Journal of Cystic Fibrosis 8 (2009) 26–30

Journal of Cystic Fibrosis

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Early referral to cystic fibrosis specialist centre impacts on respiratory outcome ☆

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Received 27 February 2008; received in revised form 11 July 2008; accepted 27 July 2008
Available online 5 October 2008

Abstract

Background: Published studies concerning the impact of specialist care on lung disease in cystic fibrosis remain limited and most are either biased due to comparison with historical controls and/or underpowered.
Methods: In this retrospective multicentric study, data from all CF children fulfilling the following criteria were collected: 1) Age 6–<18 at the end of 2003; 2) diagnosis before 8 y; 3) follow-up in an accredited CF Belgian centre; 4) at least 1 spirometry and respiratory culture available for 2003. Group A included children referred ≥2 years after the diagnosis. Patients from Group A were then matched with a single early referred patient on the basis of 2 criteria: same centre, as closest age as possible (Group B).
Results: Data from 217 children were collected (Group A: 67/217). Late referred patients had a lower FEV_1 (77.2% ± 22.4 *vs* 86.7% pred. ± 19.4, $p=0.01$) and a higher prevalence of *Pseudomonas aeruginosa* (38.6 *vs* 17.5%, $p<0.05$).
Conclusion: In this population of CF children, a delay of 6.1 y (*vs* 0.1 y) between diagnosis and referral to a specialist clinic resulted in poorer respiratory outcome at age 13.

Keywords: Specialized care; Respiratory outcome; *Pseudomonas* prevalence; Early referral; Children

1. Introduction

The prognosis of cystic fibrosis (CF) is mainly determined by pulmonary disease and has dramatically improved over the last few decades. In the United States, the mean life expectancy increased from 6 months when the disease was first described, to 35 years in 2005 [1,2]. Using a mathematical model to describe this improvement, a life expectancy of 40 years has been estimated for children born in 1990 and referred early to a specialist centre [3]. Recently, a life expectancy of 50 years has been claimed for children born around the year 2000 and this appears realistic [4]. CF is a multi-systemic and complex disease. It is commonly assumed that specialist management is the best way of guaranteeing enough experience on this multifaceted condition and making available a dedicated team as well as the numerous specialist interventions that might be necessary. It also facilitates large enough clinical trials, which remains a critical issue [5]. Early referral to a specialist healthcare centre is considered as an important prognostic factor as highlighted in consensus reports on optimal management of CF [6–8]. It is also supported by those who convincingly advocate for efficient neonatal screening, universally coupled with immediate referral

☆ Presented in part at the 29th European Cystic Fibrosis Conference (Copenhagen, Denmark, June 2006).

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doi:10.1016/j.jcf.2008.07.005

to a specialist centre. Surprisingly however, published studies concerning the impact of this centralization on lung disease remain limited and except for one [9] are either biased due to comparison with historical controls, and/or probably underpowered [10–15]. Mahadeva et al. [9] compared two groups of adults who had either received continuous care from paediatric and adult CF centres ($n=50$) or had received neither paediatric nor adult centre care for their CF ($n=36$). Excluding body mass index as a covariate, FEV_1 was significantly better in the first group. However, these patients where significantly more often colonized with *Pseudomonas aeruginosa* (PA) and this colonization occurred 5 years earlier. Studying this topic further might be especially relevant as PA colonization adversely affects the prognosis of CF and also because even though a growing number of western regions or countries are about to implement newborn screening for CF, some primary care physicians still wish to retain the clinical management responsibilities at least until the patients become obviously ill.

This study was conducted to test the hypothesis that children suffering from CF who are early referred to a specialist centre have a more favourable respiratory outcome than those referred later on. As there is no definition of what a late referral is, a cut-off level of 2 years was chosen based on the estimation that the diagnosis of CF by screening anticipates diagnosis by more than a year in 50% of cases [16] and after a preliminary analysis in a single centre.

2. Methods

2.1. Overall model of CF care in Belgium

Since 1999, seven CF centres have been officially accredited and financially supported by the national health system. All are based in academic hospitals. Centres had to fulfill a number of qualitative criteria (facilities and resources) closely derived from the Cystic Fibrosis Trust's 1996 guidelines [17]. A minimum of 50 patients on full care was required. Shared care is not considered as an option in this small country. Despite a few local initiatives, there is no national neonatal screening program.

