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A prospective study of nasal disease in adult cystic fibrosis

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Abstract
Twenty-six adult cystic fibrosis patients were studied to compare nasal disease with their laboratory correlates including skin testing, immunoglobulin and *Aspergillus fumigatus* precipitin levels, saccharin testing and sputum cultures. Six patients were asymptomatic and all of these had negative skin tests, normal IgE levels and negative *Aspergillus fumigatus* precipitins. Thirteen patients had rhinitis, 12 had positive skin-testing for common allergens, 10 elevated IgE levels and nine positive *Aspergillus fumigatus* precipitins. Seven patients had polyps, all had normal IgE levels and negative *Aspergillus fumigatus* precipitins, six had positive skin testing for common allergens. There also appeared to be a relationship between *Pseudomonas* spp. colonization and positive skin testing.

Key words: Cystic fibrosis; Nasal polyps; *Pseudomonas* infections; *Aspergillus fumigatus*

Introduction

Cystic fibrosis (CF) or mucoviscidosis was first described by Anderson.[1] It is a systemic disease in which the alimentary and respiratory tracts are involved with the production of abnormally viscid mucus by hyperplastic and dilated mucus glands. It is the most common recessive disease affecting people of northern European extraction, with an incidence of approximately one in 2500 live births.[2]

Patients have abnormal chloride transport across the apical cell membranes of epithelial cells. This results from a defective small chloride conductance channel regulated by cyclic AMP. The disease is caused by mutations in a gene located on chromosome 7 which codes for the chloride channel protein. The gene is known as the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Seventy per cent of CF chromosomes harbour a three base pair deletion that removes the phenylalanine at codon 508 (ΔF508) and the commonest CF genotype (49 per cent of patients worldwide) is homozygosity for this transmutation.[3]

The incidence of nasal disease in cystic fibrosis was first described by Pennington[4] in 1956 and varies from three to 36 per cent.[5–7] The main complaints are polyposis, sinusitis and rhinitis and the incidence of associated allergy varied from 42 per cent to 88 per cent.[8,9] In a retrospective analysis of 450 cases Cepero *et al.*,[10] found nasal polyposis and sinusitis in 10 per cent and 11 per cent of patients respectively. In another study, Drake-Lee and Morgan[11] studied 18 CF children with nasal disease and found no correlation between sinus washout cultures and corresponding sputum samples. They also found no relationship between the severity of the polyposis and the degree of atopy.

The improvement in medical care has led to the emergence of an adult cystic fibrosis population.[12] We, therefore, conducted a study to assess the incidence of nasal disease in an adult CF group and the relationship to the atopic state.

Materials and methods

Twenty-six sequential cystic fibrosis patients attending the Adolescent and Adult Cystic Fibrosis Clinic at Birmingham Heartlands Hospital were studied. A full otolaryngological history including nasal symptomatology was taken and a rhinological examination performed noting presence of nasal polyps, nasal mucosal abnormalities and assessment of the nasal airway. The mucociliary clearance was assessed by performing a saccharin test. A fragment of saccharin was placed 1 cm behind the anterior margin of the inferior turbinate and the patient instructed to sit with his head inclined forward by 10 degrees. The time taken to taste the tablet was noted.

Skin testing for the common allergens house dust mite, *Aspergillus fumigatus*, grass pollen, cat and dog dander was assessed using Bencard skin test antigens and a control. Reactions were examined at 20 minutes and were considered positive when a flare reaction greater than 5 mm diameter and a wheal greater than 3 mm diameter were obtained. No

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TABLE I
INCIDENCE OF ATOPY IN CYSTIC FIBROSIS

Reference	*n*	% Atopic	% Positive skin test reactions			
			A fumigatus	HDM	Pollens	Animal dander
Allan *et al.*[23]	30	76	37	33	7	0
Counahan *et al.*[25]	23	56	35	26	13	26
Warner *et al.*[26]	123	59	33	19	33	10
Barron *et al.*[24]	33	63	27	18	42	18
Van Asperen *et al.*[8]	78	42	28	15	10	14
Tobin *et al.*[9]	25	88	72	56	28	52

HDM = House dust mite.

patients reacted to the control solutions. *Aspergillus fumigatus* precipitin and immunoglobulin levels were performed and standard sinus X-rays taken.

