Growth and lung function in Asian patients with cystic fibrosis

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ORIGINAL ARTICLE

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Correspondence to: Dr B Callaghan, Portex Unit, Level 6, Cardiac Wing, Institute of Child Health, 30 Guilford St, London WC1N 1EH, UK; b.callaghan@ich.ucl.ac.uk

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Background: The incidence of cystic fibrosis (CF) in Asians is rare. How these patients fare in terms of morbidity and mortality in the UK compared to their non-Asian peers is not well documented.
Aims: To retrospectively study annual reviews of 31 Asian CF patients from three London paediatric CF centres.
Methods: Disease severity was assessed by lung function, age at first infection with *Pseudomonas aeruginosa*, and body mass index (BMI). The Asian children were compared with 143 matched non-Asian patients with CF. Matching criteria used were same sex and treatment centre as the Asian index patient. In addition, the controls were matched so that their date of birth, date of diagnosis, and date at annual review were within 12 months of the index patient.
Results: There was no significant difference in age at diagnosis or age at annual review between the Asian and non-Asian children. Mean Z-scores for FEV_1 and FVC were significantly lower for the Asian girls. There was no significant difference in Z-scores for BMI between the Asian children and their controls. Age at first isolation of *Pseudomonas aeruginosa* in Asian girls was significantly later than for their controls (8.3 years compared to 5.6 years for non-Asian girls).
Conclusions: While the Asian boys' lung function seems comparable with that of their non-Asian peers, the Asian girls emerge as a potentially vulnerable group and more work is required to discover why this is the case.

Although the first cases of Asian children diagnosed with CF on clinical grounds were reported in the UK 30 years ago, CF remains a rare disease among this ethnic group. The incidence of CF in Asian immigrants to Britain has been estimated at 1:10 000.[1]

Central Asia is a domain on the interior of Asia and includes Turkey, Iran, and Lebanon. Southern Asia is south of the Caucasus and Caspian Basin and encompasses India, Pakistan, and Bangladesh. Southern Asians are Caucasian.

Eighty eight patients from Southern Asia had been entered into the UK CF database registry by 2002.[2] Yet studies of how Asian patients with CF fare in childhood are scarce. A British study of nine Asian children with CF[3] suggested that Asian children suffered a more severe clinical course than their non-Asian peers. This larger study aimed to investigate whether Asian children with CF really fare worse than their non-Asian counterparts.

METHODS

Annual review notes were studied at three London paediatric CF centres: Royal London Hospital (RLH), Royal Brompton Hospital (RBH), and Great Ormond St Hospital for Children, (GOSH). All Asian CF patients from the three London paediatric CF centres were evaluated. Forty Asian children were found between the three centres. Thirty one of them had received annual reviews and had performed lung function tests within the previous 12 months. Eight were treated at the RLH, 10 at the RBH, and 13 at GOSH.

Each Asian patient was sex matched with non-Asian peers from the same CF treatment centre. The controls were chosen if their dates of birth, dates of diagnosis, and dates of annual review were all within 12 months of each Asian index patient. At least two controls from the same treatment centre were required in order to adequately match each Asian index patient. A total of 143 non-Asian controls were studied: 16 from RLH, 64 from RBH, and 63 from GOSH.

The following measurements were extracted from the computer databases and patients' notes, and then analysed: age at diagnosis, age at annual review, weight, height, genotype, lung function (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)), and age at first isolation of *Pseudomonas aeruginosa*. Anthropometric and lung function measurements were expressed as Z-scores to account for differences in gender and height, using the standard reference ranges obtained from British children.[4 5] Body mass index (BMI), a measure of body fat storage related to height and weight, was calculated by dividing weight (kg) by height (m^2).

Ethical approval for this study was obtained from the ethics committees of all three hospitals.

