
The role of allergy in manifestations of respiratory disease in adult cystic fibrosis

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Background: Variability is present in the expression of the clinical phenotype in cystic fibrosis (CF). Part of this variability may be explained by the coexistence of allergy in CF.

Objective: To determine the rate of allergy in adult CF and evaluate the association between allergy and the manifestations of upper and lower airway disease.

Methods: We performed a cross-sectional study of consecutive patients enrolled in a university hospital adult CF clinic. Allergen specific IgE was determined by radioallergosorbent and skin prick tests to common aeroallergens. We characterized features of upper and lower airway disease by clinical evaluation of rhinitis and spirometry before allergy testing.

Results: The study population consisted of 55 patients. Allergen specific IgE was present to at least 1 aeroallergen in 67% by skin prick testing and 80% by radioallergosorbent testing. Rhinitis occurred in 50% of the population and was associated with immediate-type hypersensitivity to aeroallergens other than molds. The frequency of rhinitis increased when there was sensitization to a greater number of aeroallergens and rarely occurred in the absence of allergic sensitization. There was no detectable difference in lung function between those with and without allergic sensitization.

Conclusions: Immediate-type hypersensitivity to aeroallergens commonly occurs in adult CF. The coexistence of allergy in CF is associated with clinical features of rhinitis. Because allergic manifestations of CF warrant appropriate therapy, individuals with CF should be evaluated for coexistent allergy.

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INTRODUCTION

Cystic fibrosis (CF) is an inherited autosomal recessive disorder that leads to chronic upper and lower airway disease. Genetic and environmental factors may influence the clinical phenotype of CF. One important factor that could affect the clinical phenotype of CF is the coexistence of allergy. Despite increasing numbers of adults with CF, there is limited information about the rate of allergy in adult CF. Predisposition to allergy in adult CF is suggested by an increased rate of allergy,¹ asthma,^{2,3} and chronic rhinosinusitis⁴ in adults purportedly heterozygous for the CF gene. Studies of allergy in children with CF have demonstrated allergy predominantly to molds, whereas sensitizations to other aeroallergens have not been increased.^{5–7}

The possibility that allergic inflammation may contribute to nasal disease in CF has been raised recently.^{8,9} Nasal disease in CF is generally attributed to abnormalities in transepithelial ion transport, increased mucoglycoprotein production,¹⁰ cytokine up-regulation,¹¹ and recurrent bacterial

infection¹²; however, recent analyses of nasal lavage fluid in CF have demonstrated features of allergic inflammation, including the release of eosinophil cationic protein (ECP)⁹ and leukotriene (LT) C₄⁸ into the nasal mucosa. There is little epidemiologic information available about the relationship between allergy and manifestations of nasal disease in CF. Although studies show that allergic inflammation may contribute to lower airway inflammation in CF,^{13,14} the relationship between allergy and lung function in adults with CF has not been determined. This study was designed to evaluate the rate of allergy in adult CF and determine if coexistent allergy is associated with clinical features of CF.

METHODS

Study Design

We conducted a cross-sectional study of 65 consecutive patients attending the adult CF clinic at the University of Washington Medical Center, Seattle, WA, during a 10-month period. The diagnosis of CF was established according to criteria of the Cystic Fibrosis Foundation, including either a sweat chloride level of greater than 60 mmol/L or a known genotype and compatible symptoms.¹⁵ Clinical history of rhinitis was determined by one of the investigators (J.W.B.) before the allergy evaluation. Clinical rhinitis was defined by nasal symptoms of sneezing or rhinorrhea during seasonal exacerbations or in response to perennial exposures such as cats and dust mites. Allergen specific IgE was determined by radioallergosorbent tests (RASTs) and skin prick tests. Spirometry was performed according to American Thoracic So-

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ciety criteria.¹⁶ The University of Washington Human Subject Review Committee approved the study.

