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. 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. Missed cases (false negatives) from screening are almost all pancreatic sufficient with minimal lung disease, and may have a consequent delay in diagnosis. 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. 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. 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.

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. ∆F508); 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 with and mild phenotypes. There are, in addition, a number of CFTR polymorphisms associated with mild phenotypes, particularly the number of TG repeats in IVS8.

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. 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 sinonasal 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.

In this issue of Thorax De Boeck et al. 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 to 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...
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. 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