Prevalence of Allergic Bronchopulmonary Aspergillosis and Atopy in Adult Patients With Cystic Fibrosis*

Jonathan W. Becker, MD; Wylie Burke, MD, PhD; Gwen McDonald, RN, MS; Paul A. Greenberger, MD; William R. Henderson, Jr, MD; and Moira L. Aitken, MD

Background: Underestimation of allergic bronchopulmonary aspergillosis (ABPA) prevalence in the cystic fibrosis (CF) population is suspected due to nonuniform diagnostic criteria, nonspecific signs and symptoms, assessment during asymptomatic intervals, and physician nonaggressiveness in making the diagnosis.

Objective: To define the prevalence of ABPA in adult patients with CF, as the increased duration of bronchiectasis may increase the probability of Aspergillus fumigatus (Af) colonization. We also sought to determine whether atopy increases the prevalence of ABPA in adults with CF.

Methods: We examined a cross-sectional population of adult patients with CF at the University of Washington for 1 year.

Results: Information was collected on 53 of 65 (82%) patients. Fifteen of 51 (29%) had an immediate skin test reaction to Af, and 30 of 51 (59%) had at least one positive skin test. Increased total serum IgE (>450 IU/mL) was present in 0 of 53; increased IgE-Af and IgG-Af were found in 12 of 53 (23%) and 9 of 53 (17%), respectively; 24 of 53 (45%) had Af-precipitins. Peripheral blood eosinophilia was present in one patient. Eight of 49 (16%) patients' sputum cultures grew Af. ABPA-CB (ABPA-central bronchiectasis) was present in one patient and ABPA-S (ABPA-seropositive) in no patients. Atopy was present in 20 of 51 (39%).

Conclusion: There was a low prevalence of ABPA in the adult CF population despite frequent immunologic responses to Af. The prevalence of ABPA was too small to determine an association with atopy.

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Key words: allergic bronchopulmonary aspergillosis; atopy; cystic fibrosis

Abbreviations: ABPA=allergic bronchopulmonary aspergillosis; ABPA-CB=ABPA-central bronchiectasis; ABPA-S=ABPA-seropositive; Af=Aspergillus fumigatus; CF=cystic fibrosis

Allergic bronchopulmonary aspergillosis (ABPA) is one of several Aspergillus-associated diseases of the lower respiratory tract. It was first described in 1952 and recognized as a complication of cystic fibrosis (CF) in 1965.1 The prevalence of ABPA is 0 to 11% in the primarily pediatric CF population.2-6 Untreated ABPA results in recurrent exacerbations of airway inflammation and can progress to end-stage pulmonary fibrosis.

Greenberger and Patterson7 have proposed two ABPA subtypes. Criteria common to both subtypes are as follows: immediate skin test reactivity to Aspergillus fumigatus (Af) antigens, Af-specific antibody responses (IgE, IgG, and precipitins), increased total serum IgE, peripheral blood eosinophilia, airflow obstruction, and recurrent infiltrates on chest radiographs. The ABPA-central bronchiectasis (ABPA-CB) group has proximal airway destruction, with central bronchiectasis on radiologic evaluation. The group termed ABPA-seropositive (ABPA-S) may have radiographic findings limited to infiltrates.8

In patients with CF, difficulty is encountered in the
diagnosis of ABPA and in subtyping into ABPA-CB or ABPA-S groups. Patients with CF have a high prevalence of atopy (24 to 59%), and hence frequently have immediate hypersensitivity responses to Af. Positive immediate skin tests to Af have been reported from 30% in Milwaukee to 58% in Rochester, NY. Central bronchiectasis is a common radiographic finding in patients with CF, regardless of sensitization to Af. Finally, there is overlap of CF and the signs and symptoms of ABPA. These considerations have led some investigators to require clinical improvement and a 35% decrease in serum total IgE by 8 weeks of corticosteroid treatment to establish a diagnosis of ABPA in patients with CF. Other investigators have placed a greater emphasis on the absolute value of the initial Af-IgE and Af-IgG antibody titers.9

The prevalence of ABPA in pediatric patients with CF ranges from 0 to 11%. The 1994 Cystic Fibrosis Foundation Patient Registry reported 272 cases of ABPA (1.8%) in 18,674 patients. Patients tabulated in the Registry had a mean age of 15.3 years, with 67% of patients being younger than 18 years old. The prevalence of ABPA within this database may have been underreported because the diagnosis of ABPA may not have been sought in the CF Centers unless that diagnosis was clinically suspected.

The prevalence of ABPA in adult patients with CF has not been established. We hypothesized that adult patients with CF would have an increased prevalence of ABPA compared with the reported prevalence in the CF pediatric population. With a median survival of 28.3 years, adult patients with CF have a longer period for potential exposure to Af, and perhaps a greater chance of developing sensitization and hypersensitivity responses to this organism. We observed ABPA in only 1 of 53 (2%) adult patients with CF despite a high prevalence of immunologic responses to Af, 35 of 53 (66%).

