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Several siblings with Cystic Fibrosis as a risk factor for poor outcome☆

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KEYWORDS
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Summary
Background: Occurrence of Cystic Fibrosis (CF) in more than one member in a family is not uncommon. The aim of our study was to assess the influence of multiple siblings with CF on disease expression and outcome.
Methods: Study group consisted of 2-siblings (2-sibs, $n = 42$) or 3/4 siblings (3/4-sibs, $n = 22$) with CF in one family. Each sibling was matched by age, mutation, and gender to a single CF patient.
Results: 3/4-sibs subgroup compared to singles showed a lower mean FEV1 with a faster decline rate (58.4 ± 27.5 vs. 72.7 ± 25.4 and -5 ± 6.4 vs. -1.7 ± 2.8 %predicted decline/year respectively, $p < .05$), more airway colonization by *Pseudomonas aeruginosa* and *Mycobacterium abscessus* (15 (68%) vs. 8 (36%) and 7 (32%) vs. 4 (18%), respectively, $p < .05$) and more lung transplants (5 (23%) vs. 2 (9%), respectively, $p < .02$). Last mean FEV1 within 3/4-sibs was significantly lower for the youngest sib ($p < .05$).
Conclusions: Three or more CF patients in one family may be a risk factor for more severe disease and poor prognosis. In our view this reflects the burden of disease on the patients and families.

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Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease characterized by loss of function of CF Transmembrane conductance Regulator (CFTR) protein, which results mainly in respiratory, gastrointestinal, and fertility manifestations. In spite of widespread use of genetic testing and newborn screening, the occurrence of CF in more than one member in a family still exists in different populations. The sick siblings differ in different aspects of disease expression and progression. Age of diagnosis of the younger sibling is often earlier due to awareness of family and caregivers [1—3]; however, newly diagnosed CF through newborn screening may promote the diagnosis of an undiagnosed older sibling with CF [4]. The early diagnosis contributes to better Pulmonary Function Tests (PFTs) later in life [3,5]; although similar clinical presentation of disease was shown between siblings [1,3,5], there is contradicting data in regard to disease progression and outcome [2,3,5]. Airway colonization by the same strain of *Pseudomonas aeruginosa* is often seen among siblings with CF [6], but it is unclear whether younger siblings are colonized earlier in life as a result of transmission from the older chronically colonized sibling [1—3]. The burden of disease in CF is tremendous [7,8] and has enormous impact on family choices of future family planning [8], especially on the decision whether to abort a second fetus with CF [9,10]. The aim of our study was to assess the influence of multiple CF patients in a single family on disease course and outcome.

Methods

Subjects

Study population consisted of patients with proven CF by clinical characteristics and identified CFTR alteration mutation and/or pathological sweat chloride test (above 60 mmol/L). All the patients are part of the National CF Center, Edmond and Lily Safra Children Hospital, Sheba Medical Center, Israel. The inclusion criterion for the study group was at least two siblings with CF in a family. Siblings were defined as sharing both maternal and parental origin. Inclusion criterion for the single group was CF patient without siblings with CF. The single subjects were age, gender, and class mutation matched to the study subjects individually.

Study design — a longitudinal cross-sectional retrospective study

We retrospectively obtained patients' data between 2001 and 2013 from records of the CF patients. The information included anthropometric data, age, gender, mutations; clinical parameters such as growth indices, CF-associated diseases, airway bacterial colonization, Forced Expiratory Flow in 1 s (FEV1), number of hospitalizations, organ transplantation; and social evaluations.

The work was approved by the appropriate ethics committee of the institution in which it was performed.

Analysis of data

Data was compared between the siblings groups and the single group in order to assess differences in disease course and outcome. Primary outcomes reflected disease progression and included PFTs, growth indices, number of hospitalizations, and organ transplantation. Secondary outcomes included CF-associated diseases such as pancreatic insufficiency (PI), CF-related diabetes (CFRD), and airway bacterial colonization. The study group included 2-subgroups — one with 2-siblings and the other with 3/4 siblings within a single family. Each subject within the groups had their own matched single patient.

Statistical analysis

The main comparison was between the sibling and its matched single. Accordingly paired *t*-tests were used to establish significance. The number of children/group having infection or related disease was analyzed separately by Fisher exact tests. $p < 0.05$ was considered significant and $p = 0.06$ was considered as trend. We used the SPSS Software statistical package.

