Neonatal screening for cystic fibrosis

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SUMMARY Two groups of patients with cystic fibrosis were compared. The screened group, detected with an improved neonatal screening assay for immunoreactive trypsin, developed fewer chest infections requiring treatment and gained more weight than the unscreened group. Early diagnosis by screening seems to affect early morbidity.

Neonatal screening for cystic fibrosis by dried blood spot has been undertaken at several centres since the development of the serum immunoreactive trypsin (IRT) assay by Crossley *et al* in 1979.[1] This test has been improved, notably by the human trypsinogen monoclonal antibody assay (HTMAB),[2] and it is effective and specific with acceptably few false positive and false negative results.[3 4] Nevertheless, controversy exists as to whether the long term benefits[5] of screening outweigh the economic and psychosocial costs.[6]

We report our experience with neonatal screening for this disease and compare the clinical progress during the first two years of life of a cohort of 28 patients with cystic fibrosis diagnosed by screening with a cohort of 23 patients who were clinically diagnosed. They were matched as closely as possible in terms of age and management.

Methods and results

Neonatal screening was introduced as a six month pilot study in two obstetric hospitals in Brisbane, Queensland in December 1982 (where 45% of Queensland births take place), and it was thereafter exended to all births throughout the state. Until December 1986 180 000 newborn babies were tested by the IRT assay method of Crossley *et al*; the last 45 000 babies were also tested by the HTMAB assay. Since July 1982, 99·9% of all newborn babies in Queensland have been tested. Table 1 shows the results and details of the programme. After a persistently raised IRT concentration diagnosis was confirmed at one month of age by at least three sweat tests (using pilocarpine iontophoresis for sample collection). Patients were managed by a centralised and standardised management programme for cystic fibrosis that was coordinated jointly from the two main paediatric teaching hospitals in the State of Queensland (Royal Children's Hospital and Mater Children's Hospital). During the study period no important changes in management protocol or philosophy of management occurred.

A comparison was made between two unselected cohorts of children with cystic fibrosis, who were born in Queensland between January 1980 and July 1985, with particular reference to illness during the first two years of life. The first cohort of 'unscreened' children (n=23) were born between January 1980 and July 1983 and were subsequently diagnosed clinically ranging from 0 months to 3·3 years (mean 0·6 years). The second cohort of 'screened' children (n=28) were born between December 1982 and July 1985. Patients presenting with meconium ileus were not included. Three (13%) patients in the unscreened group were (relatively) asymptomatic at diagnosis because they were diagnosed only after a sibling index case was found by screening. Clinical data concerning the first two years of life were collected retrospectively in both groups by a combination of data from the cystic fibrosis clinic medical record review, parent interview, and postal questionnaire. A comparison between the two groups is shown in table 2 and indicates items where a difference was found. No

Table 1 *Details of the cystic fibrosis neonatal screening programme in Queensland*

	Immunoreactive trypsin assay	*Human trypsinogen monclonal antibody assay*
Total No screened	180 000	45 000
Resample rate	8/1000	4/1000
Rate at which children are referred for clinical evaluation	3·6/10 000	3·5/10 000
Predictive value positive at one month (probability affected)	0·85	0·9
False reassurance rate (cases missed)	0·23/10 000	—

Table 2 *Comparison of closest possible match of patients with cystic fibrosis diagnosed during the screening programme with those diagnosed clinically with particular reference to morbidity in the first two years of life*

	Screened (n=28)	*Unscreened (n=23)*	*Result of statistical analysis*
Male/Female ratio	1·5/1·0	1·3/1·0	
Age at diagnosis (in years) mean (range)	0·1 (0·02–0·12)	0·6 (0·03–2·3)	
Symptoms at diagnosis No (%) patients	3 (14)	21 (91)	p<0·001 Fisher's exact test
Average time from onset of symptoms to diagnosis (years)	—	0·5	
Medical consultations before confirmed diagnosis (No (%))			
None	26 (93)	2 (9)	
1–2	2 (7)	5 (22)	p<0·001
3–10	0	7 (30)	χ^2=3·77
≥11	0	9 (39)	
Treated chest infection at 2 years of age (No (%))			
Up to 2	19 (68)	9 (39)	χ^2=5·56
3–10	9 (32)	12 (52)	p<0·1>0·05
≥11	0	2 (9)	p<0·025 Fisher's exact test
Hospital admissions at <2 years of age (No (%))*			
Up to 2	20 (72)*	16 (70)	
3–5	41 (14)	5 (22)	NS
6–10	4 (14)	2 (9)	χ^2=0·739
Mean (SD) body weight (kg)			
Birth	3·2† (0·14)	3·1 (0·42) (n=22)	NS
6 months	7·0 (1·1)	6·3 (0·70) (n=15)	p<0·001 (Student *t* test)
12 months	9·5 (1·28)	9·0 (1·15) (n=13)	NS
24 months	12·3‡ (1·35)	11·8 (1·59) (n=20)	

