Cystic Fibrosis in Adults: A Changing Scene

Hannah Blau MBBS, Moshe Livne MD and Huda Mussaffi MD

Kathy and Lee Graub Cystic Fibrosis Center and Pulmonary Unit, Schneider Children's Medical Center of Israel, Petah Tiqva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Abstract

Background: Cystic fibrosis is no longer a terminal illness of childhood and mean survival is now over 30 years. Adult patients with atypical CF are increasingly being diagnosed. In Israel, all patients are still followed in pediatric centers.

Objectives: To describe our experience with adult CF, stressing the importance of adult-related health and psychosocial issues.

Methods: Twenty-five CF patients aged 20–50 years, constituting 44% of the 57 patients followed at our center, were analyzed for pulmonary and extrapulmonary features and management.

Results: Nineteen were diagnosed as children and 6 as adults. Nineteen were pancreatic-insufficient and 6 were pancreatic-sufficient, including 5 diagnosed as adults. Pulmonary status was usually stable, with forced expiratory volume in 1 second 66.3 $\pm$ 21% (mean $\pm$ SD) and no difference between pancreatic-sufficient and insufficent patients. The latter had more hemoptysis, *Pseudomonas* infection, intestinal obstruction, liver disease and diabetes. Two patients died of malignancy and two of advanced lung disease. A majority received continuous inhaled and oral antibiotics, bronchodilators, Dnase, physiotherapy and periodic home intravenous antibiotics. Psychosocial functioning was excellent: 60% were employed, 36% were married and 40% had children (none with CF). Patients diagnosed as adults had mild multisystem disease or isolated severe lung disease.

Conclusions: CF adults generally have a good quality of life. Advances in understanding the CF defect and a plethora of new treatment modalities bode well for the future. Patients must be maintained in optimal condition to reap the benefits, and there is an urgent necessity for adult physicians to develop expertise in CF.

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Cystic fibrosis is the most common lethal autosomal recessive disorder in Caucasian populations [1]. Over 1,000 mutations lead to dysfunction in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene expressed in epithelial cells [2], leading to viscous secretions within ducts. This results in a multisystem disease including bronchiectasis, chronic sinusitis, nasal polyposis, pancreatic insufficiency, focal biliary cirrhosis, male infertility, and recurrent bowel obstruction.

Remarkable progress in understanding the pathogenesis of CF and in therapy has resulted in steadily increasing median survival from under 2 years of age in 1938 [3] to over 30 years today [4]. In Israel, CF affects about 400 people, with a prevalence that varies markedly with ethnic origin [5]. At least 30% of patients are now over 18 years old (information from the Israel Cystic Fibrosis Foundation), which compares with the best statistics internationally [6]. At present, all patients in Israel are still cared for within pediatric CF centers. As the awareness of the broad spectrum of CF phenotypes increases, more adults with atypical disease are being diagnosed [7]. These patients may have mild multisystem disease expression limited to a single organ [8] or isolated but advanced lung disease [9]. Occasionally, diagnosis is even delayed to pre-lung transplant evaluation.

The present study describes our changing experience with adult CF patients over the past decade, emphasizing the increasing stability of lung disease in patients treated intensively and now reaching adulthood. The importance of adult-related health and psychosocial issues in these patients is highlighted. Particular genetic and clinical features in patients diagnosed with atypical CF in adulthood are demonstrated.

Patients and Methods

Twenty-five adult patients with CF have been followed at the Kathy and Lee Graub CF Center, Schneider Children's Medical Center of Israel over the past decade. This constitutes 44% of the 57 patients followed in our clinic during this time. Twelve of the adults were male and 13 were female. Data for this study were gathered from patients' medical charts.

At diagnosis, sweat tests were repeated at least four times and CF genotyping was performed in all cases. This procedure minimized the possibility of technical errors in order to leave no doubt about the diagnosis of this life-shortening disease. Where results were inconclusive, patients were referred for nasal potential difference measurement [10]. In addition, pancreatic function was evaluated in all patients by 72 hour fecal fat collection and/or fecal elastase measurements.

