Asians with cystic fibrosis in the UK have worse disease outcomes than clinic matched white homozygous ΔF508 controls

Jonathan McCormick a, *, Simon A. Ogston b, 1, Erika J. Sims a, Anil Mehta a

a United Kingdom Cystic Fibrosis Database, Maternal and Child Health Sciences, Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland DD1 9SY, United Kingdom

b Public Health Section, Community Health Sciences Division, LGF29 Mackenzie Building, Kirsty Semple Way, Dundee DD2 4AD, United Kingdom

Received 28 July 2004; accepted 2 November 2004

Abstract

Background: We tested the hypothesis that the Asian cystic fibrosis (CF) phenotype is comparable to the commonest genetic form of CF found in 50% of the white UK CF population using the UK CF Database, a national disease-specific patient registry.

Methods: 50 Asian CF patients were matched by Centre with 143 white homozygous ΔF508 patients for gender, age and chronic Pseudomonas aeruginosa status (a marker of morbidity). The authors compared FEV1 and FVC% predicted, mean height, weight and BMI Z scores.

Results: FVC% predicted, weight and BMI Z scores were significantly worse in the Asians. Asian male/female FVC% predicted (p-value, 95% CI) \( -15.1 \) \( (p=0.001, -24.0, -8.8)/-15.2 \( (p=0.014, -27.1, -3.3) \) compared with white controls. Asian females also had significantly worse FEV1% predicted compared with controls \( (-14.9, p=0.025, 95\% \text{ CI: } -27.8, -2.0) \). Asians had significantly lower raw Z scores for weight (males \( p=0.002 \), females \( p=0.013 \)) and BMI (males \( p=0.002 \), females \( p=0.008 \)).

Conclusions: These data suggest that the Asian CF phenotype is as severe as the white controls with the homozygous ΔF508 phenotype but is worse in some outcomes, especially in Asian females. Socio-cultural factors and rare CF genotypes may contribute to the severity of CF in this vulnerable group.

© 2004 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Cystic fibrosis; Phenotype; Asian; Lung function; Growth

1. Introduction

Cystic fibrosis (CF) is usually thought of as a Caucasian disease [3,4] although Asians from the Indian subcontinent constitute 1 in 60 of the UK CF population [5]. Their clinical presentation is similar to the white population despite a different spectrum of cystic fibrosis transmembrane conductance regulator (CFTR) genotypes [5,6].

Pseudomonas aeruginosa (Pa) infection is a marker of excess morbidity in CF and a single centre small study of nine patients suggested that Asian CF patients have an earlier acquisition of Pa infection, poorer lung function and lower weight centiles compared with age and gender matched non-Asian controls [7]. Our objective was to test this association between poor clinical outcomes and ethnicity using the national database. Here, the clinical status of UK Asian CF patients is compared with white CF patients homozygous for the severe genotype [8] that constitute around 50% of the UK CF population. The hypothesis tested was that the clinical severity of CF in Asians was comparable to the commonest form of CF in the white population in the setting of modern treatment in tertiary CF Centres. We show that FVC% predicted, weight and BMI Z scores are lower in the Asian CF patients compared with these white ΔF508/ΔF508 controls. Because it remains controversial whether such outcomes should be corrected for ethnicity, we conducted sub-analyses with and without such adjustments. Our data
suggest that further investigation is needed into the effects of CF in the Asian population.

2. Methods

The operation of the UK Cystic Fibrosis Database or UKCFD, which covers around 95% of specialist UK CF Centres and smaller CF clinics, and its data verification procedures have recently been described [9]. For a given year, the UKCFD ‘active’ patients are defined as the subgroup of ‘registered’ patients with basic biographical data who have additional clinical data in the preceding 12 months [9]. Here, the UK CF registered population was divided into white Caucasian and non-Caucasian populations. Within the predominantly ethnically mixed non-Caucasian population, we identified an Asian CF population consisting of all ‘active’ Pakistani, Indian, Bangladeshi and Asian/other patients [5].