Materials and Methods

Subjects

From December 1990 through November 1991, we examined adult patients with CF at the University of Washington CF Center for the presence of ABPA using published criteria. All subjects met the CF Foundation guidelines for diagnosis of CF with a sweat chloride value of greater than 60 mmol/L by pilocarpine iontophoresis and/or recognized genotype. To establish the diagnosis of ABPA-S, all of the following criteria had to be present: positive immediate skin test by epicutaneous or intradermal to Af, increased total serum IgE, increased Af-specific IgE and IgG, Af precipitins, airflow obstruction, and peripheral blood eosinophilia. To establish the diagnosis of ABPA-CB, central bronchiectasis also had to be present.

Patients who wished to be screened were interviewed for atopic history, skin testing was performed, and blood was drawn for absolute eosinophil count and Aspergillus serologic tests. Their National Institutes of Health score, a measure of clinical severity in CF, was determined by the criteria of Taussig et al. Spirometry was performed by American Thoracic Society standards.17 Current and prior spirometry findings were reviewed to document airflow obstruction. Posteroanterior and lateral chest radiographs were reviewed for presence of infiltrates and central bronchiectasis by a reader blinded to the serologic and skin testing results. Sputum was obtained and was cultured for fungi as previously described.

Atopic Status

Atopy was defined by the presence of a history of atopic disease (eg, allergic rhinitis or asthma) and positive immediate IgE-mediated hypersensitivity skin test responses to commercial extracts of common aeroallergens, including Aspergillus (Hollister-Stier Corp, Division of Miles Inc; Spokane, Wash). Skin test techniques (epicutaneous and intradermal) and interpretation were performed as previously described. For Aspergillus testing, a mixture of species (Aspergillus fumigatus, flavus, and niger) was utilized for epicutaneous testing and, if negative, an A fumigatus extract was used for intradermal testing. Intradermal testing was performed only if the epicutaneous test result was negative. Additional skin tests for common aeroallergens included dust mites, animal proteins, fungi, and tree, grass, and weed pollens. Controls consisted of histamine and normal saline solution intradermal skin tests. All skin testing was performed by one of two investigators (J.W.B. or G.M.). Subjects did not ingest antihistamines or tricyclic antidepressants for at least 48 h prior to testing, and they had to have a positive histamine response. Food allergy was recorded when ingestion of specific foodstuffs was associated with the immediate onset of symptoms consistent with allergy or anaphylaxis, including urticarial rash, nausea, vomiting, diarrhea, laryngeal edema, or shock.

Immunologic Tests

Serum samples for Af-specific IgE, IgG, and precipitins, and total serum IgE were stored at −20°C until assayed as previously described. Specific antibody was quantified by enzyme-linked immunosorbent assay, standardized against control serum samples of Af-sensitive patients with asthma without ABPA (positive test was an index >2.0). Precipitins were scored by the number of precipitin lines in citrate-treated agar by the Ochterlony technique. Total peripheral blood eosinophil counts were obtained. The diagnosis of ABPA-S or ABPA-CB was established by presence of all criteria for each subtype.

Statistical Analyses

The data are reported as the mean±SD. The age and pulmonary function of patients who were not screened were compared to those who were with an unpaired Student’s t test. All patients with CF performed spirometry as routine care at each clinic visit.

Results

Sixty-five patients with CF came for routine clinical care to the CF clinic during that year and 53 patients agreed to be screened. Of those not included, 10 had patient time constraints or did not wish to have skin testing, one patient was younger than 18 years old, and another was developmentally delayed. None of these 12 patients was believed to have ABPA prior to or subsequent to completion of the study. The 53 patients who were evaluated did not differ significantly from those who were not in age (25.8±6.5 vs 25.2±6.8 years; p=0.81), gender (47% female vs 60% female), or pulmonary function (FEV1, 1.73±0.91 L vs 1.89±0.85 L; p=0.62; FVC, 2.84±1.22 L vs 2.81±1.01 L; p=0.95). The age range of the 53 patients evaluated was 18 to
50 years. The mean National Institutes of Health score of the 53 patients was 69.2±16.7.

A history of symptoms of seasonal/perennial rhinitis was found in 22 of 53 (42%) patients. Atopic dermatitis and food allergy were reported by none and 6 of 53 (11%), respectively. Drug allergy or intolerance was reported in 17 of 53 (32%). Only one patient reported his pulmonary symptoms as those of asthma. The other patients attributed their subjective pulmonary symptoms as CF. However, 37 patients were prescribed an inhaled bronchodilator by their physician.

