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Cystic fibrosis and survival to 40 years: a case-control study

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ABBREVIATIONS

BMI = body mass index

CF = cystic fibrosis

CFRD = cystic fibrosis-related diabetes

CFTR = cystic fibrosis transmembrane conductance regulator

CI = confidence interval

FEV_1 = forced expiratory volume in 1 second

FVC = forced vital capacity

GP = General Practitioner

IV = intravenous

OR = odds ratios

RBH = Royal Brompton Hospital

SES = socioeconomic status

ABSTRACT

The clinical course of patients with cystic fibrosis (CF) is variable and probably determined by many interacting factors. We aimed to examine the influence of early social and clinical factors on long-term survival.

A case-control design of adult CF patients was used to compare long-term survivors (aged ≥40; cases) with patients who died before reaching 30. Each case (n=78) was matched by birth date with at least one control (n=152) after exclusion of 'late diagnosis' patients. Probability weighted logistic regression models were used to identify influences on survival.

Factors resulting in increased probabilities of survival included: high BMI (OR=1.76, 95% CI 1.40-2.22), FEV_1 (OR per 5% increase=1.54, 1.32-1.80), and FVC (OR per 5% increase=1.54, 1.33-1.78) at transfer to the adult clinic and the exclusive use of oral antibiotics (OR=8.31, 3.02-22.88). Factors resulting in decreased probabilities of survival: *P. aeruginosa* acquisition (OR=0.18, 0.05-0.65) or pneumothorax before transfer to the adult clinic (OR=0.02, 0.004-0.08) and referral from a paediatric clinic in a deprived area (OR=0.13, 0.04-0.38).

Long-term survival is associated with the clinical features present by the time of referral to an adult clinic; even 'early-diagnosis' disease appears to have different phenotypes, possibly independent of CF gene function, that have different survival patterns.

INTRODUCTION

The life expectancy of patients with cystic fibrosis (CF) has been steadily increasing despite the lack of a cure for the underlying cellular defect. Patients born today are expected to have a median survival into their 6th decade.[1] The improvement has been explained in several ways including by the introduction of pancreatic enzymes, by better nutrition, specialist-centre care, improved physiotherapy and more intensive antimicrobial treatment.[2-4]

CF covers a wide spectrum of disease from milder phenotypes with 'non-classic' disease (with pancreatic sufficiency, milder lung disease and a later diagnosis) to more severe cases with a 'classic' phenotype.[5] However, even within different groups there is variation in the rate of disease progression; some patients with features of classic disease run a mild course and indeed an important proportion of patients with the common 'severe' ΔF508 mutation survive beyond 40 years of age with relatively well maintained lung function and weight.[6;7]

Thus it has been hypothesised that other factors influence survival in CF. These include variations in the function of the responsible gene – the cystic fibrosis transmembrane conductance regulator *(CFTR)* – and other independent genetic factors ('modifier' genes); none, however, have yet been shown directly to influence survival.[8] Other potential, non-genetic, determinants of survival are so-called environmental influences – these cover a diverse range of factors, broadly divided into biological effectors (eg. microorganisms, nutrition, gender and pollutants), social and cultural influences (eg. socioeconomic status (SES) and adherence to treatment) and health-care related factors such as access to care and inter-clinic treatment variations.[9] Evidence for or against these factors is variable and knowledge of when they are most influential, or when an individual is most vulnerable to them, is

not well understood. In view of this, we conducted a case-control study of long-term survival among patients registered with a specialist adult CF clinic; with the aim of identifying early potential influences of long-term survival in patients diagnosed with CF in childhood.

METHODS

Subjects

Since 1965, details of all patients referred to the adult unit at Royal Brompton Hospital (RBH) and confirmed to have CF have been entered onto a database. The diagnosis is based on clinical features and a positive sweat sodium (>70 mmol/L) or chloride (>60 mmol/L) test or, in cases with a borderline or negative sweat test result, the presence of a known disease-causing mutation on each *CFTR* gene or of an abnormal nasal potential difference measurement. Patients were referred as adults from an adult physician or by their general practitioner (GP), or directly through transition (~15 years of age) from paediatric clinics. Clinical and demographic details are collected at the first consultation and are subsequently updated at annual review.

