

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND CYSTIC FIBROSIS

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1. ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is a disease affecting patients with asthma as well as those with cystic fibrosis. The clinical picture of ABPA is characterized by symptoms of wheezing, pulmonary infiltrates, bronchiectasis, and in later stages, pulmonary fibrosis. Since patients with cystic fibrosis may have several of these clinical features as part of their disease process, it is important to distinguish the overlap of this entity so that therapy may be instituted in a timely manner. This paper will discuss the clinical diagnosis, immuno-pathology and treatment of ABPA as it affects patients with cystic fibrosis.

2. INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) may affect between 1 and 2% of asthmatic patients but figures related to patients with cystic fibrosis (CF) are higher and range between 1 and 15% (1-4). ABPA appears to develop as a result of sensitization to *Aspergillus* spores which have colonized the bronchial tree of susceptible individuals. The presence of *Aspergillus* hyphae or fungal elements in the airways triggers an immune response characteristic of both allergic (IgE) as well as inflammatory T cell mechanisms. The early diagnosis and treatment of ABPA is important in order to avoid and prevent irreversible lung damage (5).

3. CLINICAL FEATURES OF ABPA AND CF

Clinically, ABPA in patients with asthma without CF is manifested by wheezing, pulmonary infiltrates, bronchiectasis and pulmonary fibrosis. Diagnostic criteria (6-8) have been established which include asthma, pulmonary infiltrates, immediate skin test reactivity to *Aspergillus fumigatus* (Af) species, elevated total serum IgE >1000 IU/L, elevated specific IgE to Af, precipitating IgG antibodies to Af, evidence of central bronchiectasis on computerized chest tomography (CT), and peripheral blood eosinophilia. Additional criteria may include expectoration of mucus plugs in which fungal elements are identified, or sputum culture positive for *Aspergillus* species.

Cystic fibrosis is the most common fatal genetic disease in man, with an inherited autosomal recessive pattern and a prevalence of one in 2500 births. The CF gene has been associated with a protein product known as the cystic fibrosis transmembrane regulator protein (CFTR). Several hundred mutations of this gene have been identified. The resulting defective transport of sodium and chloride across the epithelial cell surface membranes of exocrine glands leads to the production of viscous secretions.

The hyperviscous pulmonary secretions seen in CF may become inspissated thus resulting in bacterial colonization and recurrent infections which are

subsequently involved in progressive pulmonary inflammation, and as a result, bronchiectasis. Common manifestations of CF include bronchiectasis, recurrent pulmonary infiltrates, pneumonias, wheezing, and colonization of diseased airways by *Aspergillus*.

The clinical features of CF overlap with the above-mentioned criteria for ABPA; hence the diagnosis of ABPA in patients with CF may be difficult which in turn may delay treatment.

3.1 Prevalence of ABPA in patients with CF

Figures relating to the prevalence of ABPA in the CF population have varied considerably since the criteria for diagnosis have varied from study to study. For example, in the United States and Canadian epidemiologic study of CF, studying 14,210 patients (9), a prevalence of 2% was found, whereas the European Epidemiologic Registry of CF involving 12,447 patients reported a prevalence of approximately 8% with a range of 2-14% (10). In the previously mentioned United States and Canadian study, there appeared to be an increased prevalence of adolescents, males, history of lower lung functions, and history of positive sputum cultures for *Pseudomonas* (9). There were also regional variations of ABPA prevalence with values ranging from 0.9% in the Southwest U.S. to 4.0% in the Western U.S. As a result, published figures in the literature have ranged from 1 to 15% (1-4, 9,10).

3.2 Associated genetic factors of ABPA and CF

It appears that patients with ABPA without CF have higher frequencies of CFTR mutations than patients with bronchitis or normal patients (11). Further studies have suggested that HLA-DR molecules DR2 and DR5 may promote susceptibility to Af induced asthma and ABPA (12) whereas HLA-DQ2 is related to resistance (13).

4. IMMUNO-PATHOLOGY OF ABPA IN PATIENTS WITH CF

Antigens from *Aspergillus* species appear to stimulate a Th2 CD4+ T-cell response in patients with ABPA, asthma, or CF (14). It is believed that following the inhalation of Af spores, entrapment in the viscous mucus of the airways occurs. The spores may then germinate, forming mycelia, with subsequent release of allergens that are processed by antigen processing cells (APC's). The Af and other species are also capable of producing various enzymes such as catalase, superoxide dismutase, enolase, and metalloproteases (15,16). Ribotoxin, gliotoxin, phospholipases and phthioic acid are also produced by a number of *Aspergillus* species (17-20). Proteases may be responsible for bronchial epithelial cell detachment (21). The local immunologic defense against the spores includes macrophages, neutrophils, monocytes, and the release of pro-inflammatory cytokines (22). Phagocytosis may be affected by various factors such as surfactant proteins and mannose binding lectin (23,24).

It appears that in patients with ABPA, Af may be found on the surface of the bronchial epithelium as well as

between the epithelial cells, without effective destruction by the local mononuclear cells or eosinophils (25). In addition, there is evidence that the damaged epithelial cell layer may be involved in the production of cytokines (26). The continual presence of Af results in the release of allergens that may cause damage to the epithelia, which result in a strong Th2 type of response marked by elevated total and specific IgE levels. Af allergens are also capable of cross linking IgE molecules which are bound to mast cells. This process results in degranulation and subsequent release of mediators, including eosinophil chemoattractants, favoring a Th2 type of response (14). The elevated levels of IgG and IgA found in ABPA may be part of this Th2 profile (27).

