Newly diagnosed cystic fibrosis in middle and later life

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ABSTRACT Four patients with cystic fibrosis diagnosed in middle and later life are presented. All had chronic bronchopulmonary infection with a high sweat sodium concentration, and chest radiographic evidence of upper zone bronchiectasis. Two patients had pancreatic dysfunction. Sputum culture grew mucoid *Pseudomonas aeruginosa* in three patients and *Haemophilus influenzae* in one. Ages at diagnosis were 63, 42, 40, and 35 years. These patients confirm the possibility of occasional longevity in cystic fibrosis and emphasise the need to consider the diagnosis at all ages. They also provide encouragement for younger patients.

The prognosis of cystic fibrosis has improved considerably over the past three decades. Previously death in the first year of life was common and very few patients with cystic fibrosis lived for more than 10 years. With the advent of systematic treatment with antibiotics and physiotherapy this outlook has changed and up to 75% of affected individuals are now reaching adult life. There are, however, some adult patients with cystic fibrosis with very mild, slowly progressive disease whose survival must be a reflection of the variable natural history of cystic fibrosis rather than the effects of treatment. In the past such patients are likely to have escaped diagnosis and some may be attending chest clinics unrecognised, or may still be undiagnosed in the community; the size of this population is unknown. The diagnosis of cystic fibrosis over the age of 30 years has been reported only rarely, although there are now many treated patients reaching this age.^{1,2} Only a handful of patients have been diagnosed after the age of 40³⁻⁷; the most recent report⁶ is of a 69 year old man with an abnormal response to the sweat test, abnormal pancreatic function, and chronic obstructive airways disease. A further four patients with cystic fibrosis diagnosed in middle and late adult life are presented here. Three of the patients were over 40 at diagnosis and one, a 63 year old, is the oldest woman with cystic fibrosis to be reported.

Method

Each patient had a sweat sodium concentration measured by the pilocarpine iontophoresis method of Gibson and Cook.⁸ It was done on both arms on at least two occasions and at least 100 mg of sweat was collected each time by a nursing sister experienced in the technique. Three patients had a suppression test using fludrocortisone⁹; they were given 5 mg of 9- α -fludrocortisone on two successive nights before sweat sodium analysis.

Exocrine pancreatic function was assessed, firstly, by faecal fat collection for three to five days while a normal diet was being taken and, secondly by the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid test.¹⁰ Half a gram of this synthetic peptide is given with 5 μ g ¹⁴C labelled *p*-aminobenzoic acid (PABA) together with 25 g of casein in 500 ml of water. PABA is released from the synthetic peptide in the duodenum in proportion to the amount of chymotrypsin available and then absorbed and excreted in the urine. Urine is collected for six hours and the amount of PABA excreted is expressed as a percentage of the ¹⁴C PABA collected. Phenacetin, paracetamol, sulphonamides, nitrazepam, and food-stuffs such as prunes and cranberries were excluded from the diet as they invalidate the test.

Results

The case histories are described below and the principal clinical details and results of investigations are summarised in the table. No consistent abnormalities emerged from routine haematological and biochemical testing.

All patients had had recurrent chest infections

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Details of the patients

Case No	1	2	3	4
Clinical details				
Sex	Female	Female	Male	Female
Age at diagnosis	63	42	40	35
Age at first clinic attendance	15	4	7	13
Gastrointestinal symptoms	Nil	Steatorrhoea	Nil	Nil
Respiratory symptoms	Persistent cough and sputum	"Recurrent bronchitis" Haemoptysis	Persistent cough and sputum	"Chronic bronchitis" Recurrent haemoptysis
Children	3 pregnancies	4 pregnancies (1 neonatal death)	None	2 pregnancies
Smoking history	++	0	0	0
Examination findings				
Height (cm)	169	162	165	168
Weight (kg)	43	44	50	47
Finger clubbing	Nil	Present	Present	Present
Chest	Widespread crackles	Crackles upper zone	Crackles upper and mid zones	Crackles mid and lower zones
Sputum	"Mucoid" <i>Pseudomonas aeruginosa</i>	<i>Haemophilus influenzae</i>	"Mucoid" <i>Pseudomonas aeruginosa</i>	"Mucoid" <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i>
FEV ₁ (l) (predicted)	0.3 (2.43)	0.6 (2.5)	1.0 (3.1)	0.9 (2.8)
Forced vital capacity (l) (predicted)	0.8 (3.30)	1.5 (3.1)	2.0 (3.8)	1.7 (3.5)
Peak flow (l/min) (predicted)	110 (390)	150 (380)	160 (540)	210 (410)
Sweat sodium (mmol(mEq)/l) *				
Left arm	100	80	92	84
Right arm	100	79	90	93
After fludrocortisone	86	97	Not done	82
Pancreatic function				
Faecal fat (g/24 h)	3.0	16.0	1.5	1.7
PABA test (over 3-5 days)†	80%	13%	Not done	54%
Glucose tolerance	Normal	Normal	Impaired	Normal
Miscellaneous				
Skin tests	Negative	Positive for common allergens	Negative	Negative
Avian and aspergillus precipitins	Negative	Negative	Negative	Negative
Immunoglobulins	Increased IgG	Normal	Normal	Increased IgM and IgG
Alpha ₁ antitrypsin	Normal	Normal	Normal	Normal

