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Diagnosing CF

Diagnosing CF: sweat, blood and years

J S Elborn, J M Bradley

Use of algorithms for the diagnosis of CF

The diagnosis of cystic fibrosis (CF) is usually straightforward. The accepted criteria for the diagnosis of CF is one phenotypic characteristic of CF (such as lung disease or pancreatic malabsorption), or a positive neonatal screening result, or a positive history of CF in a sibling *plus* a raised sweat chloride level, positive nasal potential difference (PD) test, or two mutations in the *CFTR* gene.[1] In countries with neonatal screening the diagnosis is made in most cases using either an immunoreactive trypsinogen (IRT) test on a heel prick blood sample or direct detection of genetic mutations.[2] Missed cases (false negatives) from screening are almost all pancreatic sufficient with minimal lung disease, and may have a consequent delay in diagnosis.[2] In countries which do not yet have neonatal screening for CF, most children present in the first year of life with failure to thrive, recurrent respiratory infections, or both.[2] For such children a sweat test is the most important investigation to confirm the diagnosis. Some patients also present with clinical disease later in childhood and into adult life and diagnosis can be more difficult for a number of reasons.

In late diagnosed patients there is a wider range of presenting phenotypes in addition to the common presentations with respiratory infection and pancreatic malabsorption.[3] Some present with single organ pulmonary disease (bronchiectasis), pancreatitis, severe sinusitis, or infertility. The explanation for this is that some mutations of the *CFTR* gene are associated with an atypical phenotype, usually with less severe lung disease. Over 1000 mutations of the *CFTR* gene have now been described, but only a proportion are associated with disease.[4]

Mutations of the *CFTR* gene which cause disease can be classified as follows: class 1, defective protein synthesis (e.g. G542X); class 2, defective protein processing (e.g. ΔF508); class 3, defective protein regulation (e.g. G551D). These three classes are considered to be severe mutations and are associated with the classic CF phenotype. Class 4 (e.g. R117H) and class 5 (e.g. 3849+10kbC→T and IVS8-5T) are associated with altered chloride conductance of CFTR or reduced expression and with mild phenotypes. There are, in addition, a number of *CFTR* polymorphisms associated with mild phenotypes, particularly the number of TG repeats in IVS8.[4]

At the most mild phenotypic extreme are people with congenital bilateral absence of the vas deferens (CBAVD) who have one or two mutations of the *CFTR* gene. The vas deferens is the most sensitive organ to CFTR dysfunction. About 50% of men who present with infertility and who have CBAVD have one or two mutations of the *CFTR* gene.[5 6] They may have a sweat chloride level of 30–60 mmol/l and a mildly abnormal nasal PD. For these individuals the pulmonary prognosis is almost certainly very good, although some may develop mild sinopulmonary symptoms related to the CF phenotype later in life. It is important to consider carefully the most appropriate diagnostic label for such individuals. This applies to other atypical presentations associated with CF such as idiopathic pancreatitis, bronchiectasis, heat exhaustion, allergic bronchopulmonary aspergillosis (ABPA), and chronic sinusitis, as all of these presentations can cause diagnostic dilemmas.[2 6 7]

In this issue of *Thorax* De Boeck *et al*[8] present two consensus algorithms from a Diagnostic Working Group of European experts on the diagnosis of CF and review the supportive diagnostic tests such as sweat testing, genotyping, nasal PD and measurements of intestinal currents. These algorithms provide a helpful approach to making the diagnosis of CF. The two algorithms can be used following clinical suspicion of the diagnosis of CF or neonatal screening. They lead to diagnostic classification of CF as classic or non-classic, or exclusion of the diagnosis of CF. A further small group of mildly affected patients might be considered as having a CFTR related disorder. This is usually single organ disease such as CBAVD, recurrent pancreatitis, or severe sinusitis. Such patients may have a single mutation of their *CFTR* gene and a normal or slightly increased sweat chloride concentration. Single organ disease such as this should not result in a diagnosis of CF, either classic or non-classic, and may be classified according to a WHO diagnostic list, though this is not an exhaustive list of diagnoses. The algorithms will also help confidently to exclude a diagnosis of CF.