This retrospective study initially involved these 7 centres. Eligible patients fulfilled the following criteria: 1) age at the last consultation in 2003 ranging from 6 to 18 years; 2) age at diagnosis less than 8 years; 3) at least one available spirometry data set and bacterial culture in 2003. Investigated data formed part of those collected for the Belgian CF registry, for which a written informed consent was obtained and included. FEV_1, weight (expressed as a percentage of ideal weight for height), *P. aeruginosa* (PA) prevalence at the end of the year 2003 were the main outcome measures. Anthropometric parameters and FEV_1 were normalized utilizing Freeman's [18] and Knudson's [19] equations respectively. Patients who did not expectorate spontaneously underwent a full session of physiotherapy, after which either expectorations were obtained or a deep pharyngeal aspiration was performed.

Patients were classified into two groups according to the delay between age at diagnosis and age at referral to an accredited centre, an early referral being defined as a delay less than 2 years. To get more comparable groups (see infra), each late referred patient (Group A, $n=61$) was then matched to a single early referred patient on the basis of 2 criteria: same centre and as closest age as possible. This defined Group B.

For the 2 groups of matched patients, additional data were collected, including: % of neonatally screened patients, number of respiratory cultures per patient in 2003, % of oropharyngeal samples (as opposed to sputum) for bacteriological purpose at the last visit of 2003, % of mucoid strains of PA and rate of chronic colonization by PA according to Lee et al. [20] at the end of 2003, number of hospitalisations and respiratory-related hospitalisations between 1999 and 2003 (including home intravenous antibiotic treatments), anthropometric data at the first visit at the centre.

Normally distributed data (when tested using the Kolmogorov–Smirnov test) were expressed as mean ± SD. Analysis of differences between groups or within groups at referral and at the end of 2003 was performed using unpaired or paired *t*-tests. Not normally distributed data are expressed as medians and differences between groups were evaluated with the Mann–Whitney test. A chi-squared test was used for categorical variables. Analysis of variance was performed to assess the impact of PA prevalence (alone or in combination with the delay between diagnosis and referral) on FEV_1 in the two groups. A p value <0.05 was considered significant.

3. Results

The 7 Belgian centres accepted to take part to the study. The smallest centre proved to be unable to gather the data within 12 months. Table 1 summarizes main clinical characteristics of 217 patients from the 6 other centres according to the delay between age at diagnosis and age at referral to a CF accredited centre.

Table 1
Main characteristics of the whole study population ($n=217$), classified according to the delay between age at diagnosis and age at referral

	>2 years: Group A	<2 years	p Value
Delay between age at diagnosis and age at referral			
N (%)	67 (30.9%)	150 (69.1%)	
M (%)	47	48	NS (0.96)
Median age at diagnosis (years)	0.2	0.2	NS (0.11)
Median delay between diagnosis and referral (years)	6.3	0.1	<0.001
Duration of follow-up in a specialized centre	6.2 ± 3.7	10.2 ± 3.4	<0.0001
PS (%)	1.5	4.7	NS (0.44)
Δ*F*508/Δ*F*508 (%)	60.7	61.2	NS (0.94)
Age (years)	14 ± 3.1	11.6 ± 3.1	<0.0001
FVC (% pred)	91 ± 21	96 ± 19	NS (0.08)
FEV_1 (% pred)	77.6 ± 22.2	88.5 ± 20.2	<0.001
BMI (Z score)	−0.94 ± 1.12	−0.62 ± 1.08	<0.05
IBW (%)	96 ± 12	97 ± 11	NS ($p=0.59$)
PA prevalence (%)	41.8	16.7	0.0001

Data are presented as mean ± SD unless otherwise stated. M: male, PS: pancreatic sufficient, Δ*F*508/Δ*F*508: patients homozygous for the Δ*F*508 CFTR mutation, FVC: forced vital capacity, % pred: % predicted, FEV_1: forced expiratory volume in one second, BMI: body mass index, IBW: ideal body weight, PA: *Pseudomonas aeruginosa*.

Most of the children (69.1%) were referred to a specialist centre less than 2 years following diagnosis and this proportion was strikingly different among 6–9 y and 15–18 y old children (88.3% *vs* 45.6% respectively, $p<0.0001$), reflecting changes in the model of CF care in Belgium in the past two decades.

