

Cystic fibrosis and allergy

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J. O. Warner, S. A. Kilburn

University of Southampton/Southampton General
Hospital, Hampshire, England

J.O. Warner, Child Health, Mailpoint 803,
Southampton General Hospital, Southampton
SO16 6YD, Hampshire, England

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Numerous reports have indicated that there is an increase in positive allergy skin prick tests, raised immunoglobulin E (IgE) and IgE antibodies in cystic fibrosis (CF) individuals compared with the general population. The prevalence of allergy in CF increases progressively with age (1). However, there does appear to be a greater variability of skin test responsiveness in such patients compared with ordinary atopic individuals with both more rapid development of new positive skin tests and sometimes loss of skin test positivity (2). The major allergic responses are to *Aspergillus fumigatus* and to a lesser extent, the other mould allergens such as *Cladosporium herbarum* and *Alternaria alternata* (3). Indeed, there is little evidence that responses to the conventional allergens such as house dust mite and grass pollen are in any way greater than in the normal population. These relatively simple clinical observations suggest that different mechanisms are involved both in sensitization and maintenance of the sensitized state in CF compared with ordinary atopic individuals.

Mechanisms

The presence of type 1 hypersensitivity in CF can be directly correlated with increasing severity of lung disease. Indeed, the highest IgE levels are associated with chronic *Pseudomonas* colonization and frequent exacerbation of infection. These data have been used to suggest either that the allergy contributes to the lung pathology or, alternatively, that heavy lung infection facilitates allergen sensitization (3, 4).

That this sensitivity occurs predominantly to mould spores is of particular interest. Spores are of relatively small size and are easily respirable. However, they are also relatively inert and will not release any allergenic proteins before they have been cleared from the airways. Thus under normal cir-

cumstances, despite fairly high concentrations of exposure, no sensitization will occur (5). Only exposure to high concentrations of hyphal elements rather than spores will have a chance of producing sensitivity, and this occurs more commonly in southern rather than northern Europe. Nevertheless, in the CF individual with progressively more severe airway inflammation, spores will become trapped and will not be cleared rapidly. There will then be sufficient time for hyphal growth to occur with consequent release of allergenic proteins, and sensitization will then take place (6). Indeed, it is quite common to be able to culture *Aspergillus fumigatus* and observe hyphal networks in the sputum of patients with CF. Our own studies have identified 30% of patients with positive cultures (7). This relatively simplistic explanation might account for the type of sensitivities that occur in CF, without proposing that the condition predisposes to atopy.

Our recent studies of broncho-alveolar lavage from CF and asthma patients have shown very much lower levels of interferon-gamma (IFN- γ) in the former than the latter. As this Th-1 cytokine has a down-regulatory effect on the Th-2 cytokine, interleukin-4 (IL-4) stimulated IgE production by B cells, this might provide a basic explanation for the excessive IgE production in CF (8). However, this is difficult to reconcile with the finding that IL-10, another Th-2 cytokine, is apparently reduced in bronchial lavage fluid from CF individuals compared with controls (9). Indeed, this latter finding is used to explain a lack of down-regulation of inflammation in CF because IL-10 suppresses macrophage production of TNF- α , IL-1 and IL-6 in response to lipopolysaccharide (10). The problem may be explained by the finding that IL-10 is constitutively expressed in normal but not CF bronchial epithelium (9). This points to an epithelial immune defect in CF, which has always been suspected. Similarly we, and others, have found very high levels of IL-8 in

sputum and bronchial lavage from CF patients, with a good correlation with disease severity (10, 11). However IL-8, which predominantly originates from alveolar macrophages and bronchial epithelial cells, also like IFN- γ , has a down-regulatory effect on IgE production from IL-4-stimulated B-cells (12). Thus, CF is associated with abnormal bronchial epithelial down-regulation of inflammation with consequent Th-1 activity in the airway lumen and consequent uncontrolled inflammation, but failure to clear both bacteria and allergens leading to very high and sustained allergen exposure, which eventually stimulates an IgE antibody response.

Another suggestion is that the high prevalence of atopy is a function of the genetic defect in CF. This has been based on one study which suggested a high prevalence of atopy in the parents (the obligate-heterozygotes) of CF children (13). This would suggest that there might be a relationship between the abnormal gene and atopy. However, one other study has failed to show such a relationship, although the difference between the two studies would appear to be in the frequency of atopy among the controls rather than the heterozygotes. There is one other study which has shown a higher prevalence of exercise-induced bronchial hyperresponsiveness in CF heterozygotes, which might suggest a role for the cystic fibrosis transmembrane conductance regulator in airway physiology (15).