At each CF Centre, an ‘active’ Asian group was compared with ‘active’ white controls for clinical outcomes in 2002 including forced expiratory volume in one second and forced vital capacity percent predicted (FEV$_1$ and FVC% predicted), height, weight and body mass index (BMI). ‘Active’ Asians were matched with up to five controls. Due to differences in the spectrum of CFTR mutations in the Asian population [5], cases and controls could not be matched for genotype. Instead, we referenced outcomes against the common and homozygous ΔF508 genotype. Each CF Centre control was an ‘active’ white patient matched for gender, age (±12 months) and chronic Pa infection status (defined as three or more isolates in the preceding 12 months). As CF-related diabetes (CFRD) is a potentially confounding variable [10], patients taking either insulin or oral hypoglycaemic agents were excluded from both groups (this excluded 11 Asian patients, 6 male) although the results remain unchanged if they were included (data not shown).

The applicability of UK reference charts on lung function and growth to children from ethnic minorities is controversial [11–14]. There is the view that “ethnic discounting” of FEV$_1$% predicted values contributes nothing, as birth weight, parental socio-economic status and maternal smoking will also influence the accurate prediction and are not accounted for in the calculation [15]. However, potentially “corrective” adjustments exist for calculating FEV$_1$ and FVC% predicted according to ethnic origin. Therefore, comparisons of lung function were performed in three ways.

Firstly, lung function was calculated using Polgar for children and Cherniak for adults [16,17] and direct comparisons of lung function were made between the Asian group and controls directly (referred to as Polgar/Cherniak). FEV$_1$% predicted was calculated from the raw FEV$_1$ data using Polgar’s equation for children <18 years (male: 0.812*height in m$^2$.77; female: 0.788*height in m$^2$.73) and Cherniak’s equation for adults >18 years (male: 0.04525*

The operation of the UK Cystic Fibrosis Database or UKCFD, which covers around 95% of specialist UK CF Centres and smaller CF clinics, and its data verification procedures have recently been described [9]. For a given year, the UKCFD ‘active’ patients are defined as the subgroup of ‘registered’ patients with basic biographical data who have additional clinical data in the preceding 12 months [9]. Here, the UK CF registered population was divided into white Caucasian and non-Caucasian populations. Within the predominantly ethnically mixed non-Caucasian population, we identified an Asian CF population consisting of all ‘active’ Pakistani, Indian, Bangladeshi and Asian/other patients [5].

At each CF Centre, an ‘active’ Asian group was compared with ‘active’ white controls for clinical outcomes in 2002 including forced expiratory volume in one second and forced vital capacity percent predicted (FEV$_1$ and FVC% predicted), height, weight and body mass index (BMI). ‘Active’ Asians were matched with up to five controls. Due to differences in the spectrum of CFTR mutations in the Asian population [5], cases and controls could not be matched for genotype. Instead, we referenced outcomes against the common and homozygous ΔF508 genotype. Each CF Centre control was an ‘active’ white patient matched for gender, age (±12 months) and chronic Pa infection status (defined as three or more isolates in the preceding 12 months). As CF-related diabetes (CFRD) is a potentially confounding variable [10], patients taking either insulin or oral hypoglycaemic agents were excluded from both groups (this excluded 11 Asian patients, 6 male) although the results remain unchanged if they were included (data not shown).

The applicability of UK reference charts on lung function and growth to children from ethnic minorities is controversial [11–14]. There is the view that “ethnic discounting” of FEV$_1$% predicted values contributes nothing, as birth weight, parental socio-economic status and maternal smoking will also influence the accurate prediction and are not accounted for in the calculation [15]. However, potentially “corrective” adjustments exist for calculating FEV$_1$ and FVC% predicted according to ethnic origin. Therefore, comparisons of lung function were performed in three ways.

