CLINICAL PRACTICE

Cystic fibrosis in black patients: Western Cape experiences

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Cystic fibrosis (CF) in non-American black Africans has only been described in case reports. CF was first reported in a South African black child with meconium ileus in 1959.[1] Ten years later Levin and colleagues[2] described twins born to a Sotho mother and a Zulu father. One twin had meconium ileus, the other had pancreatic insufficiency.

Not long after the identification of the cystic fibrosis transmembrane conductance regulator (CFTR) gene in 1989, molecular genetics proved that CF in Africa was a CFTR mutation-based disease. A study of 3 CF cases in black South Africans included clinical data and the results of a systematic investigation of the CFTR gene in each case.[3] Four genes had the 3120+1G→A mutation that is significantly prevalent in African Americans. Another carried a different mutation (G1249E) and the last carried a previously unidentified 54 base pair deletion in exon 17a.

Subsequently Padoa and colleagues[4] searched for the 3120+1G→A mutation and 3 other mutations found in African Americans, among 208 San and 1 152 unrelated healthy black Africans from southern, western and central Africa. In southern African black groups, eight 3120+1G→A heterozygotes were found out of 728 subjects, giving a carrier frequency for this mutation of 1 in 91 (1.1%, 95% confidence interval (CI) 0.51 - 2.17%).

Given this prevalence, surprisingly few cases have been diagnosed. Is CF different in black African patients or is it not being thought of in patients with suggestive symptoms in South Africa's health services? Padoa and colleagues[4] suggested that black African CF cases might be dying diagnosed as having had malnutrition or pneumonia. The following sequence of 5 case reports from the Red Cross War Memorial Children's Hospital (RCCH) in Cape Town over 20 years illustrates the evolution of understanding of clinical CF among black Africans in South Africa.

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Case 1: 'Cystic fibrosis unlikely because of race', 1984

This child of a Xhosa-speaking mother presented at 2 months of age with anaemia and growth faltering. She was hypoproteinaemic and had a lower respiratory tract infection with peripheral airways obstruction. Weight gain in hospital was very poor and the respiratory infection persisted. Gastro-oesophageal reflux (GOR) was demonstrated. She was readmitted a month after discharge with another chest infection. A diagnosis of early kwashiorkor was also made. GOR was thought to be a significant factor in her chest disease although a pH study was negative. In view of persistent poor weight gain and chest signs a sweat test was performed (Table I). As this was abnormal, it was repeated. Tests for malabsorption were undertaken: fat globules were seen, tryptic activity was normal, and faecal fat testing was unsuccessful. The gastroenterology team felt that the child's ethnic origin made CF unlikely. She stayed in hospital for 6 months, gaining some weight on an elemental formula. By the time of discharge, 5 positive sweat tests had been obtained. After a 6th positive test, the CF clinic followed up the case but was unwilling to give a definitive CF diagnosis. Two more sweat tests were positive (Table I). At 2½ years of age, the child rapidly succumbed to a severe respiratory infection. Autopsy demonstrated a *Pseudomonas* pneumonia with air trapping. There were typical CF changes in the pancreas.

This child never received a positive diagnosis of CF and therefore could not benefit from definitive treatment. The diagnosis was proved by postmortem examination but was not taken further by way of family studies. A subsequent offer of genetic testing was turned down by the child's mother.

Case 2: 'Do a sweat test', 1993

This child presented at 3 months of age with pneumonia and failure to gain weight. His mother was Xhosa-speaking. His

Table I. Sweat test results for case 1

Sweat sodium (mmol/l)	Sweat chloride (mmol/l)	Sweat mass (mg)
82	134	162
67	108	131
83	122	157
73	96	280
68	101	374
73	102	386
78	110	427
95	131	206