Immunological Evaluation

Skin prick tests were performed as previously described¹⁷ to 14 environmental aeroallergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat hair, dog (hair and dander), *Helminthosporium interseminatum*, *Aspergillus fumigatus*, *Cladosporium cladosporioides*, *Penicillium notatum*, red alder, white birch, English plantain, and orchard, timothy, and velvet grass (Hollister-Stier, Spokane, WA). Antihistamines and tricyclic antidepressants were restricted for 48 hours before testing. A wheal-and-flare response of 3 mm or greater with or without pseudopodia was considered a positive test result. Venous blood was analyzed for total eosinophil count using a Coulter counter (Beckman Coulter, Fullerton, CA) and total and allergen specific IgE. Total IgE was determined by radioimmunoassay (Pharmacia, Piscataway, NJ). Allergen specific IgE was measured by RAST to 17 environmental aeroallergens (BAI Allergy Reference Laboratory, Chicago, IL): *D farinae*, *D pteronyssinus*, cat, *Alternaria tenuis*, *A fumigatus*, *Cladosporium herbarum*, *Helminthosporium sativum*, *Mucor racemosus*, *Penicillium notatum*, *Pullularia pullulans*, mountain cedar, California scrub oak, Ponderosa pine, Kentucky bluegrass, perennial ryegrass, English plantain, and short ragweed. The RAST results were converted from counts per minute into classes, with a class of 2 or higher considered positive for this study. Class 2 corresponded to 1,600 to 3,600 cpm.

Statistical Analysis

The frequency of rhinitis in participants with and without allergic sensitization was evaluated with a χ^2 test; a Fisher exact test was used in instances where the number in a single category was less than 5. Differences in IgE level and eosinophil count in those with and without rhinitis were evaluated with a Mann-Whitney *U* test. Differences in lung function in those with and without rhinitis and allergic sensitization were evaluated with a *t* test. Agreement between skin test and RAST results was evaluated with the Cohen κ coefficient. Correlations were performed using a Pearson correlation coefficient. Statistical significance was defined as a 2-tailed $P < .05$.

RESULTS

Study Population

The study population consisted of 55 of 65 consecutive patients attending the CF clinic during a 10-month period (Table 1). Ten patients declined allergy testing because of time constraints. All patients underwent pulmonary function testing. RASTs were completed in 50 and skin prick tests in 37 patients. Thirty-seven patients underwent both RAST and skin prick tests. Thirty-six patients had clinical evaluation of rhinitis. Patients who completed allergy tests were similar to those who did not complete allergy tests in age (26 vs 25 years, $P = .73$), sex (55% vs 40% male, $P = .71$), and forced

Table 1. Characteristics of Study Population

Characteristic	Result (N = 55)
Age, mean $\pm$ SD, y	25.6 $\pm$ 6.5
Sex, No. (%)	
Male	30 (54.5)
Female	25 (45.5)
Clinical rhinitis, No. (%)	18 (50.0)*
Lung function	
FEV ₁ , mean $\pm$ SD, %	47.4 $\pm$ 22.6
FEV ₁ /FVC ratio, mean $\pm$ SD	0.60 $\pm$ 0.12
Median total IgE, IU/mL	53
Median eosinophil count, cells/ μ L	160
Medications, No. (%)	
β_2 -agonist	36 (69.2)†
Inhaled corticosteroid	8 (15.4)†

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

* Assessment of clinical rhinitis was completed in 36 patients.

† Prescription medications were recorded for 52 patients.

expiratory volume in 1 second (FEV₁) (47% vs 55% predicted, $P = .78$). The frequency of rhinitis was similar in those who did and did not complete RASTs (47% vs 75%, $P = .60$) and skin tests (50% vs 50%, $P = .70$). Patients who were evaluated for clinical rhinitis were similar to those who were not evaluated for clinical rhinitis in age (26 vs 25 years, $P = .56$), FEV₁ (48% vs 49% predicted, $P = .23$), frequency of β_2 -agonist use (64% vs 79%, $P = .35$), frequency of inhaled corticosteroid use (15% vs 16%, $P > .99$), IgE level (47 vs 53 U/mL, $P = .79$), and eosinophil count (170 vs 145 cells/ μ L, $P = .17$).

Prevalence of Allergic Sensitization

One or more skin prick test results were positive in 67% of patients skin tested (Table 2). At least 1 RAST result was positive in 80% of the patients tested by RAST (Table 2). There was good agreement between skin and RAST methods to detect allergen specific IgE for dust mite, cat proteins, and tree, grass, and weed pollens ($\kappa = 0.41$ – 0.69 , $P \leq .01$) but poor agreement for molds ($\kappa = -0.11$, $P = .36$).

