Cystic fibrosis in Asians

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Abstract

The clinical course of cystic fibrosis in nine Pakistani Asians was compared with 18 non-Asian age and sex matched controls. The Asian patients grew *Pseudomonas aeruginosa* at an earlier age (4.0 v 7.5 years), tended to have lower respiratory function test results (forced vital capacity 58.5 v 76.8% predicted; forced expiratory volume in one second 79.8 v 100.3% predicted), and had significantly greater concentrations of immunoglobulin IgG (13.4 v 10.1 g/l). They had a lower weight for age (78.4 v 95.7%) and weight for height (90 v 98.5%) despite similar intakes of dietary energy. Four of the nine Asians carried the δ F508 mutation compared with 17 of 18 controls. All the Asian patients were born in the UK; seven of their mothers were born in Pakistan and had moderate or severe difficulties with the English language. It is concluded that Asian patients may have a more severe clinical course than matched controls and that genetic and environmental factors may be contributory.

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There are few reports of cystic fibrosis affecting people of Asian origin.^{1 2} It is our impression that cystic fibrosis management problems are more common in Asian patients compared with those born to non-Asian families.

The present study analyses our experience with nine Pakistani Asians with cystic fibrosis.

Patients and methods

Nine Asian patients with cystic fibrosis have been seen at the Leeds regional cystic fibrosis unit (six boys, three girls; mean age 10.7 years, range 0.96-22.5 years). Their diagnosis was confirmed by typical clinical features and sweat sodium and chloride values greater than 60 mmol/l.³

For each Asian patient two age and sex matched non-Asian controls with cystic fibrosis were selected; all had birth dates within 11 months of the index subject. The case notes and computerised database for all the subjects were reviewed.

Pulmonary disease was assessed (when possible) from the forced vital capacity and forced expiratory volume in one second using a Vitalograph compact spirometer. The measurements were compared with known standards for age, height, and gender.⁴ The patients' most recent immunoglobulin IgG concentration was

used. A recent chest radiograph was scored by two observers using the method of Chrispin and Norman,⁵ and the Shwachman score, a clinical index of disease severity, was determined for each patient.⁶

Growth was assessed from the most recent measurements and percentage weight for age, height for age, and weight for height were calculated on a desktop computer using the standards of Tanner and Whitehouse.⁷ The patients' most recent dietary assessment was used to estimate energy intake. Faecal fat was analysed by the method described elsewhere.^{8 9} Compliance was estimated from a consensus view of members of the cystic fibrosis team, taking into account the families' understanding of cystic fibrosis and how well treatment recommendations appeared to be carried out. Genomic DNA analysis was performed on all patients to determine the presence of the δ F508 mutation.

The results were compared using the Mann-Whitney U test and Fisher's exact test where appropriate.

Results

DIAGNOSIS

The mode of presentation for the groups was similar. Only one Asian patient presented with meconium ileus. The sibling of another Asian patient died of this complication in the neonatal period. Five controls and two Asian patients were detected by neonatal screening, which has been undertaken at our hospital since 1977.¹⁰ A sweat test was performed on one control patient because his sibling was known to have cystic fibrosis. The remaining patients presented with chest symptoms (3/9 v 2/18) or with gastrointestinal symptoms, including failure to thrive (3/9 v 9/18). When the patients diagnosed by screening were excluded there was no significant difference in the age of onset of symptoms (0.1 v 0.06 years), the age at diagnosis (0.83 v 0.5 years), or the diagnostic delay (0.42 v 0.32 years).

RESPIRATORY DISORDERS

The forced expiratory volume in one second (58.5% predicted v 76.8%) and the forced vital capacity (79.8% predicted v 100.3%) were lower in the Asian patients, but these differences were not significant. Six of the Asian patients and 13 of the controls were able to perform respiratory function tests satisfactorily. Only one Asian patient was receiving either prednisolone by mouth or inhaled budesonide or beclomethasone

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treatment for symptoms of bronchial lability compared with five controls.