We studied only patients with a diagnosis of CF before the age of 17. These were identified from the database and classified as cases or controls as follows:

Cases (long-term survivors) were all patients with complete records who had reached 40 years of age without transplantation by 31st December 2004.

Controls were selected from all patients with complete records who had died before 30 years of age or required transplantation at <30 years of age by 31st December 2004. We excluded controls (n=27) who had died from a non-CF related cause (eg. road traffic accident).

Eighty cases and 400 controls were identified from the original population. To ensure that cases and controls were similar in terms of era of birth, as it is likely that this would have influenced the nature of care received, cases were matched by date of birth (± 365 days) to all eligible controls. Of the 80 cases identified, 78 were matched to at least one control. Each control was matched with as many cases as eligible and controls could be matched to more than one case. Of the 400 controls identified, 152 were matched to at least one case.

Information on source of referral, guardian's occupation, genotype and clinical state (weight, height, lung function, sputum microbiology, diabetic status, use of pancreatic enzymes, previous pneumothoraces, episodes of major haemoptysis and number of previous hospital admissions/antibiotic courses) prior to and at referral was collected from the initial assessment at the adult clinic; the remaining data were collected from annual reviews (school disruption, number of Advanced (or 'A') level school examinations and number of siblings). Antibiotic treatments before first attendance at the adult clinic were categorised as oral, aerosolised or intravenous (IV).

Statistical analysis

Differences between cases and controls were described by frequencies and proportions for categorical variables, and medians and inter-quartile ranges for continuous variables. Development of CFRD and the acquisition of *S. aureus*, *P. aeruginosa* and *H. influenzae* were assessed in terms of whether the patient developed these conditions before the age of 16 years or not. As such, analyses of these variables are limited to those who arrived at RBH by 16 years of age (69 cases and 109 controls). Physical measurements at initial assessment and history of antibiotic use and number of hospital admissions prior to initial assessment were limited to those arriving at RBH by the age of 15 years (73 cases and 131 controls).

We used probability weighted logistic regression models to assess the association between possible predictors and survival to 40 years of age (case status). Using this method, controls were weighted according to the cases they were matched to, thus making the distribution of the matching variable (date of birth) similar in both groups. Each control was weighted by the sum, across its matched case, of 1/(number of controls the case is matched to). Cases were allocated a weight of 1. Model results are presented as odds ratios (OR) and 95% confidence intervals (95% CI). Since patients transferred to the adult clinic at varying ages, ORs for physical measures and medical history prior to initial assessment* were adjusted for age at assessment. ORs for physical measures were also adjusted for gender. Analyses were conducted in SAS v9.1 (SAS Institute, Carey, US) or STATA (StataCorp LP, College Station, US).

*Use of antibiotics, prior hospital admissions, history of pneumothorax and major haemoptysis prior to initial assessment

Ethics

All patients consented for their anonymised data to be included in the database for research purposes. The study was approved by the Royal Brompton Hospital Research Ethics Committee.

RESULTS

Clinical characteristics

Half of the participants were born between 1960 and 1965 and most (80.4%) were diagnosed with CF before the age of five years (Table 1). Seventy percent were first seen in the adult clinic before the age of 21 years. Ninety-seven percent were pancreatic insufficient and there were similar proportions of men in cases (long-term

survivors) and controls. Genotyping was only possible for patients surviving beyond 1989 (ie. the year *CFTR* was discovered); therefore genetic data was available for 74 patients (67 cases). Of the long-term survivors genotyped (86%), 32 (48%) were homozygous ΔF508, 13 (19%) were compound heterozygous ΔF508 and 19 (28%) were heterozygous ΔF508 (with an unidentifiable second CF mutation). The remaining three cases were 621+1G→T, R553X (both with unidentifiable second genes) and R347P/3659delC. The seven controls genotyped were homozygous ΔF508.

Features significantly associated with case status (ie. long-term survivors) included diagnosis after the age of five. Patients whose initial presentation had been with respiratory disease were significantly less likely to be cases. Patients who had suffered a pneumothorax prior to referral to the adult clinic were significantly less likely to be cases after adjusting for age at first attendance. There was little heterogeneity in the distributions of pancreatic insufficiency, haemoptysis and CF-related diabetes (CFRD) prior to referral; none were associated with case status. After adjusting for age at initial assessment and gender, the probability of survival to 40 years increased with increasing height, weight, body mass index (BMI), FEV_1 and FVC as recorded at the initial assessment in the adult clinic.

