Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study

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Abstract

Objectives: To assess the effect on clinical outcome of managing paediatric and adult patients with cystic fibrosis at specialised cystic fibrosis centres.
Design: Cross sectional study.
Setting: Two adult cystic fibrosis centres in the United Kingdom.
Subjects: Patients from an adult cystic fibrosis centre in Manchester were subdivided into those who had received continuous care from paediatric and adult cystic fibrosis centres (group A), and those who had received paediatric care in a centre not specialising in cystic fibrosis followed by adult care in a cystic fibrosis centre (group B). Group C were referrals to the new adult cystic fibrosis centre in Cambridge who had received neither paediatric nor adult centre care for their cystic fibrosis.
Main outcome measures: Body mass index (weight (kg)/height (m^2)), lung function (forced expiratory volume in one second (FEV_1 percentage of predicted)), the Northern chest *x* ray film score, and age at colonisation with *Pseudomonas aeruginosa*.
Results: A prominent stepwise increase in body mass index was associated with increasing amounts of care at a cystic fibrosis centre; 18.3, 20.2, and 21.3 for groups C, B, and A respectively ($P < 0.001$). Improved nutritional status was correlated with a higher FEV_1 and better (lower) chest *x* ray film scores; $r = 0.52$ and -0.45 respectively ($P < 0.001$ for both).
Conclusion: These findings provide the first direct evidence that management of cystic fibrosis in paediatric and adult cystic fibrosis centres results in a better clinical outcome, and strongly supports the provision of these specialist services.

Introduction

Cystic fibrosis is the commonest autosomal recessive genetic disorder in North Europeans. The complex multisystem nature of the disease has led to the management of affected individuals in centres specialising in cystic fibrosis.[1 2] The cystic fibrosis centre provides care from a multidisciplinary team consisting of a clinical nurse specialist, ward staff, dietician, physiotherapist, social worker, and clerical staff coordinated by a specialist physician. There is close liaison with other specialists, and facilities for both inpatient and outpatient management and for clinical research. Since its first recognition as a disease entity in the 1930s cystic fibrosis has improved from a 70% one year mortality rate such that the median survival is predicted to be 40 years for a child born in the 1990s.[3 4] Better nutrition and antibiotic treatment have contributed to the improved survival, and although there is supportive evidence for the value of the cystic fibrosis centre there is no direct evidence that its availability alters prognosis.[5–9]

The development of a new adult cystic fibrosis centre in Cambridge in 1994 presented a unique opportunity to study the effect of centre care on the clinical outcome of cystic fibrosis. The absence of a cystic fibrosis centre within the region inevitably led to many patients being cared for in general clinics and by general practitioners. We compared these referrals to the new centre with patients who had received care in both paediatric and adult cystic fibrosis centres, and with patients who had received paediatric care in a centre not specialising in cystic fibrosis followed by adult care in a cystic fibrosis centre.

Methods

Patient assessment

Ninety seven patients from the Manchester adult cystic fibrosis centre were recruited for the study. The patients were divided into two groups depending on their previous paediatric care. Group A consisted of individuals who had received paediatric care at a cystic fibrosis centre (from two paediatric centres), and group B consisted of patients who had not received paediatric care in a cystic fibrosis centre. Groups A and B were followed up by the Manchester adult cystic fibrosis centre for a median of 89.5 months (interquartile range 43-115.5 months) and 55 months (18-97 months) respectively. Of 47 first year referrals to the new Cambridge centre 36 constituted group C as they had received neither paediatric nor adult centre care for cystic fibrosis.