Results

The sibs group included 64 patients: 21 pairs of 2-sibs, 6 sets of 3 sibs, and 1 set of 4 sibs. In the single group there were 64 single CF patients. Altogether data was analyzed from 128 patients, 12 to 47 years-of-age. There were no significant differences between the sibs group and the singles in anthropometric data, growth indices, airway bacterial colonization, and CF-related conditions. No differences were found in last mean FEV1 and mean number of hospitalization (67.3 ± 25.1 vs. 70.8 ± 23.3 %predicted and 1.8 ± 2.2 vs. 1.8 ± 1.9 hospitalizations per year, respectively, NS). Number of lung transplantations for the sibs and the singles was 8 (14%) and 5 (9%), respectively (NS), with an average age for transplantation of 23.2 ± 9.2 and 31.8 ± 9 years, respectively (NS). The only difference between the groups was more religious patients in the siblings compared to the singles (35/64 vs. 15/64, respectively, $p < 0.03$).

Subgroup analysis for 21 pairs of 2-sibs with their individually matched singles also showed more religious patients in the 2-sibs compared to the singles (17/42 vs. 7/42, respectively, $p = 0.0286$). Anthropometric data, growth indices, airway bacterial colonization, and other CF-related conditions or social parameters were similar. Last mean FEV1 was 63 ± 30.3 %predicted for 2-sibs and 72.2 ± 22.4 % predicted for singles (NS), and rate of decline of FEV1 was also similar (-1.3 ± 5.8% vs. -1.2 ± 2% per year, respectively, NS). Mean number of hospitalizations was 2.1 ± 2.2 hospitalizations per year for the 2-sibs and 1.7 ± 2.1 hospitalizations per year for the singles (NS). Number of lung transplantations for the 2-sibs and the singles was 5 (12%) and 3 (7%), respectively, (NS) (Table 1).

Subgroup analysis for 7 sets of 3 sibs and 1 set of 4 sibs with their individually matched singles showed that in the 3/4-sibs group there was more airway colonization by *P. aeruginosa* and *M. abscessus* compared to their matched

Table 1 Comparison between the 2-sibs subgroup and matched singles.

	2-siblings ($n = 42$)	Singles ($n = 42$)	p value
Age (yrs)	26.1 ± 9.2	25.4 ± 9.4	NS
Gender (m/f)	21/21	21/21	NS
Mutation I–III (y/n)	34/8	34/8	NS
Height (cm)	165 ± 13	164 ± 12	NS
Weight (kg)	55 ± 15	54 ± 11	NS
P. aeruginosa – *n* (%)	33 (79)	33 (79)	NS
Staphylococcus aureus – *n* (%)	15 (36)	18 (43)	NS
Mycobacterium abscessus – *n* (%)	17 (40)	16 (38)	NS
Aspergillus fumigatus – *n* (%)	12 (29)	15 (36)	NS
Associated diseases – *n* (%)	35 (83)	38 (90)	NS
CFRDM– *n* (%)	13 (31)	16 (38)	NS
PI – *n* (%)	28 (67)	35 (83)	NS
Dios – *n* (%)	14 (33)	10 (24)	NS
FEV1 (%predicted)	63 ± 30.3	72.2 ± 22.4	NS
Rate of decline of FEV1 (%/y)	−1.3 ± 5.8	−1.2 ± 2	NS
Hospitalization (*n*/yrs)	2.1 ± 2.2	1.7 ± 2.1	NS
Lung transplantations – *n* (%)	5 (12)	3 (7)	NS
Religious families – n (%)	17 (40)	7 (17)	=0.0286

BMI – Body Mass index, CFRDM – CF related Diabetes mellitus, DIOS –Distal intestinal obstruction syndrome, PI – Pancreatic Insufficiency.

Table 2 Comparison between the 3/4-sibs subgroup and matched singles.

	3/4 siblings ($n = 22$)	Singles ($n = 22$)	p value
Age (yr)	23.1 ± 11.5	23.6 ± 10.7	NS
Gender (m/f)	9/13	9/13	NS
Mutation I–III (y/n)	12/10	12/10	NS
Height (cm)	158 ± 17	160 ± 19	NS
Weight (kg)	50 ± 14	52 ± 16	NS
P. aeruginosa – n (%)	15 (68)	8 (36)	=0.0329
S. aureus – *n* (%)	8 (36)	9 (41)	NS
M. abscessus – n (%)	7 (32)	4 (18)	=0.0332
A. fumigatus – *n* (%)	8 (36)	6 (27)	NS
Associated diseases – *n* (%)	17 (77)	19 (86)	NS
CFRDM – *n* (%)	10 (45)	9 (41)	NS
PI – *n* (%)	15 (68)	13 (59)	NS
Dios – *n* (%)	5 (23)	3 (14)	NS
FEV1 (%predicted)	58.4 ± 27.5	72.7 ± 25.4	=0.0495
Rate of decline of FEV1 (%/y)	−5 ± 6.4	−1.7 ± 2.8	=0.0125
Hospitalization (n/yr)	1.7 ± 1.8	0.9 ± 1.2	=0.0547
Lung transplantations – n (%)	5 (23)	2 (9)	=0.0113
Religious families n (%)	18 (82)	8 (36)	=0.05

