Atopy and bronchial reactivity in older patients with cystic fibrosis

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ABSTRACT We studied 25 adolescent and adult patients with cystic fibrosis (CF) and 25 control subjects to determine if the prevalence of atopy and bronchial hyperreactivity was increased in this disease. Results showed that atopic symptoms, as defined by history, were more frequently present in the CF patients. Prick testing of the skin produced positive reactions in 88% of the CF group and 36% of the control subjects (p < 0.001), and the mean number of reactions per subject was significantly higher in the former group (p < 0.001); reactions to fungal antigens were strikingly positive in the CF group. The CF patients had a significantly higher mean serum IgG_4 (p < 0.001), IgE (p < 0.01), and higher mean eosinophil count (p > 0.05). Clear-cut bronchial hyperreactivity was demonstrated in the CF group compared with control subjects. Bronchial provocation with 400 μg of histamine led to a greater than 15% fall in the preinhalation FEV₁ in 35% of the CF subjects compared with 4% of the control group, with a mean percentage fall of 15% and 3% respectively (p < 0.001). In the CF group a greater than 15% rise in PEFR occurred in 32% after inhalation of the parasympatholytic, ipratropium bromide (54 μg), and in 27% after inhalation of the sympathomimetic, fenoterol (400 μg). No correlation was found between bronchial reactivity and atopic status, HLA phenotype pattern, or disease severity. The cause of the increased prevalence of atopy and bronchial reactivity in CF patients remains unknown. However, it is clear that a trial of bronchodilator therapy is warranted in adolescents and young adults with CF.

An increased prevalence of atopy in patients with cystic fibrosis (CF) was first reported by Lowe in 1949. Since that time, a number of authors studying a variety of atopic indices have published results, some confirming the association, others disputing it. Because of these conflicting results, and because of the difference in methodology used to assess atopy, we undertook a study to define the prevalence of atopy in a group of adolescents and young adults with CF, by examining a comprehensive range of atopic indices. Furthermore, we carried out HLA phenotyping to determine if those CF patients with atopic features constituted a separate, genetically linked subgroup.

The related problem of bronchial reactivity was studied by spirometric measurements before and after inhalation challenge with a bronchoconstrictor, histamine, and two bronchodilators, a beta₂ adrenergic agonist, fenoterol, and a parasympatholytic, ipratropium bromide.

Methods

Twenty-five documented CF patients, with an age range from 10 to 32 years (mean 17 yr) were studied. A control group consisted of 25 healthy individuals, with an age range from 10 to 28 years (mean 15-2 yr). The male–female ratio was identical in each group (2:1:1). The patients were divided into three groups of severity on the basis of clinical and radiological findings. Consent to carry out the study was obtained from parents of all subjects under 18 years of age.

ALLERGIC PROFILE

Both patients and control subjects were questioned about a history of wheezing, allergic rhinitis, eczema, “hives”, angioneurotic oedema,
drug allergy, nasal polyposis, and a family history of allergy. Skin hypersensitivity tests were performed with a diluent control, a positive control (histamine acid phosphate), and the following 13 Bencard allergen extracts: house-dust, *D pieronysinus*, grass pollen, Timothy grass, tree pollen, feathers, cat fur, *Aspergillus fumigatus*, *Aspergillus terreus*, *Cladosporium herbarum*, and three mixed mould extracts, M5, M10, and M11. The skin tests were performed by the modified prick method on the volar aspect of the forearm, and the weal size in millimetres was recorded 20 minutes after the introduction of the allergen.

Total blood eosinophil counts were determined by the chamber method, using an eosin-acetone diluent. The total serum IgE was determined by the radioimmunoassay technique, and serum IgG4 by a microscale version of a radial immunodiffusion method (antisera obtained from Seward Laboratories, London). These tests were performed without knowledge of the patients' skin reactivity. Precipitins against *Aspergillus fumigatus* were determined by the agar-gel diffusion technique, as described by Longbottom and Pepys.

**GENETIC STUDIES**

HLA phenotyping was performed by the microlymphocytotoxicity technique. The following HLA-A, -B, and -C antigens were determined.

