

Eight-year study of allergic bronchopulmonary aspergillosis in an Indian teaching hospital

Acht-Jahres-Studie zur allergischen bronchopulmonalen Aspergillose in einem indischen Lehrkrankenhaus

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Schlüsselwörter. *Aspergillus*, Aspergillose, ABPA, Epidemiologie.

Summary. A total of 651 patients with clinically suspected allergic bronchopulmonary aspergillosis (ABPA) were evaluated during the 8-year period from January 1991 to December 1998. Overall, 338 cases (51.9%) were positive either by sputum microscopy/culture (66 of 203 patients), by skin reactivity (150 of 309 cases), or by precipitating antibodies (122 of 338 patients) against *Aspergillus* species. However, in 89 patients, diagnosis of ABPA was confirmed on the basis of Rosenberg's criteria. Clinical profile and laboratory findings of those patients were analysed. The disease was found to be more common among males. Poor control of asthma, constitutional symptoms, mucopurulent expectoration, increased dyspnoea and wheezing and rhonchi were the main presenting features. Skin reactivity against aspergillin was seen in 73 (82%), precipitating antibodies against *Aspergillus* species were positive in 64 (72%) and sputum microscopy/culture was positive in 56 (63%) of those 89 patients. Central bronchiectasis and fleeting shadows were the most common radiological findings. This study highlights the importance of ABPA in north India and draws attention to the need for further analysis of

criteria to use in the diagnosis of patients with ABPA.

Zusammenfassung. Von 651 Patienten des Zeitraums Januar 1991 bis Dezember 1998 mit klinischem Verdacht auf allergische bronchopulmonale Aspergillose (ABPA) waren insgesamt 338 (51.9%) entweder mikroskopisch und/oder kulturell in Sputumproben *Aspergillus*-positiv (66 von 203 Patienten) oder in Hautreaktionen (150 von 309 Patienten) oder im Nachweis präzipitierender Anti-*Aspergillus*-Antikörper (122 von 338 Patienten). Bei 89 Patienten wurde Diagnose ABPA auf Grund der Rosenberg-Kriterien gestellt. Die Krankheit war bei Männern häufiger. Asthma, verminderter Allgemeinzustand, mukopurulentes Sputum, erhöhte Dyspnoe, Keuchen und Rasselgeräusche waren die Hauptsymptome. Bei dem Rosenberg-Teilkollektiv waren 73 (82%) in der Hautreaktion gegen Aspergillin positiv, 64 (72%) hatten präzipitierende Anti-*Aspergillus*-Antikörper, und 56 (63%) waren mikroskopisch und/oder kulturell *Aspergillus*-positiv. Zentrale Bronchiectasien und flüchtige Verschattungen waren die häufigsten radiologischen Befunde. Die Studie akzentuiert die epidemiologische Bedeutung von ABPA in Nordindien.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction to the presence of *Aspergillus* species colonizing the bronchial tree. In 1952, Hinson *et al.* [1] were

the first to describe ABPA in Britain. Reports from Australia [2], North America [3] and parts of Asia [4] followed. It was first reported from India in 1971 [5] and a few case series have subsequently been documented [6–10]. We have previously reported 35 cases of ABPA from our institute during 1986–90 [7]. Major criteria for the diagnosis of ABPA include: bronchial asthma, immediate skin test reactivity to *Aspergillus fumigatus*, elevated total serum immunoglobulin E (IgE), pulmonary infiltrates, central bronchiectasis, peripheral blood eosinophilia, and positive serum precipitins (IgG) against *Aspergillus* antigen. None of these is specific for ABPA [11], there is still no consensus on the number of criteria needed for diagnosis, and patients in different stages of ABPA may not fulfil all these criteria. Thus many cases of ABPA can be missed. The present study is a retrospective analysis of clinically suspected ABPA cases seen over 8 years (January 1991 to December 1998) and an evaluation of different parameters for diagnosis of those cases.