Documented airflow obstruction was found in 46 of 53 subjects (87%). Airflow obstruction was mild in 6 of 53 (11%), moderate in 9 of 53 (17%), and severe in 31 of 53 (58%). Methacholine challenge testing was not performed in these patients to document airway hyperresponsiveness.

The prevalence of an immunologic response to Af was high (66%) with an immunologic response defined as one or more of the following: positive immediate skin test to an Aspergillus mix of Af, increased total serum IgE, increased Af-specific IgE and IgG or Af precipitins.

Immediate skin test reactivity to Af was present in 15 of 51 (29%) subjects by either a positive epicutaneous or intradermal test. Eight of 51 had a positive epicutaneous and a further 7 of 51 a positive intradermal test. Immediate skin test response to at least one allergen was present in 30 of 51 (59%), of whom 4 of 13 (31%) were positive only to Af. The most common IgE-mediated response was to the dust mite Dermatophagoides pteronyssinus, 18/46 (39%). Immediate skin test response to Helminthosporum species was found in 2 of 46; to Hormodendrum species in 1 of 46; and to Penicillium species in 1 of 46. Seven patients were not skin tested for aeroallergens and two patients were not skin tested to Af because of time constraints in the clinic, one patient declined skin testing, and one had persistent antihistamine-induced wheal suppression.

The total eosinophil count was within the normal reference range (<500 cells per cubic millimeter) in 52 of 53 patients: 1 patient had an eosinophil count of 560 cells per cubic millimeter. Total serum IgE (>200 IU/mL) was present in 5 of 53 (9%) subjects, but no patient had an IgE level greater than 450 IU/mL. Increased Af-specific IgE and IgG (index >2.0) were noted in 12 of 53 (23%) and 9 of 53 (17%) patients, respectively, and 24 of 53 (45%) subjects had positive precipitins.

Eight of 49 (16%) sputum fungal cultures grew Af and 1 of 49 grew Aspergillus fumigatus. Candida albicans and Penicillium species were recovered in 28 of 49 (57%) and 3 of 49 (6%), respectively. Four patients did not have sputum sent for culture; two patients did not produce sputum and collection was omitted in two patients.

One patient had recurrent infiltrates on chest radiograph, localized to the right middle lobe. Tramlines and ring shadows, consistent with the radiologic diagnosis of central bronchiectasis, were seen in 52 of 53 patients. Mucus plugging and diffuse interstitial changes consistent with the diagnosis of CF were seen frequently and appeared to correlate with the severity of pulmonary dysfunction.23 One patient had a normal chest radiograph.

Using the criteria of Greenberger and Patterson,7 one patient (previously diagnosed in 1984) met the criteria for ABPA-CB. This patient had corticosteroid-dependent ABPA-CB, with the following criteria for ABPA: asthma, chest radiograph with infiltrate, positive epicutaneous skin test to Aspergillus mix, total serum IgE level of 358 IU/mL, total eosinophil count of 140 cells per cubic millimeter, (elevated eosinophil count at time of diagnosis prior to corticosteroid therapy), FEV1 of 1.57 L, Af-IgE index of 0.75, Af-IgG index of 2.11, and negative precipitins. No patient met the criteria for ABPA-S.

Atopy was found in 20 of 51 (39%) of our study population. A positive skin test was found in 30 of 51 patients. Of these 30 patients, none reported symptoms of asthma and 20 had symptoms of seasonal/perennial rhinitis. However, 37 patients were prescribed an inhaled bronchodilator by their physician. Of these 37, 22 had a positive skin test. If more patients had reported their pulmonary symptoms as asthma rather than CF, atopic prevalence may have risen to 22 of 53 (42%) in our study population.

The association of atopy and ABPA could not be determined as only one patient had ABPA.

**DISCUSSION**

We found a 2% prevalence of ABPA-CB in adults with CF in Washington state. The prevalence was lower than that reported in previous series of pediatric CF patients from other geographic areas, but was the same as that reported to the Cystic Fibrosis Foundation Registry.15 The prevalence of an immunologic response to Af was high (66%).

