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Other risk factors associated with mortality in moderate and severe cystic fibrosis patients

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Summary

Aim: Severe pulmonary disease is responsible for over 80% of deaths associated with cystic fibrosis. Our aim was to evaluate the other risk factors associated with mortality in patients with cystic fibrosis who have moderate and severe lung disease.

Material and Method: Among 200 patients with cystic fibrosis who were followed up in our clinic, 35 patients with moderate and severe lung disease (%FEV1 predicted ≤60) were included in the study. Demographic data, pulmonary function tests, high resolution thorax tomography, modified Bhalla score, blood gas analysis and nutritional status of the patients were evaluated.

Results: Requirement for respiratory support was 31.4% in moderate and severe lung disease. Lower pulmonary function, requirement for non invasive ventilation, presence of diabetes mellitus, a $Sa0_2$ value of <95, a value of pCO_2 >50 mm Hg and requirement for frequent IV antibiotics were significantly related with increased mortality.

Conclusions: This is a single centre study conducted in patients with cystic fibrosis who had moderate and severe lung disease and who had not received lung transplantation. We evaluated the clinical outcome and other factors that were associated with mortality. *(Turk Arch Ped 2012; 47: 263-267)*

Key words: Child, cystic fibrosis, risk of mortality

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease which is observed frequently in the Caucasian population and which shortens the life time. The incidence of this disease is 1/2 500-1/3500 in the Caucasian population and 1/17000 in African Americans (1,2,3). Although the definite incidence in Turkey is not known, it is found to have an incidence of 1/4000 in Greece and 1/5000 in Israel (4).

The disease occurs as a result of mutations in CF transmembrane regulator protein (CFTR) coded by CF gene. Currently, 1910 mutations which cause CF have been defined (3). The most common mutation is F508del mutation and its frequency ranges between 30% and 80% according to the ethnic origin (4,5,6). In Turkey, the frequency of F508del mutation is 20.4%-28.4% (7,8,9,10). It is known that mutation distribution is very heterogeneous in Turkish patients and it is thought that clinical findings and prognosis show variance because of this (7,8,9,10). With development of efficient supportive treatment methods the mean survival time in cystic fibrosis has increased from 30 years to 38,3 years in the last decade. 80% of the deaths in cystic fibrosis are caused by lung disease (3). Lung transplantation is recommended as a treatment option in patients with a very low life quality and a two-year survival expectation below 50% (11,12). The most important reason for lung transplantation in children is CF.

The first study related to the mortality risk in cystic fibrosis was performed in 1992 by Kerem et al.(13) and the two-year survival rate was reported to be 50% in conditions where FEV1-expected ≤30% and CO_2 pressure >50 mmHg and O_2 pressure <55 mmHg in arterial blood gases. In this study, the most valuable variable in determining the prognosis was found to be FEV1 percent. Following this study many studies have been performed to determine the mortality risk in patients with cystic fibrosis (14,15,16,17,18,19,20,21,22). The aim of these studies was to make a right selection for the patients who needed lung transplantation, because even if transplantation is performed, there is a morbidity and mortality risk related to early and late complications (22).

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In Turkey, risk factors related to CF have not been investigated. In addition, lung transplantation in pediatric patients can be performed in a limited number of centers and in limited number of patients. The aim of our study was to determine the other factors related to mortality in CF patients with moderate or severe lung involvement who have different mutations and who have not undergone lung transplantation.

Material and Method

Clinical findings and laboratory data of 35 patients with a diagnosis of CF followed up in Marmara University, Division of Pediatric Pulmonary Disease who had a FEV1 value of <60% and a follow-up time of at least two years were collected retrospectively from patient files. The diagnosis of cystic fibrosis was made by presence of clinical findings and a positive sweat test (CL>60 mEq/L).

In 30 of the patients, 36 CFTR mutations were screened using "strip assay" method which is based on reverse hybridization method.

The diagnosis of pancreatic failure in cystic fibrosis was made by presence of clinical exocrine pancreatic dysfunction and a fecal elastase-1 level of <100 mg/g in the stool (23).

Hepatic involvement in cystic fibrosis was defined as hepatomegaly, fatty changes or cirrhosis on hepatobiliary ultrasonography and increased liver enzymes (21).

