IMPACT OF OTHER RISK FACTORS THAN AGE AT DIAGNOSIS ON OUTCOME IN CYSTIC FIBROSIS PATIENTS

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Abstract

Cystic Fibrosis (CF) is a complex disease requiring early diagnosis and treatment in order to improve survival. Objective: to determine the impact of risk factors (RF) other than age at diagnosis on outcome in CF patients.

Methods: Retrospective study of 24 clinical files of CF patients (age: birth-22 years) followed up during a 7 year period (1999-2006) correlated with age at diagnosis and associated RF: early *P aeruginosa* acquisition; frequent pulmonary exacerbations; del F508 homozygous; poor socioeconomic status (PSES); severe malnutrition at diagnosis (SMD); associated conditions; age when started follow up. Study population was divided in group A (early diagnosis <1 year of age) and group B (late diagnosis).

Results: Mean age at diagnosis was 4.2 months in 20/24 patients (group A) vs. 4.3 years in 4/24 patients (B). 9 patients (A) died, the majority under the age of 1 year. Major RF for deceased patients was PSES and SMD. Age for first acquisition of *P aer* (A) was 4.2 years compared to 5 years (B). There was no correlation between genotype and outcome, 75% patients had severe mutations. 50% patients (A) had frequent exacerbations compared to 25% (B). PSES was an independent RF for not deceased patients. 66% patients (A) had SMD, percentage diminished after inclusion in standard care program. LF was performed in 5/14 patients with mean decline of 4%/year, variation depending on complications of disease. Patients with early diagnosis and follow up had significantly better outcomes.

Conclusions: early *P aeruginosa* acquisition, PSES and associated conditions adversely affected outcomes. Late age when starting follow up independently of age at diagnosis predicted worse outcome.

Key words: cystic fibrosis, risk factors, outcome

Introduction

Cystic Fibrosis (CF) is the most common autosomal recesive inherited disease in the caucasian population, with a frequency of one in 2500-3000 live births and a heterozygote carrier rate of approximately one in 25. The mutation is found in the CF transmembrane conductance regulator (CFTR) gene on chromozome 7. Over 1300 different mutations have been identified.

Without normal CFTR protein there is excess sodium and defective chloride transport across the apical membrane of secretory epithelial cells with dehydration of the surface epithelium and abnormal ion concentrations in the surface liquid. Diagnostic tests for CF exploit this ionic imbalance. The clinical consequence is a multisystem disease involving predominantly the respiratory, gastroenterology, hepatobiliary and male reproductive systems. Patients are susceptible to recurrent respiratory infections with a variety of microorganisms but especially *Pseudomonas aeruginosa, Burkholderia cepacia* complex, *Staphylococcus aureus, Haemophylus influenzae* and *Aspergillus* species. Respiratory failure is the cause of death in approximately 80% of patients (1). Lack of pancreatic enzymes and bicarbonate results in steatorrhoea and malnutrition. Abnormal gut motility results in acute obstruction. Liver disease may progress from focal biliary fibrosis to cirrhosis with splenomegaly, varrices and cirrhosis. Men with CF are universally infertile due to bilateral absence of vas deferens.

Treatment is mostly directed at the life-threatening aspects aspects of this multisystem disease: preventing respiratory infections as much as possible, minimizing lung damage by prompt treatment of acute infective exacerbations and use of antiinflammatory therapies, maintaining normal growth and nutrition and potentially reducing the risk of liver disease.

Patients with CF should be monitored at regular and frequent intervals, at least every 3 months, for early detection of deterioration (2).

Early diagnosis, regular monitoring and aggressive treatment protocols in CF have shown their benefits in terms of better lung function, higher life span an improved quality of life.

Objective

The objective of the study was to determine the impact of other risk factors (RF) than age at diagnosis on the outcomes of CF patients.

Methods

The study was represented by the retrospective evaluation of 23 clinical file of CF patients.

Age range of patients was from birth to 22 years.

The study was carried out in the Children's Hospital of Brasov during a seven years period: 1999-2006.

The evaluation of clinical parameters and outcomes were correlated with several risk factors: age at diagnosis and associated RF: early *P aeruginosa* acquisition; frequent pulmonary exacerbations; del F508

homozygous; poor socioeconomic status (PSES); severe malnutrition at diagnosis (SMD); associated conditions; age when started follow up.

Study population was divided in two groups: group A (early diagnosis <1 year of age) and group B (late diagnosis).

Results

Table 1, reprezents the patient demographics and baseline characteristics of the study population.