<table>
<thead>
<tr>
<th>HLA-A:</th>
<th>-1, -2, -3, -9(w 23, w 24), -1 (25, 26)</th>
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<tbody>
<tr>
<td></td>
<td>-11, -28, -29, -w 23, -w 24, -w 30, 31, 32.</td>
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</table>

<table>
<thead>
<tr>
<th>HLA-B:</th>
<th>-5, -7, -8, -12, -13, -14, -15, -17, -18, -27, -40, -w 16, -w 21, -w 22, -w 35.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-C:</td>
<td>-w1, -w2, -w3, -w4.</td>
</tr>
</tbody>
</table>

**BRONCHIAL CHALLENGE**

The spirometric measurements made included determination of peak expiratory flow rate (PEFR) using a Wright Peak Flow meter, forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) using a dry spirometer (Vitagraph). The best of three attempts was recorded and corrected to BTPS. Not all measurements could be made in all patients during every phase of the study. Routine bronchodilators were previously withheld according to the protocol of Chai et al. No patient was receiving antihistamine therapy at the time of the study. Both groups were challenged with the bronchoconstrictor, histamine acid phosphate 400 µg, taken as four individual puffs from a metered inhaler (courtesy of Riker Laboratories). Forced expiratory volume in one second and FVC were performed before the challenge and repeated five minutes later; the percentage change was recorded. On two separate days, the CF group, but not the control subjects inhaled bronchodilators. On the first day, the beta2 adrenergic agonist, fenoterol (400 µg), was inhaled in two puffs, and on the second day, the parasympatholytic, ipratropium bromide (54 µg) was inhaled as three puffs from a metered dose inhaler. Forced expiratory volume in one second, FVC, and PEFR were performed at 15, 30, and 60 minutes after administration of each of the two bronchodilators; the maximum rise was recorded, and the percentage change from baseline was calculated.

Differences between groups were tested with Students' *t*, Mann-Whitney U, chi2 and Fisher's exact probability tests, as appropriate. Linear regression analysis was used to look for correlation between values.

**Results**

The results of the atopic questionnaire are shown in table 1. All atopic features were reported more commonly in the CF patients, including a marked increase in the reported prevalence of such features in their first degree relatives.

**ALLERGIC PROFILE**

The CF group had significantly more positive skin tests than the control subjects, 88% compared with 36% (*p*<0.001) and the mean number of reactions per individual, 5.5 and 1.5 respectively, was also significantly higher (*p*<0.001). Both groups were similar in having the greatest number of positive reactions to house-dust, but the CF group had a far greater number of reactions to the fungal antigens — *A fumigatus, A terreus, C herbarum*, and a group of mixed moulds (table 2). The two groups showed

<table>
<thead>
<tr>
<th>Table 1 Atopic questionnaire in cystic fibrosis patients and control subjects</th>
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<tr>
<td>Cystic fibrosis patients (n=25)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Wheeze/asthma</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Hives</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Nasal polyposis</td>
</tr>
<tr>
<td>Angioneurotic oedema</td>
</tr>
<tr>
<td>Family history of atopy</td>
</tr>
</tbody>
</table>

*Fisher's *exact* probability test. Cystic fibrosis patients versus control subjects.

NS = not significant.
little difference in the degree of reactivity to pollens and feathers, antigens frequently associated with common atopic disorders. In contrast to the high prevalence of positive reactions to *A fumigatus* extract, only one patient had precipitins to the fungus in his serum.

Serum immunoglobulin E was increased above 100 U/ml in 46% of the CF patients, compared with 21% of the control subjects (figure) and the mean level was significantly higher in the former group (p<0.01). Total blood eosinophil count was elevated above 400 cells/mm³ in 33% of the CF subjects compared with 16% of the controls, and the mean count in the former was higher (375/mm³ and 268/mm³ respectively), although this difference did not reach statistical significance. Similarly, mean serum IgG₄ was significantly higher in the CF patients than the control group (p<0.001, figure). A significant correlation between the subject's age and the level of IgG₄ was found in the CF patients (r=+0.547, p<0.01) but not the control subjects. No significant correlation was detected between serum IgG₁ and IgE levels.

