Variability of airways hyper-reactivity and allergy in cystic fibrosis

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SUMMARY The importance of bronchial hyper-reactivity and allergy, and treatment with bronchodilators and corticosteroids, in the management of patients with cystic fibrosis is poorly understood. Three tests generally regarded as useful in the diagnosis of asthma were evaluated in 25 children with cystic fibrosis. The constancy of a child's response was assessed by histamine bronchial provocation, exercise challenge, and tests of skin allergy during a 6-month period. Although a positive response to these tests was related to impaired pulmonary function, 44% of children had variable responses to histamine, 56% to exercise, and 24% to skin tests which were unrelated to exacerbations of chest infection or to changes in pulmonary function. These results show the complex nature of airways hyper-reactivity and allergy in cystic fibrosis, and suggest that 'anti-asthma' therapy is not justified solely on the basis of one positive response to these tests.

Cystic fibrosis (CF) is now the most common cause of chronic suppurative lung disease in children of European origin and occurs in 1 live birth in 2500,¹ while features of asthma are found in up to 1 child in 5.² Respiratory allergy and airways hyper-reactivity have been reported in both conditions, but there are conflicting data on the frequency and importance of allergy and airways hyper-reactivity in CF.^{3,4}

Between 24 and 68% of children with CF have been shown to have positive responses to histamine bronchial provocation,^{3,5} and between 36 and 73% have been shown to have positive responses to exercise.^{5,6} Unlike children with asthma, the feature characteristic of a positive response to exercise is an increase rather than a decrease in peak expiratory flow rates.^{6,7}

Positive results to tests of skin allergy have been reported in between 43 and 77% of children with CF.^{8,9} It is not clear whether the increased hypersensitivity is secondary to lung damage or is an inherited phenomenon. Warner *et al.*¹⁰ found a high incidence of positive skin tests in heterozygotes which suggested a genetic basis, but others have found an incidence similar to the normal population.¹¹

These tests are generally regarded as useful in the diagnosis of asthma. It is important to determine their significance in patients with CF since one of the problems in the management of CF is the

identification of patients likely to benefit from 'anti-asthma' therapy.

The present study was designed to assess the constancy of an individual's response to histamine bronchial provocation, exercise challenge, and tests of skin allergy in a group of children with CF, and to relate any variability to changes in clinical status and pulmonary function.

Subjects and methods

Sixteen boys and 9 girls, aged between 9 and 18 (mean 12.1) years, with CF proved by estimation of sweat electrolytes¹² were studied. Eight children had medical histories indicative of asthma, and 22 had positive family histories on the basis of asthma, hay fever, eczema, rhinitis, urticaria, or skin tests. Patients were graded according to the presence of cough, sputum production, chest x-rays, and tests of pulmonary function (Table 1), from grade 0 (minimal lung disease) to grade 4 (severe lung disease). Patients with grade 4 were too ill to perform all the tests satisfactorily, so only patients with grades 0 to 3 were studied. Their distribution and results of tests of prechallenge pulmonary function are shown in Table 2. The children continued their normal treatment, except that bronchodilators were withheld for at least 6 hours before each test. One child received corticosteroids throughout the study. Informed consent was obtained from all patients

Table 1 *Cystic fibrosis. Grading according to pulmonary status*

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4 (severe)
Cough	No persistent cough	Persistent cough	Persistent cough	Persistent cough	Chronic cough
Sputum	None	None	< 10 ml/day	10-100 ml/day	> 100 ml/day
Chest radiograph	Normal	Minimal streaking	Bronchial wall thickening and minimal hyperinflation	Patchy infiltrates, cysts, and moderate hyperinflation	Widespread infiltrates and pronounced hyperinflation
Pulmonary function FEV ₁	> 80% predicted	65-80% predicted	65-80% predicted	50-65% predicted	< 50% predicted

Grade 0 = presence of all 4, grade 1 = any 1, grades 2-4 at least 2.

Table 2 *Distribution of patients, and results of tests of prechallenge pulmonary function (mean $\pm$ SD)*

	Grade 0 (n = 6)	Grade 1 (n = 5)	Grade 2 (n = 7)	Grade 3 (n = 7)
Baseline FEV ₁ (% predicted normal)	85.9 $\pm$ 11.8	87.7 $\pm$ 12.9	61.9 $\pm$ 13.6	49.9 $\pm$ 11.6*
Baseline PEFR (% predicted normal)	92.5 $\pm$ 10.3	96.2 $\pm$ 10.8	75.2 $\pm$ 21.0	60.5 $\pm$ 17.2*

*Significantly lower than each of the others ($P < 0.01$).

and their parents. The procedures complied with the ethical requirements of the institution.

Each child was seen on four occasions, at 6-weekly intervals, during a 6-month period from March to September. Each assessment included histamine inhalation challenge, standard exercise test, skin allergy tests, and collection of a weekly diary card. Each patient was tested at about the same time of day each time to lessen any effect of diurnal variation.

