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Long term outcome of cystic fibrosis patients with multisystem evaluation

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ABSTRACT

Introduction: Cystic fibrosis is a chronic disease with multiple organ involvement and chiefly results in chronic respiratory infections, pancreatic insufficiency and associated complications. The age at diagnosis, clinical presentation, rate of disease progression and prognosis is variable among patients. This study is designed to evaluate the behavior of disease to provide epidemiologic data for early recognition and proper management.

Material and methods: The study was designed as an active surveillance of 192 patients diagnosed with cystic fibrosis in a tertiary lung disease centre between 2008 and 2015. The diagnosis of cystic fibrosis was established in all patients accordingly to conventional criteria, including two positive sweat chloride tests and clinical signs and symptoms. Demographic, clinical and laboratory data were obtained from these patients in each hospitalization and also every follow-up visit and carefully evaluated for complications of this chronic disease.

Results: The majority of patients showed positive culture for Pseudomonas aeroginosa. Bronchiectasis was the most prevalent finding in chest CT scan. 44.3% of patients had been treated for allergic bronchopulmonary aspergillosis and all had sinus disease. Increased pulmonary artery pressure was observed in 40% of patients with cystic fibrosis. 33 patients died which consisted 17.1% of all the patients.The mean age of mortaliy was 18.15 year.

Conclusions: The clinical outcome of cystic fibrosis is variable in different countries which may reflect environmental influences and the role of early diagnosis on long term outcomes. However, the role of early diagnosis in long-term outcomes of the disease can not be ignored.

Key words: cystic fibrosis, outcome, long-term, morbidity, mortality

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Introduction

Cystic fibrosis is a disease with multiple organ involvement that mainly results in chronic respiratory infections, pancreatic insufficiency and associated complications. The long-term outcome of multi-organ involvement has been studied by several researches; however, the point of care for these patients should be determined by the specific organ involved and the nature of pathogen microorganism.

Cystic fibrosis has an autosomal recessive pattern of inheritance conditioned by a mutant gene on the long arm of chromosome 7 which encodes cystic fibrosis transmembrane conductance regulator (CFTR). With any modification of

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CFTR, the ion transfer in the epithelium is altered. Therefore, the thickening of epithelial secretions increases and also a significant reduction of the action of mucociliary transport and beta-defensing ensues. The result is an increased pro-inflammatory activity which is the initiation point of many complications of cystic fibrosis. Age at diagnosis varies widely among these patients. Median age at diagnosis according to literature is 6–8 months. Respiratory symptoms may include cough, recurrent wheezing, atypical asthma, dyspnea on exertion and chest pain. Physical signs depend on the progression of disease such as tachypnea, respiratory distress with retractions, wheeze or crackles, increased anteroposterior chest diameter, clubbing, cyanosis, hyperresonant chest on percussion and nasal polyps. The diagnosis of cystic fibrosis is based typically on clinical manifestations, family history, and positive sweat chloride test results.

The course of disease and prognosis is tremendously variable among patients due to variability in organ involved. According to the literature there is a gender gap in cystic fibrosis, with males tending to do better than female counterparts [1, 2]. The lungs are normal at birth and after birth, before the onset of infection and inflammation. Infections become established with a distinctive bacterial flora. Failure of opsonophagocytosis leads to bacterial persistence. The most common bacterial pathogens isolated from the sputum culture of patients with cystic fibrosis are *Hemophilus influenza*, *Staphylococcus aureus*, *Pseudomonas aeroginosa*, *Burkholderia cepacia*, *E.coli* and *Klebsiella pneumoniae*. *S.aureus* is one of the three most common organisms in cystic fibrosis lung infections and is associated with advanced pulmonary disease. Colonization with *P.aeroginosa* is an unfavorable event in the clinical course of the patients with cystic fibrosis.

Typically, peripheral airway involvement resulting from cystic fibrosis, manifests as an obstructive defect with air-trapping and hyperinflation. Progression of the disease has been correlated with a change in forced expiratory volume in one second (FEV_1) [3]. It has been reported that exposure to second-hand smoke adversely affects both cross-sectional and longitudinal measures of lung function in individuals with cystic fibrosis [4]. Allergic bronchopulmonary aspergillosis affects approximately 7–9% of patients with cystic fibrosis. It is relatively uncommon in childhood. The clinical criteria for the diagnosis of allergic bronchopulmonary aspergillosis development have been recently proposed and a certain number of these criteria should be present to make the diagnosis of allergic bronchopulmonary aspergillosis. A problem with applying the criteria in children with cystic fibrosis is that many of the criteria could also be due to the underlying disease. Cystic fibrosis may express itself in the classical manner or in an atypical way. Inflammation of the paranasal sinuses has been found in 74–100% of patients and nasal polyps in 6 to 44%.