Materials and methods

The hospital records of patients clinically suspected of having ABPA (i.e. patients with poorly controlled asthma, cough, purulent sputum, wheezing, dyspnoea, fever and malaise, chest pain and haemoptysis or expectoration of golden brownish sputum), between January 1991 to December 1998 were studied. Patients were evaluated for fulfilment of the criteria as suggested by Rosenberg *et al.* [12]. We sought a minimum of four major criteria and one minor criterion to fulfil before accepting the diagnosis of ABPA.

Major criteria

The major criteria were the following:

- Bronchial asthma
- Immediate skin test reactivity to *Aspergillus fumigatus*
- Elevated total serum IgE
- Pulmonary infiltrates
- Central bronchiectasis
- Peripheral blood eosinophilia
- Positive serum precipitins (IgG) against *Aspergillus* antigen.

Minor criteria

The minor criteria were the following:

- Expectoration of golden brownish sputum plugs
- Positive sputum culture for *Aspergillus* species
- Late (Arthus-type) skin reactivity to *A. fumigatus*.

Other characteristics evaluated

Clinical history, laboratory data, skin test, fungal serology, chest skiagram, spirometry and treatment received by the patients were evaluated.

Serology

Fungal serology for detection of precipitating antibodies was performed by Ouchterlony's gel diffusion techniques [13] using metabolic antigen of *Aspergillus fumigatus*, *A. flavus* and *A. niger* prepared according to Longbottom and Pepys [14]. Fungal serology was performed in 399 patients.

Sputum

Sputum samples were examined (smear and culture) for any pathogenic fungus in 203 patients. All the sputum samples were treated with *N*-acetyl-L-cysteine (NALC) and were inspected for fungal hyphae using calcoflour dye with potassium hydroxide and cultured using Sabouraud glucose agar medium. Mycelial fungi were further identified using a slide culture technique.

Skin test

Skin prick tests were performed using *Aspergillus fumigatus* antigen (Aspergillin, Hollister-Steir, USA) in 309 patients and were read every 15 min for 1 h and then after 6–8 h. For delayed-type reactions, it was read after 24, 48 and 72 h. Interpretation was as follows: Type I, wheal and erythema develops within a minute, is maximal after 10–20 min and resolves within 1–2 h; Type III, reaction was read after 6 h, any amount of subcutaneous oedema was considered positive; Type IV, delayed type of hypersensitivity was read after 48–72 h, induration more than 5 mm was considered positive.

Radiological studies and spirometry

Chest radiographs were reviewed for any fleeting shadows (pulmonary infiltrates) and central/proximal bronchiectasis in 89 patients whose Rosenberg criteria were fulfilled for diagnosis of ABPA.

Pulmonary function test [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak expiratory flow rates] were performed in 46 of those 89 patients, using a portable spirometer (Clement Clarke, UK). FEV₁ was measured from the best of three to five efforts. Reversibility of airflow obstruction was tested by repeating the expiratory manoeuvre 15 min after inhalation of 200 µg salbutamol through a spacer device. It was considered as reversible when the

improvement was greater than 20% from the initial value. Restrictive defect was observed in those with FEV₁/FVC more than 80% and FVC less than 75%. The grading of the pulmonary function defect followed the guidelines of the American Thoracic Society [15].

Results

Out of 651 patients clinically suspected of ABPA, 338 cases (51.9%) were positive either by sputum microscopy and culture or skin reactivity or by precipitating antibodies against *Aspergillus* species. Sputum by microscopy and culture was positive for *Aspergillus* species in 32.5% (66 of 203 cases). Skin reactivity was seen in 48.5% (150/309) and precipitating antibodies against *Aspergillus* species were found in 36% (122/338). However, only in 89 patients, were Rosenberg's criteria fulfilled (Table 1). Clinical profile and laboratory data of these 89 patients are shown in Tables 2 and 3.

Disease was found to be more common in males (53 male vs. 35 females). The mean age of these patients was 36.4 ± 10.8 years (range 14–64). Sputum microscopy was positive in 55 (62%) of the 89 cases. However, sputum culture was positive in 56 (63%) of the 89 cases. *Aspergillus flavus* was most common species isolated, i.e. in 62%. However, sputum was negative for acid-fast bacilli in these patients. The skin test was positive in 75 patients (85%) and a Type I response was most common (56%). Precipitating antibodies against *Aspergillus* species were found in 64 (71%) patients.