Firstly, lung function was calculated using Polgar for children and Cherniak for adults [16,17] and direct comparisons of lung function were made between the Asian group and controls directly (referred to as Polgar/Cherniak). FEV$_1$% predicted was calculated from the raw FEV$_1$ data using Polgar’s equation for children <18 years (male: 0.812*height in m$^2$.77; female: 0.788*height in m$^2$.73) and Cherniak’s equation for adults >18 years (male: 0.04525* height in cm$-0.03509*age-2.59946$; female: 0.04071* height in cm$-0.02147*age-2.56958$). FVC were similarly calculated from the raw FVC data using Polgar’s equation for children <18 years (male: 1.004*height in m$^2$.72; female: 0.946*height in m$^2$.61) and Cherniak’s equation for adults >18 years (male: 0.06584*height in cm$-0.02954*age-5.12451$; female: 0.05557*height in cm$-0.00793*age-4.89036$). Secondly, the ethnic discounting of lung function was applied according to the guidelines of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists (referred to as BTS/ARTP), which recommends that the predicted values of FEV$_1$ and FVC of Indian and Pakistani subjects should be multiplied by a factor of 0.9 [18]. Lastly, our own formula incorporating the impact of nutrition on lung development were used in a malnourished population in India as a reference base [19] (referred to as Ong). The latter was applied to the Asian and control groups equally, assuming malnourishment would exist in both CF populations (predicted FEV$_1$ = exp(2.83*ln(height in cm) − 13.43). There are no equivalent formulas for FVC calculations.

With respect to height, another reason for using data without specific adjustment for ethnicity is the secular trend towards an increasing height in succeeding generations especially where third generation immigrants and intermarriage has occurred permitting reference against national data [14]. However, we also adjusted Asian data based on the corrective factors published on a population of UK Pakistani patients aged 4–14 years [13]. Adjustments to the height, weight and BMI Z scores from the Asian CF group were made as follows: male height +0.3, female height +0.4, male weight +0.3, female weight +0.5, male BMI +0.4, female BMI +0.5. The daily amount of pancreatic replacement enzymes taken by pancreatic insufficient (PI) patients were also compared.

Matching was allowed for in the analysis by assuming the presence of additive random effects for each stratum (group of case and matched controls) and a fixed effect representing case-control difference. The SPSS mixed model procedure was used to estimate the systematic effects of gender and the case-control differences while allowing for random variation at the level of the case-control stratum as well as variation at the level of the individual subject. Analyses were performed using Microsoft Access and Excel 97 (Microsoft Corporation, Redmond, Washington, USA), SPSS for Windows version 11.5 (SPSS Inc., Chicago, IL, USA) and graphical representations were prepared using SigmaPlot (SigmaPlot for Windows version 4.01; SPSS Inc., Chicago, IL, USA).

3. Results

The UKCFD has 114 ‘registered’ Asian CF patients (age range 0.3 years to 34.3 years) from which we identified 50 ‘active’ Asian CF patients (30 male) with corresponding
‘active’ white controls at the same CF Centre/clinic. Asians were excluded if they had no clinical data submitted in 2002, if no matching controls were identified or if they had CFRD (36, 17 and 11 patients, respectively). The controls consisted of 143 white Caucasians (92 male). The 50 ‘active’ Asian subgroup (35 with lung function data) was representative of the 114 Asian CF ‘registered’ population (62 with lung function data) with no significant differences in the age at diagnosis ($p=0.40$), height ($p=0.52$), weight ($p=0.38$) or BMI Z scores ($p=0.39$), FEV$_1$% predicted ($p=0.35$), FVC% predicted ($p=0.46$) or in the proportions with chronic Pa infection ($p=0.28$). The ‘active’ Asians included 34 Pakistani/Pakistani, 10 Indian/Indian, 3 Bangladeshi/Bangladeshi, 2 Asian other/Asian other and 1 Pakistani/Bangladeshi. The UKCFD does not contain data on parental consanguinity. The Asian chromosomes were classified using the Welsh and Smith classification of CFTR mutations: class I=8, class II=26, class III=0, class IV=0, class V=3 and unknown=63, whereas the control group patients all had class II mutations [20]. A third of the CFTR mutations in the Asians remain undetectable by commonly available screening methods. There were 14 Asian patients (8 male) who carried at least one copy of the ΔF508 mutation, 12 of these were homozygous for ΔF508 (7 male). Chronic Pa infection was recorded in 19 (38%) of the Asians who were matched with chronic Pa infected homozygous ΔF508 controls.