Sociodemographic factors and patients' educational background

Associations between long-term survival and measures of socio-economic status and educational attainment are shown in Table 2. Patients referred from clinic B were less likely to be cases. Those whose guardians were in managerial or manual (skilled or unskilled) occupations were more likely to be cases than those in professional occupations but the difference was not statistically significant. Patients classified as having 'mildly' or 'grossly' disrupted schooling were statistically more likely to be controls but there was no association between case status and the number of 'A'

levels achieved. We found no association between sibling number (with or without CF) and case status.

Sputum microbiology, antibiotic courses and hospital admissions

Table 3 displays the association between long-term survival and sputum microbiology, antibiotic courses and hospital admissions prior to referral to the adult clinic. Acquiring *Pseudomonas aeruginosa,* but not *Haemophilus influenza*e or *Staphyloccus aureus,* in the sputum prior to 16 years of age, was associated with a reduced probability of being a case.

Patients who had received oral antibiotics (as intermittent courses and/or long-term/prophylaxis) and had not received aerosolised or IV antibiotics were significantly more likely to be cases than those who had not taken oral antibiotics. Conversely, the prior use of aerosolised or IV antibiotics was inversely associated with case status. Patients requiring annual or more frequent hospital admissions were significantly less likely to be cases.

DISCUSSION

This carefully matched case-control study is the first to report on the potential early influences of long-term survival in patients diagnosed with cystic fibrosis in childhood. Patients with a later diagnosis (ie. at 5 – 16 years), those whose CF did not present with respiratory disease and those with higher weight, height, BMI and lung function (% predicted) at the time of their first assessment at the adult clinic were statistically more likely to reach 40 years of age. Acquiring *P. aeruginosa*, but not *H. influenza*e or *S. aureus*, in the sputum prior to 16 years of age, was associated with a reduced probability of long-term survival. Factors that did not influence long-term survival included gender, parental occupation and major haemoptysis or the development of

diabetes before the age of 16 years. These findings suggest that the long-term survival of adults diagnosed with CF in childhood is determined predominantly by an intrinsically severe phenotype in early life with little evidence of major modification by socio-economic influences; and that maintaining good health in childhood is an important determinant of long-term survival.

We elected to study only patients whose disease had been diagnosed during childhood and thus remove the bias associated with the good prognosis of disease diagnosis in adulthood.[10;11] Moreover, by studying long-term survivors under the care of a single institution and by matching them with 'controls' born within a year of their birth date we reduced the effects of different adult treatment strategies between centres and changing strategies over time, each of which may have independent effects on survival.[9] We may, in this way, have 'over-matched' patients leaving insufficient heterogeneity of exposure to examine some important determinants of survival. For example, it is widely accepted that socioeconomic factors have a strong influence on prognosis [9;12;13] but our findings demonstrated only limited evidence of this. In contrast to a previous UK study in 1989, we found no correlation of parental occupation – an index of family socio-economic status - with long-term survival.[14] The association of poor survival with referral from paediatric clinic B (situated in an area of relatively low socio-economic status) may reflect differences in resources and provision of care, as well as patients' socio-demographics.

However, the present study provides an important extra dimension to published studies on predictors of mortality. The earliest, observational, studies recognised the association of poor nutritional status and low FEV_1 with a worse outcome.[15-17] Since then more robust epidemiological studies have confirmed this correlation, including a large population study of the Canadian Patient Data Registry.[3] More recently, an Irish study investigated factors relating to mortality in their adult patients,

concluding that lower FEV_1 and BMI, and higher infection rates of *P. aeruginosa* and *Burkholderia cepacia,* were associated with patients who had died.[18] They assessed differences in predetermined clinical parameters between patients who died during a 10-year period and those who remained alive, therefore making it difficult to draw conclusions about the timing of the events (ie. when they were most influential). Our study adds to this by clearly showing the importance of these factors at an early stage.