*Control <70 mmol(mEq)/l.

†Normal >70%.

from early childhood. Chest radiographs in each case showed hyperinflation and bronchial wall thickening that was predominantly in the upper zones, consistent with the diagnosis of cystic fibrosis. Sputum culture showed "mucoid" *Pseudomonas aeruginosa* repeatedly in three patients. Sweat sodium concentrations were consistently high and there was no suppression below 65 mmol/l with 9- α -fludrocortisone in those patients in whom the test was performed. One patient had unequivocal evidence of pancreatic insufficiency, and a second had an abnormal response to the *N*-benzyl-L-tyrosyl-*p*-aminobenzoic acid test.

CLINICAL HISTORIES

Case 1: woman aged 63

This woman had been described as a chesty child with frequent chest infections and daily cough and sputum, and at school she was unable to do any

sport. Her symptoms improved during her teenage years, puberty occurring normally with menarche at the age of 13. She was told on several occasions that she had an abnormal chest radiograph but that this was not due to tuberculosis. In her 20s she had three successful pregnancies and episodes of pleurisy and pneumonia. Pleurisy occurred again at the age of 42 and she had a bronchogram, details of which are not available. She remained relatively well until she was 58, when she developed cough and sputum after an influenza like illness. She deteriorated after this, becoming more breathless over the subsequent years with daily cough and sputum that was controlled with postural drainage.

At present she is short of breath after walking five metres and daily produces about 10 ml of yellow sputum. She denies having had any abnormality in her bowel motions at any time and opens her bowels two to three times a day. She smoked 10 cigarettes a day until she was 58.

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Case 2: woman aged 42

This woman had daily cough and sputum production from the age of 2, with frequent exacerbations resulting in many hospital admissions as a child. A shadow on her chest radiograph led to treatment with isoniazid and aminosalicylic acid (PAS) for one year. From the age of 5 she had frequent bowel motions and steatorrhoea and was started on a gluten free diet, to which she adhered incompletely. By her 20s she was taking a normal diet with no worsening of her symptoms. Over the last few years she had again had frequent pale stools, which were sometimes difficult to flush away; and she had been losing weight steadily for two years.

She had four pregnancies; the second child died in the neonatal period. After the birth of the fourth child when she was 35 her sputum production increased to a cupful a day with intermittent haemoptysis. At present she can walk up one flight of stairs and can cope with the housework. There is no family history of chest disease and she is a non-smoker.

On examination she was thin. After a normal jejunal biopsy specimen was obtained she was treated with pancreatic extract (Pancrex V). Her bowel motions became normal and she gained 4 kg in weight.

Case 3: man aged 40

As a child this man had had frequent chest infections and at the age of 20 he was told that he had "bronchitis." Subsequently he had recurrent chest infections and a gradual increase in sputum volume. In 1966 a bronchogram showed bilateral apical and right middle lobe bronchiectasis. He continues to have courses of antibiotics and his exertional breathlessness is increasing.

Case 4: woman aged 35

This woman had "pneumonia" at the age of 2 and had cough and sputum intermittently throughout her childhood; they became persistent after the age of 10. During her teens and early 20s she had persistent cough and sputum, which resulted in further investigation. She had two courses of antituberculous treatment despite negative sputum cultures and a negative response to the Mantoux test. Sputum persistently grew *Pseudomonas aeruginosa* and *Haemophilus influenzae* had also been cultured. She continues to have daily sputum production—up to half a cupful a day—and episodes of haemoptysis, necessitating frequent treatment with antibiotics; and she is short of breath on climbing stairs. Past illnesses include a thyroidectomy at the age of 28 for tracheal compression. She has had two successful singleton pregnancies. There is no

family history of chest disease and she has never smoked.