Spirometry was performed using a 9-litre water-filled spirometer (Godart Expirograph EP 62001) with the patient seated in accordance with standard guidelines.¹³ Results at BTPS were expressed as percentage predicted for height and sex.¹⁴⁻¹⁶

As an independent preliminary investigation had shown there was no appreciable difference in the response to histamine provocation and exercise challenge when both tests were carried out on the same day in that order whether separated by 60 minutes or 4 hours, a 1-hour interval was allowed.

Histamine inhalation challenge was performed using 8 dose steps from 0.03 to 10 mg/ml according to standard guidelines.¹⁷ A positive response was defined as a 20% or greater fall from baseline forced expiratory volume in one second (FEV₁). The test was terminated with a positive response or, if none occurred, with the highest concentration.

The children ran for 6 minutes on a treadmill (Avionics Pty Ltd) which was set at a 10% grade. The treadmill speed was determined on the basis of an estimate of the work load necessary to achieve a heart rate of 170 beats per minute.¹⁸ Peak expiratory flow rate (PEFR) was measured before, at 3-minute intervals during, and at 5-minute intervals for 20 minutes after the run, using a Wright peak flow

meter (Air-Med Ltd, England). A positive response was defined as one or more of a >14.3% fall in PEFR, a >19.0% rise in PEFR, or an exercise lability index of >22.5%.¹⁸

Skin allergy prick tests were performed using 10 common local allergens.¹⁹ Saline was used as a negative control, and histamine (1 mg/ml) as a positive control. Reactions were read at 10 minutes, and a weal of 3 mm diameter greater than a negative control was considered as a minimum positive response.

A diary card, which included questions on frequency of cough, wheeze, and production of sputum, was completed weekly by a parent for each child.

The data were analysed using Student's unpaired *t* test, χ^2 test with Yates's correction for continuity, and analysis of variance of regression.²⁰ A non-parametric analysis (Wilcoxon's signed rank sum test) was used to analyse the diary cards. The level of significance was taken as $P < 0.05$.²¹

Results

The frequency of positive responses to each challenge on the four occasions is shown in Fig. 1. Table 3 shows the number of children who had positive responses to the tests on all four occasions, the number who had negative responses on all four occasions, and the number who had positive responses some days but negative ones on others. There were significantly more positive histamine bronchial provocations, positive exercise tests, and positive skin allergy tests in patients with grade 3 disease (Table 4).

Fig. 1 Proportion of positive histamine, exercise, and skin tests on each of the four occasions.

Table 3 Pattern of response to histamine, exercise, and skin tests on the four occasions

	Number		
	Always positive	Always negative	Variable
Histamine response	10	4	11
Exercise tests	5	6	14
Skin tests	12	7	6

Table 4 Response to histamine, exercise, and skin tests in the 4 grades

	Grade 0	Grade 1	Grade 2	Grade 3	
Histamine response					
Total number					
Positive tests	10	11	15	24	$\chi^2=13.36$
Negative tests	14	9	12	3	$P<0.01$
Exercise tests					
Total number					
Positive tests	4	7	12	16	$\chi^2=10.68$
Negative tests	18	13	14	9	$P<0.05$
Skin tests					
Total number					
Positive tests	12	13	11	25	$\chi^2=16.32$
Negative tests	12	7	17	3	$P<0.001$

Children who had positive histamine, exercise, and skin tests on all four occasions had significantly lower mean results to tests of baseline pulmonary function ($P<0.01$) than children in whom results were always negative. The baseline pulmonary function of the children with variable responses to histamine ($P<0.02$) and variable responses to exercise ($P<0.001$) was significantly greater than those who always had positive results. The baseline pulmonary function of the children with variable responses to skin tests ($P<0.02$) and variable

Table 5 Responses to histamine, exercise, and skin tests on the four occasions (mean $\pm$ SD)

	Always positive	Always negative	Variable
Histamine response			
Baseline FEV ₁ (% predicted)	61 $\pm$ 18	83 $\pm$ 10	72 $\pm$ 22
Exercise tests			
Baseline PEFR (% predicted)	56 $\pm$ 18	93 $\pm$ 12	83 $\pm$ 18
Skin tests			
Baseline FEV ₁ (% predicted)	66 $\pm$ 18	80 $\pm$ 17	66 $\pm$ 21

responses to skin tests ($P<0.01$) was significantly lower than for those who were always negative (Table 5). The baseline pulmonary function of the children with variable responses to the tests was lower but not significantly different on the days when they had positive responses compared with the days when they had negative ones.

Children with severe disease (grade 3) and lower prechallenge FEV₁ tended to respond at lower and more variable doses of histamine than children with mild disease (grade 0) (Fig. 2).

There were 39 positive exercise tests, 20 being

Fig. 2 Histamine dose compared with prechallenge pulmonary function (a) in 4 children with mild disease, and (b) in 7 children with severe disease. (Numbers show individual cases).

positive on the basis of increased flow rates, 11 due to decreased flow rates, while 3 were associated with both significant increases and decreases in flow rates. Five were positive on the basis of the exercise lability index alone. The baseline PEFR of children with positive results based on increased flow rates was significantly lower than those with positive results based on decreased flow rates (63.1 ± 17.3 compared with 83.2 ± 24.6 $P < 0.02$). The predominant response to exercise was an increase in PEFR and there was a significant correlation between the percentage rise in PEFR during exercise and impaired lung function ($P < 0.01$) (Fig. 3).