Pseudomonas aeruginosa had been isolated from the sputum of six of the Asian patients and 13 of the controls. This had occurred at a significantly younger age in the Asian subjects (4.0 v 7.5 years; $p<0.05$). None of the Asian patients had grown *Xanthomonas maltophilia* compared with two of the controls, and no patient from either group had grown *Pseudomonas cepacia*. The level of serum immunoglobulin IgG was significantly greater in the Asian patients (13.4 v 10.1 g/l; $p=0.01$). An additional diagnosis of hypogammaglobulinaemia has since been made in one of the control patients; her IgG concentration was not included in this comparison. The median Chrispin-Norman chest radiograph scores were similar for the two groups (5 v 6). The median Shwachman clinical scores were lower in the Asian patients (80 v 90; $p=0.07$) and respiratory disease was the most important factor accounting for this.

NUTRITION AND GASTROINTESTINAL

The weight for age of the Asian patients was significantly less than the controls (78.4 v 95.7%; $p<0.05$), as was the weight for height (87.0 v 98.8%; $p=0.01$). There was no significant difference in height for age (94.7 v 97.4%). There was also no significant difference between the energy intake at the most recent dietary assessment (111 v 120.5% of estimated average requirements¹¹; $p=0.3$). The groups were taking similar numbers of pancreatic enzymes (20 v 24.5) and there was no significant difference in their faecal fat outputs (11.9 v 13.6 g/day).

COMPLICATIONS AND GENETICS

There were surprisingly few complications of cystic fibrosis in the Asian patients (table). One Asian child whose cystic fibrosis presented with meconium ileus was noted to have hepatomegaly in the neonatal period. This has not subsequently resolved. His sibling, born to the same consanguineous parents, does not have cystic fibrosis but has severe and as yet unexplained liver disease.

Two Asian patients had other genetic disorders. One had glucose-6-phosphate dehydrogenase deficiency and the second had distal renal tubular acidosis and β thalassaemia trait. The latter patient has been the subject of a previous report.¹² Four of the nine Asian patients carry the $\delta F508$ mutation (all homozygotes) compared with 17 of 18 controls (12 homozygotes).

Complications in Asians and controls with cystic fibrosis

Complication	No of patients with complications at any one time	
	Asians	Controls
Liver disease		
Clinical	1	4
Biochemical	1	2
Distal ileal obstruction syndrome	1	4
Glucose intolerance or diabetes mellitus	0	0
Allergic bronchopulmonary aspergillosis	0	1
Nasal polyps	0	4
Rectal prolapse	0	3
Pseudo-Bartter's syndrome	0	3

SOCIAL AND ENVIRONMENTAL FACTORS

Four of the nine Asian patients were considered to be poor clinic attenders compared with six of the controls. Three Asians had prolonged periods without regular medical care, two as a result of visits to Pakistan. The chest disease of one and the weight centile of another deteriorated considerably during these periods away from specialist cystic fibrosis care. More of the Asian families were considered to be either moderate or severe non-compliers with treatment (6/9 v 6/18). There was no difference in the median number of admissions to hospital over a 24 month period for the two groups (three v one).

The Asian patients were all born in the UK. Two pairs are cousins. They come from significantly larger families than the non-Asian group (median number of siblings: three v one; $p<0.05$). Their families originate from Pakistan where seven of their mothers and six of their fathers were born. Whereas all the fathers now have no difficulties communicating in English, all their mothers continue to have at least moderate communication difficulties.

All nine Asian families are social class III, IV, or V, compared with 14 of the 18 controls.¹³ Five of the parents of the Asian patients are unemployed and the fathers of the other four are employed as an engineer, a butcher, a taxi driver, and a factory worker. None of the Asian families were considered to live in unsatisfactory housing and smoking was significantly less common in the Asian families (1/9 v 14/18; $p<0.05$).

Discussion

Cystic fibrosis is the most common potentially lethal genetic disorder in white populations, but it is considerably less prevalent in other ethnic groups. Several reports suggest differences of expression of cystic fibrosis in non-whites and these have been recently documented in North American black subjects.¹⁴⁻¹⁶ Descriptions of cystic fibrosis in Asians are few, however. Goodchild *et al* reported three Asian children from the West Midlands and estimated an incidence of cystic fibrosis in Asians of approximately 1:10 000.¹ Schwarz *et al* found that three of six patients in Lancashire Pakistani families carried the $\delta F508$ mutation²; all were homozygotes.