Patients were reviewed in the multidisciplinary CF clinic every 1–3 months and underwent regular lung function tests, sputum cultures, oxygen saturation measurements, nutritional evaluation, psychosocial assistance and updating of physiotherapy techniques for daily home care. Annual chest radiograph, liver function tests, blood count, oral glucose tolerance tests, abdominal ultrasound and, more recently, bone densitometry studies were performed.

Statistics

The differences between PI and PS patients regarding *Pseudomonas aeruginosa* colonization, hemoptysis and extrapulmonary complications were evaluated using the Fisher exact test. An unpaired Student *t*-test was used to compare values for lung function (FEV1 % of predicted) between PI and PS patients. A mixed model was

CF = cystic fibrosis

PI = pancreatic-insufficient
PS = pancreatic-sufficient
FEV1 = forced expiratory volume in 1 second

used to analyze longitudinal data for FEV1% predicted, for patients above 6 years of age and able to perform spirometry, as recently described [11].

Results

The 25 patients were above 20 years old: 13 aged 20–30 years, 8 aged 31–40 years and 4 aged 41–50 years. Of the 19 patients diagnosed as children, 9 were diagnosed before 1 year of age and 8 by 4 years of age. Six patients were diagnosed as adults. Nineteen patients (76%) were pancreatic-insufficient and 6 (24%) were pancreatic-sufficient, including 5 of the patients diagnosed as adults.

Pulmonary status

Figure 1 is a plot of the population regression line (thick line) and the individual regression lines (thin lines) resulting from a mixed model analysis using the 262 FEV1% predicted values for the 49 clinic patients able to perform spirometry. Results were extremely variable between patients, with stability or even improvement over the decade in many. However, the regression slope for the population as a whole was -0.7143% predicted FEV1/year ($P < 0.0001$), indicating a significant decline in FEV1 with time, for the entire group. Patients with severe disease (FEV1 <40%) at presentation to our clinic tended to deteriorate more rapidly. One patient required lung transplantation and is doing well, with normal lung function 10 years later. Two patients died from advanced lung disease.

There was no significant difference in FEV1% predicted between pancreatic-sufficient and insufficient patients (67 ± 20%, and 65 ± 22% respectively). Similarly, the prevalence of *Pseudomonas aeruginosa* colonization appeared less in PS patients but did not reach significance. Massive hemoptysis was significantly decreased in PS patients compared to PI ($P = 0.021$) [Table 1]. In most cases, pulmonary management was more aggressive than required for pediatric patients, although patients were rarely admitted to hospital. Sixty-two percent received continuous oral antibiotics, 58% continuous inhaled antibiotics, 83% inhaled bronchodilators, 54% inhaled Dnase and 46% inhaled steroids. Only 8% received courses of oral steroids. Over the past year, of 17 patients requiring courses of intravenous antibiotics for pulmonary exacerbations, 13 received home therapy for 2–4 weeks, and only 4 were admitted initially, continuing at home after 2–7 days when their situation stabilized.

