

The variability of skin test hypersensitivity reactions in cystic fibrosis and asthma

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Summary

Cystic fibrosis (CF) children had a greater variability of skin prick test response compared with asthmatic children, when the tests were performed on two occasions. This suggests that there is a different cause for the allergy in the two groups, perhaps because the asthmatics have a transient period of susceptibility to sensitization in infancy and the CF children a persistent vulnerability. Amongst the asthmatic children, clinical improvement was associated with loss of some skin prick test reactions, and clinical deterioration with an increase in the number of positive reactions. Thus continuing allergic reactions may maintain a mucosal defect, resulting in a persistence of susceptibility to allergen sensitization, and control of the reactions may re-establish normal mucosal defence mechanisms.

Introduction

A failure of antigen exclusion at mucosal surfaces leading to overstimulation of IgE-producing lymphocytes has been proposed as the underlying defect which predisposes to the development of allergy (Soothill, 1974). Two such abnormalities of mucosal function have been associated with a high incidence of allergy; namely transient IgA deficiency in infancy (Taylor *et al.*, 1973) and in cystic fibrosis (CF) (Warner *et al.*, 1976). Taylor *et al.* (1973) suggested that there is a brief period of vulnerability to sensitization by allergens in early infancy and that transient IgA deficiency may precede much childhood atopy. Whilst allergic reactions might maintain an abnormal mucosal permeability, one might expect that individual allergies would remain consistent over long periods in atopic children. In CF, however, the mucosal abnormality is permanent and therefore increasing exposure to a greater variety of allergens would be expected to produce an increasing spectrum of different allergies.

A group of house-dust mite allergic asthmatic children and a group of CF children were, therefore, studied on two occasions, to ascertain the consistency of prick test responses.

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Patients and methods

Sixty-two CF children, who were amongst the 123 children who participated in a preceding study (Warner *et al.*, 1976), and forty-three house dust mite sensitive asthmatics, participating in a therapeutic trial, had prick tests on the forearms with seven Bencard antigens (Table 1) and a control solution. Antihistamine therapy was stopped for at least 24 hr before prick tests. They were performed on two occasions separated by approximately 6 months. The weal diameter was measured after 20 min using a gauge, and a 2 mm diameter or greater weal was labelled positive. On the three occasions that a positive reaction occurred with the control solutions, a weal diameter of 2 mm greater than the control was accepted as positive. The clinical progress of the patients during the 6 months between tests was also examined. For the CF patients this involved a review of the bimonthly out-patient notes and a questionnaire from the patients; and for the asthmatics, a daily card symptom score and bimonthly clinical review.

The CF children were aged 2½–11 years (mean 8·6) when first tested, being forty-three males and nineteen females. The asthmatics were aged 5½–14 years (mean 10·0), being thirty-two males and eleven females. Their asthma was moderately severe and a bronchial provocation test to *Dermatophagoïdes pteronyssinus* was positive (Warner, 1976). Statistical analyses were done by Fisher's exact test.

Results

At the first testing, thirty-six (58%) of the sixty-three CF children had one or more positive prick tests, and on the second test 6 months later, forty-three (69%) were similarly allergic. Seven children developed positive prick tests, having formerly had negative responses. Two of these children also developed wheezing episodes, with bronchodilator-reversible airway obstruction, for the first time between the two tests. Many patients lost or gained individual allergies but none converted from the allergic to totally nonallergic status.

The numbers of CF and asthmatic children who gained or lost individual reactions are shown in Table 1. Significantly more CF children had gained skin responses compared with asthmatic children to *Dermatophagoïdes pteronyssinus* ($P<0\cdot01$), feathers ($P<0\cdot01$) and cat fur ($P<0\cdot01$). There were no significant differences for the acquisition of reactions to milk, Timothy grass, *Cladosporium herbarum* and *Aspergillus fumigatus*. Furthermore, there were no significant differences between the two groups of patients for the loss of any allergen sensitivity on the second skin tests. In general, both CF and asthmatic patients maintained large weal reactions but were more likely to alter their allergy if the reaction was relatively small.

Severe chest infections during the 6 month interval between prick tests occurred equally in the allergic, sixteen out of forty-three (37%), and nonallergic, six out of nineteen (32%), CF patients. There was also no greater incidence of severe infections in those CF patients who gained positive prick tests on the second occasion, ten out of twenty-six (38%). Marginally more children in the allergic group, thirty-eight out of forty-three (88%), than the non-allergic group, fifteen out of nineteen (79%), required antibiotics during the same 6-month period.