Statistical analysis

A power calculation was made to detect 15% absolute change in FEV_1 % predicted between the two groups. If the control group was to be at least twice the size of the index group, a study sample of 94 Asian CF children and 187 Caucasian CF children would be needed for a study to reach 95% power with a significance level of 0.01. This far exceeds the Asian paediatric CF population cared for between these three London centres. We therefore performed a retrospective power calculation on our study, using the formula for unequal sample sizes. Analysis of results from the 31 patients in our index group and their 143 controls, has 80–90% power at the 5% significance level to detect a difference of one standard deviation (SD) in estimates of FEV_1 and FVC between the two groups, after adjusting for potential confounding factors. Therefore, we would expect to obtain

Abbreviations: BMI, body mass index; CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOSH, Great Ormond St Hospital for Children; RBH, Royal Brompton Hospital; RLH, Royal London Hospital

Table 1 Background characteristics and respiratory function for Asian girls and their non-Asian matched peers

	Asian girls (n = 17)	Non-Asian girls (n = 77)	95% CI (Asian girls–non-Asian girls)	p value
Mean age at diagnosis, years	2.8 (4.6)	1.8 (2.8)	−3.52 to 1.32	0.35
Mean age at annual review, years	11.1 (3.8)	11.2 (3.4)	−1.95 to 1.74	0.91
Growth parameters				
Height Z-score	−1.3 (2.3)	−0.7 (1.8)	−1.7 to 1.9	0.53
Weight Z-score	−0.8 (1.1)	−0.6 (1.0)	−0.7 to 0.3	0.87
Body mass index	18.4 (5.7)	17.1 (3.0)	−0.6 to 3.2	0.20
Respiratory parameters				
FEV_1 Z-score	−2.2 (1.7)	−1.3 (1.6)	−1.7 to −1.4	0.05
FVC Z-score	−1.9 (0.9)	−0.8 (0.8)	−1.9 to −0.3	<0.01
Age at first PA infection, years	8.3 (4.3)	5.6 (3.7)	0.2 to 5.2	0.03

Anthropometric and respiratory function Z-scores calculated according to Freeman *et al*[4] and Rosenthal *et al*,[5] respectively.
CI, confidence interval; PA, *Pseudomonas aeruginosa*.
Figures in brackets = 1 standard deviation (SD).

a false positive result 5% of the time and to detect a difference if one actually exists 80% of the time.

The data were recorded onto an SPSS spreadsheet using double entry for quality control. Comparisons of group characteristics and respiratory function between the groups were performed using SPSS for Windows (release 10.03); *t* tests were performed to obtain p values with their attendant 95% confidence intervals, and $p < 0.05$ was considered statistically significant.

RESULTS

Complete data was available for 31 Asian children with CF; 17 were girls (55%) and 14 were boys (45%). A total of 143 non-Asian sex matched controls from the same treatment centre were studied: 77 (54%) were girls and 66 (46%) were boys.

All the children studied had pancreatic insufficiency. There was no significant difference in median age at diagnosis between the Asian children (0.73 years, range from birth to 15.27 years) or the non-Asian children (0.4 years, range antenatal diagnosis to 13.2 years). The median age at annual review was 11.0 years (range 4.5–17.1 years) for the Asian children and 11.4 years (3.1–16.7 years) for the non-Asian children. There was no significant difference in height Z-scores, weight Z-scores, or BMI between the Asian and non-Asian children (tables 1 and 2).

Lung function tests

The Asian girls had significantly lower mean FEV_1 Z-scores and FVC Z-scores than their non-Asian female controls (table 1). The Asian boys were noted to have a trend towards lower mean FVC Z-scores than the non-Asian boys but the difference was not statistically significant. There was no significant difference in FEV_1 Z-scores between the Asian and non-Asian boys (table 2).

Mean age at first isolation of *Pseudomonas aeruginosa*

The Asian girls had their first isolation of *Pseudomonas aeruginosa* significantly later than the non-Asian girls ($p = 0.03$) (table 1). There was no difference between the boys ($p = 0.66$) (table 2).

