Allergic Bronchopulmonary Aspergillosis in Patients With Cystic Fibrosis*

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In order to determine the incidence of allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis (CF), we reviewed the records of 236 patients followed up at the Duke CF Center. Sixty patients (25 percent) had colonies of Aspergillus fumigatus. These patients were older and had more severe disease as assessed by lower Schwachman-Kulczycki (S-K) scores than the patients who did not have evidence of A. fumigatus. In 15 of the patients with A. fumigatus (6.5 percent of the total population), the diagnosis was ABPA. Age and S-K scores were not significantly different from those of patients with A. fumigatus without ABPA. Diagnostic features of the affected patients included wheezing refractory to bronchodilator therapy, persistent pulmonary infiltrates, peripheral eosinophilia, positive skin reactivity to an A. fumigatus antigen and elevated total serum IgE levels. Steroid therapy was started for all patients, and clinical improvement was noted within 1 month as evidenced by decreased symptoms and weight gain. Chest x-ray films usually showed improvement. Vital capacity improved in all but two patients. Total IgE did not consistently decrease in response to therapy. Although the diagnosis of ABPA may be difficult to establish, ABPA commonly is associated with CF. Most patients respond to steroid therapy; however, the effect of therapy on the course of the disease is difficult to assess.

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Patients and Methods

During a 6-month period in 1985, we reviewed records of 236 patients with CF who were diagnosed and followed up at the Duke CF center. These patients had blood counts, chest x-ray films, and sputum or throat swab specimens submitted for culture as part of their routine care. The sputum specimens were plated on routine blood agar nonenhanced media. Spirometric testing was performed on patients old enough to cooperate and forced vital capacity, FEV1, and mean forced expiratory flow during the middle half of forced vital capacity were determined on a computerized water seal spirometer (W. Collins, Braintree, Mass). Patients suspected to have ABPA on clinical grounds and a selected control group underwent a workup consisting of skin testing with an A. fumigatus antigen (1:1,000) injected intradermally (Greer laboratories, Lenoir, NC) with readings at 20 min and 6 h and determination of total serum IgE and precipitating antibodies to A. fumigatus. The latter was determined initially in our laboratories by the double-gel diffusion techniques of Ouchterlony, then at the Mayo Medical Laboratories (Rochester, Minn) because of poor yield. In addition, specific IgE to A. fumigatus was determined by radioallergosorbent testing at the Mayo Medical Labs.

The diagnostic criteria for ABPA in our CF patients were as follows: (1) bronchial obstruction—asthma; (2) pulmonary infiltrates; (3) elevated total serum IgE level greater than 400 IU/ml; (4) blood eosinophilia more than 500/mm3; (5) immediate hypersensitivity to A. fumigatus.

Patients fulfilling these criteria were treated with prednisone, 2 mg/kg/d, and their disease activity was followed up by medical history, physical examination, pulmonary function testing, chest x-ray films, and total serum IgE levels. Statistical significance was determined by using the one-way analysis of variance.

Results

The patients ranged in age from 1 to 41 years, with a mean age of 14.5 years. All patients were white; there were 11 male and only 4 female patients, with a ratio of 2.7:1. Their Schwachman-Kulczycki (S-K) scores13 ranged from 35 to 100 with a mean of 78.5. Sixty patients (25 percent of the population) were found to have colonies of A. fumigatus, as evidenced

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ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; S-K = Schwachman-Kulczycki.
by growth on the sputum culture. These patients were significantly older (p < 0.0002) and had more severe disease, as assessed by a lower S-K score (p < 10\(^{-6}\)), than the patients without evidence of *A. fumigatus* (Table 1). In 15 patients (65 percent of the population), the diagnosis was ABPA. Their ages ranged from 8 to 39 years, with a mean of 14.5 years. Their S-K scores ranged from 63 to 87, with a mean of 76. Age and S-K scores were not significantly different from those of the patients with evidence of *A. fumigatus* who did not have ABPA.