Our small study suggests that this group of Asian patients may have a more severe clinical course than matched non-Asian controls. *P. aeruginosa* was grown from sputum at a significantly earlier age in the Asian patients and this may adversely affect prognosis.¹⁷ Increased serum IgG concentrations also suggest increased activity of the chest infection,¹⁸ as do the reduced respiratory function tests and Shwachman scores.

As a group the Asian patients were significantly underweight, which has been recognised as an important prognostic factor in cystic fibrosis.^{19 20} This does not appear to be due to more severe intestinal malabsorption or reduced energy intake. Increased energy utilisation as a result of more severe pulmonary disease²¹ and genetic factors may have contributed to their lower weight.

Tanner-Whitehouse standards were used in this study in the absence of more specific reference data for UK Asians. In Indian children, however, in the 0–5 year period it has been suggested that socioeconomic and environmental factors determine differences of growth performance rather than genetic factors and therefore Tanner-Whitehouse standards can be used for Indian children.^{22–23} Nevertheless, this does not indicate that Tanner-Whitehouse standards are necessarily applicable to other ethnic groups.²⁴

Genetic factors may be important in determining differences between the groups. Since the cystic fibrosis mutation was located in 1989^{25–27} many studies have sought to correlate clinical phenotype with the genotype of the patient with cystic fibrosis. The most common cystic fibrosis mutation, known as $\delta F508$, has its highest incidence in northern Europe and the USA.²⁸ A total of 78.5% of cystic fibrosis mutations are accounted for by $\delta F508$ in native English subjects from north west England.² Only four of the Asian patients studied carried the $\delta F508$ mutation; all were homozygous and two were cousins. Five Asians did not carry this mutation. The presence of cystic fibrosis mutations other than $\delta F508$ may have contributed to the differences of clinical phenotype in the Asian group studied.

The distribution of cystic fibrosis mutations in the Asian population is likely to be strongly influenced by a high incidence of parental consanguinity,²⁹ moreover it increases the probability of other genetic disorders, which were found in two children. This contrasts with the small number of complications of cystic fibrosis observed among the Asian patients. Other genetic diseases in addition to cystic fibrosis should be carefully considered in Asian patients.

Social and environmental factors are also likely to have contributed to the differences observed. All seven of the mothers born in Pakistan had moderate or severe communication problems in English. Communication difficulties render education of the Asian family considerably more difficult even when interpreters are available. It may also delay the presentation for treatment during acute respiratory exacerbations of cystic fibrosis, increasing the likelihood of pulmonary damage. No significant delay was noted between the initial onset of symptoms and the clinical diagnosis of cystic fibrosis in the Asian patients, but our study numbers were small and neonatal screening prevented delays in the diagnosis of two Asian patients and four controls. Language difficulties could delay counselling for the prenatal diagnosis of cystic fibrosis and may impede families obtaining state benefits, exacerbating financial hardship.

All of the Asian families were social class III, IV or V, compared with 14 of the 18 controls. This may have been a source of bias in our study.³⁰ None of the Asian families lived in poor housing conditions, however, and the adverse factor of tobacco smoking at their homes was uncommon.

We conclude that Asian patients may have a

more severe clinical course than matched controls and that genetic and environmental factors may be contributory. These families should be given additional help from the cystic fibrosis team to assist in overcoming language and cultural difficulties. A social worker from the same ethnic background as the patient is desirable.