Chronic P.aeruginosa (PA) colonization was defined as isolation of PA for three times in the last six months in sputum (21).

Noninvasive ventilation was administered to the patients in cases of hypercarbic acute lung exacerbation, nocturnal desaturation and/or nocturnal hypercarbia (24).

Nasal O_2 support was given, when nocturnal hypercarbia did not accompany and O_2 saturation was below 92% (25).

The diagnosis of acute exacerbation of cystic fibrosis was made, when at least two of the following conditions were present: fever, newly-onset or increased cough or sputum production, hemoptysis, dyspnea, chest pain, fatigue, loss of appetite, a decrease of more than 10% in FEV1 or FVC and deterioration of pulmonary sounds (26). Patients with a diagnosis of acute exacerbation who had stable clinical findings were treated with oral antibiotics. Patients who did not respond clinically to oral antibiotic treatment or who had unstable clinical status, a O2 saturation of <94% or a CO_2 pressure above 45 in blood gases at presentation were hospitalized and given intravenous antibiotic treatment. In our study, respiratory function tests were performed using Winspro PRO 2.8 (MIR, Italy) device in patients who were older than 6 years. The test was performed by making the patient to blow upon the reader of the spirometer by a forced expiration following a forced inspiration maneuver. The test was repeated at least for three times, three acceptable spirometer values were obtained and the highest values were recorded (27).

High resolution thoracic tomography (HRTCT) images of the patients were evaluated by a radiologist who did not know the clinical states of the patients using modified Bhalla method. The values ranged between 0 and 31 according to the presence and extent of ordinary findings. A value of 0 was considered to be normal according to the Bhalla method. A score of 1-10 was considered to be mild, a score of 11-21 was considered to be moderate and a score of 22-31 was considered to be severe (28). When the descriptive characteristics of the patients were evaluated, data with a normal distribution were expressed as mean and standard deviation and data which did not have a normal distribution were expressed as median and the least-the highest. In investigation of the factors related to mortality, Pearson correlation, Spearman correlation and chi-square tests were used. In all statistical analyses, a p value of <0,05 was considered to be significant.

Informed consent was obtained from the families, if needed and approval was obtained from the local ethics committee (24.06.2010/number:690/no:09.2010.0035).

Results

The mean age of 35 patients included in the study was 15.8±6.1 years and 19 of these patients were female (54%). The median age was 1.75 years at the time of diagnosis (25th and 75th percentiles, 0.25-6.5 years). The most common findings before diagnosis included failure in growth and development and respiratory findings (Table 1).

Genetic analysis was done in 30 of the patients (83.3%) and CFTR mutation was found in 63.5% of the patients. The most commonly found mutation was F508del. It was found heterozygously in 6 of the patients (20%) and homozygously in 5 of the patients (16.7%). No mutations was found in 36.5% of the patients.

The rate of chronic PA colonization was found to be 35% in CF patients followed up in our clinic, whereas the same rate was found to be 88.6% in the study group (p=0.001).

In 29 of the patients (80.6%), modified Bhalla scoring was done by HRCCT; moderate lung involvement was found in 91.3% of the patients and severe lung involvement was found in 8.7%. The clinical properties of the patients are shown in Table 2.

Table 1. Demographic properties of the patients

Female / Male (n)	19/16
Mean age (years)	15.8±6.1
Median age at the time of diagnosis (years)	1.75 (20 days-27 years)
Mean follow-up time (years)	6.8±4.0
Genotype	
(F508del homozygous) (n / %)	5 (%16.5)
(F508del heterozygous) (n / %)	6 (%20)
Other (n/%)	8 (%26)
Undetermined	11 (%36.5)
Died/survived (n)	8/27

Eight (23%) of the patients included in the study group were lost during the follow-up period. When the lost patients were compared with the patients who survived, diabetes mellitus (DM), need for noninvasive ventilation, $Sp0_2$ <%95, pCO_2>50 mmHg and intravenous antibiotic requirement for three times or more in the last one year were related with increased mortality (Table 3). No relation was found between mortality and liver involvement, age at the time of diagnosis and follow-up period. No significant difference was found between patients with and without CFTR mutation in terms of mortality, chronic PA colonisation, liver involvement, DM, noninvasive ventilation requirement, SpO_2 and pCO_2 levels.