The diagnostic features of our patients who had ABPA included wheezing refractory to bronchodilator therapy, acute drop in spirometric test results, and persistent pulmonary infiltrates which were unresponsive to antibiotic therapy, physical therapy, and occasionally bronchoscopy. All patients who had ABPA had cultures positive for *A. fumigatus*, peripheral eosinophilia, immediate cutaneous reactivity to *A. fumigatus*, and elevated total serum IgE levels. Thirteen patients had a late cutaneous reaction to *A. fumigatus*. Precipitins to *A. fumigatus* were consistently negative in all patients tested in our laboratory, but positive in 8 out of 11 patients who were tested elsewhere. Nine of 12 patients had an elevated specific IgE to *A. fumigatus*.

Review of the clinical records of the 15 patients who had ABPA indicated 86 percent of the patients (13 of 15) had a history of asthma or allergic rhinitis, or both, and approximately 50 percent of the patients (7 of 15) had a history of significant asthma.

Eighty-seven patients of the total CF population underwent skin testing with an *A. fumigatus* antigen injected intradermally. Thirty-eight (47 percent) had a positive immediate reaction. Of these, 12 (31.5 percent) showed no growth of *A. fumigatus* on the sputum culture. The late reaction could be ascertained in 80 patients and was positive in 23 (29 percent). Twenty-nine patients were tested for *A. fumigatus* precipitins, and 9 (31 percent) showed positive results.

For the patients considered to have ABPA, steroid therapy was started with an initial dose of 2 mg/kg/d of prednisone. This dosage was reduced progressively, as allowed by the clinical course, the radiologic and spirometric changes, and the IgE levels. Thirteen patients had appropriate follow-up examinations, ranging from 12 to 48 months (mean, 29 months). They received a total of 22 courses of steroids, ranging from 2 weeks to 38 months (mean, 13 months). All patients reported symptomatic improvement and had weight gain within 1 month of initiation of therapy. Pulmonary function tests improved in most patients (Table 2). Total serum IgE levels decreased in six patients where paired levels were available, while it increased in three patients and did not change in two (Table 2). The changes in total serum IgE levels did not consistently correlate with the clinical, radiologic, or spirometric changes.

Radiologic changes varied between no change, resolution of localized mucus plugging, and generalized improvement.

In patients requiring long courses of steroids, every effort was made to reduce their dosage. However, these patients experienced exacerbations for which steroid dosage had to be increased again. In one patient, ketoconazole therapy was started in an attempt to decrease his steroid dependence; however, success was limited.

**DISCUSSION**

Cystic fibrosis is an autosomal recessive disease involving dysfunction of the exocrine glands. One major target organ is the lung where the presence of thick tenacious secretions favor the growth of certain microorganisms, especially *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The secretary products of these microorganisms along with the inflammatory

### Table 1—Aspergillus fumigatus: Colonization Status of Cystic Fibrosis Population Studied

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>With Colonies</th>
<th>Without Colonies</th>
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<tbody>
<tr>
<td>Age range, yr</td>
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<td>1-37</td>
</tr>
<tr>
<td>Mean</td>
<td>18.3</td>
<td>13.3*</td>
</tr>
<tr>
<td>S-K score range</td>
<td>35-92</td>
<td>40-100</td>
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<tr>
<td>Mean</td>
<td>72</td>
<td>81†</td>
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*p = <0.0002.*

†p<10\(^{-4}\).

### Table 2—Immunoglobulin E Levels and FEV\(_1\), Before and After Steroid Therapy

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response initiated by their presence result in lung damage involving predominantly the upper lobe.

Allergic bronchopulmonary aspergillosis is a hypersensitivity lung disease induced in predisposed individuals by the ubiquitous fungus, *A. fumigatus*. The clinical course is characterized by wheezing, which is usually unresponsive to bronchodilator therapy, and recurrent pneumonia. Chest roentgenograms usually show evanescent pulmonary infiltrates, bronchiectatic changes, and branching shadows of mucoid impaction with "tramline" shadows of thickened bronchial walls, occurring most commonly in the upper lobes.