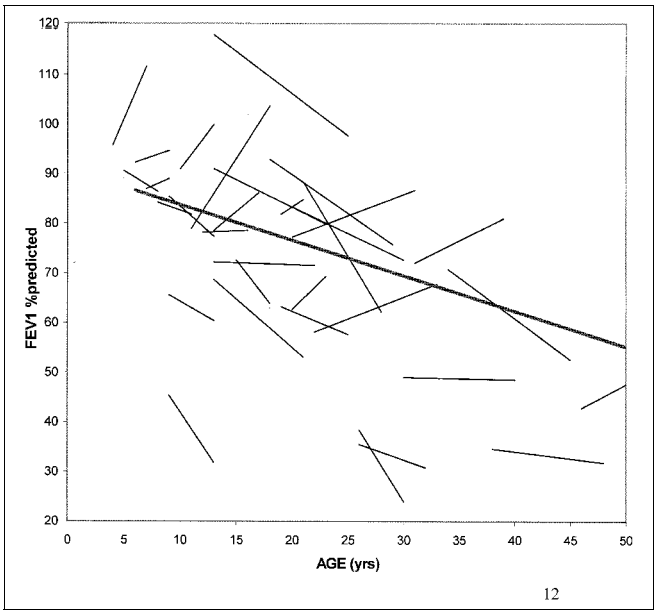

Figure 1. FEV1 (% predicted) decline with age shows a mean regression slope of -0.7143%/year for all patients able to perform spirometry ($P < 0.0001$). The population regression line (thick line) and the individual regression lines (thin lines) result from a mixed model analysis using the 262 FEV1 values for these 49 clinic patients.

Table 1. Pulmonary status of adult CF patients

	PI (n=19)	PS (n=6)	*P* value	Total (n=25)
Pseudomonas aeruginosa	18 (94%)	4 (67%)	NS*	22 (88%)
Hemoptysis	14 (73%)	1 (16%)	<0.05	15 (60%)
FEV1% predicted (mean ± SD)	65 ± 22	67 ± 20	NS	66 ± 21

* No significant difference between PI and PS patients
P value calculated for hemoptysis and *P. aeruginosa* using Fisher's exact test.
P value calculated for FEV1 using an unpaired Student *t*-test.

Table 2. Extrapulmonary complications in adult cystic fibrosis patients

	Liver disease	Glucose intolerance*	Diabetes	Arthralgia/ arthritis	Rib fracture	DIOS	Malignancy	Total
PS (n=6)	1 (16%)	0	0	0	1 (16%)	0	0	2/6
PI (n=19)	7 (37%)	2 (11%)	3 (16%)	2 (11%)	2 (11%)	13** (68%)	2 (11%)	19/19***

* Pathologic oral glucose tolerance test
** $P < 0.005$ (PI compared to PS patients; Fisher's exact test)
*** $P < 0.001$ (PI compared to PS patients; Fisher's exact test)
DIOS = distal intestinal obstruction syndrome
Total = total number of patients with extrapulmonary complications

Table 3. Patients with atypical CF diagnosed as adults

Gender/ Age*	Presentation	Sputum	CXR	FEV1	Sinus CT	PI/PS	Sweat Cl^-	Mutations	NPD
M/34	CBAVD	*Staph. aureus*, MAC	Nl	83%	Nl	PI	49	D1152H/ D1152H	–
M/20	↑LFT	*Staph. aureus*, *Enterobacter*	Nl	85%	Polyp	PS	40	W1282X/5T	Nl
M/24	Salt loss	*Staph. aureus*; *Streptococcus* group G	Nl	75%	Nl	PS	95	?/?	CF
M/46	Lung disease, pancreatitis	*P. aeruginosa*	Bronchiectasis	39%	Sinusitis	PS	123	W1282X/ D1152H	Nl
F/38	Lung disease	*P. aeruginosa*	Bronchiectasis	50%	Sinusitis	PS	55	Δ F508/ D1152H	Atypical CF
F/40	Lung disease	*P. aeruginosa*	Bronchiectasis	45%	Sinusitis	PS	50	3849 /W1282X	CF

* Age at diagnosis (years)

CBAVD = congenital bilateral absence of vas deferens, LFT = mildly raised liver enzymes, CXR = chest radiograph, Nl = normal, NPD = nasal potential difference measurement, MAC = *Mycobacteria avium* complex.