BMI – Body Mass index, CFRDM – CF related Diabetes mellitus, DIOS –Distal intestinal obstruction syndrome, PI – Pancreatic Insufficiency.

singles (15 (68%) vs. 8 (36%) and 7 (32%) vs. 4 (18%), respectively, $p < .05$). FEV1 was significantly lower for the 3/4-sibs subgroup with a faster decline rate compared to singles (58.4 ± 27.5%predicted vs. 72.7 ± 25.4%predicted for last mean FEV1 and −5 ± 6.4 vs. −1.7 ± 2.8%predicted per year, respectively, $p < .05$). Lung transplantations were significantly more prevalent in the 3/4-sibs subgroup (5 (23%) vs. 2 (9%), respectively, $p < .02$) There were more religious patients in the 3/4-sibs compared to the singles (18/22 vs. 8/22, respectively, $p < .05$). A trend toward more hospitalizations was found in the 3/4-sibs group (1.7 ± 1.8 vs. 0.9 ± 1.2 hospitalizations per year, respectively, $p = 0.0547$) (Table 2).

We further compared FEV1 within siblings and found that last mean FEV1 was significantly lower for the youngest sib as shown in Fig. 1 ($p < .05$).

Discussion

This study compares disease expression and outcome in families with multiple CF patients compared to families with only one CF patient. We found that patients from families with 3 or more siblings with CF show lower FEV1, a faster decline rate of FEV1, more bacterial airway colonization, increased frequency of lung transplants, and a trend towards more hospitalizations compared to single CF patients in a family. However, 2-sibs within one family did not have such an impact.

The significant determinants of disease progression in CF may include severe genotype, poor growth, pulmonary exacerbations, meconium ileus, and infection with mucoid *P. aeruginosa* [11]. In this study we show that multiple family members with CF are another risk factor for poor prognosis as shown by a lower FEV1 with a faster rate of decline of FEV1 and ultimately by more lung transplants.

Airway colonization with *P. aeruginosa* has been associated with a more rapid decline in pulmonary function

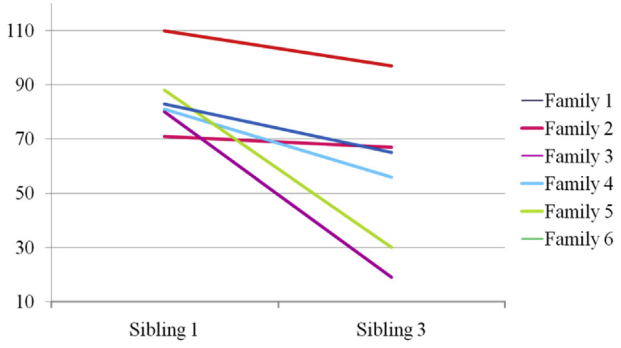

Figure 1 Last mean FEV1 within the family in the 3/4-sibs subgroup.

[11—15]. Indeed, in our study Pseudomonas was more prevalent in the 3/4-sibs. This may be attributed to either cross-transmission between family members or acquisition from common environmental exposure. Since families share the same household it may be assumed that once one of sibs is infected by an airway pathogen, the other sibs are likely to also be infected. A prior study of siblings done in Israel by Picard et al. showed that when Pseudomonas was isolated from the first-born patient, 91% of the second siblings were also positive for Pseudomonas colonization [1]. Moreover, younger siblings tend to be colonized with Pseudomonas at an earlier age [3]. The cross-infection is also supported by studies showing that siblings share the same genotypes of strains of *P. aeruginosa* [6,16—20]. Apart from Pseudomonas there are other bacterial pathogens that are associated with a worse clinical outcome such as *M. abscessus*, which was also more prevalent in our group of patients. As previously shown, *M. abscessus* is also associated with a faster lung function decline [21]. Whole genome sequencing has revealed frequent transmission of multidrug resistant NTM between patients with cystic fibrosis attending the same clinic despite conventional cross-infection measures [22], so it may be expected that siblings sharing the same household might also cross-infect each other with the same strain of Mycobacterium.