The diagnosis of ABPA in patients with CF frequently is overlooked because the signs and symptoms of each disease mimic each other. With a high index of suspicion, the physician should be alert to the possibility of ABPA whenever the CF patient presents with new infiltrates, *A. fumigatus* in respiratory secretions, and eosinophilia. Prick or intradermal skin testing with *A. fumigatus* antigen provides a screening test for ABPA, since a negative test means the patient does not have ABPA. A positive test suggests a tentative diagnosis of ABPA; confirmation requires evidence of elevated total serum IgE, elevated anti-*A. fumigatus* IgE, and the presence of *A. fumigatus* precipitins. Although immunologic tests are important in confirming the diagnosis of ABPA, final diagnosis needs to be made by clinical assessment. Using these criteria, in 15 of our 236 patients with CF (6.5 percent) the diagnosis of ABPA was made. This incidence is slightly lower than the 10 percent reported in the literature. Thus, ABPA represents a relatively common problem among patients with CF, and the disease is characterized by remissions and exacerbations.

Patients with CF frequently manifest laboratory and immunologic features of ABPA. Multiple studies have demonstrated the presence of precipitins to *A. fumigatus* in CF patients. In our study, none of our patients had precipitins when the assays were performed in our laboratory; however, when the patient's sera subsequently were tested elsewhere, *A. fumigatus* precipitins were noted. Although *A. fumigatus* precipitins may vary with time, this discrepancy probably was due to the use of more potent *A. fumigatus* antigens by more experienced technicians. Because of these variations we did not require the presence of *A. fumigatus* precipitins for the diagnosis of ABPA. Attention also must be given to the significance of an elevated total serum IgE level in fulfilling the laboratory criteria for ABPA. Although patients with ABPA characteristically have markedly elevated total serum IgE levels, patients who have CF but not ABPA also may have high total serum IgE levels, probably due to atopy. Nevertheless, an elevated level of total serum IgE is an important immunologic finding in establishing the diagnosis of ABPA in the CF patient.

Patients who have CF frequently manifest immediate and late cutaneous reactivity to *A. fumigatus* antigens. Among our CF patients who had skin tests, 47 percent had an immediate reaction and 29 percent had a late reaction, findings which are similar to the observations reported in the literature. All of our CF patients who had ABPA demonstrated positive immediate reactions to *A. fumigatus*.

Cystic fibrosis patients frequently have evidence of *A. fumigatus*. Nelson et al documented that 57 percent of their patients had colonies of *A. fumigatus*, compared with 25 percent of our population. The lower incidence of colonization in our patients most likely is due to a selection effect, since their patients were older than 5 years, while our population included infants and younger children in whom *A. fumigatus* is not present or cannot be recovered. Variation in laboratory technique also could account for this discrepancy. All of our CF patients who had ABPA had intermittent colonization of *A. fumigatus*.

The high rate of colonization in CF patients is due to the propensity of *A. fumigatus* to grow in thick secretions in diseased lungs. Colonization leads to chronic antigenic stimulation through diseased respiratory mucosa with subsequent sensitization in a susceptible host such as an atopic patient. Patients with ABPA usually are atopic, as seen in our series where 13 of the 15 patients had a history of allergic rhinitis or asthma or both.

The objective of treatment of ABPA in CF patients is to control acute exacerbations and to prevent permanent lung damage. The treatment of choice is systemic corticosteroids. In contrast to the usual dose of prednisone (0.5 mg/kg/d), we administered an initial dose of 2 mg/kg/d for 2 weeks in order to enhance the initial clinical response. After this induction period, the dose was reduced 0.5 mg/kg/wk, and when the daily dose reached 0.5 mg/kg, this dosage was continued for 1 to 2 months. Subsequent doses of prednisone, including alternate-day therapy, were determined by the clinical status of the patient. Corticosteroids usually produce a satisfactory clinical and immunologic response. The disease activity must be carefully monitored since many of our patients experienced exacerbations requiring increased doses and prolonged therapy with corticosteroids. Inhaled corticosteroids are ineffective in the treatment of ABPA.