CF gene analysis results are shown in Table 4. Since CF gene analysis was not done in four of eight patients who were lost, the relation between CF mutation and mortality was not evaluated. Since the number of patients was inadequate, logistic regression analysis was not done.

Table 2. Clinical properties of the patients

	n (%)
Chronic PA colonisation	31 (88.6%)
Staphylococcus infection	12 (34.3%)
B. cepacia infection	1 (3%)
Atypical mycobacterium infection	1 (3%)
Allergic bronchopulmonary aspergillosis	3 (8.5%)
Pancreatic failure	35 (100%)
Diabetes mellitus	6 (17%)
Liver disease	7 (20%)
Noninvasive ventilation	11 (31.4%)
Nasal O2 requirement	4 (11.5%)
Mean FEV1-expected	%40.8±13.7
FEV1 % reduction value	3.7±2.6
Mean SpO2 (%)	93.6±4.2
Mean PaCO2 (mmHg)	43.5±8.3
Weight median Z-score	-2.5 (quarter deviation: -3.4-1.7)
Height mean Z-score	-1.9±-1.2
Mean HRCCT score	18±3.0
Number of acute execerbations in the last year	4.14±2.27
Number of hospitalizations in the last year	1.71±1.56

PA: P. aeruginosa
FEV1: Forced expiratory volume in 1 second
SpO_2: Oxygen saturation
$PaCO_2$: carbondioxide pressure
HRCCT: High resolution chest computarized tomography

Discussion

In cystic fibrosis, the clinical course shows marked variance form patient to patient even in patients with the same genetic mutation. Therefore, it is considerably difficult to predict the prognosis. In a retrospective study performed by Kerem et al. (13) in 1992, it was reported that the two-year mortality was above 50%, if FEV1-expected was ≤30%, PaO_2 was <55

Table 3. Variables related to mortality

	lost (n)	survived (n)	p value
noninvasive ventilation requirement	no 2 yes 6	22 5	0.003
DM	no 4 yes 4	25 2	0.016
$FEV_{1\text{-expected}}$	<%30 6 ≥%30 2	6 21	0.011
SpO_2	<%95 8 ≥%95 0	6 21	0.000
PCO_2	<%50 3 ≥%50 5	23 4	0.015
Intravenous treatment (in the last 1 year. ≥3)	no 3 yes 5	22 5	0.031
Liver involvement	no 6 yes 2	22 5	0.69

DM: Diabetes mellitus
FEV_1: Forced expiratory volume in 1 second
SpO_2: Oxygen saturation
$PaCO_2$: Carbondioxide pressure

Table 4. Cystic fibrosis transmembrane regulator mutation analysis results

Mutation	(n)
Homozygous	10
F508del	5
1677delTA	3
N1303K	2
Heterozygous	8
F508del, L571	1
F508del, 2789+5G>A	1
F508del, 2183AA--G	1
F508del, 1262insG	1
F508del,1507del	1
F508del,N1303K	1
G542X, 15406>A	1
G542X,R560T	1
Could not be determined	11
Yok	6

mmHg and Pa CO_2 was >50 mmHg. In this study, FEV1 was reported to be an important marker in determining the mortality and survival rate (14,15,16,17,18,19,20,21,22). In our study, a FEV1-expected % value of ≤30 was related with increased mortality risk and 75% of these patients were lost in an average period of 2.5 years.

Recent studies have reported that annual FEV1 reduction rate is a better marker in predicting the prognosis (29,30). In our patients, the annual FEV1 reduction rate was found to range between -1,5 and -3,6 (30). The CF patients included in our study who had moderate and severe lung involvement had a higher annual FEV1 reduction rate, but this was not found to be related to mortality.

Chronic PA colonisation is one of the variables related to mortality in patients with cystic fibrosis. Chronic PA colonisation was found to be related to a more severe clinical course, low pulmonary functions, low weight, decreased height and body mass index and increased hospitalizations. Therefore, it is recommended that the patients should be treated in accordance with treatment protocols included in the international guides, when PA is found for the first time (31). In CF patients, the frequency of chronic PA colonisation increases with advanced age and reaches 80% at 25 years of age (3). In our patient group, chronic PA colonisation was found in 31 of the patients (88.6%). The rate of chronic PA colonisation was found to be 35% in all of our CF patients. Chronic PA colonisation was found to be significantly higher in our study group. Although chronic PA colonization was found to be significantly higher in our patient group compared to all CF patients followed up in our clinic, it was not found to be related to mortality. This finding is probably related to the low number of patients.