Early referred patients had a significantly better FEV_1 (88.5% pred ± 20.2 *vs* 77.6% pred ± 22.2, $p<0.001$), lower prevalence of PA ($p=0.0001$) and higher BMI ($p<0.05$). However it was necessary to refine this comparison for three reasons: 1) early referred patients were significantly younger (11.6 years ± 3.1 *vs* 14 years ± 3.1, $p<0.0001$); 2) the proportion of early referred patients was very variable between centres, ranging from 26% in centre numbered 5 to 86% in centre numbered 3; 3) there were striking differences in outcomes from different centres (Fig. 1). In order to take into account these confounding variables, each later referred patient was matched based on same age to a single early referred patient attending the same

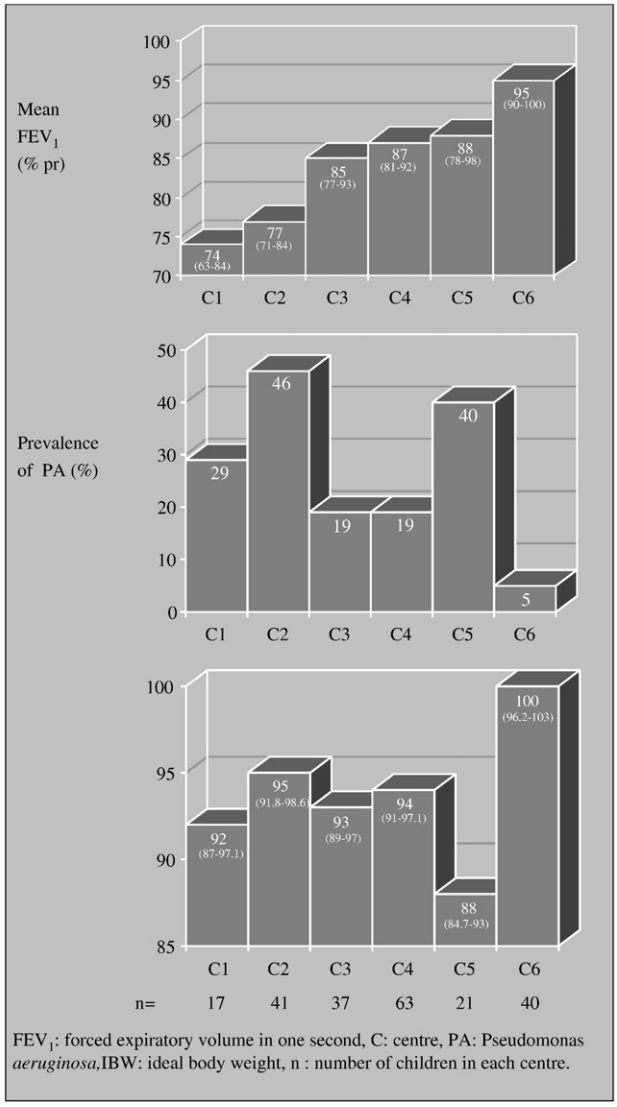

Fig. 1. Major outcome parameters of the paediatric populations (6–17 years) from the 6 main Belgian centres at the end of the year 2003 (mean — 95% confidence interval for the mean).

Table 2
Main characteristics of children after matching, based on same age, late referred patients (Group A) to a single early referred patient attending the same accredited centre (Group B)

	>2 years: Group A	<2 years: Group B	*p* Value
Delay between age at diagnosis and age at referral			
N	57	57	
Median delay between diagnosis and referral (years)	6.1	0.1	<0.0001
Neonatally screened patients (%)	15.8	10.5	NS (0.57)
M (%)	47	42	NS (0.70)
Median age (years) at diagnosis (IQR)	0.2 (0–0.6)	0.3 (0.1–1.82)	NS (0.13)
Mean duration of follow-up in a specialized centre	6.4 ± 3.7	11.4 ± 3.3	<0.0001
PS (%)	1.8	5.3	NS (0.61)
Δ*F*508/Δ*F*508 (%)	60	63.2	NS (0.87)
Age (years)	13.6 ± 3.1	12.9 ± 2.9	NS (0.24)
FVC (% pred)	91 ± 21.6	94 ± 16.1	NS (0.41)
FEV_1 (% pred)	77.2 ± 22.4	86.7 ± 19.4	0.01
Weight (% IBW)	92 ± 14	95 ± 19	NS (0.33)
BMI (*Z* score)	−0.82 ± 1.04	−0.62 ± 1	NS (0.30)
Weight (*Z* score)	−0.82 ± 1.14	−0.66 ± 1.15	NS (0.45)
Height (*Z* score)	−0.25 ± 1.40	−0.27 ± 1.15	NS (0.91)
Median number of respiratory cultures in 2003	5	5	NS (0.87)
Bacteriology: % of OP aspirates	30	42.1	NS (0.25)
PA prevalence (%)	38.6	17.5	0.021
Prevalence of mucoid PA (%)	24.6	12.3	NS (0.15)
Chronic colonization by PA (%)	33.3	21	NS (0.2)
Median number of hospitalisations for respiratory problems in the past 5 years	1	1	NS (0.53)