Extrapulmonary complications

There was a marked increase in episodes of distal intestinal obstruction syndrome, from 9% in children to 68% in adults ($P < 0.001$). Other complications included glucose intolerance and diabetes, cystic fibrosis-related liver disease (as expressed by abnormal liver ultrasound and/or increased liver enzymes) and arthropathy. These complications usually began in adolescence, as described by others [12]. Three patients suffered from pathologic fractures of ribs due to osteoporosis. As shown in Table 2, pancreatic-sufficient patients had significantly fewer extrapulmonary complications, reflecting their milder phenotype ($P < 0.001$). In particular, the prevalence of distal intestinal obstruction syndrome was significantly higher in PI patients as there were no cases in PS patients ($P < 0.05$).

In this adult population two patients died from malignancies: a 33 year old man with esophageal carcinoma probably related to gastroesophageal reflux; and a 44 year old woman who had secondary adenocarcinoma in the liver, with unknown primary. Unrelated to CF was atherosclerotic heart disease requiring coronary artery bypass operation in a 50 year old man. He did well postoperatively.

Patients diagnosed with CF as adults

The six patients diagnosed with CF as adults have atypical disease [Table 3]. Presenting symptoms included male infertility, dehydration and salt depletion, liver dysfunction and lung disease. All but one patient were pancreatic-sufficient and all had good nutritional state, which may have decreased the index of suspicion for CF. In three of the six patients lung disease was mild and asthma-like, though requiring intensive treatment with antibiotics and physiotherapy during exacerbations. Three patients had more severe lung disease and *P. aeruginosa* colonization, requiring intensive treatment including continuous antibiotics, inhalations and daily, prolonged physiotherapy. Genetic mutations were either those associated with mild disease, e.g., D1152H [13], the splice mutations 5T and 3849+10kb C→T [10,14], or unknown.

Psychosocial adjustment

Our patients were functioning at an excellent level, not very different from the healthy population. Most importantly, 60% were employed, although often in part-time jobs to enable the time-consuming daily cystic fibrosis care. Careers include journalism, engineering, computer science, teaching, art therapy, psychology, social work, speech therapy, secretarial work and commerce. A further 28% were students, consistent with their age. Thirty-two percent had a long-term partner and 36% were married.

Fertility and parenthood

Ten of the 25 adult patients had children: 5 had 1 child, 4 had 2 children and one mother had 3 children. All the couples had genetic counseling prior to conception and none of the children had CF. Five patients had children who were conceived naturally. Two of the males underwent microaspiration of testicular sperm followed by in vitro fertilization with intracytoplasmic sperm injection. One of the mothers had CF-related cirrhosis and portal hypertension, which contraindicated pregnancy. She had twins born to a surrogate mother. Two patients elected to adopt children, including one single mother.

In all cases, having children brought tremendous satisfaction and the adults made excellent parents. However, the necessity for adequate support from the spouse and extended family, as well as home help, was emphasized. Having children often proved a motivation to increase adherence to therapy in order to maintain CF nutritional and pulmonary status. Where this was not the case, disease frequently destabilized.

Discussion

CF is no longer a terminal illness of childhood. In the past, children with CF did not plan for or dream of their future. Today, as a result of early diagnosis and aggressive management by a multidisciplinary team, as was recommended by Shwachman et al. 25 years ago [15], almost 50% of patients at our CF center are now adults. In developed countries, median survival now exceeds 30 years [6] but

varies dramatically even within one country, from 17 to over 40 years [16]. Socioeconomic factors and resource availability are critical. Follow-up in a specialized center, preventive care and attention to detail vastly improve prognosis.

With disease progression, complications related to advanced CF develop and require expertise. CF-related diabetes often requires adequate insulin to enable good control without food restriction, since late diabetic complications may occur. Distal intestinal obstruction syndrome is common in adult patients with PI, but is generally manageable with conservative treatment. Prevention includes emphasis on adequate dosing of pancreatic enzyme supplements. Osteoporosis and even recurrent rib fractures develop due to multiple CF-related factors in both PI and PS patients. Factors include malnutrition, chronic inflammation, inadequate calcium and/or vitamin D intake and absorption, decreased physical activity and steroid use [17]. As elsewhere, we provide bone density screening, nutritional counseling, and treatment with bisphosphonates where needed. Finally, as patients with CF live longer, gastrointestinal malignancies are noted to increase [18], demanding a high index of suspicion.