Colonisation with B.cepacia is an indicator of poor prognosis in cystic fibrosis (32). In our study, one patient was colonized with B.cepacia and was lost because of Cepacia syndrome. However, no comment can be made about a relation with mortality risk, since only a single patient was lost because of this syndrome.

F508del mutation is the most common mutation in CF. Its frequency shows variance according to ethnic groups and ranges between 30% and 80% (4,5,6). When compared with patients in Europe and America, the frequency of F508del mutation in our country ranges between 20.4% and 28.4% in different studies (7,8,9,10). In our study, the frequency of homozygous mutation was found to be 16.7%. No mutation causing CF could be found in 36.5% of the patients included in our study group. CF mutations in our country are very heterogeneous. Lakeman et al. (33) reported 31 different mutations in Turkish patients in a study they performed in the Turkish and North African people living in Europe and a mutation causing CF could be found only in 64.2% of these patients. No mutation causing CF could be found in 35.8% of the Turkish patients. These results are similar to our results. It is thought that these differences in the genotype of cystic fibrosis also affect the phenotype. The diagnosis delays because of all these variations and absence of neonatal screening. In our patients, the median age at the time of diagnosis was found to be 1.75 years (20 days-27 years). In USA, 58% of the patients are diagnosed by neonatal screening and 75% are diagnosed until they are two years old (3). In our study, 4 patients (11.4%) were diagnosed after the age of 10 and the mean FEV1-expected % value of these patients at presentation was <60. In our study, no relation was found between the age at the time of diagnosis and mortality. We thought that this finding was related with the limited number of patients.

As the life time of CF patient gets longer, the frequency of development of CF-related diabetes increases (34,35). The frequency of diabetes is 50% at the age of 30 and reaches 70% at the age of 40 (36). In our study, presence of DM was related to be increased mortality in CF. Four (17%) of six patients with diabetes were lost during the follow-up period. In our study, a significant relation was also found between noninvasive ventilation requirement and the mortality risk. 28% of the patients needed noninvasive ventilation. In 8 (80%) of these patients %FEV1expected was found to be ≤30. Six of the eight patients who were lost during the follow-up period were receiving noninvasive ventilation.

Fauroux et al. (24) reported 168 patients with noninvasive ventilation requirement in 36 CF centers in France. In all patients with a diagnosis of CF, noninvasive ventilation was started because of stable diurnal hypercapnia leading to exacerbation of severe hypercapnic breathing or sleep disturbance. In our study patients, noninvasive ventilation was started because of exacerbation of hypercapnic breathing, stable hypercapnia and/or decreased SpO_2. An oxygen saturation below 95 in room air during the daytime was found to be related to increased mortality risk.

As the lung involvement gets more severe in cystic fibrosis, the frequency of acute exacerbations and need for antibiotics increase (34). In our patients, requirement of antibiotic use for three or more times in the last one year was found to be related to increased mortality risk.

Although this study is a retrospective study, it is the first study from our country which investigates the factors related with mortality in CF patients with moderate and severe lung involvement. In our patients, FEV1-expected %≤30, requirement for noninvasive ventilation, presence of DM, SpO_2<95, pCO_2>50 mmHg and history of intravenous antibiotic use for three times or more in the last one year were found to be related with increased mortality risk. Logistic regression analysis was not done, since the number of patients was inadequate.

Numereous patients with CF live in Europe and America and the clinical findings related to these patients are being reported by CF centers. However, it is very important that we produce the information related to our own patients, since the patients in our country show genetic and phenotypic variance. In this study, the clinical course was evaluated in CF patients with moderate and severe lung involvement followed up in a single center who had different mutations and who had not undergone lung

transplantation and the factors related to mortality were reported. In our country, lung transplantation is not being performed, yet. This study is significant, since CF patients are the patients who need lung transplantation with the highest rate. We believe that similar multi-center studies should be performed.

Conflict of interest: None declared.

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