Table 1. Diagnosis of 89 patients with ABPA by Rosenberg's criteria (major and minor)

	No. of patients (%)
Major criteria	
Bronchial asthma	80 (90)
Immediate skin test reactivity to <i>Aspergillus fumigatus</i>	73 (82)
Elevated total serum IgE	ND ^a
Pulmonary infiltrates	38 (43)
Central bronchiectasis	61 (69)
Peripheral blood eosinophilia	89 (100)
Positive serum precipitins (IgG) against <i>Aspergillus</i> antigen.	64 (72)
Minor criteria	
Expectoration of golden brownish sputum plugs	61 (69)
Positive sputum culture for <i>Aspergillus</i> species	56 (63)
Late (Arthus-type) skin reactivity to <i>A. fumigatus</i>	23 (26)

^aND, not done.

Radiology showed that central bronchiectasis only was present in 13 cases (14%), fleeting shadows were found in 28 cases (31%), and both central

Table 2. Clinical profile of 89 cases of ABPA

Total no. of cases	89
Male (n = 53) to female (n = 35) ratio	1.5 : 1
Age (years)	
mean	36.4 ± 10.8
range	14–64
No. with bronchial asthma	80
Duration of bronchial asthma	
mean	12.06 years
range	6 months to 38 years
Treatment received (before presentation)	
bronchodilators only	31
antitubercular drugs	26
corticosteroids	13
antibiotics + bronchodilators	6
Clinical presentation	
constitutional symptoms	28
mucopurulent expectoration	61
poor control of asthma	64
increase of dyspnoea	13
wheezing and rhonchi	79
Clinical stage of ABPA during presentation	
acute stage	74 (83%)
remission stage	6 (7%)
complications	9 (10%)

Table 3. Detailed laboratory data in 89 patients of ABPA

Radiological findings	89/89
central bronchiectasis (CB)	13 (14%)
fleeting shadows	28 (31.4%)
CB + fleeting shadows	38 (42.7%)
CB + complication	10 (11%)
Sputum culture	56
<i>A. fumigatus</i>	14 (25%)
<i>A. flavus</i>	29 (61.6%)
<i>A. niger</i>	2 (3.7%)
<i>A. flavus</i> + <i>A. niger</i>	4 (7.1%)
<i>A. fumigatus</i> + <i>A. flavus</i>	7 (12.5%)
Skin test	75
against Aspergillin ^a	
Type I	50 (56.1%)
Type I + III	15 (16.9%)
Type IV	2 (2.2%)
Type I + III + IV	8 (8.9%)
Serology against	64
<i>A. fumigatus</i>	3
<i>A. flavus</i>	20
<i>A. niger</i>	2
<i>A. flavus</i> + <i>A. niger</i>	3
<i>A. fumigatus</i> + <i>A. flavus</i>	26
<i>A. fumigatus</i> + <i>A. flavus</i> + <i>A. niger</i>	10

^aType I, erythema and wheel within 1 h; Type III, any amount of subcutaneous oedema after 6 h; Type IV, induration of more than 5 mm diameter after 24 h.

bronchiectasis and fleeting shadows were seen in 38 cases (43%). However, 26 patients were misdiagnosed as having pulmonary tuberculosis.

Spirometry was performed in 46 patients. A mild to moderate obstructive pattern was observed in 24 cases and a restrictive defect was observed in eight cases, while 14 patients showed mixed patterns.