Table 1. Patient demographics and baseline characteristics:

	Group A (dg<1y) (n=20)	**Group B (dg>1y) (n=4)**
Male	13	1
Female	6	3
Del F 508 homozygous	10 (41.6%)	1 (4.16%)
Del F508 heterozygous (severe)	4 (16.6%)	2 (8.33%)
Other mutation (severe/severe)	1 (4.16%)	0
Undetermined mutations	5	1
Mean age at diagnosis (months/years)	4.2 months	4.3 years
Mean age I-st CF symptoms	2 months	3 months
Mean age when started follow up	3 months	3.5 years
Mean age I-st *Paer* acquisition	4.2 years	5 years
Deceased<1 year of age	6	0
Deceased >1 year of age	3	0
Mean Schwachman score*	71.16	74.6
Mean Chrispin-Norman score*	4.25	5
Associated conditions **	10	0

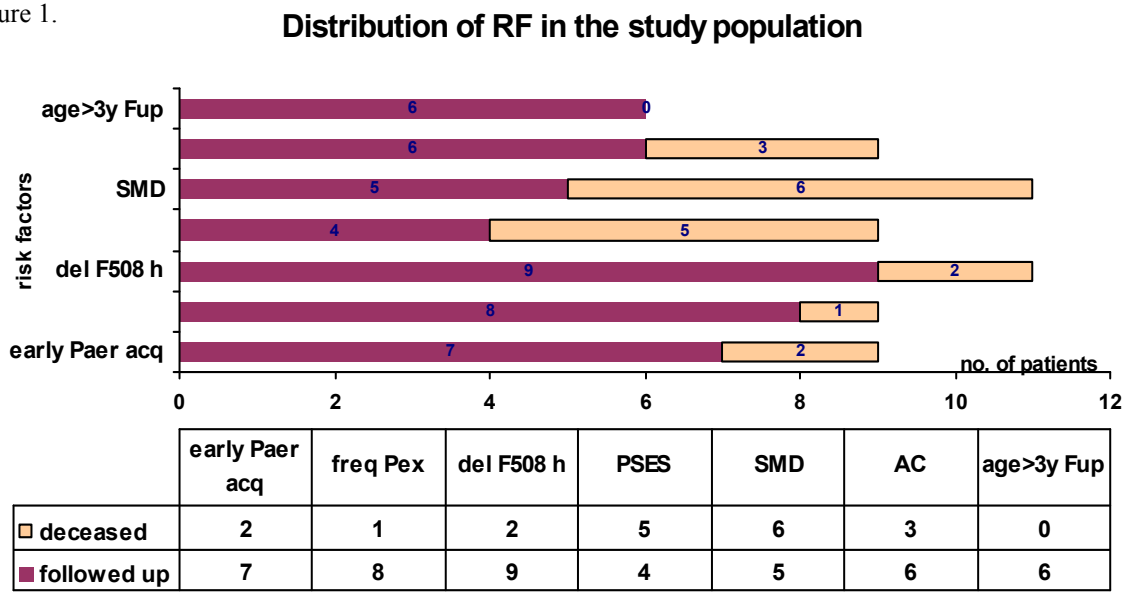
**Evaluation done at the end of the study period*
*** MI, ABPA, CFRLD, other*

At that moment of the study, the following observations were done:

- There was no correlation between genotype and clinical outcomes (as seen in Schwachman scores and incidence of severe mutations)
- 75% of patients had severe mutations (42% del F508 homozygous)
- There was no significant difference between Schwachman scores and Chrispin-Norman scores (p=0.20)

The distribution of evaluated risk factors is shown in figure 1.

Figure 1.



	early Paer acq	freq Pex	del F508 h	PSES	SMD	AC	age>3y Fup
deceased	2	1	2	5	6	3	0
followed up	7	8	9	4	5	6	6

Among the evaluated risk factors, being a del F508 homozygous seemed to have a major impact in the study population, as well as early colonisation with *P aeruginosa* (as mentioned in the literature).

Deceased patients (37.5% of the study population) had a greater impact on worse outcome by poor socio-economic status (the majority being from rural areas with low incomes of the families and poorer understanding of the chronic condition of disease. Severe malnutrition at diagnosis (SMD) was also predominent in this group of patients, probably correlated as well with the socio-economic status.

There was a significant difference between ages when I-st symptoms of CF occurred and age when diagnosis was done (age when diagnosis was done usually corresponded with age when follow up started) as it is illustrated in figure 2.

Late age by starting follow up and associated conditions have had influenced outcomes as observed in figure 3.

Figure 2.