The response pattern of the skin allergy is summarised in Table 6. The allergens that elicited a positive response most often were *Dermatophagoides pteronyssinus* and *Aspergillus fumigatus*. There was a significant relationship between the severity of lung disease and a positive response to *A. fumigatus* but not to *D. pteronyssinus*. Children who had positive reactions to *A. fumigatus* on all four occasions had a mean FEV₁ which was significantly lower than those

Fig. 3 Increase in PEFR during exercise compared with prechallenge pulmonary function. A significant correlation exists ($r = -0.65$, $P < 0.01$). The regression line is shown.

Table 6 Response pattern of skin allergy tests on the four occasions

Allergen	Total number positive tests	Number of patients		
		Always positive	Always negative	Variable
Yorkshire fog pollen	21	5	18	2
Rye grass pollen	25	4	17	4
Cat fur	27	5	15	5
Dog hair	13	0	20	5
<i>Dermatophagoides pteronyssinus</i>	38	7	13	5
Cows' milk	1	0	24	1
Sheep wool	5	0	20	5
<i>Aspergillus fumigatus</i>	37	4	12	9
<i>Candida albicans</i>	2	0	23	2
Whole egg	0	0	25	0

who were consistently negative ($P < 0.001$), while children with variable responses had a mean FEV₁ which was significantly lower than those who were always negative ($P < 0.001$), but not different from those who were always positive. The FEV₁ of the children who were always positive to *D. pteronyssinus* was no different from those who were always negative nor was it different in those children whose responses varied.

Analysis of the diary cards showed no correlation between histamine bronchial provocation, exercise challenge, and results to tests of skin allergy and changes in clinical status—as assessed by wheeze, cough, or sputum production.

Discussion

This study demonstrated that for many patients with CF the response to histamine bronchial provocation testing, exercise challenge, and skin allergy testing varied over a 6-month period. In 44% the response to histamine was variable, as it was in 56% to exercise, and in 24% to skin testing. The variability did not relate to exacerbations of chest infection or to changes in pulmonary function. There were more positive responses in patients with impaired lung function, and more negative responses in those with normal lung function, but these two groups overlapped greatly. In an individual patient, a test could be positive on all four occasions, negative on all four, or variable. Furthermore, an individual could show a positive response to all 3 tests on one day, be negative to all 3 on another, or be positive to 1 test and negative to others. No clear correlation could be found between these differing responses. The implication of these findings is that the responses of children with CF grouped on the basis of prechallenge pulmonary function could be predicted, but variability of response precluded such a prediction in any one child.

A previous report³ stated that a patient with CF who had normal pulmonary function had a uniformly negative response to histamine. It concluded that histamine challenge could be used to diagnose asthma only in patients with normal FEV₁. The present study found that 4 who responded to histamine, 4 to exercise, and 3 to skin testing had normal lung function, but that 2 of them had symptoms and 5 a family history of asthma. This suggests that latent hypersensitivity of the bronchial tree may be more characteristic of CF than previously had been thought and the relationship to asthma is far from clear.

The predominant response to exercise challenge was an increase in PEFR as has been noted previously.^{6,7} This is different from the findings in asthma

where up to 80% of subjects show a predominant fall in PEFR.²² The most likely explanation for the rise in CF is the rapid emptying of the large dead space.^{23, 24} Decrease of bronchomotor tone is perhaps a further factor,⁷ and this is the explanation given for the small rise in PEFR seen in asthma. The fall in PEFR in asthma is presumed to be due to bronchoconstriction, and the fall in flow rates seen in about 30% of the CF exercise tests may also be due to bronchoconstriction.

The high incidence of positive responses to *D. pteronyssinus* unrelated to the severity of lung disease has not previously been reported and its significance is unclear. While the overall trend was for positive skin sensitivity to relate to severity of lung disease as previously reported,^{4, 25} this was due mainly to the association of skin sensitivity to *A. fumigatus* with impaired lung function.

The variability of response to histamine bronchial provocation, exercise challenge, and skin testing in this group of patients indicated the difficulty of interpreting a response found on a single occasion. Institution of 'anti-asthma' therapy—such as bronchodilators, sodium cromoglycate, corticosteroids, and hyposensitisation in a patient with CF on the basis of a positive response on one occasion is unjustified. At present such a decision must be made on the clinical history, physical examination, and the demonstration of a bronchodilator response to an inhaled sympathomimetic drug.²⁶

The inter-relationship of bronchial hyper-reactivity to histamine, response to exercise, and skin sensitivity to environmental allergens in CF would seem to be complex. Each test probably measures a different phenomenon and it is unwarranted to use tests to characterise allergy and airways hyper-reactivity of the asthmatic type in patients with CF.

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