Misdiagnosis of cystic fibrosis

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SUMMARY On reassessment of 179 children who had previously been diagnosed as having cystic fibrosis seven (4%) were found not to have the disease. The importance of an accurate sweat test is emphasised as is the necessity to prove malabsorption or pancreatic abnormality to support the diagnosis of cystic fibrosis.

During the past six years we have provided a referral service for children and adults with cystic fibrosis in the Yorkshire region. They are referred by the consultant undertaking their long term care for a comprehensive assessment.

We describe seven children who had been diagnosed as having cystic fibrosis and who were receiving treatment. The diagnosis was not confirmed and we suggest ways by which such mistakes can be avoided.

Patients

Table 1 gives details of the seven children who were referred from different district hospitals. They had been diagnosed as having cystic fibrosis and treated for periods ranging from five months to eight years. All seven had received daily physiotherapy and six

were taking pancreatic supplements and antibiotics regularly. Three were on low fat diets. The commonest reasons for diagnosing cystic fibrosis were recurrent chest infections and failure to thrive. One child had a sibling with cystic fibrosis and another a maternal cousin with the disease.

All seven children were considered to have abnormal sweat tests at the time of the original diagnosis. Four (cases 1–4), however, had at least one equivocal sweat test result. Five children were over the age of 3 when the diagnosis was made. Three children had no gastrointestinal symptoms and of three who had trypsin or chymotrypsin activity estimated in the faeces, only one (case 1) was abnormal.

Results

Table 2 shows the results obtained during reassessment at our unit. All the children had normal sweat tests with sodium and chloride concentrations of less than 60 mmol/l.

All seven children had chymotrypsin activity estimated in faeces after pancreatic supplements had been stopped and the results were within the normal range (120 µg/g or above). Six children had their faecal fat output estimated and all were normal. Faecal fat output was determined using a non-

Table 1 *Clinical details of children wrongly diagnosed as having cystic fibrosis*

Case No	Age at initial diagnosis (years)	Symptoms	Original sweat tests (mmol/l)		Duration of treatment of cystic fibrosis	Other factors
			Sodium	Chloride		
1	9 months	Chest infections	82	30	8 years	Low faecal trypsin activity
2	1½	Failure to thrive; chronic diarrhoea; abdominal distension	98	65	2 years	Mental handicap
3	3	Failure to thrive; recurrent chest infections; offensive stools	56	37	8 months	
			62	46	4 years	Maternal cousin had cystic fibrosis
			88	67		
			75	55		
4	3½	Failure to thrive; recurrent chest infections	67	68	5 years	—
			70	57	6 months	
			53	32		
5	3½	Recurrent chest infections; persistent cough	80	66	3 months	—
			109	77		
6	4	Underweight; recurrent abdominal pain	119	96	3½ years	Sibling had cystic fibrosis
7	7	Recurrent chest infections; offensive stools; underweight	130	115	3 months	—
			175	117		

Table 2 *Results of reassessment of children wrongly diagnosed as having cystic fibrosis*

Case No	Sweat tests (mmol/l)		Faecal chymotrypsin activity µg/g	Faecal fat excretion gm/day	Result of ultrasonography of pancreas	Vitamins (µmol/l)		Suspected diagnosis
	Sodium	Chloride				A	E	
1	45 32	29 23	225 188 225	2.0	Not done	2.4	25	Asthma
2	32 35	24 24	530	Not done	Pancreas not visualised	1.14	14.7	Failure to thrive; mental handicap
3	33 48	29 28	370	0.9	Mildly abnormal	5.1	41	Asthma
4	48	29	120	3.0	Normal	1.5	12.3	Failure to thrive; recurrent chest infections
5	30 32	16 11	725	2.7	Normal	1.4	22.3	Recurrent chest infections
6	56 43	50 40	240 840	1.7	Normal	1.5	9.5	Normal child
7	44 58	29 47	280 520	1.1	Normal	3.42	24.3	Small asthmatic child
Normal ranges	<60	<60	>120	<5g	Normal	2.83 (1.8) mean (SD)	17.6 (4.0)	

absorbable faecal marker, polyethylene glycol 4000, (250 mg or 500 mg three times daily for seven days). Fat and polyethylene glycol were estimated in the stools collected on days 6 and 7, and the daily faecal fat then corrected to the equivalent of 750 mg or 1500 mg of polyethylene glycol daily. Although in five cases this was done while the children were taking pancreatic supplements (case 7 was not receiving pancreatic supplements) their outputs of fat were low and not characteristic of patients with cystic fibrosis receiving treatment. Five children had ultrasound examinations of the pancreas of which only one was possibly abnormal. Fat soluble vitamin concentrations were estimated in all seven patients after they had fasted and omitted their daily supplements. Five had mean (SD) vitamin E concentrations well within the normal range (17.6 (4.0) µmol/l) and all seven had mean (SD) vitamin A concentrations within the normal range (2.83 (1.8) µmol/l). Although the children were receiving routine vitamin supplements, none was taking more than 4000 IU of vitamin A daily and none was taking supplementary vitamin E.

