Cystic fibrosis presenting in adults

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Cystic fibrosis is a common genetic disease occurring in children. Milder forms of cystic fibrosis are increasingly being recognized as presenting in adults as well. This article describes the various ways in which cystic fibrosis can present in adult patients.

Cystic fibrosis (CF) is the most common autosomal recessive, potentially lethal disease in Caucasian populations. Most patients present in childhood and paediatricians will recognize the classical symptoms of steatorrhoea, failure to thrive and recurrent chest infections. However, occasional cases of CF presenting in adults have been described, and over the last two decades it has emerged that CF encompasses a wider spectrum of disease severity than was previously recognized, including mild and atypical disease that can present for the first time in adulthood. It can present at any age, even being reported in the elderly (van Biezen et al, 1992; Rosenbluth and Goodenberger, 1997), and with a variety of different clinical presentations. Many clinicians are unaware that this genetic disorder can present later in life, leading to potential delayed or missed diagnosis (Amorosa et al, 1995). This article reviews the various presentations of CF in adults that have been described.

INTRODUCTION

The CF gene was identified in 1989 and is located on chromosome 7. The gene product is a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR), which functions as a c-adenosine monophosphate (cAMP)-regulated chloride (Cl^-) channel in the apical membrane of epithelial cells. Since the discovery of the gene, over 750 disease-causing mutations have been identified, the most common mutation being a deletion of a phenylalanine residue at position 508 on the amino acid sequence, designated ΔF508. This mutation occurs on about 70% of all CF chromosomes, but this varies from over 90% of patients from Northern Europe to less than 50% of Mediterranean patients (Johansen et al, 1991).

Discovery of the various mutations causing CF has led to better understanding of the variations in disease phenotype. Some mutations (e.g. ΔF508) produce absent or very low cellular levels of CFTR, leading to a severe phenotype and early presentation. Other mutations (e.g. R117H, A455E) produce some functional CFTR and the resulting phenotype is milder, particularly for respiratory function, airway colonization by *Pseudomonas aeruginosa* and pancreatic status. Patients with mild phenotypes also present at a later age (Hubert et al, 1996).

In a study comparing patients diagnosed in childhood with those diagnosed over the age of 16 years, all ΔF508 homozygotes were diagnosed by the age of 13 years, whereas 39% of patients without this mutation were diagnosed after 16 years of age (Gan et al, 1995).

Correlation of levels of CFTR activity with varied disease expression led to the discovery of a hierarchy of organ sensitivity to CFTR deficit. Levels of cellular CFTR greater than 10–12% of normal are compatible with a normal phenotype. At lower levels the first organ to be affected is the genital tract (see section on congenital absence of the vas deferens). Genotypes producing CFTR levels between 1% and 5% of normal lead to pulmonary disease but the pancreas is unaffected. At levels less than 1% (usually ΔF508 homozygotes), the classical CF phenotype with severe lung disease and pancreatic insufficiency occurs (*Figure 1*). However, even within the same genotype, variations in disease severity are seen, suggesting that other genetic loci or environmental factors contribute to disease expression (Burke et al, 1992).

DIAGNOSIS OF CYSTIC FIBROSIS

Since 1959, the 'gold standard' for the diagnosis of CF has been finding raised levels of sweat

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electrolytes by means of the sweat test (Di Sant'Agnese et al, 1953). Sweat electrolyte levels are higher in adults than in children, so CF should only be diagnosed in adults when two measurements of sweat sodium (Na^+) are above 70mmol/litre or sweat Cl^- above 60mmol/litre (Hodson et al, 1983). In borderline cases, a fludrocortisone suppression test improves the accuracy of diagnosis. There are a number of conditions besides CF that can cause elevated sweat electrolytes, and these are listed in *Table 1*.

Since 1975, there have been occasional reports of patients with clinical symptoms suggestive of CF but normal sweat electrolytes (Stern et al, 1978). Until discovery of the CF gene it could not be determined whether these patients had a form of CF or a distinct disease entity. In 1991, a new mutation in the CFTR gene, designated G551S, was found in two such patients, confirming that they had CF (Strong et al, 1991). Subsequently another mutation (termed 3849+10kb C⇒T) was identified in patients (mainly adults) with typical CF pulmonary disease and normal sweat electrolytes (Highsmith et al, 1994). This mutation was described in three different ethnic groups and so may be relatively common. Therefore patients with a pattern of pulmonary disease suggestive of CF, but normal sweat electrolytes should undergo further diagnostic testing.