It is difficult to make the diagnosis of ABPA in patients with CF as there is no definitive test, but rather a group of findings that establish the diagnosis. These criteria rely heavily on serologic responses to Af, which vary by disease stage (summarized in Table 1). By these criteria, ABPA-CB stages 1 (acute) and 3 (exacerbation) have more criteria for diagnosis present than stages 2 (remission), 4 (corticosteroid-dependent), and 5 (fibrotic), which are quiescent in terms of chest radiographic infiltrates. The assessment of patients for ABPA at a single point in time may underdiagnose the
disease if the patients have quiescent stage 2, 4, or 5 disease or are being treated with systemic corticosteroids. Many of our patients had multiple criteria present at the time of evaluation, but not sufficient to establish a diagnosis of ABPA. All but one of our patients had central bronchiectasis. She did not fulfill the criteria of ABPA-S. She had a negative skin test to Af, no Af precipitins, a total IgE level of 394 ng/mL, but Af-specific IgE and IgG levels were not increased, a normal eosinophil count, and no infiltrate on chest radiograph. Only one of our patients carried the previous diagnosis of ABPA stage 1. None of our patients had ABPA-CB stage 2. In our study population, only one patient had symptoms with asthma test negative. Twelve patients had a reduced FEV1 vital capacity ratio and a positive skin test to Af (12/53, 23%). The authors believe that a positive skin test to Af alone should not make the diagnosis of ABPA when airflow obstruction can be explained on the basis of CF. In addition, stage 1 disease would have had to have been missed in the past. No patient fulfilled criteria for stage 3. Stage 4 ABPA-CB is defined as dependence on systemic corticosteroid therapy to control symptoms. Only one patient fell into this category. Stage 5 ABPA-CB is characterized as the end-stage disease with fibrosis secondary to ABPA. In stage 5, one would have presumed that this diagnosis would have been made at a younger age because the large majority of the patients with CF had received their care from CF centers and we believe this to be unlikely. CF caregivers are aware of the reportedly high prevalence of ABPA and readily seek to make this diagnosis. One patient with previously documented ABPA-CB was using systemic corticosteroids. No other patient was using systemic corticosteroids at the time of skin testing.

The relatively low prevalence of ABPA in the 1994 CF registry may reflect the lack of standardized criteria for diagnosis of ABPA from center to center. Patients must be followed up longitudinally to be confident of not missing the diagnosis of ABPA. The patients included in our series were followed up closely before and after the screening period at the CF center, yet the clinical, serologic, and radiologic findings do not support ABPA-CB. Corticosteroids supress some markers of immune responses to Af such as total serum IgE concentration. Only the one patient with previously diagnosed ABPA was using systemic corticosteroids (20 mg on alternate days) at the time of our evaluation.

We found only one case of ABPA-CB, but immediate skin test reactivity in 29%, and a 66% prevalence of an immunologic response to Af. Zeaske et al24 and Laufer et al4 reported a prevalence of ABPA in 11% and 10% with immediate skin reactivity in 59% and

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<th>Table 1—Diagnostic Criteria of ABPA by the Stage of Disease*</th>
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<td>Asthma</td>
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<td>Positive skin test to Af</td>
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<td>Elevated total serum IgE</td>
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<td>Af precipitins</td>
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<td>Elevated IgE, IgG to Af</td>
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<td>CXR1 infiltrate</td>
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*Adapted from Greenberger and Patterson.2
1CXR=chest radiograph.

53%, respectively. Zeaske et al24 reported immunologic responses in 77% (Table 2). The age range of the patients in the Zeaske et al24 report was 5 to 36 years old (mean, 14 years) and that of Laufer et al4 was 2 to 36 years old (mean, 14 years). Laufer et al4 and Zeaske et al24 conducted their studies in Wisconsin, and the difference in findings between their studies and ours may reflect the Aspergillus species spore counts or virulence in Wisconsin as compared with Washington.25,26 The antigen used for skin testing differed between studies. Zeaske et al24 and Laufer et al4 used Af from a lyophilized dialysate from a laboratory (Dr. V.P. Kurup, PhD; Medical College of Wisconsin) while we used a commercial extract (Miles Inc; Spokane, Wash). The difference in extract may explain the difference in skin test results, as serologic testing was similar in all three studies.

We were unable to determine whether the prevalence of ABPA is higher in adult patients with CF as we did not examine the prevalence of the disease in the pediatric population of Washington state.26 However,
the prevalence of ABPA in the pediatric population at our institution, as defined by three of four of the following—increased eosinophilia, positive precipitins, positive skin test, increased IgE—is approximately 2%, ie, 4 of 200 patients, which is the same prevalence as the adult population. The 2% prevalence of ABPA observed in our adult CF population was lower than that reported in pediatric patients with CF from the states of Wisconsin and New York.

A high prevalence (59%) of reactivity to aeroallergens was found in our patients consistent with the presence of atopy in the CF population (24 to 59%). Sensitization to both indoor (eg, dust mites, cat protein) and outdoor (eg, trees, grasses) allergens was common. The high prevalence of atopic responses in patients with CF remains unexplained. Hypotheses are that the airway epithelium is disrupted in patients with CF allowing access for aeroallergens, and the presence of AF in the mucus may stimulate immunologic responses by activation of local immune cells, including Th2 lymphocytes.

In conclusion, we showed that there was a low prevalence of ABPA in our adult population of patients with CF. However, immunologic responses to AF were high (66%). Further study is needed to determine whether this cohort of patients will develop ABPA-S or ABPA-CB over a longer period of clinical evaluation.

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