Details of age, sex, age at diagnosis, pulmonary function, colonisation status and age at onset of colonisation with *Pseudomonas aeruginosa*, pancreatic status, diabetes mellitus, smoking history, and liver function were obtained by patient interview and from case notes. Colonisation was defined as two consecutive

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positive sputum cultures six months apart. Patients were classified according to their need for pancreatic enzyme supplements as pancreatic sufficient or pancreatic insufficient. The presence of liver disease was established from clinical features, interpretation of liver function tests, and liver imaging. Severity of pulmonary disease was documented as the patient's best forced expiratory volume in one second in the previous six months compared with age and sex matched controls, expressed as a percentage of predicted values (FEV_1). A chest *x* ray film taken when the patient was stable was assessed using the Northern scoring system by a radiologist who was blinded to the patients' care.[10] This system scores a posteroanterior chest *x* ray film out of a maximum of 20 with higher scores representing more profound radiographic abnormalities.

Cystic fibrosis genotypes were determined by the Department of Clinical Genetics, Addenbrooke's Hospital, Cambridge and the Department of Molecular Genetics, Royal Manchester Children's Hospital. α_1 Antitrypsin phenotypes were determined by isoelectric focusing, and were classified as deficient (at least one S or Z allele) or non-deficient (phenotype M).[11]

Statistical analysis—Differences in patient characteristics between groups A, B, and C were assessed by three tests: the Kruskal-Wallis, χ^2 test for contingency tables, and one way analysis of variance. Analysis of covariance assessed the effect of centre care on body mass index (weight (kg)/height (m^2)) and on lung disease severity (FEV_1). The covariates evaluated were age, sex, age at diagnosis, cystic fibrosis genotype, pancreatic status, smoking status, diabetes mellitus, colonisation status with *P aeruginosa* and *Burkholderia cepacia*, liver disease, and α_1 antitrypsin phenotype. Each covariate was individually assessed for its effect on the outcome measure, and the most powerful combination was used to obtain the final model and the adjusted means for each analysis. The effect of centre care on chest *x* ray film scores was assessed using the Kruskal-Wallis test with the Mann-Whitney U test incorporating the Bonferroni correction to identify differences between the groups. The one way analysis of variance test assessed the effect of patient group on age at onset of colonisation with *P aeruginosa* as no covariates were found to be important in this model. Further to this the least significant difference technique for multiple comparisons was used to identify which groups were significantly different. The relation between FEV_1, body mass index, and chest *x* ray film scores was assessed by Pearson's correlation coefficient. Comparison of the body mass index and FEV_1 before and after 18 months' management in the Cambridge adult cystic fibrosis centre was by the non-parametric sign test and the paired *t* test respectively. A P value of less than 0.05 was taken to be statistically significant in all analyses.

Table 1 Characteristics of three groups of cystic fibrosis patients* (P value represents any difference between the three groups)

Variable	Group A (n=50)	Group B (n=47)	Group C (n=36)	P value
Mean and SD of age (years)†	22.9 (4.49)	27.5 (7.50)	25.0 (6.42)	0.002
Median and interquartile range of age at time of diagnosis (months)‡	6.0 (22.0)	15.0 (81.0)	12.0 (34.5)	0.088
Sex (%)¶:				
Male	28 (56.0)	23 (48.9)	26 (72.2)	0.097
Female	22 (44.0)	24 (51.1)	10 (27.8)	
Cystic fibrosis genotype (%)§¶:				
508/508	32 (63.3)	25 (55.5)	17 (56.7)	0.199
508/Other	12 (26.5)	19 (42.2)	9 (30.0)	
Non-508/non-508	5 (10.2)	1 (2.2)	4 (13.3)	
Liver disease (%)¶:				
Not present	43 (86.0)	41 (87.2)	30 (83.3)	0.879
Present	7 (14.0)	6 (12.8)	6 (16.7)	
Pancreatic status (%)¶:				
Insufficient	48 (96.0)	40 (85.1)	35 (97.2)	0.057
Sufficient	2 (4.0)	7 (14.9)	1 (2.8)	
Diabetes mellitus (%)¶:				
Not present	39 (78.0)	38 (80.9)	27 (75.0)	0.814
Present	11 (22.0)	9 (19.1)	9 (25.0)	
Pseudomonas aeruginosa (%)¶:				
Not colonised	5 (10.0)	5 (10.6)	10 (27.8)	0.043
Colonised	45 (90.0)	42 (89.4)	26 (72.2)	
Burkholderia cepacia (%)¶:				
Not colonised	31 (62.0)	39 (83.0)	32 (88.9)	0.007
Colonised	19 (38.0)	8 (17.0)	4 (11.1)	
Smoking status (%)¶:				
Non-smoker	43 (86.0)	45 (95.7)	33 (91.7)	0.243
Current or ex-smoker	7 (14.0)	2 (4.3)	3 (8.3)	
α_1 Antitrypsin phenotype (%)¶:				
Normal	42 (85.7)	39 (83.0)	29 (85.3)	0.926
Deficient	7 (14.3)	8 (17.0)	5 (14.7)	

