



Diagnosing cystic fibrosis in South Africa

Cystic fibrosis (CF) occurs in all South Africa's population groups. While well described in the white and coloured populations, its presence in black African populations is less well known. Recent evidence from the group of CF patients in the Western Cape suggests an incidence of 1 in 3 000 and 1 in 10 300 live births in the white and coloured populations respectively.¹ In black South African populations, carrier frequency estimates have been used to project an incidence of 1 in 4 624 live births.² Further evidence of the presence of CF in these populations is presented in this issue of the *Journal*.³

While considering or being aware of the diagnosis is the first step in identifying CF, diagnosing the disease presents challenges at clinical and laboratory levels in South Africa. In simple terms, the diagnosis of CF requires a patient to have suggestive clinical features as well as 2 positive sweat tests and/or 2 identified disease-causing CF transmembrane conductance regulator (CFTR) gene mutations.

The classic triad of clinical features associated with CF consists of recurrent or persistent respiratory symptoms, pancreatic insufficiency and poor weight gain. A recent study of 181 CF patients in South Africa showed that only 4.6% of patients had all 3 features at presentation. Only one-third had recognised malnutrition and one-third of patients did not have respiratory symptoms at the time of diagnosis.⁴ The range of symptoms that may suggest CF is very wide. In the fetus or neonate there may be intestinal obstruction; infants may present with anaemia and oedema, hypochloraemic metabolic alkalosis, rectal prolapse, severe 'bronchiolitis', or conjugated hyperbilirubinaemia; children may have nasal polyposis or uncontrolled 'asthma'; adults may present with bronchiectasis, chronic obstructive airways disease, recurrent pancreatitis or infertility.⁵ Therefore only thinking of CF in certain ethnic groups or when features of the classic triad of CF are present will result in too low an index of suspicion for CF in South Africa.

Once CF is suspected, the diagnosis should be confirmed or refuted. In South Africa, reliable sweat testing, the gold standard, is only available in major centres and it can be difficult to collect enough sweat in young infants. Molecular testing for CFTR gene mutations is often requested as a substitute. Without testing for multiple mutations, molecular testing in South African subjects is usually insufficiently sensitive to identify the diagnostic 2 CFTR mutations in true cases of CF.⁶ Even the most clear-cut scenario – testing for the commonest mutation in white persons, namely deltaF508 – yields a diagnostic genotype (deltaF508/deltaF508) in only 58% of white CF patients.⁶ If molecular testing is to be done, the South African panel of mutations as described in Goldman *et al.*⁶ should be tested for. These mutations (from

the more than 1 100 identified worldwide) have been shown to give the best results in South Africa at present, although further mutation detection studies are necessary to improve the detection rate in coloured and black African CF patients where the current mutation detection rates with the panel are 74% and 46%, respectively. Even using the panel, 16% of white CF patients, 38% of coloured CF patients and 50% of black CF patients will only have 1 identifiable CFTR mutation and some will have no mutation identified.⁶ Therefore the inability to identify 2 disease-causing CFTR mutations does not exclude the diagnosis of CF. Requesting molecular analysis instead of doing a sweat test may confirm a diagnosis of CF, but cannot exclude it. Molecular testing should be performed by a laboratory familiar with genetic testing, and in particular CF molecular testing, as the methodology and standardisation used and the interpretation of the result are crucial. Sweat testing that includes a chloride estimation must remain the gold standard for the diagnosis in South Africa.⁷ With the increasing evidence that CF occurs at a significant frequency throughout South Africa, sweat testing needs to be made more available. The accuracy of sweat conductivity in confirming the diagnosis of CF is unproven⁷ but it may be a useful screening test.

If molecular testing is done, the following potentially perplexing or problematic scenarios may confront the clinician. Only 1 CFTR gene mutation may be identified. There are 3 possibilities in this situation.

In the first scenario the patient has typical CF. Genetically such a patient is a compound heterozygote, having a different mutation in each of the 2 CFTR genes, only one of which is identified by molecular testing. In this situation, CF can and should be confirmed with a sweat test. Because of the importance of accurate diagnosis, the case should be discussed with an expert in CF, especially if sweat testing is not available. Pancreatic insufficiency, present in about 85% of typical CF cases, can be proved by testing a stool sample for faecal human pancreatic elastase-1.⁸ Typical micro-organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* may be found in respiratory secretions.

In the second scenario, the patient has atypical CF. In this situation, the patient often has mild symptoms and equivocal sweat test results. This patient is also a compound heterozygote but the unidentified mutation is responsible for the mild phenotype. The World Health Organization has classified a number of CFTR-associated clinical syndromes, only 2 of which are 'typical' CF.⁹ Again, such a patient should be discussed with an expert in CF. Sophisticated testing may be the only way to confirm the diagnosis. Symptomatic treatment, careful genetic counselling and follow-up are required.



The third scenario is that the patient has another disease and carries a CFTR mutation. Except in occasional cases of atypical CF, sweat electrolyte levels are rarely normal in CFTR-related disease. Carriers of a CFTR mutation have normal sweat electrolyte levels. The patient is identified as at risk of having a child with CF. This information should only be given to the patient in association with genetic counselling. If the patient is a child, the parents should be told that the testing has excluded CF. The child's carrier status should not be revealed to the parents.

Since molecular testing always carries the possibility of revealing carrier status, this situation should be anticipated and discussed with the child's parents before the test is done. The right of the child to decide in the future whether or not to know his or her carrier status at a time of his or her choosing is taken as paramount in current guidelines on the molecular testing of children.^{10,11} These guidelines are based on the ethical principle of non-maleficence, the presumption being, in the absence of clear evidence to the contrary,¹² that harms are likely to outweigh benefits in these situations. They also reflect the primacy of the best interests of the child as set out in the Convention on the Rights of the Child and the South African Constitution. Autonomy is another ethical principle that would be circumvented if such information were provided before the child was able to decide what he or she wished to know. Therefore the practitioner should counsel the parents on the purpose of the test, namely to confirm the diagnosis of CF. If fewer than 2 mutations are identified the test has simply not confirmed the diagnosis. The practitioner will need to decide whether it is appropriate to take the issue further with the patient when he or she grows up.

Practitioners in almost all fields of medicine in South Africa need to consider CF in the differential diagnosis of all patients presenting with common symptoms. The diagnosis should be confirmed with a sweat test and not by sweat conductivity alone. Molecular testing should include the South African panel of CFTR gene mutations as appropriate for the 'ethnic' origin of the patient. The potential meaning of the results

of such testing in different clinical situations needs to be understood.

The South African Cystic Fibrosis Consensus Document is available from the South African Cystic Fibrosis Association, PO Box 16891, Atlasville 1465.

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