These algorithms are likely to be helpful in addressing the question: ''Is this disease CF?'' For example, in patients attending a general respiratory clinic (paediatric or adult) with symptoms or signs suggesting bronchiectasis, the diagnosis of CF should be considered. Patients with bronchiectasis who have a history of symptoms starting in childhood should all have a sweat test and the diagnostic algorithm used from there. In particular, patients from whom typical organisms of CF such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or a member of the *Burkholderia* genus are isolated should have a sweat test to determine if their disease is related to CFTR dysfunction. The sweat test is the most straightforward first investigation in such patients and then the first diagnostic algorithm should be followed as appropriate. Confirmatory genotyping can then be undertaken to

determine the specific mutations. A small number of people carry mutations associated with sweat chloride levels in the normal range. If suspicion of CF is high, genotyping should be undertaken in such patients.

There are also a small number of children who have a label of CF following neonatal screening but in whom little or no phenotypic manifestations of CF develop over subsequent years, calling into question the diagnosis (false positives). The second diagnostic algorithm is helpful in such patients as they are likely to have had a *CFTR* DNA test with only one or no mutations, but may not have had a sweat test since the time of diagnosis. This is not a common occurrence but the algorithm will be helpful in those cases. The sweat test should be repeated and other investigations arranged as appropriate to explore other diagnoses.

In the two algorithms the authors argue that the traditional upper limit for sweat chloride of 40 mmol/l should be lowered to 30 mmol/l. From their literature review this seems to be a reasonable suggestion, but care in the interpretation of sweat chloride tests in this range will be important in order to avoid false positive diagnoses. Most national guidelines still recommend that levels below 40 mmol/l are normal.[9 10]

The paper also explores the value of adjunctive diagnostic investigations such as nasal PD measurements. These are not widely available and are difficult measurements to make accurately and reproducibly. A number of centres in the UK offer this service and it can be of some value, particularly in confirming that there is no CFTR dysfunction in a patient with an equivocal sweat chloride concentration who has a phenotype suggestive of CF but in whom only one or no mutations can be identified. It is likely that such patients have some other cause for their bronchiectasis. It is unnecessary for every CF centre to have this test available. The performance of nasal PD testing is technically challenging and it is preferable that a few centres develop this expertise. Intestinal current measurements are also valuable but are available at even fewer centres. This involves taking a small biopsy sample from the lower gastrointestinal tract and measuring the electrical current under different conditions. This assessment gives similar information to nasal PD and can confirm or refute dysfunction of the CFTR chloride channel.

The spectrum of the diagnosis of CF and related disorders has widened considerably and should be considered in all patients with bronchiectasis, idiopathic pancreatitis, severe sinusitis, nasal polyps, ABPA and CBAVD, and investigated as appropriate. These algorithms will be a help to clinicians considering or reconsidering the diagnosis.

Thorax 2006;**61**:556–557.
doi: 10.1136/thx.2005.056309

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Funding: none.

Competing interests: none declared.

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The burden of lung disease

The burden of lung disease

R Hubbard

A timely reminder of the needs of people with respiratory disease in the UK

The range of clinical conditions included under the umbrella of "respiratory medicine" is wide. From cancers to obstructive sleep apnoea, interstitial lung disease to airways disease, occupational lung disease to respiratory infections, there is a variety present in respiratory medicine not seen in other hospital based specialties. This diversity makes respiratory medicine a deeply rewarding specialty in which to work, but also means that it is not easy to quantify the full impact of lung disease on the health of the British public.

For this reason, the British Thoracic Society has produced the second edition of "*The Burden of Lung Disease*" which includes a number of statistics that may be startling to the casual reader and of interest to those involved in resource allocation in the NHS.[1] For example, of the 580 000 deaths each year in the UK, one in five is due to respiratory disease with 35 000 deaths from lung cancer, 34 000 from pneumonia, and 27 000 from COPD. Respiratory disease now accounts for more than 845 000 hospital admissions each year and is second only to injury and poisoning as a cause of emergency admission to hospital. Asthma remains the most common chronic illness in children. The estimated cost to the UK of respiratory disease in 2004 was a staggering £6.6 billion. Clearly, the impact of lung disease is huge.

The report also provides evidence of health inequalities in lung disease. The socioeconomic gradient in death rates from respiratory disease is steeper than that for all cause mortality, highlighting the great potential to prevent deaths from lung disease. Worryingly, the report also suggests that respiratory medicine in the UK is falling behind other specialties and other countries. For example, the death rate from ischaemic heart disease in the UK has