Lung function was available in 35 Asians (21 male) and 81 controls (52 male). Fig. 1 shows that the range of values for mean FEV$_1$% predicted in Asian males was between 3% and 12% worse compared with controls. However, this trend was of borderline significance dependent on the equation used: Polgar/Cherniak ($p=0.072$, mean difference $-10.0$ (95% confidence intervals (CI): $-20.9, 0.9$)), BTS/ARTP ($p=0.588$, mean difference $-2.9$ (95% CI: $-13.7, 7.8$)) and Ong methods ($p=0.061$, mean difference $-12.6$ (95% CI: $-25.8, 0.6$)). In contrast, Asian females had between 9% and 17% worse FEV$_1$% predicted compared with controls (Fig. 1), a deficit that remained significant using two of the three “corrective” equations: Polgar/Cherniak ($p=0.025$, mean difference $-14.9$ (95% CI: $-27.8, -2.0$)), BTS/ARTP ($p=0.127$, mean difference $-9.5$ (95% CI: $-21.9, 2.9$)) and Ong methods ($p=0.024$, mean difference $-17.1$ (95% CI: $-31.8, -2.4$)). Using the Polgar/Cherniak method, Asian patients also had significantly worse FVC% predicted compared to controls (Fig. 2); Asian males compared with the controls calculated using the Polgar/Cherniak ($p=0.001$, mean difference $-15.1$ (95% CI: $-24.0, -6.2$)) and the BTS/ARTP methods ($p=0.083$, mean difference $-8.0$ (95% CI: $-17.1, 1.1$)); Asian females compared with the controls calculated using the Polgar/Cherniak method ($p=0.014$, mean difference $-15.2$ (95% CI: $-27.1, -3.3$)) and the BTS/ARTP method ($p=0.165$, mean difference $-8.5$ (95% CI: $-20.8, 3.7$)).

Asians had significantly lower unadjusted Z scores for BMI at diagnosis ($p=0.022$) and BMI at the age at diagnosis ($p=0.028$). No difference between Asians and controls was represented by the dotted line. FEV$_1$% predicted calculations: unadjusted (as per Polgar/Cherniak, filled symbols), ethnicity adjustment (BTS/ARTP, unfilled symbols) and malnourishment adjustment (Ong, grey symbols).

![Fig. 1. Mean differences in FEV$_1$% predicted between Asian patients and controls for male (squares) and female (circles). Data based on 21 male Asian CF patients with 52 matched controls, and 14 female Asian CF patients with 29 matched control patients. No difference between Asians and controls is represented by the dotted line. FEV$_1$% predicted calculations: unadjusted (as per Polgar/Cherniak, filled symbols), ethnicity adjustment (BTS/ARTP, unfilled symbols) and malnourishment adjustment (Ong, grey symbols).](image1)

![Fig. 2. Mean differences in FVC% predicted between Asian patients and controls for male (squares) and female (circles). Data based on 21 male Asian CF patients with 52 matched controls, and 14 female Asian CF patients with 29 matched control patients. The dotted line represents no difference between the Asian and Caucasian groups. Filled and unfilled symbols represent data unadjusted and adjusted for ethnicity, respectively.](image2)
the 15 Asian PI female patients, mean lipase units/kg/day=9322 compared with the 8605 in the 42 PI female control patients (p=0.48). There were no significant differences in the proportions of male or female Asian patients exceeding the recommended 10,000 lipase units/kg/day [21,22] compared with the control patients (male Asian patients 29.6%, p>0.05; female Asian patients 40.0%, p>0.05).

4. Discussion

The interpretation of outcomes and the prediction of morbidity in Asian CF are problematic due to the lack of consensus over adjusting raw data for ethnicity when comparing lung function and anthropometric data between different ethnic groups. Therefore, we took the pragmatic approach of comparing growth parameters, directly and with ethnicity adjustment and compared lung function using three separate formulae to adjust for ethnicity and malnourishment. Ethnicity adjustments lack precision associated with variations in height, weight, etc. of Asian people from different regions and different socio-cultural groups within the Indian subcontinent [6] and the trend towards taller final height in succeeding generations of immigrant populations [14]. We find that Asians with CF had poorer FVC% predicted (but only poorer FEV$_1$% predicted in females), weight and BMI Z scores than the homozygous ΔF508 white controls. There was no difference in height between Asian and control patients and, although our study was not designed to explain this observation, it could be a result of dietary influences, similar levels of pancreatic insufficiency, or because the null hypothesis is true. Although FEV$_1$% predicted was not significantly worse in male Asians, the difference bordered on significance and may be a reflection of the patient numbers in our study. Larger patient numbers would be achievable with an international CF database (which we have proposed [23]), and better evidence could come from prospective studies once neonatal screening is universal. The majority of Asian CF patients live in England where there are only a few hospitals with pilot newborn CF screening programmes. It remains to be shown whether these patients may differentially benefit from its introduction. The possible reasons for no difference between the male Asians and white controls include a difference due to ethnicity (cultural differences in the gender roles in Asian society), nutritional factors or an influence such as consanguinity producing a type II error. Therefore, we suggest that the Asian CF phenotype is as severe as the homozygous ΔF508 phenotype in white patients but may be worse.