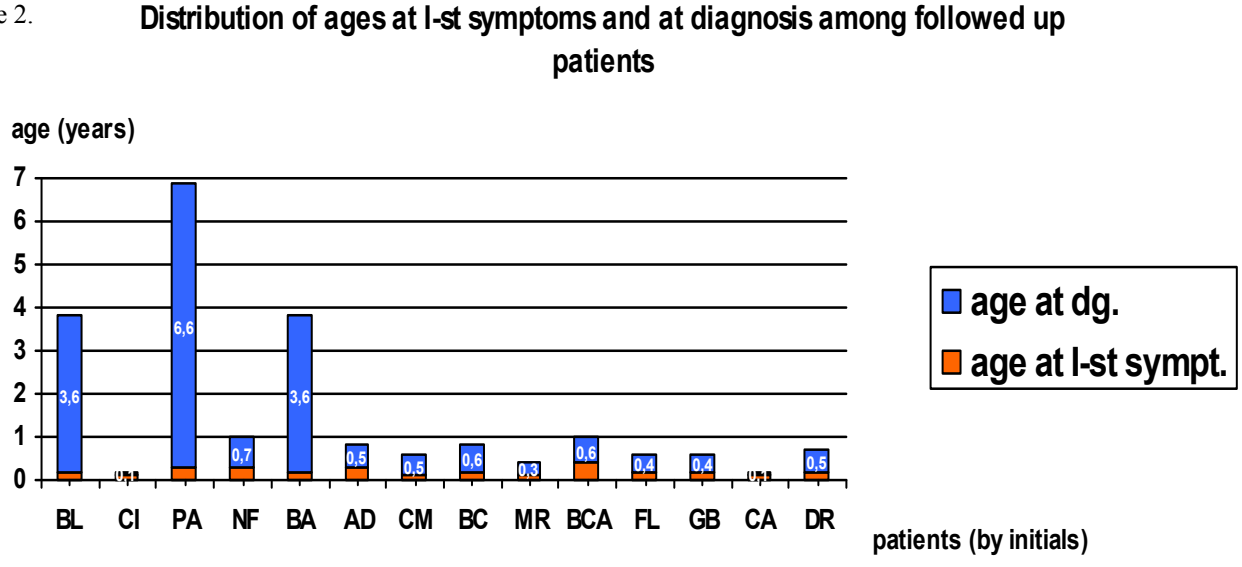
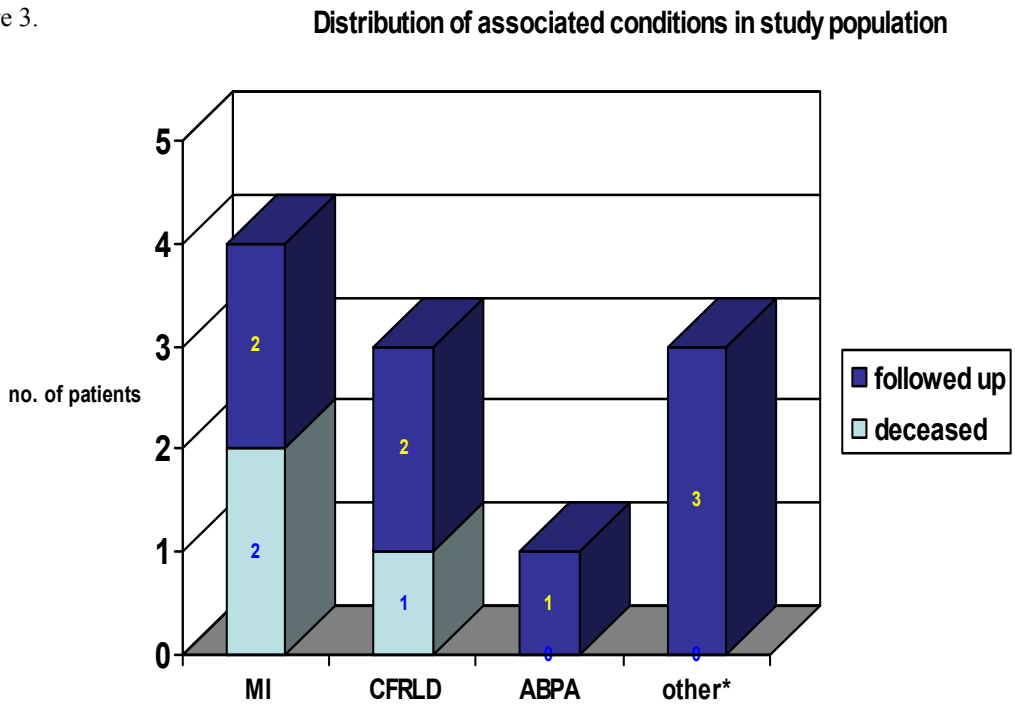
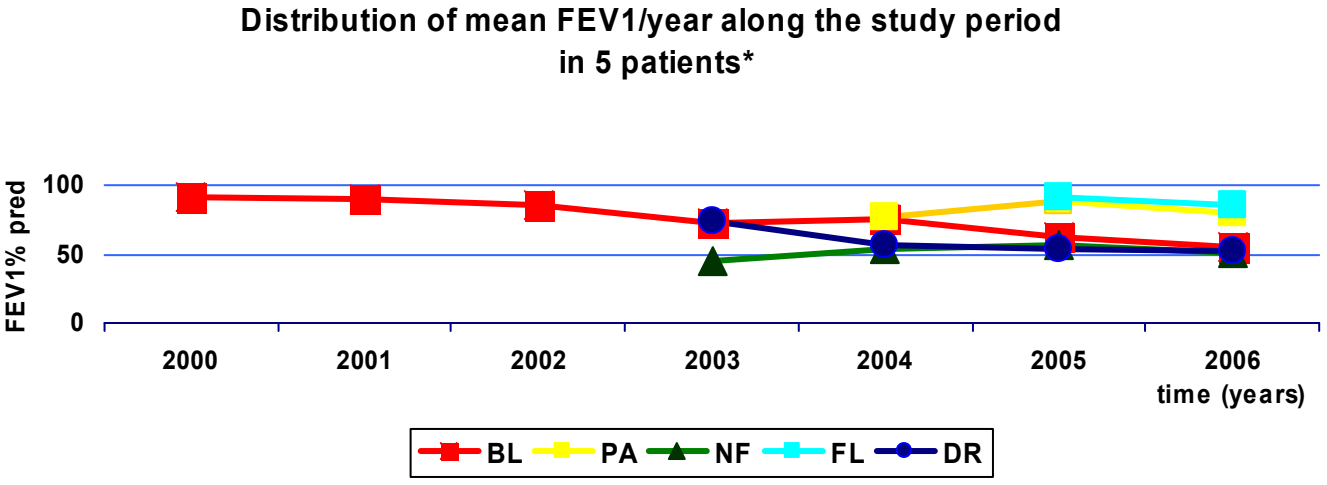