*Group A patients had had both paediatric and adult care in a cystic fibrosis centre; group B patients had not had paediatric but had had adult care in a cystic fibrosis centre; group C patients had had no care in a cystic fibrosis centre. †One way analysis of variance. ‡Kruskal-Wallis test. §Not available for one, two, and six patients in groups A, B, and C respectively. ¶χ^2 test.

Results

At the time of the study the Manchester adult cystic fibrosis centre cared for 81 patients who had received continuous cystic fibrosis centre care—that is, paediatric care followed by adult care in a cystic fibrosis centre. The patients had a mean body mass index of 21.3 (SD 2.6), mean FEV_1 of 65.0 (SD 23), and a mean age of 23.2 years (SD 4.9). Fifty of these patients were recruited into group A. The 31 subjects not recruited into group A had a mean body mass index of 21.3 (SD 2.8) and mean FEV_1 of 72.5 (SD 20.8). The mean body mass index of these patients did not differ from those included in the study but their mean FEV_1 was significantly better than those included in the study (mean observed FEV_1 60.5); 12% difference, P = 0.025. Hence the FEV_1 values in group A patients would tend to underestimate the FEV_1 of all the patients attending the clinic who had received continuous care in a cystic fibrosis centre.

Eighty patients from the Manchester clinic had received paediatric care in a centre not specialising in cystic fibrosis followed by adult care in a cystic fibrosis centre. The patients had a mean body mass index of 20.4 (SD 2.3), mean FEV_1 of 56.6 (SD 22.1), and median age of 25 years (interquartile range 23.0-29.8 years). Forty seven of these patients were recruited into the study. The 33 patients not included in group B had a mean body mass index of 20.6 (SD 2.2) and a mean FEV_1 of 61.3 (SD 21.5), which did not differ from those included in the analysis.

Table 1 shows the characteristics of patients in groups A, B, and C. Differences in characteristics between the groups were taken into account if the particular factor had an important effect on the outcome measure under evaluation. This method corrects for any imbalances between the groups that could affect

outcome, such as the difference in the ages of the patients between groups A and B, which would have an important confounding effect on outcome if it were not included as a covariate.

Body mass index—The patients who had any form of centre care for cystic fibrosis (groups A and B) had a significantly higher body mass index when compared with patients who had had no centre care for their cystic fibrosis (group C); 21.2, 20.0, and 18.8 for groups A, B, and C respectively (difference between A and C 2.4, $P<0.001$; and between B and C 1.2, $P=0.019$). Moreover, patients who had received both paediatric and adult centre care for their cystic fibrosis (group A) had significantly better nutritional status compared with patients who had received non-specialist paediatric care followed by adult centre care for their cystic fibrosis (group B, $P=0.005$). Although a positive correlation was found between FEV_1 and body mass index ($r=0.520$, $P<0.001$) the differences in body mass index between the groups persisted after adjusting for the effect of FEV_1 (Table 2).