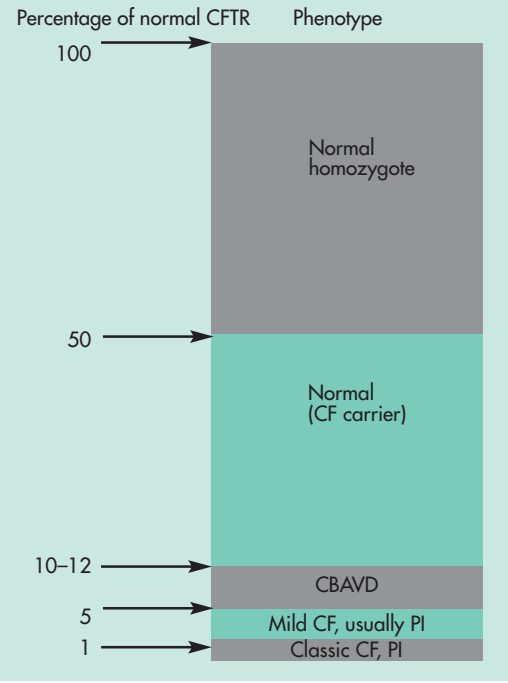

Figure 1. Correlation of cellular levels of cystic fibrosis transmembrane regulator (CFTR) with cystic fibrosis (CF). CBAVD = congenital bilateral absence of the vas deferens; PI = pancreatic insufficiency.

TABLE 1.
Diseases other than cystic fibrosis causing raised sweat electrolyte concentration

Untreated hypoadrenalism
Untreated hypothyroidism
Malnutrition
Ectodermal dysplasia
Nephrogenic diabetes insipidus
Glycogen storage disease type I
Glucose-6-phosphate dehydrogenase deficiency
Hypogammaglobulinaemia

The diagnosis in these patients can be made either by assessment of the CF genotype or by measuring the nasal potential difference (NPD). The NPD measures the voltage across the nasal epithelium. This correlates with the movement of Na+ across cell membranes and is raised if the CFTR function is abnormal (Stern, 1997). The response to perfusion with amiloride and isoproterenol increases the sensitivity of the test, which assesses CFTR function more directly and reliably than the sweat test. However, it is time consuming, more difficult to perform than sweat testing and is only available in specialized centres.

PULMONARY DISEASE

Respiratory disease is the major cause of mortality and morbidity in CF. Patients with classical, childhood CF usually develop recurrent chest infections in infancy, and severe, suppurative lung disease by their teens. Most patients described who were diagnosed as adults presented with chest symptoms (Gan et al, 1995), but their disease is milder and progresses more slowly than that of classical CF. The most common presentations are recurrent chest infections and chronic cough and sputum production. Symptoms may first occur in childhood but their significance is often overlooked, especially when other symptoms of CF (e.g. malabsorption) are absent (Hunt and Geddes, 1985). Disease may be mild enough to be compatible with a normal lifespan (Su and Beanblossom, 1989; Van Biezen et al, 1992), regular employment and successful pregnancies in women (Hunt and Geddes, 1985; Knowles et al, 1989).

Chest X-ray abnormalities, such as bronchiectasis, atelectasis, pulmonary infiltrates and hyperinflation are common. Involvement of the upper lobes of the lungs is characteristic of CF. Before the diagnosis of CF was made, patients had been given diverse diagnoses, such as chronic obstructive pulmonary disease, asthma, sarcoid and tuberculosis (Stern et al, 1977; Hunt and Geddes, 1985).

The lungs of CF patients are colonized by a specific microbiological flora, consisting mainly of *Staphylococcus aureus*, *Haemophilus influenzae*, and most characteristically, *P. aeruginosa*. *P. aeruginosa* has been shown to demonstrate increased adherence to airway epithelial cells in CF patients, especially those with the ΔF508 mutation (Saiman and Prince, 1993). The recovery of mucoid *P. aeruginosa* from sputum is so characteristic of CF that it has been suggested that it is a 'sign' of CF in adults with chronic pulmonary disease (Reynolds et al, 1976).

CF patients have a high incidence of bronchial hyperreactivity and asthma, and asthmatic symptoms have been described in patients with atypical CF. Kerem et al (1997) suggested that a particular mutation (the 5T allele) is associated with a high incidence of asthma-like symptoms.