Statistical analysis was by the Student's *t*-test.

Results

Twenty-six adults (11 males and 15 females) aged 14–31 years of age (median 21) were assessed.

History

Six patients were asymptomatic and 20 suffered from perennial nasal obstruction (of the latter, eight had seasonal exacerbation). Nineteen complained of non-purulent rhinorrhoea, seven of hyposmia and only one patient had suffered from sinusitis since childhood.

Examination

The nasal cavities were examined by rigid nasal endoscopy. Twenty patients had an obstructed nasal airway, seven due to bilateral polyps arising from prolapsed oedematous mucosa from the ethmoidal air cells. In 19 cases the obstruction was due to enlarged inferior turbinates, the mucosa being hyperaemic. Only six patients had non-purulent mucous strands in the nasal cavity.

From the history and examination six patients were asymptomatic with a non-obstructed airway, seven had nasal polyposis and 13 had rhinitis with nasal obstruction and rhinorrhoea secondary to generalized mucosal swelling. Clinical examination and the consequent allocation of patients into these three clinical groups preceded skin testing for atopic status. The examiner was therefore effectively blinded to the atopic status of these patients at the time of examination.

Investigations

Saccharin test. All were within the normal limit (less than 20 minutes). The time ranges from five to 10 minutes with a mean of seven minutes.

Sinus X-rays. All the sinus X-rays were similar. The maxillary and ethmoidal air cells were opaque and the frontal sinuses hypoplastic.

Skin testing. Eighteen patients had a positive skin test for more than one allergen, the incidence for each allergen being *Aspergillus fumigatus* – 86 per cent, house dust mite – 86 per cent, pollen – 57 per cent and animal dander – 50 per cent. The incidence of atopy in other series is shown in Table I.

Aspergillus fumigatus *precipitins and immunoglobin levels.* Nine patients had positive *Aspergillus fumigatus* precipitin levels. All patients had normal IgA and IgM levels (normal range IgA 0.75–4.0 g/l, IgM 0.25–2.0 g/l) and slightly elevated IgG levels (normal range 6–16 g/l). The IgE level differences between the three groups were statistically significant (mean values: asymptomatic group 33 ± 3.6 u/l, polyp group 117 ± 5.9 u/l and rhinitis group 994 ± 28 u/l). However IgE was only elevated in the rhinitis group (normal range less than 200 u/l).

In the asymptomatic group (six patients) all had negative skin testing, normal IgE levels and negative *Aspergillus fumigatus* precipitins. The polyp group had normal IgE levels, negative *Aspergillus fumigatus* precipitins and six out of seven had multiple allergens on skin testing. In the rhinitis group (13 patients) 12 had multiple allergens, 10 elevated IgE levels (up to 1000 IU/ml) and nine had positive *Aspergillus fumigatus* precipitins.

The relationship between *Pseudomonas* colonization and atopy is shown in Table II. In the 20 patients with *Pseudomonas* colonization 17 had multiple allergens and three were non-allergic. Only one patient had a positive skin test out of the six patients not colonized by *Pseudomonas* sp.

TABLE II
RELATIONSHIP BETWEEN PSEUDOMONAS COLONIZATION AND SKIN TESTING

Asymptomatic group	5 non-*Pseudomonas*	5 negative skin test
	1 *Pseudomonas*	1 negative skin test
Rhinitis group	13 *Pseudomonas*	12 positive skin test
		1 negative skin test
Polyp group	6 *Pseudomonas*	5 positive skin test
		1 negative skin test
	1 *non-Pseudomonas*	1 positive skin test

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Discussion

The symptomatology, clinical examination and laboratory investigations allow the patients to be divided into three groups: asymptomatic (23 per cent), polyposis (27 per cent) and rhinitis (50 per cent).

In the asymptomatic group all the patients had a good nasal airway and all had negative skin testing, normal IgE levels and negative *Aspergillus fumigatus* precipitins. Only one patient had been colonized by *Pseudomonas*.