Genotype

Twenty seven of the Asian children were from Southern Asia and four were from Central Asia. All the Asian children and 94% of the non-Asian children studied had undergone genotype testing. Six (20%) of the Asian children were ΔF508 homozygous, compared to 69 (51%) of the non-Asian children. All of these patients were from Southern Asia; ΔF508 homozygosity therefore occurred in 33% of the Southern Asian group. Seventeen per cent of the Asian children were ΔF508 heterozygous compared to 13% of the non-Asian children. Twelve (39%) of the Asian children had unidentified genotypes. Seven (5%) of the non-Asian European children in this study had unknown genotypes. The genotype distribution seen here is similar to the genotype frequency reported by the CF database registry of patients from the Indian subcontinent and non-Asian Europeans.[2] It also supports the findings of other studies in Asian patients with CF which have reported the frequency of ΔF508 mutations at 25–54%.[6 7]

DISCUSSION

Differences in outcome between Asian and non-Asian CF patients are often attributed to later diagnosis in Asian patients. To overcome such bias, this study closely matched paediatric Asian CF patients with non-Asian peers to investigate whether there was an intrinsic difference in lung function between Asian and non-Asian children with CF. This study reveals that Asian girls with CF have significantly lower lung function measurements than non-Asian girls with CF. No significant difference in lung function exists between the Asian and non-Asian boys.

Lung function in children with CF has previously been shown to be associated with poor nutrition.[8] All the Asian children in this study were British born and, as has been previously reported in migrant communities, have assumed similar growth patterns to their white European peers.[9] There was no significant difference in weight, height, or BMI between the Asian and non-Asian children. From a growth point of view, the Asian children fare as well as their non-Asian peers. Poor nutrition is not a cause for the reduced lung function seen in the Asian girls.

There was no significant difference in mean age or median age at diagnosis between the Asian and their non-Asian matched controls. The mean age at diagnosis for all the children in this study was later than that reported in larger studies.[10] This is not surprising. Patients referred to tertiary centres often have delayed diagnoses, as the ranges of age at diagnosis seen here demonstrate.

We hypothesise that intrinsic ethnic differences in lung function between British born Asian and non-Asian females exist and should be explored. The Asian boys' sample size is

Table 2 Background characteristics and respiratory function for Asian boys and their non-Asian matched peers

	Asian boys (n = 14)	Non-Asian boys (n = 66)	95% CI (Asian boys–non-Asian boys)	p value
Mean age at diagnosis, years	2.1 (2.8)	1.2 (2.1)	−2.7 to 0.67	0.22
Mean age at annual review, years	10.9 (4.1)	11.6 (3.7)	−2.9 to 1.6	0.57
Growth parameters				
Height Z-score	−0.67 (1.45)	−0.54 (1.52)	−1.0 to 0.8	0.77
Weight Z-score	−0.4 (1.2)	−0.6 (1.0)	−0.3 to −0.5	0.64
Body mass index	18.0 (3.2)	17.5 (2.7)	−1.2 to 2.1	0.56
Respiratory parameters				
FEV_1 Z-score	−0.38 (2.5)	−0.54 (2.3)	−1.2 to 1.5	0.81
FVC Z-score	−2.1 (1.6)	−1.2 (1.6)	−1.8 to 0.06	0.07
Age at first PA infection, years	4.5 (3.8)	5.1 (3.7)	−3.3 to 2.1	0.66

Anthropometric and respiratory function Z-scores calculated according to Freeman *et al*[4] and Rosenthal *et al*,[5] respectively.
CI, confidence interval; PA, *Pseudomonas aeruginosa*.

smaller and may have led to a type II error since no difference between the Asian and non-Asian boys' lung function was found. A larger study of boys should be undertaken to investigate the Asian boys' lung function further.