Pregnancy in CF requires close follow-up by both the CF team and the high risk pregnancy unit. The emphasis is on maintaining stability of lung disease and optimal nutritional state, while avoiding antibiotics and other medications dangerous to the fetus. This frequently is not an easy task, but prognosis can be good [19].

Effective coping styles are essential to enable a smooth transition to independent responsible care as patients progress through adolescence to adulthood [20]. Survival is no longer the only aim of management. Patients expect to enjoy life as productive adults functioning well in society. By constantly grappling with time, the adult CF patient attempts to carefully balance his or her 'normal' daily life with his 'CF world'. The former frequently includes a busy schedule of studying, work, social life, home management, marriage and children. The latter may require up to 2–3 hours/day of chest physiotherapy, 1–2 hours/day of nebulized drug treatments, frequent high calorie meals with food supplements, vitamins, up to 80 capsules of pancreatic supplements, continuous oral and periodic intravenous antibiotics, regular exercise and daily rest [21]. Achieving the best balance requires a hopeful but realistic support system within the specialized cystic fibrosis center. Otherwise, patients struggling with slowly deteriorating health may sink into resignation or avoidant coping styles.

Late diagnosis of CF is increasing rapidly, due to awareness of the broad spectrum of CF phenotypes, as well as increasing availability of genotyping and nasal potential difference measurements for diagnosis of atypical cases [22]. Patients may have mild multisystem disease or expression limited to a single organ, e.g., congenital bilateral absence of vas deferens [8] or chronic pancreatitis. However, as shown in our patients, some have advanced lung disease although they may be pancreatic-sufficient with male fertility [9]. Thus, as a group, pulmonary function is not significantly different in atypical or PS patients. Occasionally, cases of classical CF are still missed and may even be diagnosed when presenting for lung transplantation. Pulmonary function in these patients often improves greatly, when multidisciplinary and aggressive CF care is instituted.

The emotional response of patients with late diagnoses varies greatly. If the illness has been severe, there is much relief that a diagnosis has been reached and appropriate treatment instituted. When disease is mild, there may be anxiety at a diagnosis of cystic fibrosis and the mistaken belief that early death is expected. Therefore, sensitive explanation and discussion are essential [23]. The process of coping is often gradual, and adherence to routines that include daily, prolonged physiotherapy is more difficult when they have not become a part of life from early childhood. These patients require a specialized CF care center attuned to the needs of adults.

As the proportion of adults with CF increases, there is a need for internists and adult pulmonologists to become acquainted with the management of this disease. Patients may develop other age-related diseases, as exemplified by our patient requiring coronary artery bypass operation. In the USA, the CF Foundation has made transitioning to adult CF care centers a prerequisite for recognition and funding [24]. This follows more than a decade of carefully planned program development, with fully committed internists or pulmonologists directing the programs. Physicians train in fellowships that include experience in established CF centers. Sensitive and gradual transitioning of patient care involves much interaction between the adult and pediatric CF centers [25]. At present, there are no such programs in Israel.

Adults with CF today can generally expect a good quality of life, as evidenced by the condition of the patients in our center. Advances in the understanding of the basic CF defect, improved modalities for diagnosing cases of atypical CF, and a plethora of new treatment modalities bode well for the future of these patients. They must be maintained in optimal condition in order to reap the benefits.

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Correspondence: Dr. H. Blau, Director, Graub Cystic Fibrosis Center and Pulmonary Unit, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tiqva 49202, Israel.
Phone: (972-3) 925-3654
Fax: (972-3) 925-3147
email: hblau@post.tau.ac.il