5. TESTS AVAILABLE FOR THE DIAGNOSIS OF ABPA IN CF

5.1. Skin testing and specific IgE antibodies to Af

Percutaneous skin testing using extracts of *Aspergillus* have been performed as a screening and diagnostic tool for ABPA. Studies have shown that between 31-59% of CF patients may have positive immediate wheal and flare reactions to Af (4,28) indicating widespread sensitization to Af antigens. Assays for specific anti-Af IgE antibodies are sensitive tests for ABPA in CF (1,2,29).

5.2. Precipitating antibodies to Af

Precipitating antibodies have been found in up to 50% of patients with CF, however, they remain part of the diagnostic criteria for ABPA (2). These antibodies are generally of the IgG isotype (30,31).

5.3. Total IgE

Total IgE levels are an important diagnostic tool in the screening and diagnosis of ABPA with or without CF. Levels used in the diagnostic criteria may vary (1,2,29). As a screening tool, changes in the total IgE level may be of importance in the diagnosis and follow-up management of ABPA in patients with CF.

5.4. Peripheral blood eosinophil counts

Peripheral circulating eosinophil counts have been felt to be of limited value in the diagnosis of ABPA in patients with CF (2).

5.5. Radiographic findings

High resolution CT is a sensitive imaging technique for the detection of central bronchiectasis, which is a major feature of the diagnostic criteria of ABPA (32). Bronchiectasis can be divided into cystic, varicose, and cylindrical varieties. Varicose and cystic bronchiectasis is seen more often in ABPA whereas cylindrical bronchiectasis is more typical of CF (33).

Pulmonary infiltrates may suggest ABPA (34), but are also commonly seen in CF (35). The clinical response to corticosteroids has been suggested as a method of identifying infiltrates due to ABPA since it would be expected that steroids would quickly improve the radiographic appearance of the lung (36). However,

Table 1 Similarities between the diagnostic criteria of ABPA and the overlapping characteristics of ABPA and CF

Classic Criteria for ABPA without CF	Overlapping Criteria for ABPA with CF
Asthma	Asthma
Positive skin test to Af	Positive skin test to Af
Elevated total IgE > 1000 IU/L	Elevated total IgE > 400 kU/L
Elevated specific IgE to Af	Elevated specific IgE to Af
IgG precipitating Ab to Af	IgG precipitating Ab to Af
Central bronchiectasis	Central bronchiectasis
Pulmonary infiltrates	
Peripheral blood eosinophilia	

Table 2. Criteria useful in the diagnosis of ABPA

Clinical deterioration of pulmonary status as characterized by increased cough, sputum or wheezing without another diagnostic cause
Appearance of a new chest x-ray infiltrates that do not respond to the usual therapies
Elevated total IgE > 1000 IU/L or significant change in elevation from baseline, usually defined as greater than two fold
Positive skin test to Af
Elevated specific IgE to Af
IgG precipitating Ab to Af

because of the variability to clinical response, most authors do not include resolution of infiltrates as a result of steroid treatment as an accepted part of the major diagnostic criteria of ABPA in CF.

6. CRITERIA FOR THE DIAGNOSIS OF ABPA IN PATIENTS WITH AND WITHOUT CF

The classic diagnostic criteria of ABPA patients without CF and the overlapping criteria frequently observed in ABPA with CF are given in Table 1. The problem presented to the clinician while treating a patient with CF who is suspected of having developed ABPA is primarily in the definition of the patients pulmonary disease status. As mentioned above, new pulmonary infiltrates are common in CF patients. Therefore, the lack of response to the usual antibiotic and chest physiotherapy treatments may be a clue that ABPA has developed. Similarly, the complexity of defining new bronchiectasis may be difficult in the CF patient, but its occurrence may raise clinical suspicion.

IgE levels that are elevated or that increase over a previous baseline value may be of significance in entertaining a diagnosis of ABPA. Some of these criteria have been summarized below in Table 2.

7. TREATMENT OF ABPA IN PATIENTS WITH CF

The goals of treatment in patients with ABPA, with or without CF are to prevent the onset of further pulmonary deterioration and the development of pulmonary fibrosis (5,37). At the present time, well controlled studies assessing the efficacy of treatment of ABPA patients with or without CF are not available.

From the clinical and experimental evidence available, the treatment of ABPA involves an attempt to reduce the inflammatory reaction created in the diseased airways. The main therapies available are corticosteroids and anti-fungal drugs. Steroids are effective in reducing eosinophilia, pulmonary infiltrates, and IgE levels while

improving pulmonary functions (37). Recommended treatment schedules present in the literature include a starting dose of 0.5-2 mg of prednisone per kg for 1-2 weeks followed by a gradual taper over the next several months, while monitoring IgE levels and response to pulmonary infiltrates (38).

Anti-fungal drugs, of which itraconazole has been studied the most, are effective in reducing the presence of fungal elements in the airways, thereby reducing the presence of persisting allergen load. It has been shown to be effective in patients with ABPA but without CF (39). In patients with CF and ABPA, itraconazole was shown to have a steroid sparing effect (38). Further studies are needed to assess the efficacy of these therapies in patients with ABPA and CF. This will be helpful in guiding the clinician in the choice of treatments options.

8. FUTURE DIRECTIONS

Further research is needed to understand the mechanisms involved in the unique host immunity of CF. In addition, further studies are needed in the areas of antigen processing, and the subsequent immune responses to the allergens and antigens of Af. Additional studies on allergen epitopes, purification, and standardization are also important. This further knowledge may help to lead to advances in the treatment and possible immunomodulation of ABPA.

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