Cystic fibrosis diagnosed in adult patients

Tanya J McWilliams, Registrar; Margaret L Wilsher, Respiratory Physician; John Kolbe, Respiratory Physician, Respiratory Services, Green Lane Hospital and Department of Medicine, University of Auckland, Auckland.

Abstract

Aim. To review the presentation, diagnosis and long-term, clinical follow-up of cystic fibrosis in adult patients diagnosed in adulthood at Green Lane Hospital.

Methods. A retrospective review of the case notes of patients with cystic fibrosis diagnosed in adulthood at Green Lane Hospital or referred there for management. Information was collected on diagnostic tests, including sweat tests and genotyping. Relevant family history was documented as were spirometry results and microbial colonisation.

Results. Six patients conclusively fulfilled the diagnostic criteria for cystic fibrosis. There was a wide range of ages at diagnosis (18-68) and half of the patients had a positive family history. A single mutation was identified in all, but in only one of the cases was the second mutation identified. All patients had evidence of bronchopulmonary suppuration and all had retained pancreatic function. Colonisation with P aeruginosa was associated with marked impairment in lung function.

Conclusion. The patients at Green Lane Hospital represent part of the broad-spectrum disease in adult patients diagnosed with cystic fibrosis and highlight the differences between this group and those patients diagnosed in childhood with the more classical phenotype. Patients generally have less severe lung disease and retain pancreatic function. Sweat testing is useful diagnostically but gene testing is of limited value in making the diagnosis.

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Cystic fibrosis (CF) is the most common, lethal genetic disease amongst Caucasians in New Zealand. It has an incidence of about 1 in 2500 live births (in New Zealand 1 in 3179 Caucasian births) and 1 person in 25 is an asymptomatic carrier. The gene responsible for CF was cloned in 1989[1] and codes for the cystic fibrosis transmembrane regulator (CFTR), a phosphorylation-regulated, chloride channel located in the apical membrane of epithelial cells.[2]

Although the disease is caused by mutations in this single gene coding for CFTR, the disease has a variable clinical phenotype. The most common mutation is ΔF508, due to a deletion of phenylalanine in the 508 position on the CFTR gene and comprises approximately 80% of the mutations in New Zealand. The classic picture of cystic fibrosis is that associated with the ΔF508 homozygote genotype and includes pancreatic insufficiency, male infertility and severe sino-pulmonary disease.[2] In such patients, colonisation with *P aeruginosa* and *S aureus* may be associated with deterioration in lung function.[3] The typical electrophysiologal picture is of abnormal transport of sodium and chloride ions across the apical membranes of affected cells. There are more than 600 mutations in the CFTR gene now identified. While clinical variation exists within a single genotype due possibly to modifying genes or environmental and management factors, it is well recognised that certain genetic types are associated with a milder phenotype, with retention of normal pancreatic function and milder lung disease.[3]

The spectrum of disease associated with the CF gene is much wider than previously thought. Some patients who have milder disease and lack the typical features are only diagnosed in adulthood. It is important that general practitioners and physicians are aware of these atypical presentations of CF so that the correct diagnosis can be made and appropriate management (including genetic counselling) and long-term follow-up instituted. To illustrate this point we reviewed patients with CF presenting in adult life in Auckland.

Methods

We retrospectively reviewed the case notes of patients with CF diagnosed in adulthood and currently under the care of Green Lane Hospital. We included patients diagnosed at Green Lane Hospital and those referred there for management. Information was collected on demographics, clinical presentation, lung function, diagnostic tests (specifically sweat tests and genotyping) and relevant family history. Exocrine pancreatic function at the time of presentation to Green Lane Hospital was assessed on history and confirmed if necessary with a three-day, faecal fat test or a faecal elastase test. Patient progress from diagnosis was followed with spirometry and microbial colonisation.

Results

The diagnosis of CF depends on presentation with an appropriate phenotype (or sibling with CF) and evidence of abnormal ion and water transport (elevated sweat electrolytes and/or abnormal nasal potential differences). Six patients fulfilling this definition have been diagnosed as adults at Green Lane Hospital.

All patients were European (one patient was born in South Africa, the others in New Zealand) and five out of six were female. None were related. The age at diagnosis ranged from 18 to 68 years. Three patients had no family history of CF. One patient was diagnosed at the age of 68 after her grandchildren (with chronic respiratory illness) were diagnosed with CF. The one male patient, diagnosed at the age of 27, had a sister with CF. The other patient had a grandmother who had died of chronic suppurative respiratory disease. Only two of our patients were smokers.

All patents presented with respiratory symptoms. Two had a history compatible with bronchiectasis. One had a long history in adulthood and was finally diagnosed with CF at the age of 31 in 1996. Two further patients had chronic cough as a presenting complaint. A further patient, diagnosed at the age of 68, primarily had sinusitis. In our group of patients computed tomography (CT) scans of the chest had been performed as part of the original diagnostic work-up some time before the diagnosis of CF was made. Three patients had CT scans showing upper lobe bronchiectasis and one had a lower lobe pattern. At least two of these patients were initially diagnosed with bronchiectasis

and a typical pattern for CF on CT was one clue to the correct diagnosis.

Diagnosis was confirmed in all by a positive sweat test (the sweat sodium results ranged from 64 to 127 mmol/L). Five out of six of these patients had an identifiable mutation in the CF gene (Table 1). All cases had normal pancreatic function. Immunoglobulin levels were uniformly normal.

Table 1. Adult patients with cystic fibrosis at Green Lane Hospital.