Furthermore, worse clinical outcome may reflect the burden of disease in families with several CF patients. The simultaneous rise in the complexity of the care regimen and the shift of care to the home means that the burden of care increasingly falls on patients and families; this requires that family caregivers provide direct and complex clinical care that was previously provided by professionals [23]. Such a shift in care requires not only greater technical skill on the part of family caregivers, but also a substantial commitment of time and energy. Parents of children with CF know the demands of the CF regimen well, and the work of parents as family caregivers for children with CF is well documented. Studies that examined the quality of life of parental caregivers and siblings of children with CF [24—27] and the relationship between family function and the health of the child with CF [28,29] showed that there is a negative correlation between the level of burden experienced by parents of children with CF and decreased pulmonary function over time. Coyne et al. described the time consuming and complex daily care for children with CF and pointed to the need to provide support for their parents [26]. The daily treatment regimen along with the frequent clinic visits and hospitalizations during pulmonary exacerbation is a lot to deal with when one child has CF. For parents with 3 or more sick children it may be assumed that the task is almost impossible, both technically and emotionally. Collaco et al. showed that parents caring for 2 children with CF divide their time and resources in caring for both children, but once the older sibling has left the home, the remaining sibling's pulmonary function is increased, perhaps as a result of increased resources being devoted to that remaining sibling [30]. In our study, a trend toward more hospitalizations was also seen in this group of patients. Frequent hospitalizations impose great burden on the patient's family, especially when more than one patient is hospitalized simultaneously. Hospitalizations also put the CF patient at risk for airway contamination and acquisition of Pseudomonas and other bacterial pathogens that enhance disease progression. Moreover, every pulmonary exacerbation enhances lung tissue destruction, which explains the lower pulmonary function seen in the 3/4-sibs group.

Another important aspect that may contribute to disease severity is that multiple siblings are found more in religious families. This finding is expected because although genetic testing is prevalent in Israel, religious parents tend to perform less genetic testing or pregnancy termination. In the current era of prenatal diagnosis and newborn screening the importance of genetic consultation for families with children with CF is of high importance. Studies exploring the choice to abort a CF fetus after already caring for a child with CF showed results ranging from 20% in some parts of the US [31] to over 50% in France, UK, and Belgium [32—34]. Several psychosocial factors underline decisions about use of prenatal diagnosis for CF among parents of affected children. Wertz et al. demonstrated that the majority of affected families reject selective abortion for CF and that many will curtail childbearing rather than use prenatal diagnosis [9]. Therefore, the choice standing before religious parents is complex and often controversial. Furthermore, religious patients may not fully adhere to treatment and follow up due to their religious beliefs in divine providence and different apprehension of disease.

Looking into each sibling's data in the 3/4-sibs group we found that FEV1 was lower for the youngest sib. Earlier studies have demonstrated lack of difference in clinical outcomes between siblings when looking at 2-siblings [2]. Moreover, although younger siblings tend to be colonized with Pseudomonas at an earlier age, they may show better lung function outcomes [3]. This may result from the fact that the second-born sibling is often diagnosed at an earlier age compared to the first-born due to high index of suspicion [1,3] and this counts as a good prognostic factor because an early diagnosis of CF is associated with better lung function after two decades of life [3]. This underscores the importance of early diagnosis with newborn screening and early referral to a specialized center in the prevention of long-term deleterious effects on lung function [3]. However, Munck et al. reported that nearly 9% of families with an infant screened for CF were unaware of an affected older sibling [4]. In contrast, our data showed that FEV1 was lower in the youngest sib in the 3/4-sib group, suggesting depletion with time of parental and family resources, and that despite the early diagnosis the enormous burden of treatments on a family of so many CF patients may impact the clinical outcome of the youngest patient. Since such results did not exist in the 2-sibs group it may be assumed that a crucial limit is crossed when a third sick child is added to the family.

There are some limitations to our study. The study was performed retrospectively in one CF center. However, our center is the national center for CF in Israel and includes the largest number of patients in Israel and the oldest patients. Although data was collected retrospectively it allowed us to follow disease progression for a long period of time until a relatively old age.

In conclusion, we suggest that 3 or more CF patients in one family may be a risk factor for more severe disease and poor prognosis as manifested by lower PFTs, a faster decline rate of PFTs, more bacterial airway colonization,

and increased frequency of lung transplant. This reflects, in our view, the burden of disease on the patients and families. Medical staff should be aware of this risk factor and consult infected families accordingly.

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