The spectrum of positive reactions is shown in Table 1 and *Aspergillus fumigatus* allergy occurred most frequently, with 81% of the allergic CF patients. However, only five CF children were allergic to this allergen alone and three of these had developed this allergy only on the second batch of tests. The percentage of positive reactions to

Table 1. The numbers of C.F. and asthmatic children who gained or lost individual skin test reactions on tests repeated 6 months after the first study

Children	<i>Dermatophagoïdes pteronyssinus</i>	Mixed feathers	Cat fur	Milk	Timothy grass pollen	<i>Cladosporium herbarum</i>	<i>Aspergillus fumigatus</i>
CF (<i>n</i> = 62)							
Positive at first test	7	6	5	4	24	13	24
Gain at second test	6	7	4	1	2	6	11
Loss at second test	0	3	1	4	4	8	3
Asthmatic (<i>n</i> = 43)							
Positive at first test	43	33	29	7	23	12	4
Gain at second test	0	3	1	3	3	1	3
Loss at second test	1	6	5	4	2	4	2

each allergen is very similar to that found in the original study of 123 CF children (Warner *et al.*, 1976).

Amongst the asthmatic children changes of prick test reactivity, irrespective of which allergens were involved, were related to the clinical progress of asthma (Table 2). The CF individuals often lost some allergies and gained others, whereas the asthmatics always either lost one or more positive skin reaction or acquired one or more. Excluding the 'no change' groups for the purpose of analysis, using a 2×2 contingency test, clinical progress was significantly related to changes in skin reactivity ($P = 0.003$). Whether improvement in asthma was due to treatment or spontaneous change, this was associated with a loss of some prick test reactions, and worsening asthma was associated with the acquisition of more positive reactions. Three out of the seven patients with worse asthma had developed a new sensitivity to *Aspergillus fumigatus* at the second test.

Table 2. Clinical progress of the asthma during the 6 months between the skin tests in relation to the changes in reactions to any allergens on repeat skin testing

Prick test reactions	Clinical progress of the asthma		
	Improved	No change	Worse
Loss of some positive reactions	10	5	0
No change	14	3	2
Increase in number of positive reactions	2	2	5

Discussion

This study has demonstrated a greater variability of prick test responses in CF compared with allergic asthma in childhood. This is consistent with the view that there is a difference of the origin of allergy in each group, perhaps because the asthmatics have a transient period of susceptibility to sensitization in infancy and the CF children have a persistent vulnerability.

Several studies have indicated that allergy is common in CF (Allen *et al.*, 1975; Warren *et al.*, 1975; Warner *et al.*, 1976). Warren *et al.* (1975) found a 70% prevalence of positive prick tests in forty-three CF patients (age 2–34 years), whereas Warner *et al.* (1976) found 59% in a younger group of patients (age 4 months–17 years, mean 8.4). The allergic patients in the latter study were older (mean 8.9) than the non-allergic group (mean 7.9). In conjunction with the present study this suggests that the older a CF individual is, the more likely it is that he or she will become allergic, presumably because of an increasing exposure to a greater variety of appropriate allergens.

There was some difference in the antibiotic requirements between the allergic and non-allergic CF patients, but there was no difference in the incidence of recent severe chest infections in either group or in those who developed positive prick tests on the second tests. Thus, chest infection is probably not the predisposing factor in the development of allergy. In the first study of 123 CF patients, allergy was associated with a greater overall incidence of severe chest infections (Warner *et al.*, 1976). Therefore, the suggestion that there is a mucosal defect in CF, which results in both susceptibility to chest infection and the development of allergy, seems more likely.

Studies have shown that allergic CF children have a greater bronchial lability on exercise testing and are more likely to have a favourable response to bronchodilators (Price, personal communication). As *Aspergillus fumigatus* and Timothy grass pollen were the only two allergens that were reasonably consistently positive in the CF patient, they were perhaps more likely to be of some clinical significance. This could only be ascertained by doing direct nasal or bronchial provocation tests.

The asthmatics had a much greater consistency of response to *Dermatophagoïdes pteronyssinus*, feathers, cat fur and Timothy grass pollen than to milk, *Cladosporium herbarum* and *Aspergillus fumigatus*. Thus the first four allergens are probably much more important in the pathogenesis of their disease.

Some asthmatic children had varying prick test responses. This may be due to the poor reproducibility of the skin prick test, as changes occurred mostly when there was a small prick reaction. However, changes in prick responses were associated with clinical changes, and probably do reflect a real change in allergic status. Clinical improvement in asthma was associated with a loss of some prick test response and deterioration with an increase in the number of positive reactions. This suggests that continuing allergic reactions in the form of asthma attacks can maintain a mucosal defect. This will allow re-sensitization to occur so that the allergies are maintained, or even new ones may develop. These observations are a further argument against the suggestion that there is a genetic link between immune response genes and specific allergen sensitivities (Levine, Stember & Fotino, 1972), where one would expect the sensitivities to persist. The data, however, is consistent with the idea that allergy results from defective mucosal exclusion of allergens!

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