A number of studies have addressed the issue as to whether CFTR mutations are involved in the aetiology of isolated respiratory syndromes. A significantly increased frequency of CFTR gene mutations has consistently been found in patients with disseminated bronchiectasis of unknown origin (Gervais et al, 1993; Pignatti et al, 1996; Girodon et al, 1997). Similar studies in patients with other lung diseases have shown less consistent results. One study initially showed an increased incidence of ΔF508 heterozygotes in patients with bronchial hypersecretion (Dumur et al, 1990b). However, subsequent studies did not find a higher incidence of CFTR gene mutations in patients with chronic bronchitis (Gervais et al, 1993; Entzian et al, 1995), and a non-significant increase in patients with asthma and non-obstructive pulmonary diseases (Pignatti et al, 1996).

Therefore patients with bronchiectasis of unknown aetiology warrant assessment of their CFTR genotype, but the involvement of CFTR mutations in other lung diseases is unproven.

UPPER RESPIRATORY TRACT DISEASE

CF patients have the same functional abnormalities in the mucosa of the nose and sinuses as the lower respiratory tract. Sinusitis is common in CF patients, with 10–20% requiring surgery, and 25% of patients have nasal polyps. Adult patients presenting with respiratory symptoms often had upper respiratory disease, which may have predated the chest symptoms (Su and Beanblossom, 1989; Stewart et al, 1995; Gregory et al, 1997). Severe sinusitis and nasal polyposis have also been described as the sole presenting complaint of CF in a 21-year-old patient (Kaplan et al, 1996).

Similar studies to those performed in patients with isolated respiratory syndromes have been conducted to assess if CFTR mutations are involved in the aetiology of nasal polyposis. Irving et al (1997) identified three carriers of CFTR mutations in 55 patients with severe nasal polyposis, an incidence not significantly higher than that of the general population. Another study found the G551D mutation to be significantly over-represented in German patients with nasal polyps, but only four patients out of 59 had this mutation (Burger et al, 1991). Therefore although some CFTR mutations may have a casual role in nasal polyposis, the majority of patients with upper respiratory tract disease will have a normal genotype. However, the possibility of CF should be considered in such patients, especially if respiratory symptoms are also present.

GASTROINTESTINAL AND HEPATOBILIARY DISEASE

Presentation of CF in adults with gastrointestinal or hepatobiliary symptoms is much more rarely described than with pulmonary disease (Gan et al, 1995). About 90% of children with classical CF have pancreatic insufficiency (PI), resulting in malabsorption and impaired growth. PI very rarely develops for the first time in adults, and patients with PI usually also develop severe pulmonary disease in childhood (Hubert et al, 1996). PI in neonates can lead to a form of intestinal obstruction known as meconium ileus. An equivalent syndrome occurs in older CF patients and is termed distal intestinal obstruction syndrome. This has only been described in previously diagnosed CF patients and no reports exist of it being the presenting symptom of CF.

A rare presentation of CF that has been described in adults is recurrent, acute pancreatitis (O'Connor and Brashear, 1985). This has been described as an isolated manifestation of CF in patients with no respiratory symptoms and who are pancreatic sufficient (Masaryk and Achkar, 1983; Gross et al, 1989).

About 15% of patients with CF develop hepatobiliary disease, including hepatic cirrhosis and gallstones. There are a few case reports of CF presenting in adults with liver disease. Presentations reported include deranged liver function tests, portal hypertension with oesophageal varices (Stern et al, 1977; Gan et al, 1995), and jaundice (Greaves et al, 1997). Therefore CF should be considered as a cause of cirrhosis in adults where more common aetiologies have been excluded.

CONGENITAL BILATERAL ABSENCE OF THE VAS DEFERENS

Over 90% of males with CF are infertile due to failure of development of the epididymis and vas deferens. In 1990, Dumur et al described 17 men

who had congenital bilateral absence of the vas deferens (CBAVD) when investigated for infertility, but did not have CF. Of these, seven (42%) were heterozygous for the ΔF508 mutation and six had abnormal sweat tests. Since this initial report larger studies have confirmed that CFTR gene mutations are involved in the aetiology of CBAVD (Anguiano et al, 1992; Chillon et al, 1995).

CFTR mutations have a greater than expected incidence in men with unilateral absence of the vas deferens (Chillon et al, 1995) and obstructive azoospermia without CBAVD (Jarvi et al, 1995). The proportions of chromosomes carrying CFTR mutations in men with CBAVD range from 38% to 81% in different studies (Donat et al, 1997). Results vary as to whether other clinical manifestations of CF are present in these patients.

Some studies have reported no symptoms or only minor respiratory symptoms (Anguiano et al, 1992; Chillon et al, 1995; Donat et al, 1997) and normal pulmonary function (Colin et al, 1996). Others have reported that over 40% of these patients have respiratory symptoms (Kerem et al, 1997) and a high incidence of sinus disease and antibodies to *P. aeruginosa* (Durieu et al, 1995). It is probable that this population of males with CBAVD and CFTR mutations is a heterogenous group, with the severity of clinical manifestations depending on the particular CFTR mutations present in each individual patient.