Table 2 Effect of three types of care for cystic fibrosis on outcome measures* (P value represents any difference between the three groups. Adjusted mean calculated after correction for imbalances of important covariates between groups)

Outcome measure	Group A (n=50)	Group B (n=47)	Group C (n=36)	P value
FEV_1 (body mass index as covariate):				
Observed mean	60.5	53.1	44.5	
Adjusted mean	53.5	53.9	50.7	0.777
Pooled within group SD	19.35			
FEV_1(without body mass index):				
Adjusted mean	61.2	54.3	42.6	0.002
Pooled within group SD	22.26			
Body mass index (with FEV_1 as covariate):				
Observed mean	21.3	20.2	18.3	
Adjusted mean	21.2	20.0	18.8	<0.001
Pooled within group SD	2.02			
Body mass index (without FEV_1):				
Adjusted mean	21.6	20.0	18.3	<0.001
Pooled within group SD	2.39			
Chest *x* ray film score†:				
Median (interquartile range)	9.0 (6.0-11.0)	10.0 (7.0-12.8)	12.0 (10.0-13.0)	0.003
	n=47	n=44	n=33	
Age (years) at colonisation with *Pseudomonas aeruginosa*‡:				
Observed mean (SD)	11.1 (5.5)	18.1 (7.3)	16.1 (9.5)	<0.001
	n=41	n=36	n=19	

FEV_1 Forced expiratory volume in one second as percentage of predicted values. *Group A patients had had both paediatric and adult care in a cystic fibrosis centre; group B patients had not had paediatric but had had adult care in a cystic fibrosis centre; group C patients had had no care in a cystic fibrosis centre. †Kruskal-Wallis test. ‡One way analysis of variance.

Lung disease

No significant difference was found between the FEV_1 for groups A, B, and C (53.5, 53.9, and 50.7% respectively) in a final model with the covariates of body mass index, age, colonisation with *P aeruginosa* and *B cepacia*, pancreatic status, smoking history, and liver cirrhosis (Table 2). In view of the strong positive correlation between FEV_1 and body mass index the effect of body mass index on the groups' FEV_1 was assessed by including and excluding body mass index as a covariate (other covariates were constant). Interestingly when body mass index was excluded as a covariate the groups' FEV_1 was strikingly different; 61.2, 54.3, and 42.6 for groups A, B, and C respectively. This indicates that the underlying differences in body mass index between the groups were the only reason for the apparent differences in FEV_1 in our study (Table 2). After exclusion of body mass index analysis showed that patients in group A who had received both paediatric and adult centre care for their cystic fibrosis had a much better FEV_1 compared with patients who had not received centre care. There was also a trend towards a better FEV_1 in group B, who received adult care for their cystic fibrosis, compared with group C patients although this narrowly missed statistical significance; 11.6% difference ($P=0.051$). No significant difference was found between groups A and B ($P=0.17$).

Groups A and B had significantly better chest *x* ray film scores than group C; 9.0, 10.0, and 12.0 for groups A, B, and C respectively (differences between A and C 3.0, $P=0.007$; and between B and C 2.0, $P=0.029$). No significant difference was found between patients in groups A and B ($P=0.229$). These scores correlated well with FEV_1 ($r=-0.69$, $P<0.001$) suggesting that they were a good indication of pulmonary disease severity. The scores were also significantly negatively correlated with body mass index ($r=-0.45$, $P<0.001$) indicating that less severe radiographic changes (and less severe pulmonary disease) were associated with a higher body mass index.

Age at onset of colonisation with *P aeruginosa*

Patients who had attended both paediatric and adult cystic fibrosis centres (group A) were more likely to be colonised with *P aeruginosa*, and were colonised with the organism much earlier (by 5 years) than patients who had never attended a cystic fibrosis centre (11.1 years for group A and 16.1 years for group C). Although patients in group B who had not received paediatric care in a cystic fibrosis centre but had received adult care in one were as likely to be colonised with *P aeruginosa* as group A patients, they acquired this organism seven years later (mean age at colonisation with *P aeruginosa* 11.5 years, 95% confidence interval 9.4 to 12.8; and 18.1 years, 15.6 to 20.6 years for groups A and B respectively), which again was significant at the 5% level (Table 2).