Association of Allergy With Features of Respiratory Disease

Clinical rhinitis was present in 50% of those evaluated for rhinitis (Table 1). Patients with rhinitis exhibited greater frequency of immediate-type hypersensitivity by skin prick test to cat proteins and tree, grass, and weed pollens (Figure 1). Similarly, patients with rhinitis showed evidence of increased allergen specific IgE by RASTs to cat hair, grass pollens, and English plantain (Figure 2). The frequency of rhinitis was similar in those with and without sensitization to molds (Figures 1 and 2). Only 10% of patients with all negative skin test results had clinical rhinitis. The frequency of rhinitis increased as sensitization to a greater number of different allergens was present (Figure 3). Similarly for RASTs, the frequency of rhinitis was 14% when all RAST results were negative but increased to 25% when 1 allergen

Table 2. Frequency of Elevated Allergen Specific IgE by Skin Prick Test and RAST

Allergen	Skin prick (≥3 mm), %	RAST (class 2 or higher), %
Dust mites		
<i>Dermatophagoides farinae</i>	30	30
<i>Dermatophagoides pteronyssinus</i>	43	39
Animal		
Cat hair	22	22
Dog (hair and dander)	6	
Molds		
<i>Aspergillus fumigatus</i>	18	10
<i>Alternaria tenuis</i>		8
<i>Helminthosporium interseminatum</i>	0	
<i>Helminthosporium sativum</i>		8
<i>Cladosporium cladosporioides</i>	3	
<i>Cladosporium herbarum</i>		17
<i>Penicillium notatum</i>	3	10
<i>Mucor racemosus</i>		10
<i>Pullularia pullulans</i>		4
Tree pollen		
Red alder	19	
White birch	19	
Mountain cedar		12
California scrub oak		12
Ponderosa pine		19
Weeds		
English plantain	17	28
Short ragweed		22
Grasses		
Orchard	28	
Timothy	28	
Velvet grass	31	
Kentucky bluegrass		39
Perennial ryegrass		35

Abbreviation: RAST, radioallergosorbent test.

was positive and to 80% when 3 or more allergens were positive. The IgE levels were within the normal reference value of 300 U/mL or less in 82% of the study population. IgE levels were correlated with the number of skin test results that were positive ($r = 0.50$, $P = .01$). The median IgE level was higher in those with rhinitis than those without rhinitis, but this relationship was not statistically significant (median IgE level, 76 vs 20 U/mL, $P = .16$). There were no significant relationships between eosinophil count and the frequency of allergic sensitization by RASTs or skin tests.

No significant differences were noted between FEV₁ in those with and without positive RAST results (mean FEV₁, 50% positive vs 38% negative; $P = .12$) and skin test results (mean FEV₁, 50% positive vs 44% negative; $P = .50$). Although the degree of allergic sensitization by the number of positive RAST results was correlated with better lung function measured by FEV₁ ($r = 0.33$, $P = .02$), this association was not demonstrated by skin tests ($r = 0.24$, $P = .16$). The

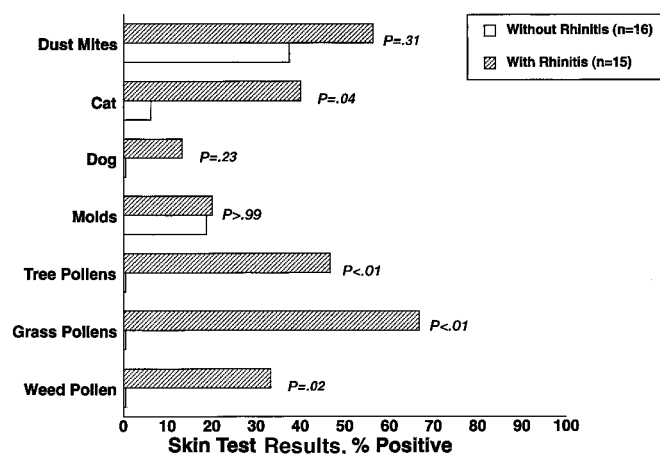


Figure 1. Frequency of allergen specific IgE by skin prick tests in adults with cystic fibrosis with and without rhinitis. The specific aeroallergens tested are described in the "Methods" section.

frequency of β_2 -agonist use was similar in those with and without positive RAST results (71% vs 60%, $P = .70$) and skin test results (64% vs 64%, $P > .99$). The use of inhaled corticosteroids was similar in those with positive RAST results (57% vs 43%, $P = .15$) and skin test results (14% vs 9%, $P > .99$) compared with those with negative test results.