The present study demonstrated a worse outcome in patients diagnosed with CF early (before 5 years of age) and also in those with an initial disease presentation of respiratory symptoms. This supports the findings of another North American registry-based study, demonstrating variable survival among patients with inherently different degrees of baseline risk – reflected by their age at diagnosis and their degree of disease severity at presentation.[19] They also showed that meconium ileus was associated with reduced survival which provides an explanation for the lack of correlation found in our study, as only a few patients presenting with meconium ileus survived to adulthood. Contrary to their findings, we found gender did not predict survival, which, in part, might be explained by the historical higher mortality among CF girls, particularly around puberty, taking its toll, thus leaving those who have a predetermined survival advantage to progress through to the adult clinic.[20] However, others have argued that the so called 'gender gap' does not exist, highlighting the complex interaction of this much debated relationship.[21] Patients with an increased baseline risk are predisposed to developing worse lung disease and an accelerated decline in their general health. Consequently they develop more complications and ultimately require more hospital admissions and IV antibiotic courses, as demonstrated by the strong correlation of these factors with control status in our study.

The negative impact on survival of *P. aeruginosa* is consistent with previous studies and although there is still some controversy regarding causality and ascertainment bias, it should be regarded as a poor prognostic factor.[22;23] The insignificant impact of *H. influenzae* and *S. aureus* is consistent with other studies. A European cross-sectional study demonstrated that *S. aurues* was not associated with worse pulmonary status and others have shown a deleterious effect on symptoms only, including the risk of massive haemoptysis.[24-26] The finding of a survival benefit for patients receiving oral antibiotics (without aerosolised or IV antibiotics) is interesting as oral flucloxicillin is usually given as long-term prophylactic anti-staphylococcal treatment, suggesting indirectly that *S. aureus* may be relevant to survival, although this association may also be an indicator of milder disease.[27]

We were unable to explore the impact on survival of specific *CFTR* mutations as the majority of controls died before the discovery of the CF gene in 1989, making regression analysis impossible.[28] However, as 48% of the long-term survivors were homozygous ΔF508 (compared to 50% in the total UK adult CF population [29]), their survival advantage cannot be attributed to 'milder' genotypes with less severe disease expression. We chose to use 17 years of age as our age criterion as it has been demonstrated previously that this differentiates two distinct phenotypes of long-term survivors.[11] We acknowledge that we cannot be certain that all non-classic phenotypes have been excluded, but combined with the genotype data, and the fact that 97% of the total study population were pancreatic insufficient, bias from genuine non-classic disease would have been minimal. Additionally, the use of a younger age of diagnosis would have further selected out 'mild' cases, but with the recognition of significant disease heterogeneity even for homozygous ΔF508, reducing the age would have excluded patients with 'classic' disease genotypes that follow a milder disease course (eg. due to gene modifiers) – the group of patients of particular interest to this study.

There are several limitations to our findings. The incidence of complications such as CFRD and major haemoptysis increase with age,[24] thus numbers were small in both groups at the time of assessment in the adult clinic, limiting the likelihood of finding an effect on survival. We were unable to assess the impact of *B. cepacia* complex as the importance of this pathogen in CF only became apparent in the mid 1980s.[30] Asymptomatic patients, diagnosed at birth through neonatal screening are also not included in this study as such programmes have only recently been introduced. The study was further limited by the data available to us and therefore, in some instances, proxy markers (for example parental occupation) had to be used and patient numbers were small, making interpretation difficult. The information on socioeconomic status was therefore limited as the broad category of 'parental occupation' and the recognised limitations of 'source of referral' do not allow for definitive conclusions to be made.

In summary, this study demonstrates the importance for long-term survival of achieving optimal growth and lung health by the time a patient attends an adult clinic. Effective clinical care is needed to facilitate this but, from our findings, we conclude that longevity is determined early, possibly by factors independent of CFTR function (eg. gene-modifiers) that determine early phenotype, disease severity and, ultimately, the probability of long-term survival.

Competing interests: None

Table 1 Early characteristics and associations with case status (long-term survival): odds ratio (OR) and 95% confidence intervals (CI). ORs derived from weighted logistic regression models.

