 40 years and with male predilection which is in correlation with the recent Indian study⁵. This discrepancy may be due to gender bias in seeking medical help, in this part of India, where social structure is comparatively less favorable for females. In correlation with an earlier study¹⁷, which showed family history of suggestive of atopic disorder in 63% patients of ABPA, our study found it in 11 (61.5%) patients of ABPA. Previous studies reported that almost half of ABPA patients were misdiagnosed and treated as pulmonary tuberculosis^{5,20}, but all of our patients were prescribed anti tubercular drugs some times in the course of their illness, which reflects the lower level of awareness among general physicians for ABPA.

The present study found radiographic shadows in 23 patients, but only 18 had ABPA. Thus radiographic shadows neither establish nor exclude the diagnosis of ABPA, as one of our patients with ABPA had normal radiograph. Radiographic infiltrates in patients of ABPA lay in correspondence with bronchial distribution, usually involving the upper lobes²¹ and are mainly fleeting in character, which is evident in our study also. Peripheral blood absolute eosinophil count above 1000cells/ μ l was found in 17 (94.4%) patients. Previous study¹⁷ found Type I reactivity to *A. fumigatus* in 87% cases and Type III reactivity in 36% cases of bronchial asthma, but present study found Type I reactivity in 30.3% and Type III reactivity in 11.5% cases, which is in close correlation to a Western study which showed Type I reaction positive in 23 to 28% patients of bronchial asthma²². Out of 74 patients with positive Type I skin test, only 18 (24.3%) were found to have ABPA. This observation in light of a previous study, which found prevalence of positive Type I skin test in 20% of general population²³, says that positive skin test, is not confirmatory of ABPA. Wide variation in prevalence of positive Type I skin test among patients of bronchial asthma, may be due to difference in local prevalence of skin reactivity in areas, where these studies are conducted. Sputum culture for *A. fumigatus*, showed positive growth in 71 patients, but only 18 (25.4%)

had ABPA.

Elevated serum titers of specific IgE²⁴ or IgG²⁵ antibody to *A. fumigatus* are strong indicator of ABPA, but in our study, out of 49 patients with positive specific IgE to *A. fumigatus*, and 41 patients with positive specific IgG to *A. fumigatus*, only 13 (26.5% and 31.7% respectively) were found to have ABPA, which again highlights the fact that, like skin test and chest radiograph, these serologic tests also lack reliability for diagnosis of ABPA if performed alone. Present study found 16.9% patients of bronchial asthma having serum precipitins to *A. fumigatus*, which is close to 10% found in another previous study,²⁶ but in our study, out of 27 patients with positive serum precipitins, only 18 had ABPA, which again demonstrates its low reliability, and like skin test it may also be detected in general population to the extent of 1%.²⁷

Thus in conclusion it could be said that among patients with bronchial asthma, prevalence of ABPA is 7.4%. Any particular test lacks reliability for establishing or excluding the diagnosis of ABPA if performed alone, due to which diagnosis of ABPA should be considered, in presence of at least five tests with positive results. Any patient of long standing bronchial asthma, with high levels of peripheral blood absolute eosinophil count, fleeting pulmonary infiltrates on serial chest radiographs, and persistently corticosteroid requirement for control of asthma, should always be investigated for ABPA. Efforts need to be intensified to improve the awareness level about this disease, among general physicians who frequently confuse it with pulmonary tuberculosis, for timely diagnosis and institution of appropriate treatment so as to avoid misuse of antitubercular drugs and prevention of end stage irreversible lung damage.

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