There are no previous reports of differences in age at *Pseudomonas aeruginosa* infection between ethnic groups. The Asian girls developed their first *Pseudomonas aeruginosa* infection significantly later than their non-Asian matched peers. Despite this, their lung function was lower, suggesting that factors other than pulmonary infection may play a prominent role in the Asian girls' lung function measurements. Non-Asian females with CF have been shown to fare worse than boys in terms of lung function, morbidity, and mortality. Females have a significantly increased risk of death and a median lifespan 3–5 years shorter than males.[11] Earlier infection with *Pseudomonas aeruginosa* and poorer nutrition have been suggested as putative causes for this reported ''gender gap''.[12] These factors cannot explain our findings of lower lung function values in the Asian girls. An intrinsic ethnic difference in lung function may explain why the Asian girls appear to be demonstrating the gender difference sooner than their non-Asian female peers.

Thirty nine per cent of the Asian children had unknown genotypes and therefore it is difficult to relate phenotype and genotype in the Asian girls. Compliance data were not collected for this study. Poor compliance is unlikely to entirely explain the differences in lung function between the Asian and non-Asian girls. The Asian children's growth was equivalent to their non-Asian peers. Anecdotally, the three London centres report good compliance by Asian parents. However, the relative rarity of CF in the Asian community and the potential stigma of revealing such a diagnosis may impact on compliance by parents of Asian CF parents and ought to be explored. Social class has been shown to exert an independent effect on time of death from CF. While the Asian children were matched with peers from the same treatment centre, tertiary centres often serve a heterogeneous group of patients in terms of socioeconomic class. Immigrant families are often socioeconomically disadvantaged and so the effect of social class on the Asian children's outcome remains to be considered.[13]

The number of Asian patients surviving into adulthood with CF continues to rise. The care they receive in established centres of excellence guides the care of Asian CF patients worldwide. While studies of Asian CF patients will often be under-powered, the opportunity to describe their pattern of illness must not be missed.

Lung function remains the primary predictor of death in CF and the yearly rate of decline of FEV_1 is the most important variable in predicting mortality.[14 15] Lung function tests are known to differ with ethnicity between adult healthy controls.[16] Healthy adult Asians have been reported as having lower lung function values than non-Asian subjects in some poorly matched studies.[17–19] Infant and preschool lung function measurements of British born Asian and non-Asian CF patients are being collected and will provide a useful baseline.[20 21] The lung clearance index (LCI) is emerging as a sensitive measure of disease progression in CF.[22]

Lung function data of healthy, British born Asian adults and children could establish much needed reference values against which British born Asian patients with respiratory diseases can be compared.[23] Such information might then help to confirm whether the lower lung function tests seen in these Asian girls are the result of intrinsic ethnic differences. Studies comparing lung function measurements between adult Asian and non-Asian CF patients remain to be carried out and may clarify whether the normal findings in the Asian boys are due to a type II error. The advent of neonatal screening for CF in the UK will help in the earlier diagnosis of some Asian children who can then undergo early lung function assessment.

What is already known on this topic

- Case reports have reported increased morbidity in Asian CF paediatric patients compared to their non-Asian peers
- Causes for increased morbidity have suggested poverty, reduced access to medical care, inadequate comprehension of disease and regimen required, and poor compliance

What this study adds

- There was no difference in BMI between the Asian and non-Asian groups, showing that Asian children with CF show similar growth patterns to their non-Asian peers
- When matched for gender and height, the Asian girls had significantly lower Z-scores for FEV_1 and FVC

The UK CF Database has recorded mortality according to ethnicity only since 2002. This mortality data will become increasingly useful in monitoring the outcome of Asian children with CF.

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Authors' affiliations

B D Callaghan, A F Hoo, R Dinwiddie, Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London, UK
I M Balfour-Lynn, Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK
S B Carr, Department of Paediatric Respiratory Medicine, Royal London Hospital, London, UK

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