DISCUSSION

In this study, we found that a substantial portion of adults with CF had evidence of allergic sensitization as demonstrated by sensitization to at least 1 aeroallergen in most of the population by RASTs and/or skin testing. Compared with the general adult population, where rates of 1 or more positive skin test results are 30% to 35% in the highest estimates,^{18,19} the rate of allergy in adult CF is likely increased. Unlike studies of allergy in children with CF where allergic

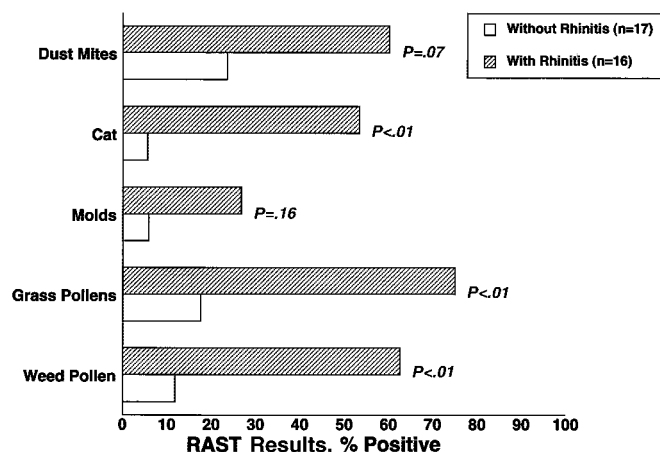


Figure 2. Frequency of allergen specific IgE by radioallergosorbent tests (RASTs) in adults with cystic fibrosis with and without rhinitis. The specific aeroallergens tested are described in the "Methods" section.

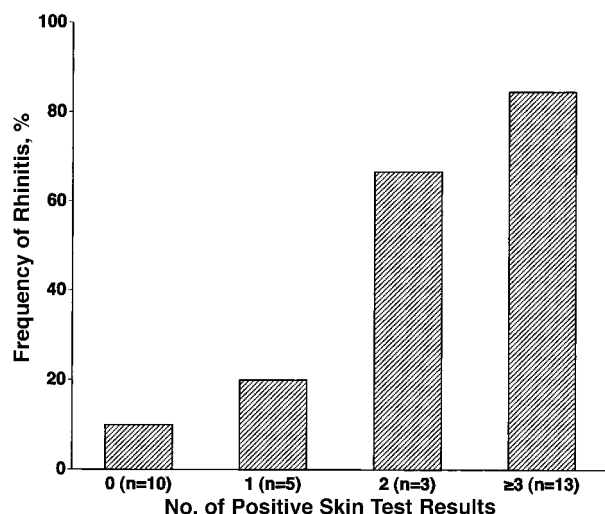


Figure 3. Frequency of rhinitis varies according to the number of positive skin test results. χ^2 test for trend across categories, $P < .01$.

sensitization was primarily to molds,^{5,7,20–25} we found that allergic sensitization occurs to a wide range of aeroallergens. The frequent evidence of allergy noted in this study could be explained by abnormalities in epithelial barrier function and mucus hypersecretion leading to retention of allergens in the respiratory tract with progressive exposure and sensitization. Alternatively, a genetic predisposition to allergy has been suggested by studies of persons heterozygous for CF.^{1–3,26} The frequency of asthma is 9% in carriers of the $\Delta F508$ CF transmembrane conductance regulator (*CFTR*) mutation compared with 6% of noncarriers.³ Missense mutations in the *CFTR* gene were found in 15% of 144 adults with asthma but none of 41 subjects without asthma.² The frequency of the HLA class II alleles *DR4* and *DR7*, which are increased in persons with atopy and asthma, are increased in CF.²⁶