After 18 months, 27 out of the 36 patients in group C were still attending the Cambridge centre: three died; four received heart-lung transplantation; one left the region; and one chose not to attend. Further assessment showed that their mean body mass index had improved significantly by 1.1 ($P<0.001$) and that they maintained their FEV_1 (geometric means 41.7 and 40.9 before and after follow up at 18 months respectively; $P=0.457$).

Discussion

Current guidelines recommend that the health care of cystic fibrosis should be delivered by a specialist team in a cystic fibrosis centre.[1,2] Previous studies have supported a clinical benefit from this approach but none has shown direct evidence to justify this system of care.[5–9] A randomised controlled trial evaluating the merits of centre care of cystic fibrosis would be impossible but the establishment of a new adult cystic fibrosis centre in Cambridge has provided a unique opportunity to perform this assessment by an alterna-

tive method. We have shown a clear advantage in clinical outcome in patients who received treatment in paediatric and adult cystic fibrosis centres. The maximum benefit was apparent in nutrition and pulmonary disease severity both of which are important determinants of prognosis, and was present to a lesser but important extent even if the patients only received treatment in a cystic fibrosis centre in adulthood.[12–14]

Our findings support the strong relation between nutrition and pulmonary disease severity in patients with cystic fibrosis.[6 13] Indeed, of all the factors assessed, nutritional state was the most predictive of FEV_1 in our group of patients. Body mass index was determined by the amount of care received for cystic fibrosis in a centre, and as body mass index was a major determinant of pulmonary function this was also closely linked to centre care. The mechanism of the effect of body mass index on FEV_1 is complex and not clearly established. Malnutrition can cause immune dysfunction and respiratory muscle weakness, and pulmonary disease could influence body mass index by increasing energy expenditure owing to a greater oxygen cost of breathing, and from the metabolic effects of chronic inflammation and sepsis.[15] The predictive effect of body mass index on lung function reinforces the importance of nutrition in cystic fibrosis but does not undermine the importance of aggressive pulmonary care, which is well known to be beneficial to pulmonary function.[16–18]

In cystic fibrosis centres cross infection with *P aeruginosa* is a controversial issue.[19–23] We found higher *P aeruginosa* colonisation rates in patients managed in cystic fibrosis centres. Those patients who received only adult centre care (group B) were colonised seven years later than those who received paediatric and adult centre care (group A). It is interesting that the benefit of centre care of cystic fibrosis occurred despite more frequent colonisation with *P aeruginosa* and *B cepacia*, which have been associated with more severe pulmonary disease in other studies.[24 25]

The wide spectrum of severity in cystic fibrosis makes it important to consider confounding factors when assessing clinical outcome. Our patients were recruited from two different regions of the United Kingdom, which makes it possible that additional genetic or environmental factors, or both, could account for the regional differences that we have seen. In addition there may have been a tendency for the most severely affected patients to have been referred first to the new cystic fibrosis centre in Cambridge. The patients in all groups were, however, well matched for most known factors that could alter the clinical course of the disease (Table 1), and the statistical methods used are the most appropriate available to account for any imbalances between the groups. Moreover the benefits of centre care are underscored by the finding that patients referred to the new adult cystic fibrosis centre in Cambridge had an improved body mass index after follow up at 18 months.

The implications of the findings from this study are considerable. Although accepted in principle this is the first time that the two main prognostic indicators in cystic fibrosis—that is, pulmonary function and nutrition—have been so clearly linked to the care of paediatric and adult cystic fibrosis in centres. The main reason for improved survival seen in adult cystic fibrosis centres is because patients come from paediatric cystic fibrosis centres which have considerably improved clinical status compared with 10 years ago. It is crucial that paediatric patients receive centre care for their cystic fibrosis at the earliest possible age if they are to gain the impetus for prolonged survival in adulthood. Patients with cystic fibrosis have already requested their care be provided by centres, and it is now the clinical responsibility of all physicians to ensure that this care begins in childhood and is continued throughout adult life.[9]