None of our patients experienced infectious complications suggestive of immunosuppression while receiving corticosteroid therapy. Two patients developed cataracts. Two other patients developed diabetes requiring insulin. However, in only one patient did insulin dependency persist when steroid therapy was discontinued. This patient, who developed portal hypertension requiring shunting, was the only patient among the steroid-treated group who showed impair-
ment of linear growth.

Patients who fail to respond to high-dose corticosteroids have been treated with ketoconazole, which was found to be beneficial in some patients.21 Ketoconazole did not significantly alter the course of our one patient requiring a high dosage of prednisone; however, it was associated with a slight reduction of his steroid dependency. No complications occurred with ketoconazole therapy.

The course of our CF patients often was complicated by increased pulmonary symptoms associated with new infiltrates. In such patients, the clinician often has a problem differentiating exacerbations of ABPA from CF with superimposed bacterial or viral infections.24 The diagnosis of ABPA also may be difficult because many features are not specific and all criteria are not fulfilled at the same time. Several factors related to A fumigatus sensitization (total serum IgE and IgE to A fumigatus) are currently being utilized to reflect disease activity of ABPA.9,10,21,25 Although these factors were usually more markedly elevated in our patients with severe disease, they did not consistently reflect the course of the disease. Since corticosteroid therapy has been documented to decrease the total serum IgE and anti-A fumigatus IgE levels, these parameters also are used to monitor the effectiveness of therapy.12,21 However, as seen in Table 2, corticosteroids produced inconsistent results, with significant reduction in the total serum IgE level occurring in less than 50 percent of our patients. In our study, the usefulness of serial total serum IgE determinations was also limited by the periodic unavailability of baseline values. Although we did not perform anti-A fumigatus IgG determinations, this test may more accurately reflect the clinical status of the patient with ABPA.25 At times, the various factors related to A fumigatus sensitization are nonspecific in the CF patient, and their elevation may not necessarily mean the symptoms are secondary to ABPA.26 Hence, the diagnosis of ABPA in the CF patient is difficult and requires careful integration of clinical and laboratory data. The clinician must make the correct diagnosis in order to initiate appropriate therapy, eg, antibiotics versus corticosteroids.

Although the incidence of allergic disease in CF patients is controversial, the presence of asthma or allergic rhinitis or both, have been documented in 12 to 24 percent of CF patients.19 Allergic rhinitis or asthma, or both, were recognized in 86 percent of our 15 CF patients with ABPA, an occurrence which is threefold greater than the frequency of atopy in CF patients. Thus, the atopic CF patient is probably at increased risk for ABPA.

Interestingly, 11 of the 15 patients with CF and ABPA were male, a male:female sex ratio of 2:75. This value is two and half times the male:female ratio of 1:09 noted in all patients seen at our CF Center. Furthermore, among the CF patients with evidence of A fumigatus, the male:female ratio also was increased—1:79. The significance of this observation remains to be determined. One can postulate the increased frequency of A fumigatus colonization and subsequent ABPA is due in part to the male having increased exposure to soil and A fumigatus spores.

The effect of ABPA on the course of patients with CF is unknown; however, numerous authors have postulated that ABPA contributes to the progression of the pulmonary disease in CF.9,10,11 Hence, early diagnosis with prompt and vigorous corticosteroid therapy is necessary to prevent the progression to severe, irreversible, and potentially fatal disease. Although our 15 patients were initially followed only for a period of 4 years, a recent review of these 15 patients by another investigator disclosed that all 15 patients were alive 7 years after the diagnosis of ABPA.27 None of the patients were experiencing remission and six were experiencing symptoms requiring corticosteroid therapy. Hence, the prognosis of ABPA in the CF patient may not be as dismal as previously predicted.

In conclusion, ABPA is a common complication of CF that may be difficult to identify and requires a high index of suspicion. Affected patients respond to corticosteroid therapy, but they frequently experience exacerbations and may require prolonged courses of therapy. Total serum IgE levels and other parameters of A fumigatus sensitization are useful but not consistent in predicting disease activity. Our 15 CF patients are alive 7 years after being diagnosed with ABPA.

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