Patients who are compound heterozygotes, have positive sweat tests and respiratory symptoms should certainly be considered as having an attenuated form of CF, and should be followed up to detect possible late complications of CF. Controversy remains as to whether men with CBAVD and CFTR gene mutations but no other clinical symptoms should be given a diagnosis of CF, with the possible negative consequences this may entail (Colin et al, 1996).

However, determining whether men with CBAVD have CFTR gene mutations — even if otherwise asymptomatic — is of more than academic interest, because sperm aspiration techniques offer them the possibility of fathering children. If the patient's partner is a carrier of a CF gene (a 1 in 25 chance in European populations), their risk of having a child with two abnormal CFTR genes is 25% for a heterozygous male and 50% for a homozygous or compound heterozygous male. Therefore genetic testing of these patients and their female partners is imperative to assess their risk of having a child with CF.

HEAT PROSTRATION

In 1953, Di Sant'Agnese and colleagues noted an abnormally high number of children with CF among those admitted to hospital with heat prostration during a heatwave. This observation led to the finding of high concentrations of Na^+ and Cl^- in the sweat of patients with CF and development of the diagnostic sweat test. Heat prostration, dehydration and metabolic alkalosis are well-recognized complications of CF in children, and may even be the initial presentation of the disease.

Two adult patients have been described in whom CF first presented in this way. In 1995, Smith et al reported a 24-year-old British soldier who collapsed twice during training in hot climates and was found to be hyponatraemic and hypokalaemic. A positive sweat test confirmed the diagnosis of CF. He had normal pulmonary and pancreatic function but was azoospermic (Smith et al, 1995). In 1997, Bates et al described a 17-year-old man who presented with a syncopal episode while engaged in heavy manual labour in a hot environment. He had previously complained of generalized fatigue and muscle cramps while working in hot temperatures. He was found to be hypotensive, hypokalaemic and had a metabolic alkalosis. A raised sweat Cl^- confirmed him as having CF. He was otherwise asymptomatic and had a normal chest X-ray and normal pancreatic function. Both patients were compound heterozygotes for the ΔF508/R117H mutations.

This is a rare presentation of CF but the diagnosis should be considered in adults presenting with these symptoms and biochemical findings. The ΔF508/R117H genotype has also been found in 15% of males with CBAVD and CFTR gene mutations (Gervais et al, 1993). These two patients and the males with CBAVD are probably phenotypically identical, but the former presented because they underwent strenuous exertion in hot climates, while the latter were diagnosed after investigation for infertility. If this hypothesis is correct, then patients with this genotype (and possibly all CF genotypes with raised sweat electrolytes) should be advised to avoid heavy exercise in hot climates.

GENETIC SCREENING OF RELATIVES OF CF PATIENTS

Once an individual is diagnosed as having CF, genetic analysis of relatives should be carried out to detect carriers and give appropriate genetic counselling. Three adult patients have been reported in whom CF was diagnosed when genetic analysis was carried out after a related child was diagnosed with the disease. The children described were compound heterozygotes inheriting a ΔF508 chromosome from their father and a mild CF mutation from their mother. However, genotyping of the mothers (and one of the mother's sisters) actually revealed them to be

compound heterozygotes for two mild CFTR mutations. One gave a history of recurrent chest infections and sinusitis and was found to have impaired pulmonary function, *Staph. aureus* in her sputum and a positive sweat test (Gregory et al, 1997). The other mother (and her sister) was minimally symptomatic, had impaired pulmonary function and positive sweat tests (Santis et al, 1990). These cases illustrate the importance of genetic screening of relatives of index patients with CF, especially if compound heterozygotes, as it may reveal previously undiagnosed CF. **HM**

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KEY POINTS

- Cystic fibrosis (CF) is now recognized to encompass a wide spectrum of disease severity, ranging from severely affected infants to minimally symptomatic adults.
- A total of 5–10% of adult CF patients present after the age of 16 years, and the disease has been described in middle-aged and elderly patients, so the diagnosis should be considered in anyone with appropriate clinical features.
- Most adult patients present with respiratory symptoms, but a number of other, rarer, clinical presentations of CF can occur, including gastrointestinal, metabolic and urogenital disease.
- CF is diagnosed by the finding of elevated sweat electrolytes. In some cases it can exist with normal levels of sweat electrolytes and further diagnostic testing is required to make the diagnosis.