*All screened patients had an initial routine admission for assessment and education. All patients were managed concurrently by a co-ordinated cystic fibrosis clinic. Patients with meconium ileus were excluded from both groups.
†Twenty fifth percentile.
‡Fiftieth percentile.

differences were found in sex ratio, birth weight, or number of hospital admissions, but significant differences were observed in the age of diagnosis, time from onset of symptoms until diagnosis, the number of medical consultations before diagnosis, and the number of treated chest infections in the first two years of life. Body weight (where known) was on average on the 25th percentile at birth in both groups, but it was significantly lower in the unscreened population at 6 months of age. By 2 years the mean body weight of the screened group was at the 50th percentile with the mean weight of the unscreened group remaining on the 25th percentile.

Discussion

Our data indicate the improving sensitivity and specificity of the screening test for cystic fibrosis with advances in the technique, and they provide evidence in support of continuation of the programme. The data, however, need to be interpreted with due consideration that the screened and unscreened cohorts were not exactly comparable, and there is the possibility that data from undiagnosed, possibly less severe cases of cystic fibrosis in children who were born during the study period were missed. Because of the age overlap of a number of cases in both groups, the older mean age of diagnoses but earlier birth dates in the unscreened group, and the concurrent management of both groups this was not a sequential study; a fact which disadvantaged earlier investigations. This, plus some data that might have been missed in the unscreened group (by virtue of diagnosis of asymptomatic cases in siblings of index cases diagnosed during the screening programme) gives confidence in comparing progress in the two groups.

We therefore agree, overall, with the conclusion from the only similar published study to date, that neonatal screening for cystic fibrosis reduces morbidity in the first two years of life.[6] The data

indicate fewer medical attendances, fewer treated respiratory chest infections, and improved overall weight gain in the screened population. We did not find significantly fewer hospital admissions. The number of days in hospital, which have been variously reported as reduced[6] or increased,[5] were not analysed. All of our screened patients were briefly admitted on diagnosis for assessment and education about their condition. The later age of diagnosis and possible lesser awareness of the importance of recognising symptoms before diagnosis in the unscreened group might have accounted for the similar admission rates in the first two years of life.

As yet there have been no adequate studies of the psychosocial implications of neonatal screening for cystic fibrosis. The potential effects of the resampling and false postive results[5] and the effects of diagnosing the disease in 'well' babies have to be considered against the observed findings in this study of repeated medical consultations and delay in diagnosis in a sick child; there is also the advantage with earlier diagnosis of genetic counselling. The psychosocial disadvantages of screening are becoming less obvious now that there is a reduced need for resampling and an increase in the predictive value of a positive result (resulting from more specific assays). There is also increasing experience with the approach to diagnosis in 'well' babies, and conversely the avoidance of delayed diagnosis now that fetal genetic diagnosis is possible.

In conclusion, the published results of screening for cystic fibrosis indicate that screening programmes deserve wider application and study.[1 4 6] In particular, as both repeated pulmonary infections and relative underweight are important adverse prognostic indicators in cystic fibrosis, a reduced morbidity should be regarded as one of the primary advantages of screening.

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Cognitive development in transposition of the great vessels

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SUMMARY Ten children who had had transposition of the great vessels (TGV) repaired, deep hypothermia, and cardiac arrest were examined. Seven children with acyanotic heart disease and 12 unaffected siblings were tested for comparison. Their intelligence, academic achievement, and behaviour was studied. The group with TGV had lower performance subscores on the intelligence test, an increase in somatic complaints, and aggressive behaviour.

Survival of children with transposition of the great vessels (TGV) improved substantially with the advent of balloon atrial septostomy[1] and intracardiac baffle.[2] Children with TGV may have associated hemiplegia due to cerebrovascular accidents,[3] or a dyskinetic movement disorder due to anaesthetic hypothermia and cardiac arrest,[4] or delayed development related to restricted cardiac reserve and chronic hypothermia and parental imposition of restrictions of the child's activities.[5] The severe neurological damage some children have made us question whether seemingly unaffected