	Age (at diagnosis)	Gender	FEV1 (% predicted) at diagnosis)	Genotype
1	37	F	42	F508/R117H
2	19	F	82	F508/
3	31	F	78	not known
4	18	F	76	F508/
5	68	F	115	R117H/
6	27	M	42	F508/

There was a range of severity of respiratory disease. In our patients one was colonised with Aspergillus species and *Mycobacterium avium intracellulare*. However, this man and another patient had *P aeruginosa* in their sputum. Both of these patients had FEV_1s below 50% predicted at diagnosis in contrast to the other four. Two patients have had a decline in lung function tests during follow-up and were the only two smokers in this group.

Discussion

Patients with cystic fibrosis diagnosed later in life rather than in childhood have variable and atypical presentations, and often have milder disease[1] and a better, long-term prognosis.[3] Correct diagnosis allows institution of correct therapy, more informed discussion of prognosis and appropriate genetic counselling. The following discussion addresses issues of the diagnosis, genetic basis and varied clinical picture of CF in these patients.

Diagnosis. All of our patients satisfied the current criteria for the diagnosis of CF, namely a compatible phenotype plus abnormal sweat electrolytes. In one patient a CF mutation could not be identified amongst the limited number of mutations tested for in New Zealand. In three patients there was also a family history of CF but in only one was this in a sibling. The range of normal values for sweat sodium and chloride, in children younger than 15 years is less than 60 mmol/L and 95% of results are less than 40 mmol/L. However, levels of sweat sodium and chloride normally rise slowly throughout childhood and early adulthood. Values of greater than 60 mmol/L are considered abnormal in adults and the causes of false positives are readily excluded on clinical grounds. In CF, levels of sweat sodium and chloride are usually in the range of 80-190 mmol/L.[3] A minimum of 0.04 g of sweat is required for a reliable result.

Genetics. Recent advances in genetic testing have identified a large number of CFTR mutations; some are becoming associated with particular phenotypes. The range of mutations includes other amino acid deletions, missense (point) mutations, e.g. R 117H, R334W and R347P,[4] nonsense (stop code) mutations and frame-shift mutations. The most common sites for clinically significant mutations are the two-nucleotide binding domains. Patients who are ΔF508 homozygotes have no CFTR in the apical membranes of their sweat glands, (although some remains in the cytoplasmic perinuclear granules) and generally have severe sino-pulmonary disease and pancreatic insufficiency.

Cystic fibrosis mutations are usually described as mild or severe depending on whether they are associated with pancreatic sufficiency[5] (R 117H, R334W, R347P, A445E and P547H) or insufficiency (AF508 and G551D[6]). In some patients one "mild" mutation is enough to preserve pancreatic function even when paired with a "severe" allele, There can also be differences in severity of disease within the IVST-8 genotype when the quantity of functioning CFTR is affected by alternative splicing of the mRNA.[7]

The relationship between genotype and phenotype is not so clear in lung as in pancreatic disease. One study[3] in the Netherlands found that patients with the A445E mutation had less severe lung disease. They had better lung function, were less likely to be colonised with *P aeruginosa*, and had less pancreatic insufficiency. This occurred even when the allele paired with A445E was one usually associated with severe disease (e.g. ΔF508, 1717-1G-A, E60X, G542X and R553X).

In our study the patients were all pancreatic sufficient as has been the case in previous studies.[1,3] Similarly, all of our patients presented late. Although four of our patients were ΔF508 heterozygotes, in only one case was the other allele able to be identified (ΔF508/R117H). The R117H allele is known to be associated with milder disease.[3]

The patients included in this review all had their genotype analysed in New Zealand. Four out of six were ΔF508 heterozygotes with the other allele being identified in only one case. All of these ΔF508 heterozygotes must have a second allele with a CFTR mutation and it is this allele that usually determines the severity of disease. Since all four of the patients who are ΔF508 heterozygotes were pancreatic sufficient we must assume that their other allele is one which has a mutation that codes for pancreatic sufficiency. One patient was a R117H heterozygote, the other did not have a genotype that can currently be identified in New Zealand. As only limited genotyping is undertaken in New Zealand, the failure to detect two mutations does in no way exclude the diagnosis of CF in this group.

Clinical features. Respiratory symptoms predominated in this group of patients, with all having retained exocrine pancreatic function. This is consistent with organ-specific variable dependence on CFTR within the sweat glands, pancreas and lungs, the lungs needing a higher functioning level of CFTR than the pancreas, The vas deferens is generally considered to require the highest functioning of CFTR of any organ and, therefore, the fertility of one of our male patients is extremely unusual.

Two of our patients were colonised with *S aureus* and *P aeruginosa* and these two both had FEV_1s below 50% predicted, at presentation. In patients who are homozygotes for ΔF508, colonisation with *P aeruginosa* and *S aureus* is usually associated with deterioration in lung function.[3]

In our patients who presented with "bronchiectasis", radiological features were helpful in making the diagnosis of CF, particularly when other potential causes such as allergic bronchopulmonary aspergillosis and immunoglobulin deficiency had been excluded. A typical CT scan in cystic fibrosis may demonstrate cylindrical bronchiectasis with peribronchial thickening, peripheral nodular opacities and ring shadows. Bronchial cysts (56%) and interstitial cysts (32%) may also be present. A distribution of apical rather than basal bronchiectasis is often a clue that cystic fibrosis, rather than idiopathic bronchiectasis, is the underlying diagnosis.

Conclusion

CF is no longer thought of as a homogeneous disease due to a single genetic abnormality as is reflected in our group of patients. The spectrum of clinical presentations is increasing, as is the identification of new genetic abnormalities underlying them. People are presenting with mild forms of

CF presumably due to the presence of a second abnormal allele, which cannot yet be detected by the genotyping available in New Zealand. The diagnosis of CF should be confirmed with a sweat test and genotyping. The latter is useful, not only for prognostic purposes but also to facilitate genetic counselling, Once the diagnosis is secure, treatment can be appropriately directed at optimising and maintaining respiratory function.

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