Discussion

ABPA is the most frequently observed clinical manifestation of allergic aspergillosis today. The disease is prevalent in north India. We observed an increase in number of ABPA cases diagnosed from this centre which is situated in north India. Eighty-nine cases were diagnosed over 8 years (1991–98), in comparison with the 35 cases reported in the previous 5 years (1986–90). This is probably a result of an increase in awareness among the clinicians of this institute and the practitioners in the neighbouring areas who referred some of these cases. ABPA is usually described in patients with pre-existing asthma which may or may not be related to fungal allergies [16]. In our study, pre-existing asthma was present in 80 patients and nine patients were nonasthmatic, indicating that pre-existing asthma is not absolutely essential. The duration of asthma (results not shown) did not effect the incidence or severity of ABPA in the present study. In 56% of the cases, a Type I skin reaction was present and 15 patients (17%) had biphasic responses. A similar observation was recorded by other authors, i.e. the type I reaction is the most common positive skin test in ABPA and approximately one-third of the patients may have a biphasic response [17]. The detection of serum precipitins in various series of ABPA patients has been variable. In our earlier studies [7, 18], we reported precipitating antibodies in 77.1% and 54% of the cases but this percentage may increase to well over 90% when threefold concentrated serum is tested [17]. Higher incidence has also been described by Chetty *et al.* [19], as compared to the low incidences reported by Khan *et al.* [6] and Sandhu *et al.* [20]. The disease was seen in all age groups and was more common in males (M : F 1.5 : 1) in contrast to our previous study [7].

In the current study, although only 89 patients fulfilled the Rosenberg criteria, our 338 cases were positive either by sputum culture/microscopy, by precipitating antibodies, or by skin reactivity which are helpful pointers to the diagnosis of disease. Patients with ABPA may be classified in to five stages: I, acute; II, remission; III, exacerbation; IV, corticosteroid-dependent asthma; and V, fibrotic end stage. In this study, 74 patients (83%)

were in the acute stage, six were in remission and nine presented with associated complications (pneumothorax, haemoptysis, or pneumonia). However, in the remission stage peripheral blood eosinophilia is usually not present and pulmonary infiltrates are absent. Similarly, precipitating antibodies against *Aspergillus* species may or may not be present in stages other than the acute stage [11]. Moreover, patients with chronic fibrotic disease may be relatively asymptomatic in spite of extensive radiological lesions. So, in our study there may be patients who were in different stages of disease and could have been missed as there are no uniformly accepted criteria regarding clinical, radiographic and laboratory analyses for the diagnosis of ABPA. In these patients, response to steroids was good (data not shown) but duration of follow-up was not long enough to determine how many patients had recurrent exacerbations and how many would have developed corticosteroid-dependent asthma.

One of the important findings in the present report was that 26 patients had been treated with antitubercular drugs before coming to this hospital as they had been misdiagnosed as cases of pulmonary tuberculosis. It may be that the radiological picture of upper-zone infiltrates seen in ABPA mimics pulmonary tuberculosis. Thus a diagnosis of ABPA can be missed because tuberculosis is the most common respiratory disease in India. Early diagnosis and therapy are important for ABPA cases to prevent the progression of the disease to fibrosis of the lung.

The roentgenographic changes in ABPA may be transient or permanent [21]. Of the permanent changes, the most important is central/proximal bronchiectasis with normal peripheral bronchi, a pathognomonic feature of ABPA. In the present study, most of the radiological findings showed central bronchiectasis and pulmonary infiltrates. However, 31% of the patients had no central bronchiectasis but they showed evidence of pulmonary infiltrate. Pulmonary function tests did not reveal any specific pattern to help in the diagnosis of ABPA. Spirometry is relatively insensitive either to define the extent of disease or to exclude it.

Although *A. fumigatus* is the organism implicated in the causation of the disease in its original descriptions, *A. flavus* was more commonly isolated in the present series. Precipitating antibodies to *A. flavus* were observed in 69% of cases as compared to antibodies to *A. fumigatus* which were found in 44% cases. This apparent difference in comparison with other series may be due to a greater presence of *A. flavus* in the environment. *Aspergillus flavus* is also the most frequent causative agent of paranasal

sinus mycoses in north India, indicating a possibly greater exposure to *A. flavus* [22].

In conclusion, a thorough discussion is still required to identify uniform criteria for the diagnosis of patients with ABPA in different clinical stages. Increased awareness among clinicians in the area of prevalence is also required to prevent misdiagnosis of cases, especially in those areas where tuberculosis is highly prevalent.

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