The rate of allergy to *Aspergillus* in this study was much lower than that reported in studies of children and adolescents with CF.^{6,7} The 2 methods of detecting *Aspergillus* sensitization in this study showed poor agreement, with skin testing being the more sensitive method of detecting *Aspergillus* specific IgE. Lack of environmental exposure to *Aspergillus* is an unlikely explanation for these findings, since *Aspergillus* sensitization occurred in 21% of adults with respiratory allergy at the same institution.²⁷ *Aspergillus* sensitization is associated with reduced lung function^{6,7,28} and may be associated with reduced survival in children with CF.²⁹ Therefore, the prevalence of sensitization in those patients who survive into adulthood could be reduced. Allergic bronchopulmonary aspergillosis³⁰ may occur as a result of *Aspergillus* colonization and sensitization of the airways, but the overall rate of allergy³¹ and the rate of lung function decline³² in CF are not influenced by allergic bronchopulmonary aspergillosis.

In CF, the frequency of nasal disease, such as rhinitis, nasal polyps, and sinusitis, is higher than in the general popula-

tion.¹² We found that rhinitis in this adult CF population was strongly associated with allergic sensitization. Rhinitis may be due to both allergic and nonallergic mechanisms.³³ Patients with allergic rhinitis have evidence of eosinophil influx^{34,35} with release of ECP,³⁴ epithelial cell activation,³⁶ and generation of LTs³⁷ in nasal lavage fluid. The origin of rhinitis in CF is generally attributed to factors other than allergy^{10,12}; however, analyses of nasal lavage fluid in CF have demonstrated the release of ECP⁹ and LTC₄⁸ into the nasal mucosa, suggesting an allergic origin. The association between rhinitis and allergic sensitization was strengthened in our study by the observation that as the number of positive RAST or skin test results increased, the frequency of rhinitis increased accordingly. Symptomatic rhinitis was rare in the absence of allergic sensitization. These data provide epidemiologic evidence that symptomatic rhinitis in adult CF is in part a result of allergic sensitization.

Pulmonary function abnormalities in CF result from airway inflammation that occurs due to cytokine dysregulation^{38,39} and persistent infection,⁴⁰ leading to bronchial wall destruction and parenchymal fibrosis. Allergy may also contribute to lower airway inflammation that is allergic in origin. Although the numbers of eosinophils are low in the lower airways of patients with CF,⁴¹ they have an increased propensity in vitro to release eosinophil granule proteins.¹³ The cysteinyl LTE₄ is increased in the urine of atopic children with CF.¹⁴ However, studies do not link allergy to decreased lung function in CF in the absence of other factors, such as persistent infection.^{20,21,42} The data in the present study suggest that lung function is not altered by the presence of allergy in CF but is not large enough to adequately adjust for factors such as age, use of anti-inflammatory medications, presence of bronchial hyperresponsiveness, CF genotype, and frequency and type of infection that could confound the relationship between lung function and allergy in CF.

This study has several important limitations. First, not all patients enrolled in the adult CF clinic completed RASTs and/or skin testing, which could have influenced the estimate of allergy prevalence. To evaluate the possibility of bias, we performed subgroup analyses to detect differences between those who did and did not complete RASTs and skin testing. The RAST results were available for 50 of the 65 patients in the CF clinic, making 62% the lowest possible rate of allergy. Second, the presence of rhinitis was based on symptoms, without objective measures of nasal airflow limitation. Third, cross-sectional data do not allow the evaluation of causality with respect to the relationship between allergy and features of CF. Finally, although this is the largest group of adults studied, we do not have an adequate sample size to adjust for additional factors that could confound the relationship between allergy and features of upper and lower airway disease in CF.

We conclude that allergy to a wide range of aeroallergens commonly occurs in adult CF. Rhinitis in adult CF is frequently present and is associated with the degree of allergic sensitization. These findings suggest that allergy is a common

factor in the development of upper airway disease in CF. Small crossover studies have shown that an inhaled corticosteroid reduces bronchial hyperresponsiveness, dyspnea, and cough in adults with CF who have bronchial hyperresponsiveness,⁴³ and a cysteinyl LT antagonist reduces serum eosinophil counts and ECP levels in children with CF.⁴⁴ Further studies with larger numbers of patients are needed to determine the role of these and other allergy medications in the subgroup of patients with CF who have concurrent allergic disease. Because allergic manifestations of CF warrant appropriate therapy, individuals with CF should be evaluated for coexistent allergy.

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