Figure 3.



All patients who could perform lung function testing* were followed up starting over 3 years of age (figure 4). Usually the lung function trendline had a descendent direction. The rate of FEV1 decline was higher than 4%/year.



Discussions

Even the study groups were not homogenous as number, there is a paradoxal difference between ages at first sugestive symptoms for CF (around 4 months of age) and the age when diagnosis was done (4.2 months vs. 4.3 years). This had a direct impact on the age when follow up on a regular basis was started. Clinical outcomes as reflected by Schwachman and Chrispin Norman scores did not vary significantly between the two groups, which was not the same for the percentage of deceased patients, the majority being from the group with early diagnosis. For that reason, it seems normal to presume that the high incidence of deaths in the early diagnosis group is correlated to some risk factors as it was shown (poor socio-economic status, severe malnutrition at the time of diagnosis and probably associated conditions as meconium ileus)

To mention the associated conditions, only one patient that had a relative favorable outcome till the moment of death (mostly in terms of lung disease and *P aer* colonisation), and died from early liver disease (CFRLD) at the age of 3years 6 months. The patient had meconium ileus and several surgical interventions, as well as recurrent episodes of dystal intestinal obstruction syndrome (DIOS).

The other deceased patients died under the age of one year and had worse nutritional status and poor socio-

economic status which probably interfered with the access to specialized care.

One patient had allergic bronchopulmonary aspergillosis (ABPA), even being from the early diagnosed ones, but started follow up on a regular basis at the age of 9 years when lung function was severely affected. ABPA worsened the outcome of lung disease with a consecutive fall in FEV_1 despite intensive treatment.

All five patients who could perform lung function testing over the time of the study period
had a fall in FEV_1 higher than 4%/year belonging to the category of late start of follow up (despite early diagnosis in some of them).

Conclusions

Late age when started follow up independently of age at diagnosis predicted worse outcomes.

There was a high rate of decline of lung function (FEV1) in older patients and also lower Schwachman scores and BMI in late followed up patients.

There was a high mortality rate, mainly influenced by associated risk factors as poor socio-economic status and severe malnutrition at the time of diagnosis which could have had influenced the outcome of lung disease.

Early diagnosis followed by regular monitoring, early and aggressive intervention regarding pulmonary infection and nutritional support could influence the outcome of CF patients.

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