**GENETIC STUDIES**

HLA phenotyping in the total CF group and in those patients with marked atopic features showed no statistically significant difference from the pattern obtained in a group of 253 Irish control subjects (Reen, unpublished data).

**BRONCHIAL PROVOCATION**

The results of spirometric testing before and after bronchial challenge with histamine and bronchodilators are shown in tables 3 and 4. The mean basal FEV₁ was significantly lower in the CF group compared with control subjects, 2.06 (60% of predicted normal value) and 3.14 (101% of predicted) litres respectively (p<0.01). After inhalation of histamine, a greater than 15% fall in the preinhalation FEV₁ was found in 35% of the CF subjects compared to 4% of the control subjects (p<0.05), with a mean percentage...
Table 3 Comparison of histamine inhalation (400 μg) in cystic fibrosis patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>CF patients</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 Mean ± SD (ml)</td>
<td>3144 ± 911</td>
<td>2058 ± 1134</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean % change ± SD</td>
<td>-28 ± 4.6</td>
<td>-15.2 ± 11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC Mean ± SD (ml)</td>
<td>3407 ± 900</td>
<td>2648 ± 1085</td>
<td></td>
</tr>
<tr>
<td>Mean % change ± SD</td>
<td>-916 ± 5.1</td>
<td>-12.9 ± 13.5</td>
<td></td>
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</table>

Table 4 Influence of bronchodilators in cystic fibrosis patients

<table>
<thead>
<tr>
<th></th>
<th>Ipratropium bromide (54 μg)</th>
<th>Fenoterol (400 μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>Pre: 22; Post: 22</td>
<td>Pre: 22; Post: 22</td>
</tr>
<tr>
<td>FEV1 Mean ± SD (ml)</td>
<td>1920 ± 1052; 2045 ± 1105</td>
<td>1925 ± 1050; 2118 ± 1058</td>
</tr>
<tr>
<td>Mean % change ± SD</td>
<td>+7.5 ± 8.2; +8.9 ± 13.2</td>
<td>+9.6 ± 6.4; +11.9 ± 10.1</td>
</tr>
<tr>
<td>FVC Mean ± SD (ml)</td>
<td>2501 ± 967; 2675 ± 938</td>
<td>2545 ± 1076; 2770 ± 1048</td>
</tr>
<tr>
<td>Mean % change ± SD</td>
<td>+8.2 ± 9.2; +8.9 ± 13.2</td>
<td>+9.6 ± 6.4; +11.9 ± 10.1</td>
</tr>
<tr>
<td>PEFR Mean ± SD (l/min)</td>
<td>309 ± 108; 331 ± 109</td>
<td>303 ± 122; 331 ± 116</td>
</tr>
<tr>
<td>Mean % change ± SD</td>
<td>+8.2 ± 9.2; +8.9 ± 13.2</td>
<td>+9.6 ± 6.4; +11.9 ± 10.1</td>
</tr>
</tbody>
</table>

fall of 15.2% and 2.8%, and mean absolute falls of 263 and 93 ml respectively (p<0.001). A trivial rise in FEV1 after inhalation of histamine occurred in one of the CF patients and five of the control subjects. A less striking effect on the FVC was observed, with a greater than 15% fall in the preinhalation value occurring in 25% of the CF patients compared with none of the control subjects (p<0.05); the mean percentage fall was 13% and 1% and the mean absolute fall was 268 and 37 ml respectively (p<0.001). The relationship between severity of the underlying airway obstruction and the response to histamine challenge was examined. Regression analysis of basal FEV1 against percentage change after histamine showed no correlation. Two patients with basal FEV1 levels which were 98% and 102% of the predicted normal values had falls of 22% and 19% in FEV1, respectively, indicating that bronchoconstriction was not confined to patients with reduced baseline values.