Epidemiological inferences based on racial categories are criticised for overlooking confounding social, economic and cultural variables [15,18]. The ethnicity of both parents of CF patients is reported within the UKCFD but not consanguinity, and the approach we report here is limited by the lack of a detailed ethnic genealogy on each patient. The fact that there are no significant differences in the age at diagnosis or major symptoms at presentation between UK white and Asian CF populations [5], despite the contrasting spectrum of CFTR mutations, suggests that Asian origin is not a barrier to early or appropriate diagnosis (nor is it a barrier in US African–American CF patients [24]). Spencer’s study in 1994 found that 5 out of 13 Asian CF children had a delayed diagnosis as a direct result of their racial origin [25]; however, our earlier work found no difference in the age of diagnosis between 88 Asian patients and 5078 Caucasians using the national database [5]. Therefore, other factors must be involved in the subsequent clinical course of Asian CF patients in the UK.

There have been relatively few studies into Asian CF patients because of the rarity of cases in any particular region. Inclusion of ethnic minorities in research is important and such research is ideally suited to a national clinical database [26,27]. This enabled us to control for important variables such as treatment differences between CF Centres and clinics, chronic Pa infection, gender, diabetic status and age in our study design. Our findings agree with the study in Leeds that compared 9 UK-born Asian CF patients with 18 non-Asian age and gender matched controls [7]. Methodologically, that study used standard reference charts for weight and height and did not adjust for ethnicity, and applied the Polgar equation for lung function to children as well as adults but had the advantage of having detailed clinical histories and socio-economic information on all their patients facilitating reporting on social class and smoking status.

South Asians living in the UK have a higher prevalence of coronary heart disease [28] though this has not been
shown to be due to differences in medical care [29]. Socio-cultural factors including diet, family income and language barriers [7,19] and health care access and quality may all contribute to the findings of our UK-wide study and can have a major impact on outcomes especially survival in CF [30–32]. CF is a complex disease to manage and insufficient patient education, cultural acceptability of genetic conditions and the impact of cultural beliefs on adherence to treatment are challenging management issues [33]. It is difficult to assess the contribution of the genotype to the Asian CF phenotype, whilst no mutations are found in approximately 40% of UK Asian patients [5] (a US study reported 50% as unidentified or unknown [34]). However, it would be useful if existing identified mutations seen in the Asian population could be classified at a cellular level so that genotype/phenotype correlations could be examined [35]. This will become more important when new CFTR-function specific therapies are introduced. Further work is needed to elucidate the factors contributing to why Asian CF patients have poorer lung function and our previous work albeit in a different setting has suggested that diet might be a factor in lung development [19]. More work is needed to explore this association between ethnicity and clinical outcome and we suggest that this vulnerable group should merit particular attention. The factors leading to these differences in lung function need to be explored but it remains to be proven that early intervention will prevent excess morbidity and mortality [36,37].

Acknowledgements

The authors are grateful for grants from the CF Trust and the National Services Division of NHS (Scotland). We thank M. Fraser and S. Krawczyk for their expert data validation and all the data entry staff and the Directors in CF Centres for their support. There are no conflicts of interest.

The authors are grateful for the financial support of the CF Trust and the National Services Division of NHS (Scotland).

This work was presented as an oral presentation at the Respiratory Session of the 8th Spring Meeting of the Royal College of Paediatrics and Child Health held in York, England in March 2004 [1].

This work has been presented as an oral and poster presentation at the 27th European Cystic Fibrosis Conference held in Birmingham, England in June 2004 [2].

References