Data are presented as mean ± SD unless otherwise stated. M: male, PS: pancreatic sufficient, Δ*F*508/Δ*F*508: patients homozygous for the Δ*F*508 CFTR mutation, FVC: forced vital capacity, % pred: % predicted, FEV_1: forced expiratory volume in one second, IBW: ideal body weight, Pc: percentile, BMI: body mass index, OP: oropharyngeal, PA: *Pseudomonas aeruginosa*.

CF accredited centre. In the 2 centres with higher proportions of late referred patients, a few of these could not be matched and were discarded. Two more homogeneous groups of later referred (Group A) or early referred patients (Group B) could then be compared. Table 2 summarizes these refined data. Belgian CF children aged from 6 to 17 years, referred earlier to a centre (less than 2 years after the diagnosis), have a more favourable respiratory outcome than those referred later on. Specifically, they had a 12% higher FEV_1 at a mean age of 13 years ($p=0.01$) and PA prevalence in this group was about two fold lower ($p<0.05$). Analysis of variance revealed a strong association between PA and FEV_1 ($p<0.0001$) but not between FEV_1 and the delay of referral. After adjustment for the presence of PA, FEV_1 was comparable in early and late referred patients ($p=0.45$).

At the end of 2003, ideal body weight (Group A: 92% ± 14, Group B: 95 ± 11) and *Z* scores for BMI (Group A: −0.82 ± 1.04, Group B: −0.62 ± 1), weight (Group A: −0.82 ± 1.14, Group B: −0.66 ↑1 1.15) or height (Group A: −0.25 ± 1.40, Group B: −0.27 ± 1.15) did not differ significantly between the 2 groups.

Anthropometric data at the first visit at the centre were available for 49 children from Group A and 43 from Group B.

Table 3
Anthropometric data at the first visit at the centre and at the end of 2003

		>2 years: Group A	<2 years: Group B	p Value
Delay between age at diagnosis and age at referral				
n		49/57	43/57	
Visit 1	Median age (y)	6.6	0.8	
	BMI	−0.80 ± 1.15	−1.31 ± 1.5	NS (0.07)
	Weight	−1.04 ± 1.38	−1.20 ± 1.57	NS (0.61)
	Height	−0.89 ± 1.57	−0.95 ± 0.58	NS (0.85)
End of 2003	Median age (y)	14.4	13.3	
	BMI	−0.75 ± 1.03	−0.67 ± 0.94	NS (0.66)
	Weight	−0.76 ± 1.15	−0.64 ± 1.02	NS (0.61)
	Height	−0.23 ± 1.44	−0.22 ± 1.06	NS (0.98)
Mean duration of follow-up (y)		6.1 ± 3.7	11.2 ± 3.1	
Δ BMI (*Z* score) at the end of 2003		0.05 ± 0.72	0.65 ± 1.73	0.03

Data are presented as mean ± SD unless otherwise stated. BMI (body mass index), weight and height are expressed as *Z* score.

Table 3 summarizes them as well as corresponding values for these subgroups at the end of 2003. From the first visit tot the end of 2003, a significant improvement was observed in early referred patients in terms of BMI ($p<0.05$), weight ($p<0.05$) and height ($p<0.01$), all expressed in *Z* score. In late referred patients, weight and height improved significantly ($p<0.05$ and <0.001 respectively) but BMI did not ($p=0.62$).

4. Discussion

While avoiding the bias of most previous studies, this retrospective multicentric work demonstrates a more favourable respiratory outcome in CF children if they are referred early to a specialist centre. It is the first time that this benefit is reported both in terms of FEV_1 and PA prevalence. The functional respiratory benefit observed in children referred early following the diagnosis is important (12% FEV_1 difference at a mean age of 13 years). As FEV_1 and PA infection are major prognostic markers in CF, these data add important objective evidence to support centralized treatment of patients with this disease.