The commonest suspected final diagnosis was asthma. In each case the referring paediatrician and the parents were told that the child did not have cystic fibrosis. In the two cases in which there was a family history of the disease the parents refused to accept the reversal of the diagnosis. The parents of one child who had received considerable welfare benefits and a trip to Disneyland in Florida because she had cystic fibrosis attempted to sue the referring paediatrician. When they finally

accepted the reversal of the diagnosis the child featured in a daily newspaper article which proclaimed that she had been cured of cystic fibrosis. The mother of the other child transferred his care to another paediatrician. Both children had been admitted to hospital on several occasions and one of them had been treated with an aminoglycoside intravenously.

Discussion

These seven children were incorrectly diagnosed as having cystic fibrosis because of initially abnormal sweat tests, respiratory tract symptoms, and other suggestive features. All sweat tests were normal when they were repeated at the regional referral unit, and a combination of indirect tests of pancreatic function strongly suggested that there was no pancreatic insufficiency.

Misdiagnosis of cystic fibrosis has been previously reported by Smalley *et al* in 14 children because of initially abnormal sweat tests.¹ They emphasised the importance of testing pancreatic function in the absence of typical clinical features. David *et al* reported seven patients in whom cystic fibrosis had been wrongly diagnosed, but surprisingly only three had abnormal initial sweat tests.²

Although a stimulated pancreatic function test using intravenous pancreozymin and secretin is the definitive test for confirming normal pancreatic function, there are several non-invasive methods which have reduced the need for this.³

Chymotrypsin activity in faeces is usually low in

untreated patients with cystic fibrosis at any age. It is more stable than trypsin in the faeces and less likely to result in false low values. Faecal collections for fat estimation are difficult but are essential if malabsorption of fat is to be proved. The diagnosis should be questioned if the faecal fat output is normal. Estimation of the concentrations of fat soluble vitamins is another useful indirect method of indicating the presence of a gastrointestinal lesion. In a previous study 28 of 30 children with cystic fibrosis who were not receiving vitamin E supplements had plasma concentrations more than two standard deviations below the control mean.⁴ In virtually all children with cystic fibrosis over the age of five years the pancreas looks abnormal on ultrasonography.

Although 5–10% of patients with cystic fibrosis do not have clinical pancreatic dysfunction, 5–10% have mild and 85% have severe pancreatic disease.⁵ The fact that the pancreatic function tests, although indirect, were normal in our patients is strong evidence against a gastrointestinal lesion and therefore the diagnosis of cystic fibrosis.

The most common diagnostic error is the uncritical acceptance of an abnormal sweat test. It is important that this test is performed by a laboratory used to carrying out the investigation and that the results are interpreted correctly in the light of the patient's age, clinical findings, and additional investigations. It is also important to analyse the chloride as well as the sodium content of the sweat, as in patients with cystic fibrosis whose sweat electrolytes are equivocal (50–70 mmol/l) the chloride concentration is usually higher than the sodium concentration, whereas in normal subjects the reverse is the case.⁶

The implications of an incorrect diagnosis of cystic

fibrosis can be extensive, the children receiving unnecessary treatment and investigations. In addition to the anxiety generated by such a diagnosis and worries regarding the child's future, there are genetic implications that may influence decisions about further pregnancies.

It is important, therefore, to reconsider the diagnosis where typical clinical features are either not present or only mild, and to have two reliable sweat tests as well as evidence of malabsorption or pancreatic abnormality (preferably both). We suggest that the sweat test should be repeated and the diagnosis reviewed in all patients with cystic fibrosis about one year after the initial diagnosis. Evaluation of problems in diagnosis is an important function of a cystic fibrosis referral centre.

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Cerebral arteriovenous malformation in a neonate: treatment by embolisation

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SUMMARY A neonate with an aneurysm of the vein of Galen was treated by embolisation using Gianturco coils. Doppler ultrasound examination showed that blood flow in the internal carotid artery

decreased while that in the pericallosal artery increased after occlusion, suggesting a 'steal phenomenon' with blood directed preferentially towards the aneurysm.