	All (n=230); n(%)	Cases (n=78); n(%)	Controls (n=152); n(%)	OR (95% CI)	Wald test p-values
Sex					
Female	103 (44.8)	34 (43.4)	69 (45.4)	1.00	
Male	127 (55.2)	44 (56.4)	83 (54.6)	1.09 (0.62, 1.92)	0.75
Original presenting features:					
Respiratory					
No	124 (55.9)	53 (68.8)	71 (49.0)	1.00	
Yes	98 (44.1)	24 (31.2)	74 (51.0)	0.44 (0.24, 0.80)	0.01
Malabsorption/failure to thrive					
No	78 (35.3)	33 (42.9)	45 (31.3)	1.00	
Yes	143 (64.7)	44 (57.1)	99 (68.8)	0.59 (0.33, 1.06)	0.08
Relative with CF					
No	189 (85.9)	63 (81.8)	126 (88.1)	1.00	
Yes	31 (14.1)	14 (18.2)	17 (11.9)	1.58 (0.72, 3.48)	0.26
Meconium ileus					
No	206 (93.6)	72 (93.5)	134 (93.7)	1.00	
Yes	14 (6.4)	5 (6.5)	9 (6.3)	1.40 (0.42, 4.61)	0.58
Other					
No	197 (90.0)	67 (87.0)	130 (91.6)	1.00	
Yes	22 (10.1)	10 (13.0)	12 (8.5)	1.67 (0.67, 4.17)	0.27
Age at diagnosis					
<5 yrs	185 (80.4)	55 (70.5)	130 (85.5)	1.00	0.02
5 yrs +	45 (19.6)	23 (29.5)	22 (14.5)	2.31 (1.17, 4.56)	
Prior to attendance at adult clinic:					
Use of pancreatic enzymes					
No	6 (2.6)	2 (2.6)	4 (2.6)	1.00	0.81
Yes	224 (97.4)	76 (97.4)	148 (97.4)	0.81 (0.14, 4.64)	
CFRD* before age 16 years.					
No	172 (97.7)	66 (97.1)	106 (98.2)	1.00	0.64
Yes	4 (2.3)	2 (2.9)	2 (1.9)	1.62 (0.22, 12.09)	
Pneumothorax (any)					
No	189 (82.2)	77 (98.7)	112 (73.7)	1.00 †	<0.01
Yes	41 (17.8)	1 (1.3)	40 (26.3)	0.02 (0.004, 0.08)	
Major Haemoptysis (>100mls)					
No	213 (92.6)	72 (92.3)	141 (92.8)	1.00 †	0.30
Yes	17 (7.4)	6 (7.7)	11 (7.2)	0.58 (0.21, 1.63)	
At presentation to adult clinic:					
Height (cm); median (IQR)	165 (158-172)	169 (162-175)	162 (157.5-168.5)	1.71 (1.04, 2.82) †† (per 10 cm)	0.03
Weight (kg); median (IQR)	49.5 (43.8-56.2)	55.5 (48.8-62.4)	45.8 (39.6-50.3)	2.25 (1.51, 3.34) †† (per 5 kg)	<0.01
Body mass index (kg/m^2); median (IQR)	17.8 (16.5-19.9)	19.6 (17.8-21.5)	16.8 (15.7-18.2)	1.76 (1.40, 2.22) ††	<0.01
FEV_1 (%predicted); median (IQR)	41.3 (24.5-69.7)	57.3 (41.5-81.6)	27.5 (20.4-42.1)	1.54 (1.32, 1.80) †† (per 5% predicted value)	<0.01
FVC (% predicted); median (IQR)	61.3 (40.3-81.4)	75.9 (60.1-94.8)	43.2 (32.3-66.3)	1.54 (1.33, 1.78) †† (per 5% predicted value)	<0.01

*CF-related diabetes mellitus. Analysis is limited to those attending from age 16 years. † OR adjusted for age at initial assessment. ††: OR adjusted for age at initial assessment and sex

Table 2 Sociodemographic factors and patients' educational background and associations with case status (long-term survival): odds ratios(OR) and 95% confidence intervals (CI). ORs derived from weighted logistic regression models.