Twenty-seven per cent of patients had polyposis. This compares favourably with other series that range from three to 36 per cent.[6,7,13] The high incidence of polyposis in the patients in our study may be due to the older population studied as it has been suggested that polyposis confers a survival advantage.[7] Although polyps may be asymptomatic many patients complain of nasal obstruction and rhinorrhoea and rarely present with facial distortion.[14] Drake-Lee and Pitcher-Wilmott reported that patients with polyps had a heavier birth weight, later presentation, milder gastrointestinal symptoms, less infection with *Staphylococcus aureus* and better vital capacities.[13] This was also noted by Fonsman and Morgan *et al*.[16] However six of our patients with polyps had lungs colonized by *Pseudomonas* sp., a feature often associated with poor lung function.[15] Kingdom *et al*.[17] found in a cross-sectional analysis of a large patient database that CF patients with nasal polyposis that required surgery formed a distinct sub-group which had slightly better pulmonary function and nutritional status but still had a higher rate of *Pseudomonas aeruginosa* colonization, more hospitalizations and a higher rate of acute exacerbations per year than did the comparison group. Allergy has been linked with the presence of polyps by others.[18] Schwachman[17] noted that allergic CF patients had a higher incidence of nasal polyps (16 per cent) than did those without allergic disease (three per cent). However, this association has been disputed by others.[15,19,20] Drake-Lee and Pitcher-Wilmott[13] found that CF children with polyps were no more allergic than controls, while Stern *et al*.[20] found that 36 per cent of 157 patients with polyps had no allergic symptoms.

Our study does not clarify the association between allergy and polyposis as although six had positive testing, the IgE levels were not raised and *Aspergillus fumigatus* precipitins were negative. Rulon *et al*.[21] proposed that the pathogenesis of polyps in CF were due to dilated glands in the nasal mucosa causing venous outflow obstruction leading to stromal oedema, prolapse and polyp formation. More recently, it has been proposed that polyps develop as a result of increased fluid absorption by the cells of the nasal mucosa which in turn is a result of the defective CFTR protein in CF, which is essentially a chloride channel. In these patients there appears to be a reduction of chloride efflux from the epithelial cell, with concomitant reduction in water transport out of the cell.[22] However, De Gaudemar *et al*.[23] found no evidence of a genetic cause for polyposis in a prospective study of 66 CF children.

Thirteen patients in our series had rhinitis (eight with seasonal exacerbation). Twelve had multiple allergens on skin testing, 10 had statistically significant elevated IgE levels and nine patients had positive *Aspergillus fumigatus* precipitins, thus supporting an allergic basis. All 13 were colonized with *Pseudomonas* sp. The incidence of positive skin testing and the allergens involved compares favourably with other series (Table I).[8,9,24–27] The higher incidence of allergy in our study compared to the others may relate to the study group consisting entirely of adults. The other groups consisted of children with the exception of Tobin *et al*.[9] whose values are closer to our own. Radiological examination of the sinuses showed pan-opacification of all sinuses in all patients. This was consistent with the findings of other researchers.[28,29]

Our study confirms previous reports of a high incidence of allergy to *Aspergillus fumigatus*,[30] however our study also confirms a high correlation between skin testing and clinical symptoms. Possible explanations for the increased sensitivity to *Aspergillus fumigatus* are increased permeability of respiratory mucous membranes, defective IgA protection of mucosal surfaces and retention of small allergen particles due to gas trapping.[31] The immunological reaction to *Aspergillus fumigatus* contributes to chronic lung damage and the development of allergic bronchopulmonary aspergillosis.[30] Cystic fibrosis patients with positive skin tests have worse lung function, higher hospital admission rates and worst chest radiograph scores.[27] Our study seems to show that there is a relationship between *Pseudomonas* colonization and allergy (Table II). *Pseudomonas* colonization may lead to increased permeability due to damage by proteases, exotoxins and other inflammatory substances.[32] The abundance of bacterial and fungal antigens in the respiratory tract may lead to enhanced IgE responses to common inhaled allergens due to an adjunctive effect, and hence to the development of atopy.[31]

Conclusions

Seventy-seven per cent of adult CF patients studied have nasal disease. There is a good correlation between clinical symptoms and tests for allergy. The development of the atopic state may be related to chronic *Pseudomonas* colonization.

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