The results of bronchodilator administration in the CF group are set out in table 4. After ipratropium bromide, a greater than 15% rise in PEFR, FEV1, and FVC occurred in 32%, 23%, and 27% respectively. The patient group as a whole showed a mean percent rise in PEFR, FEV1, and FVC of 8.2%, 7.5%, and 8.9%, and a mean absolute rise of 22 l/min, 125 ml, and 174 ml respectively. Inhalation of fenoterol induced a greater than 15% rise in PEFR, FEV1, and FVC in 27%, 14%, and 18% of the patients, with a mean percentage rise of 12.2%, 9.6%, and 11.9%, and a mean absolute rise of 28 l/min, 193 ml, and 225 ml respectively.

Grading of Disease Severity
The patients were divided into three groups in increasing order of severity: group 1 consisted of 10 patients, group 2 of six, and group 3 of nine. In these three small subgroups, it was not possible to relate clearly the severity of disease with the number of atopic features present, or the degree of bronchial reactivity.

Discussion
This comprehensive study of atopic indices in CF, has permitted us to confirm and extend previous observations on this association. Our CF patients, compared with control subjects, demonstrated a striking prevalence of atopic features as judged by prick testing of the skin, total serum IgE levels, total eosinophil counts, serum IgG4 levels, and an atopic questionnaire. The related problem of bronchial reactivity has been similarly defined in more detail, using a variety of bronchoconstrictor and bronchodilator challenges. Comparing our data with results of previous studies, interesting differences and similarities are noted.

Positive skin tests were observed more frequently in the CF group than in the control group, 88% and 36% respectively, and the former also had significantly more reactions per individual. In contrast to the previous reports of a relatively low frequency of reactions to house-dust and house-dust mite in CF patients,6 14 15 they produced the greatest number of positive reactions in our patients. The increased sensitivity to house-dust and house-dust mite noted in our
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patients may reflect the fact that they were older than the patients in other studies. This is in accordance with the results of another study of ours which showed that the frequency of positive skin tests in CF increases with age. An increased prevalence of sensitivity to fungal antigens, as observed in our study, has been noted by previous authors. Total IgE levels were significantly higher in the CF group. This supports a similar finding by Wallwork, but contrasts with Bardana’s report of normal IgE values in a study of 61 CF patients. In the present study, elevated IgE levels were found predominantly in subjects displaying the greatest degree of skin reactivity.

Serum IgG₄, the IgG subclass known to be associated with some atopic reactions, again was significantly higher in the CF group. This confirms a similar finding by Shakib. We found no significant correlation between individual IgE and IgG₄ levels, which suggests that each immunoglobulin reflects a different pathway in the pathogenesis of atopy in CF.

The reason for the increased prevalence of atopy in CF is unknown. One possibility is that the phenomenon is acquired as a result of increased antigen access to the IgE producing cells in the submucosa. Mechanisms which might be responsible include abnormal mucosal permeability, a defective secretory IgA system, trapping of antigen in infected areas of the lung, or failure of antigen clearance because of a ciliotoxic factor. An alternative explanation is that there is a genetic linkage between the CF gene and genes controlling atopic response. In our study, there was a significantly increased family history of atopy in the CF group. However, one must have reservations about comparisons between historical data derived from frequently interviewed patients, and those obtained from healthy control subjects. Although Warner found an increased personal history of atopy and positive skin tests in a study of obligate heterozygotes, a separate study of ours suggests that there is no significant difference between positive skin tests in obligate heterozygotes and control subjects. In view of Soothill’s finding of an increased prevalence of HLA-A1 and B8 among infants with positive skin tests, we examined the HLA phenotype pattern of our patients, but failed to detect linkage of atopy to any particular HLA antigen.

The frequent association of bronchial hyper-reactivity with atopy has led a number of investigators to study the response to inhaled bronchoconstrictors and bronchodilators in CF. Haluszka and Mellis performed bronchial provocation in CF, using varying doses of histamine, and found a positive response in 68% and 24% respectively. In contrast, we used a fixed dose of histamine (400 µg) and demonstrated a greater than 15% fall in FEV₁ in 35% of the CF group, compared with 4% of the control group, with a mean percentage fall of 15% and 3% respectively. We found no significant correlation between bronchial reactivity to histamine and the degree of airway obstruction in our CF patients. Indeed, two patients with basal FEV₁ levels which were 98% and 102% of the predicted normal values showed marked drops of 22% and 19% respectively. This contrasts with the assertion of Mellis that significant bronchoconstriction only occurred in those patients whose basal pulmonary function was abnormal.