Discussion

The first reported case of cystic fibrosis to be newly diagnosed over the age of 20 was by Hellerstein in 1946¹¹; this was of an American Negro who died at the age of 35. Subsequent case reports of cystic fibrosis diagnosed in adulthood are rare; there are still few published reports of patients newly diagnosed over the age of 30 and only a handful of patients older than 40. The oldest reported survivors with cystic fibrosis are a 52 year old American woman and a 69 year old Norwegian man.⁴⁻⁶

The diagnosis of cystic fibrosis depends on several features, including chronic bronchopulmonary infection, pancreatic insufficiency, a high sweat sodium concentration, and a family history of cystic fibrosis; not all patients have all these and in particular pancreatic insufficiency is absent in up to 15%.¹² Stern *et al* have recently suggested modifications dividing the diagnostic criteria into major and minor criteria, following from their work on obstructive azoospermia.¹³ The diagnosis is established by the presence of one major with two minor or two major findings; the two criteria for diagnosis must include different organ systems. All our patients fulfill these criteria.

A sweat sodium concentration of over 60 mmol (mEq)/l in a child is usually considered diagnostic of cystic fibrosis, but sweat sodium concentrations tend to increase with age and show wide variability between individuals.¹⁴ There are several series reporting sweat sodium concentrations in normal people from older age groups.^{15 16} In McKendrick's series of 110 normal adults only five had a concentration greater than 80 mmol/l.¹⁴ Recent work by Hodson *et al* suggested that cystic fibrosis should be diagnosed in adults when two measurements of sweat sodium are above 70 mmol/l, and diagnostic accuracy was improved in borderline cases by a suppression test using fludrocortisone.⁹ All our patients had sweat sodium concentrations greater than 80 mmol/l and no suppression below 65 mmol/l with 9- α -fludrocortisone occurred in the three patients in whom the test was done. When the baseline sweat sodium concentration was plotted against the lowest concentration all results were well above the best discriminatory line as described by Hodson *et al*.⁹

The clinical pattern of chest disease in these patients was typical of cystic fibrosis. All had a long history of respiratory infections that started in childhood, the chest radiographs showed changes of bronchiectasis predominantly affecting the upper zones, and bacteria cultured from the sputum were also typical. Exocrine pancreatic insufficiency was

demonstrated in two of our patients; another had an abnormal response to the glucose tolerance test. In di Sant 'Agnese's series of adult patients with cystic fibrosis² 95% had pancreatic insufficiency but, in contrast to the younger patients, it was seldom symptomatic and in many cases dietary restrictions were unnecessary. Chronic pulmonary diseases has been the predominant cause of morbidity in our patients. No patient had a family history of cystic fibrosis but this is only a minor diagnostic criterion and is usually not found.

The most interesting feature of these four patients is their longevity. While this may reflect only the mild end of a continuous spectrum of clinical disease, there are other possible explanations, including a mild variant of cystic fibrosis and an improved prognosis in those without pancreatic insufficiency. There is little evidence to support genetic heterogeneity in cystic fibrosis, although it is possible that other genes modify the clinical expression of the disorder. The absence of pancreatic disease resulting in better nutrition may protect the chest from rapid deterioration seen in the most severely affected. At present the relative contributions of chest and pancreatic dysfunction to the clinical expression of cystic fibrosis is uncertain.

All our patients had been attending specialist clinics for some years before the diagnosis of cystic fibrosis was made. This suggests that there must be many others in the clinic population who are as yet undiagnosed. Wood¹⁷ looked at 24 emphysematous patients, of whom five had an abnormal sweat chloride concentration and impaired absorption of neutral fat; the mean chloride concentrations, however, were only on the borderline of abnormality. Karlish and Tarosky¹⁸ made a search for cystic fibrosis in adults attending a chronic lung disease clinic and found that 11 of 33 adults previously diagnosed as having bronchitis, emphysema, asthma, or bronchiectasis had abnormally high sweat electrolyte concentrations that were consistent with cystic fibrosis and some also had abnormal bronchograms. It is uncertain how many, if any, of the patients from those two studies had cystic fibrosis. The patients we report have excellent positive evidence of cystic fibrosis and emphasise the need to consider this diagnosis in any patient with persistent unexplained chest infections, particularly if combined with malabsorption. A sweat test should form part of the diagnostic investigation regardless of the age of the patient.

Finally, these patients are important for two other reasons. Firstly, they confirm that longevity is poss-

ible with cystic fibrosis, which should provide encouragement for younger patients; and secondly, the identification of long survivors may well contribute to an understanding of the aetiology and pathophysiology of the disease.

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