Key messages

- Management of patients with cystic fibrosis in paediatric and adult cystic fibrosis centres results in an improved clinical outcome
- Improved clinical outcome occurred in cystic fibrosis centres despite earlier and more frequent colonisation with *Pseudomonas aeruginosa*
- Nutritional status is an important predictor of lung disease in cystic fibrosis

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Contributors: RM and KW helped with the study design and data collection and interpretation. RW helped with the statistics and data interpretation, NC scored the chest *x* ray films, MD helped with data collection and interpretation, and DB and DL helped with the study design and data interpretation.

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Conflict of interest: None.

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Commentary: Management in paediatric and adult cystic fibrosis centres improves clinical outcome

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Mahadeva et al provide evidence that management of cystic fibrosis in a paediatric centre specialising in such care and subsequent transfer to an adult centre results in better objective measures of clinical status (body mass index and forced expiratory volume in one second (FEV_1) as a percentage of predicted values) in adults with cystic fibrosis than management in general paediatric or adult clinics. The authors found that it was the type of paediatric care that made the biggest difference. Of course the patients who receive care in a paediatric clinic are a heterogeneous group some of whom will have been receiving treatment in a centre since birth while others may have been referred to the centres comparatively late in childhood. The methodology can also be criticised in several other ways including the selection bias inherent in the exclusion from the original birth cohorts of patients who have died. In all major studies of cystic fibrosis, female mortality rates are higher than those of males, which may be reflected by the higher proportion of males in the group who had not received centre care.

There are other important and confounding sex differences in cystic fibrosis. Recent papers have reported that females with cystic fibrosis surviving into adulthood maintain their body mass index better than males,[1] although among a Canadian group (which included those who died) female patients showed a much steeper decline in pulmonary function than males.[2]

Care should be taken before generalising from these audit data. Cystic fibrosis centres vary considerably in leadership, resources, and outcomes, and the original United Kingdom survey that reports a survival benefit conferred by centre care defined centres only in terms of clinic size.[3] We still need better understanding of the components of specialist care that make the difference.

Three positive messages emerge from this paper. Firstly, the maintenance of good nutritional status in cystic fibrosis is important, and the authors' opinion was that "body mass index was a major determinant of pulmonary function." It is paradoxical that no dietician was included in the authorship. Secondly, although there is more opportunity for cross infection between patients in large centres, in particular the spread of *Pseudomonas aeruginosa* (this study confirmed that patients attending the cystic fibrosis centres were indeed more likely to be colonised with the organism), nevertheless the superiority of the large centres over patients in non-specialist centres was maintained. The lesson seems to be that bacterial infection can be controlled by aggressive treatment. Finally, it has once again been shown that fatalism is not appropriate in dealing with this disease. The Cambridge patients had considerably improved nutritional and lung function measurements after 18 months of specialist care. None the less the Cambridge patients still lagged behind the Manchester patients, who had been given a head start by centre care in childhood.

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One hundred years ago

An expedition without medical aid

It is not a matter for surprise that strong comments should have been made on the disastrous consequences attending the despatch of military expeditions in Uganda without any medical aid. Relating the circumstances in which Captain Dunning, SDO, Royal Fusiliers, lost his life in Uganda, the *Army and Navy Gazette* says: "Here was an expedition actually sent on active service without a doctor to look after the sick and wounded; Captain Dunning was seriously wounded and lived for some days in great agony, but his life would have been spared, there is every reason to believe, if he had received even ordinary medical care."

Our contemporary condemns the Foreign Office for "the cruel neglect of those who have entered its service. There seems to have been no attempt made to protect life." The story is almost incredible. Even though the Army Medical Department has been allowed by the ineptitude of the War Office to dwindle far below its proper strength, yet it is certain that the Foreign Office could have at once obtained medical volunteers in this country by holding up its hand. The public, we imagine, are becoming heartily sick of these recurring scandals.
(*BMJ* 1898;i:1096)