This bronchoconstrictor response may result either from a direct local effect on airway smooth muscle or from vagally mediated reflex bronchoconstriction. Empey demonstrated marked histamine reactivity after an upper respiratory tract infection, presumably the result of epithelial damage and exposure of nerve endings. Possibly, in CF there may be increased sensitivity of the bronchial mucosal receptors caused by chronic infection. Furthermore, the ability to form histamine is increased in chronic inflammatory conditions, because of adaptation in the production of histidine decarboxylase, and this might also contribute to the bronchial hyperirritability in this disease.

There have been conflicting reports on the response to bronchodilators in CF. After inhalation of nebulised adrenaline or isoprenaline, some found a reduction in airway obstruction, others noted no change. The parasympathetic antagonist atropine sulphate was used in one study and found to be superior to isoprenaline. As isoprenaline and atropine are now unsuitable for clinical use, we examined the response to a selective beta₂ adrenergic agonist, fenoterol, and a parasympatholytic, ipratropium bromide. Both were administered by metered dose inhalers, in which they are routinely prescribed, and so the results have more direct implications than if the drugs were administered from a special nebuliser or by a positive pressure device. Although the mean rise in PEFR after each agent was undramatic, almost half the patients experienced a greater than 15% rise in PEFR after inhalation of ipratropium bromide or fenoterol or both. Such an increment is often clinically worthwhile, particularly in those patients with reduced baseline values. The fact that more patients responded to

bronchoconstrictors and bronchodilators in CF.
the parasympatholytic, ipratropium bromide, than to fenoterol is in accordance with Mitchell's observations,\textsuperscript{39} that 51% of unselected CF patients had a positive response to methacholine. The more selective responsiveness to a parasympatholytic agent in our patients is similar to the pattern observed in chronic bronchitis by some workers.\textsuperscript{40} \textsuperscript{41} The cause of the bronchial hyperreactivity in cystic fibrosis is unknown. Although there is a disputed association between bronchial hyperreactivity and atopic status, the current study found no association between atopy and bronchial responsiveness to histamine, fenoterol, or ipratropium bromide in our cystic fibrosis subjects. This contention is supported by two other studies in CF, which have shown no correlation between exercise-induced bronchial lability\textsuperscript{4} or histamine-induced bronchoconstriction\textsuperscript{57} and atopic status.

Authors have contended that atopy ameliorates,\textsuperscript{5} \textsuperscript{14} worsens,\textsuperscript{5} \textsuperscript{17} or has no effect\textsuperscript{6} \textsuperscript{42} on the natural history of CF. In the present study, a wide spectrum of disease severity was observed, and no clear relationship with either atopic status or bronchial reactivity was observed. It is difficult, however, to draw conclusions from the small number of patients studied.

Our results show that there is a higher prevalence of atopy in CF as determined by a comprehensive group of atopic indices. The cause of atopy in this disease remains unknown. It may be caused by increased antigen access or there may be genetic linkage between atopy and CF. No relationship was found between atopic status and severity of the underlying condition, suggesting that atopic status is not of prognostic value in CF. Likewise, the degree of atopy did not correlate with the degree of bronchial reactivity. As a significant proportion of the patients show reversibility in airway obstruction, a trial of bronchodilator therapy, with a beta\textsubscript{2} adrenergic agonist or a parasympatholytic or both, should be considered in adolescent and young adults with cystic fibrosis.

We are grateful to the Medical Research Council of Ireland who supported this study. We are indebted to the control subjects and the patients who took part in this study and without whose co-operation it would not have succeeded. We thank Mr L Daly, Department of Community Medicine and Epidemiology, University College, Dublin for providing statistical guidance, and Mr M Cogan, Mrs G Lawless, and Mrs N Martin for technical assistance.

References

17 Allan JD, Moss AD, Wallwork JC, McFarlane
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