Relationship between atopy and airway damage

There has been much dispute about the causal relationship between immune responses to *Aspergillus fumigatus* and lung disease because the presence of allergy is often coincident with the appearance of *Pseudomonas* colonisation. However, it has been proposed that there is a causal association between both *Aspergillus* IgE (16) and IgG (17) antibody titres and decreasing lung function. Indeed, our own studies would suggest that patients with increasing IgE levels to *Aspergillus fumigatus* do have a more rapid progression of their disease than those without such an increase (18). There are, however, a number of published studies which have failed to show such effects (4, 14). It is obviously difficult to disentangle the influences of the *Pseudomonas* from that of the *Aspergillus*.

However, allergic bronchopulmonary aspergillosis (ABPA) does occur in up to 10% of patients with CF, and this is very clearly associated with a more rapid decline in lung function (7). Sometimes this leads to the development of proximal bronchiectasis in addition to the more peripheral airway damage that usually occurs in CF. Once developed, ABPA tends to recur even though initially responsive to steroid therapy. The condition is characterised by

airway colonisation with *Aspergillus fumigatus* which produces an intense allergic response and is, therefore, associated with a very sudden and dramatic rise in total IgE and usually also IgG antibodies. We have shown that a fourfold rise in total IgE is strongly indicative of ABPA in CF (19). Unfortunately, it is often difficult to identify ABPA as the classical features of this condition, including respiratory symptoms with wheezing, fleeting pulmonary shadows, blood and sputum eosinophilia, raised total serum IgE, and raised IgE and IgG antibodies to *Aspergillus fumigatus*, can occur in isolation in many CF patients. Thus, up to 75% of adolescent and adult CF patients have positive prick skin tests and IgE antibodies to *Aspergillus fumigatus*. We have found in a paediatric population 30% with positive skin tests, 23% with IgE antibodies, 19% with IgG antibodies, but only 9% fulfilled all the criteria for ABPA (7).

We have recently demonstrated that one of the antigens of *Aspergillus fumigatus* which produces the major IgE response is of high molecular weight but is released in fairly high concentrations in *Aspergillus* cultures, beginning approximately 3 days after establishing the culture at 37°C (20). Interestingly, it appears to be selectively released when *Aspergillus* is co-cultured with *Pseudomonas*, and this may explain the relationship between colonisation with these two organisms and the subsequent development of allergy.

Bronchial hyperresponsiveness

Bronchial hyperresponsiveness (BHR) is a common finding in CF, though this does not necessarily correlate well with skin test reactivity or IgE antibodies (21). The lung hyperresponsiveness on bronchial provocation testing has considerable intra- and inter-individual variability, depending on the degree of mucosal inflammation due to bacterial infection rather than allergy (22). It is part of an overall airway instability defect which develops with increasingly severe disease in CF (23). Nevertheless, one study showed that 15 CF children had positive allergen bronchial challenges with half having late reactions, though only 1 had clinical asthma (24). This suggests that the allergy may indeed contribute to airway inflammation even in the absence of asthma, particularly if it is associated with the generation of a late reaction which results in recruitment of both neutrophils and eosinophils to the airway.

Eosinophils

Eosinophil counts are frequently raised in CF blood and sputum (7). Furthermore, a recent study has suggested that eosinophil activation may occur very

commonly in CF and be associated with a greater degree of lung function abnormality. This would appear to sway the argument in favour of a causal relationship between atopy and lung damage in CF (25). However, the observation was based on the assumption that eosinophil cationic protein (ECP) is released in large quantities from activated eosinophils. There is now evidence that this may also be released by neutrophils. Indeed, in our own studies of bronchial lavage in CF, we have found a strong correlation between ECP levels and total cell counts with a stronger correlation with neutrophil rather than with eosinophil counts. Thus, ECP may merely be identifying the increased neutrophil-mediated inflammation consequent upon infection and release of IL-8 rather than representing a type 1 hypersensitivity phenomenon.

Conclusion

In conclusion, the evidence remains very conflicting on whether atopy *per se* contributes to the lung problems in CF. However, when this leads to allergic bronchopulmonary aspergillosis, there is no doubting the increased rapidity of decline in lung function. Tests which could identify the early development of this complication, thus facilitating early effective intervention, would be of considerable benefit in up to 10% of CF patients. Detection of the high-molecular-weight antigen in respiratory secretions may provide an appropriate early indicator (20). At present, the most sensitive and specific test for ABPA is recombinant *Aspergillus fumigatus* (major allergen 1) antibody assays (26). However, much can be learnt about the control of IgE production by further studies on patients with CF.

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