	All (n=230); n(%)	Cases (n=78); n(%)	Controls (n=152); n(%)	OR (95% CI)	Wald test p-value
Source of referral					
Adult consultant/GP	102 (44.9)	47 (61.0)	55 (36.7)	1.00	0.01
clinic A*	26 (11.5)	9 (11.7)	17 (11.3)	0.78 (0.31, 1.97)	
clinic B*	47 (20.7)	4 (5.2)	43 (28.7)	0.13 (0.04, 0.38)	
other paediatrician	35 (15.4)	11 (14.3)	24 (16.0)	0.56 (0.24, 1.28)	
other	17 (7.5)	6 (7.8)	11 (7.3)	0.65 (0.22, 1.92)	
Guardian's occupation					
professional	19 (14.8)	6 (11.3)	13 (17.3)	1.00	0.87
managerial	48 (37.5)	21 (39.6)	27 (36.0)	1.61 (0.51, 5.03)	
skilled	50 (39.1)	21 (39.6)	29 (38.7)	1.54 (0.49, 4.81)	
partly-skilled/unskilled	11 (8.6)	5 (9.4)	6 (8.0)	1.53 (0.32, 7.33)	
School disruption					
none	105 (49.8)	51 (66.2)	54 (40.3)	1.00	<0.01
mild	76 (36.0)	17 (22.1)	59 (44.0)	0.32 (0.16, 0.63)	
gross	30 (14.2)	9 (11.7)	21 (15.7)	0.51 (0.21, 1.23)	
Number of 'A' levels					
0	115 (70.1)	47 (71.2)	68 (69.4)	1.00	0.88
1-2	24 (14.6)	10 (15.2)	14 (14.3)	0.92 (0.37, 2.29)	
≥3	25 (15.2)	9 (13.6)	16 (16.3)	0.79 (0.31, 1.99)	
Number of siblings; median (IQR)	2 (1-3)	2 (1-3)	2 (1-2.8)	1.06 (0.89, 1.26)	0.50
Any siblings with CF					
No	133 (58.9)	45 (57.7)	88 (59.5)	1.00	0.89
Yes	93 (41.2)	33 (42.3)	60 (40.5)	1.04 (0.59, 1.84)	

*Clinic A = Paediatric clinic in high SES area
*Clinic B = Paediatric clinic in low SES area

Table 3 Sputum microbiology, antibiotic treatment and hospital admissions prior to referral to the adult clinic and associations with case status (long term survival): odds ratios (OR) and 95% confidence intervals (CI). ORs derived from weighted logistic regression models.

	All (n=230); n(%)	Cases (n=78); n(%)	Controls (n=152); n(%)	OR (95% CI)	Wald test p-value
Microbiology (acquisition before the age of 16 years)					
*S. aureus**					
No	148 (84.6)	61 (91.0)	87 (80.6)	1.00	0.06
Yes	27 (15.4)	6 (9.0)	21 (19.4)	0.40 (0.15, 1.06)	
*P. aeruginosa**					
No	151 (85.8)	65 (95.6)	86 (79.6)	1.00	0.01
Yes	25 (14.2)	3 (4.4)	22 (20.4)	0.18 (0.05, 0.65)	
*H. influenzae**					
No	159 (90.3)	63 (92.7)	96 (88.9)	1.00	0.42
Yes	17 (9.7)	5 (7.4)	12 (11.1)	0.63 (0.21, 1.92)	
Oral antibiotics**					
No oral antibiotics	54 (28.6)	8 (11.4)	46 (38.7)	1.00 †	<0.01
Only oral antibiotics	63 (33.3)	40 (57.1)	23 (19.3)	8.31 (3.02, 22.88)	
Oral and other antibiotics	72 (38.1)	22 (31.4)	50 (42.0)	1.05 (0.34, 3.18)	
Aerosol antibiotics**					
No	138 (69.0)	59 (83.1)	79 (61.2)	1.00 †	<0.01
Yes	62 (31.0)	12 (16.9)	50 (38.8)	0.16 (0.06, 0.48)	
Intravenous antibiotics**					
No	124 (63.3)	52 (73.2)	72 (57.6)	1.00 †	<0.01
Yes	72 (36.7)	19 (26.8)	53 (42.4)	0.15 (0.05, 0.42)	
No. of previous hospital admissions					
0	16 (8.3)	13 (18.8)	3 (2.4)	1.00 †	0.01
1-5	178 (91.8)	56 (81.2)	122 (97.6)	0.17 (0.04, 0.70)	

*analysis limited to those attending from age 16 years. **analysis limited to those attending from age 15 years. † OR adjusted for age at initial assessment.

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