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- Goodchild MC, Insley J, Rushton DI, Gaze H. Cystic fibrosis in three Pakistani children. *Arch Dis Child* 1974;**49**:739–41.
- Schwarz MJ, Super M, Wallis C, et al. $\delta F508$ testing of the DNA bank of the Royal Manchester Children's Hospital. *Hum Genet* 1990;**85**:428–30.
- Gibson LF, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilising pilocarpine iontophoresis. *Pediatrics* 1959;**23**:545.
- Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards*. Philadelphia: Saunders, 1971.
- Chrispin AR, Norman AP. The systematic evaluation of the chest radiograph in cystic fibrosis. *Pediatr Radiol* 1974;**13**:101–6.
- Shwachman H, Kulczycki LL. Long term study of one hundred and five patients with cystic fibrosis. *AMA J Dis Child* 1958;**96**:6–15.
- Tanner J, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity and stages in puberty. *Arch Dis Child* 1976;**51**:170–9.
- Van de Kamer JH, Bokkel Huinink H ten, Weyers HA. Rapid method for the determination of fat in faeces. *J Biol Chem* 1949;**177**:347–55.
- Gilbert J, Kelleher J, Walters MP, Littlewood JM. Markers for faecal fat estimation in the monitoring of steatorrhoea in cystic fibrosis. *Gut* 1988;**29**:1286–8.
- Evans RT, Little AJ, Steel AE, Littlewood JM. Satisfactory screening for cystic fibrosis with the BM meconium procedure. *J Clin Pathol* 1981;**34**:911–3.
- Department of Health. *Dietary reference values for food, energy and nutrients for the United Kingdom*. London: HMSO; 1991. Reports on health and social subjects: 41.
- Fallon JS, Brocklebank JT, Simmonds EJ, Littlewood JM. Cystic fibrosis and renal tubular acidosis. *Arch Dis Child* 1989;**64**:1054–5.
- Office of Population Census and Surveys. *Classification of occupations*. London: HMSO; 1980.
- Kulczycki LL, Schauf V. Cystic fibrosis in blacks in Washington, DC. *Am J Dis Child* 1974;**127**:64–7.
- Stern RC, Doershuk CF, Boat TF, Tucker AS, Primiano FP, Matthews LW. Course of cystic fibrosis in black patients. *J Pediatr* 1976;**89**:412–7.
- McColley SA, Rosenstein BJ, Cutting GR. Differences in expression of cystic fibrosis in blacks and whites. *Am J Dis Child* 1991;**145**:94–7.
- Wilmott RW, Tyson SL, Matthew DJ. Cystic fibrosis survival rates. *Am J Dis Child* 1985;**139**:669–71.
- Wheeler WB, Williams M, Matthews WJ, Colten HR. Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels: a 5-year longitudinal study. *J Pediatr* 1984;**104**:695.
- Kraemer R, Rüdeberg A, Hadorn B, Rossi E. Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand* 1978;**67**:33–7.
- Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr* 1982;**100**:857–62.
- Vaisman N, Pencharz PB, Corey M, Canny GJ, Hahn E. Energy expenditure of patients with cystic fibrosis. *J Pediatr* 1987;**111**:496–500.
- Agarwal KN, Agarwal DG, Benkappa SM, et al. *Growth performance of affluent Indian children (under fives)*. New Delhi: Nutrition Foundation of India; 1991. Scientific report: 11.
- A measure of agreement on growth standards [Editorial]. *Lancet* 1984;**i**:142–3.
- Black J. Growth performance of affluent Indian children under 5 years of age. *Arch Dis Child* 1992;**67**:666.
- Rommens JM, Ianuzzi MC, Kerem B-S, et al. Identification of the cystic fibrosis gene; chromosome walking and jumping. *Science* 1989;**245**:1059–65.
- Riordan JR, Rommens JM, Kerem B-S, et al. Identification of the cystic fibrosis gene; cloning and characterisation of complementary DNA. *Science* 1989;**245**:1066–73.
- Kerem B-S, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene; gene analysis. *Science* 1989;**245**:1073–80.
- The cystic fibrosis genetic analysis consortium. Worldwide survey of the $\delta F508$ mutation. *Am J Hum Genet* 1990;**47**:354–9.
- Gillies DRN, Lealman GT, Lumb KM, Congdon P. Analysis of ethnic influence on stillbirths and infant mortality in Bradford 1975–81. *J Epidemiol Community Health* 1984;**38**:214–7.
- Britton JR. Effects of social class, sex and region of residence on age at death from cystic fibrosis. *BMJ* 1989;**298**:483–7.