father, said to be from the same group, had been murdered. Tests for tuberculosis (TB) were done and follow-up was arranged. The child presented soon afterwards with collapsed right middle and left lower lobes and severe air trapping. There was some response to broad-spectrum antibiotics but severe peripheral airways obstruction persisted. A pulmonologist requested a sweat test. The ward staff viewed this suggestion with incredulity but went ahead. The result was positive (sweat mass 77 mg, sodium (Na) 78 mmol/l, chloride (Cl) 114 mmol/l), as was a second test (sweat mass 153 mg, Na 94 mmol/l, Cl 104 mmol/l). Because he was a black African child, a third test was requested. It was also positive (sweat mass 299 mg Na 83 mmol/l, Cl 103 mmol/l). Molecular testing by the Department of Genetics at the South African Institute of Medical Research/National Health Laboratory Services (SAIMR/NHLS) in Johannesburg, with the help of colleagues in France, identified 2 CFTR mutations. One was the 'African mutation', 3120+1G→A, and the other was a unique mutation, 3196del54.[3] This child has shown a typical CF course with pancreatic insufficiency and *Staphylococcus aureus* and mucoid *P. aeruginosa* in the chest. He was 13 years old at the time of writing.

Case 3 now benefited from the RCCH's experience with CF in the Xhosa-speaking population.

Case 3: 'Not HIV, so what is the cause of the problem?', 1995

This infant, born in King Williamstown to Xhosa-speaking parents, had not grown since birth and was severely wasted. He had persistent changes on his chest radiograph, with marked air trapping. He had a firm hepatomegaly. He had been investigated for TB and HIV infection, with repeated negative results in Port Elizabeth and was transferred to RCCH for further testing. CF seemed likely despite the child's ethnicity and was proved within a few days – 2 sweat tests were positive (test 1: sweat mass 371 mg, Na 80 mmol/l, Cl 107 mmol/l; test 2: sweat mass 356 mg, Na 82 mmol/l, Cl 99 mmol/l), there was a high faecal fat level, and mucoid *P. aeruginosa* and *S. aureus* were grown from the sputum. The 3120+1G→A mutation was not present.

This case, following hard on the heels of case 2, was rapidly diagnosed at RCCH. The child's diagnosis brought the message of CF occurring in black African children to paediatricians in the Eastern Cape.

Case 4: A typical case in atypical 'race', 2001

This male child of Xhosa-speaking parents presented at age 2 years with repeated pneumonia and failure to thrive from 9 months of age. Investigations for TB and HIV were negative. He had had diarrhoea intermittently from infancy. On admission he had lung hyperinflation and respiratory distress. Chest radiograph confirmed air trapping and there were opacifications in the right upper lobe and perihilar regions. Sweat chloride was 52 mmol/l. Repeat tests showed variable (but abnormal) results (test 2: sweat mass 209 mg, Na 101 mmol/l, Cl 94 mmol/l; test 3: mass 220 mg, Na 53 mmol/l, Cl 45 mmol/l). Tests for fat malabsorption were unsuccessful. Mutation analysis covering common South African mutations including 3120+1G→A was negative. CF was thought probable but was not proved. With a respiratory infection 2 months later, mucoid *P. aeruginosa* was grown from his sputum, increasing the likelihood of CF. The patient was treated with pancreatic enzyme supplementation, nutritional advice and physiotherapy. A year later, during which time he had had a few mild respiratory infections and had gained weight, a 4th sweat test was again equivocal (test 4: sweat mass 265 mg, Na 56 mmol/l, Cl 55 mmol/l). His radiograph showed persistent air trapping and perihilar infiltrates.

With this patient, CF in black Africans joined the mainstream – recurrent chest infections leading to an investigation of CF and a complex of suggestive symptoms and test results but no absolute proof. Ethnicity was no longer a factor against the diagnosis.

Case 5: Typical presentation in infancy; instant diagnosis, 2003

This male infant of Xhosa-speaking parents presented at 2 months of age with dehydration and diarrhoea. There were no chest signs or symptoms and no significant family history. Investigation revealed a hypochloraemic metabolic alkalosis. Sweat tests were requested by junior doctors in the Rehydration Unit and the diagnosis of CF was confirmed. Mutation analysis showed the child to be a compound heterozygote with 1 copy of the 3120+1G→A mutation.

This encouraging case illustrates that CF is part of the differential diagnosis of all children, irrespective of ethnic origin, presenting with suggestive features in contemporary Cape Town. The challenge presented 22 years ago when case 1 was born has begun to be met – CF occurs in black Africans and is being considered in appropriate clinical situations by non-experts.

Since this article was written, a 6th child, presenting with respiratory signs and growth faltering, has been diagnosed at 7 weeks of age.

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