While it is currently considered as unacceptable for an isolated clinician to only refer a patient for severe complications or when the disease has progressed too far [6], a complete centralization for the care of CF patients can also present some obstacles, including distances between a centre and a patient's home – which is virtual in such as small country as Belgium – and the problem of financing patient healthcare in specialist centres [21]. Moreover, the possibility of an increased risk of cross-infection for patients followed up in the centres has to be taken into account. It is especially dreaded for PA infection because chronic colonization by this bacteria has been associated with the loss of nearly a third of life expectancy [22], a less favourable FEV_1 and an accelerated decline of this parameter [23,24], an increased treatment load affecting quality of life and much higher treatment costs [25]. A link between attendance at a centre and colonization by PA has been documented [26], including in the context of neonatal screening [27]. In the latter study, increased colonization by this organism could have masked part of the benefit derived from early diagnosis and early specialist intervention.

Mahadeva's [9] study currently provides the most often cited published evidence for early centralized care in CF patients. These authors reported a better FEV_1 and chest X-ray score in CF adults who had received continuous care from paediatric and adult CF centres as compared to adults who never received centre care or only received paediatric care at a CF centre.

Our work confirms the main conclusion of this study: earlier specialist CF care is associated with a better FEV_1. It strengthens it in that the mean delay before referral in the late referred group is much shorter (6.1 y) than in the Mahadeva's study.

In contrast to the findings of Mahedeva et al. however, we observed that PA prevalence, mucoid PA prevalence and chronic colonization rate by PA according to Lee all were lower in the group of early referred patients though the difference was only significant for PA prevalence. This was not obtained at the price of a greater number of hospitalisations for respiratory problems in the last 5 years of follow-up (see Table 3). Moreover, statistical analysis showed that the benefit observed in terms of FEV_1 in this group was explained by the lower PA prevalence. This suggests that a major contribution of early specialist CF care in Belgium consisted of this achievement of lower PA prevalence. It is actually now realized that a link between attendance at a centre and earlier acquisition of PA is not a fatality, neither during regular specialist CF care nor in the context of neonatal screening [28,29]. In reality it is largely manageable with a policy of patient segregation based on bacteriology (applied to ambulatory as well as hospitalised care), regular systematic bacteriological surveillance and early intervention once this organism is detected [30]. Such policies have been put into practice in the 6 Belgian centres studied, for more than 17 years in one centre and more than 7 years in 4 others, contributing to a low number of clusters in this country [31] and a remarkably low prevalence of chronic colonization by Pseudomonas in one centre [32].

Most anthropometric parameters of children significantly improved from the first visit at the centre to the end of 2003. The latter are in accordance with those reported in the literature [1] but in contrast to Mahadeva's results the differences between early and late referred patients were not significant. This finding was unexpected since the benefit of early intervention in CF, in particular as a result of neonatal screening, was first and mainly demonstrated through nutritional aspects [33]. Looking further at the data at the first visit shows that the BMI (*Z* score) of early referred patients tended to be worse ($p=0.07$). Taken together, the data suggest that the nutritional aspect of the treatment was pretty well managed by the general paediatricians before referral.

Another point highlighted by this work is the heterogeneity of the outcomes variables obtained from the different centres. Such differences have been recognized for a long time [34]. Their amplitude can be astonishing in such a small country but is comparable to that shown at the level of large epidemiological studies and national registries during the past few years. These differences are now drawing considerable attention as they may provide an opportunity to develop quality improvement

initiatives [35]. Accordingly, a recent ESCF study led to the identification of a link between better lung function in 6- to 12 year-old children and clinical care patterns in infants in previous years [36]. Yet, a comprehensive attempt to identify specific care patterns associated with better outcome was beyond the scope of this study.

Assuming an acceptable mean annual decline in FEV_1 of 1–3%, a 20% difference in this major outcome variable between children with a mean age around 13 years from different centres is impressive. It has such survival implications that it might even pose ethical concerns at the level of the National CF patients Association, rising the question of the access of patients and/or their parents to this information.

From a different point of view, these results, which plead for an early referral to specialist centres, are in agreement with the accumulated body of evidence for neonatal screening, currently in place or considered in a growing number of western countries.

In conclusion, this retrospective multicentric study clearly shows that earlier referral of children suffering from CF to specialist care is associated with a significant pulmonary benefit, as demonstrated by a markedly better FEV_1 and lower PA prevalence at 13 years. The study also confirms, in a small country such as Belgium, a wide disparity of results from different centres.

Acknowledgment

The authors wish to thank G. Reychler for assisting in data collection and help in statistical analysis.

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