This study is designed to provide epidemiologic data useful for better evaluation and treatment of cystic fibrosis.

Material and methods

The study was designed as an active surveillance of 192 male and female patients diagnosed with cystic fibrosis in a tertiary referral lung disease centre (National Research Institute of Lung Disease) between 2008 and 2015.

The study was reviewed and approved by the Shahid Beheshti University of Medical Sciences Ethics Committee. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 2000 Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm) and its later amendments. Information about the study was given comprehensively both orally and in written form to all patients or their accompanying adult. They gave their informed written consents prior to their inclusion in the study.

The diagnosis of cystic fibrosis was established in all patients accordingly to conventional criteria, including two positive sweat chloride tests and clinical signs and symptoms. Demographic, clinical and laboratory data were obtained from these patients in each hospitalization and also every follow-up visit and carefully evaluated for complications of this chronic disease. Follow-up visits were set every 6 months if patients had no incidents of any exacerbation. If patients were admitted to hospital due to an emergency situation, their lab and radiologic data were reclaimed through National Health System from their admission file. At every visit, all necessary physical exam, laboratory or radiological exams were acquired if requested by physician.

Results

Total number of 192 patients with confirmed diagnosis of cystic fibrosis were enrolled in the

Table 1. Demographic variables of patients

Variable	
Age at the time of diagnosis	2.5 year
Sex (male/female)	60.4%/39.6%
Age at onset of the initial presentation	
> 5 year	20.2%
1–5 year	10.6%
< 1 year	66.2%

Table 2. Pathogenes cultured positive in lung sputum of cystic fibrosis patients (%)

Sputum culture	Positive
Pseudomonas aeroginosa	72.0
Staphylococcus aureus	25.4
Candida albicans	9.6
Aspergillus fumigates	8.8
E.coli	1.5
Klebsiella pneumoniae	1.5
Burkholderia cepacia	0.5

study. Demographic variables are presented in Table 1. The median age at diagnosis was approximately 2.5 year, and 60.4% of the patients were male and 39.6% of them were female. From 192 patients, 67.6% of the patients belonged to consanguineous families.

Sputum culture isolates

Sputum cultures were obtained during each hospitalization or at every visit. All the cultures were evaluated generally (not specifically individualized in each patient). From all the sputum specimens, 72% showed positive culture for *Pseudomonas aeroginosa*, 25.4% for *Staphylococcus aureus*, and 9.6% for *Candida albicans*. Surprisingly only one out of 192 patients showed positive sputum culture for *Burkholderia cepacia* (Table 2). 18.8% of our patients with second-hand smoke exposure had positive sputum cultures for methicillin-resistant *Staphylococcus aureus* (MRSA). Computed tomography (CT) findings in sputum culture positive patients for Aspergillosis were classified and 97% of patients with hyperinflation and 76.9% with collapse were positive for Aspergillosis.

HRCT scan findings

Various chest CT findings in cystic fibrosis patients were recorded during follow-up time.

Table 3. High-resolution computed tomography (HRCT) scan findings of cystic fibrosis patients (%)

HRCT scan findings	Positive	Negative
Bronchiectasis	96.5	3.5
Consolidation	83.3	16.7
Collapse	81.2	18.8
Hyperinflation	98	2

Table 4. Various clinical findings during follow-up time in cystic fibrosis patients (%)

	Positive	Negative
Allergic bronchopulmonary aspergillosis	44.3	55.7
Sinus disease	100	0
Failure to thrive (FTT)	89.5	10.5
Vitamin D deficiency	49	51
Diabetes	2.5	97.5
Increased pulmonary artery pressure (PAP)	40	60
High serum IgE	44.3	55.7

These chest CT findings are depicted in Table 3. The most prevalent finding is bronchiectasis observed in 96.5% of patients.

Clinical findings

Various clinical findings during follow-up time are depicted in Table 4. During their admission, 44.3% of patients had been treated for allergic bronchopulmonary aspergillosis (ABPA) and 100% had sinus disease during the course of their disease. Increased pulmonary artery pressure (PAP) was observed in 40% of patients with CF during 7 years follow-up time.

Mortality rate

During follow-up, 33 out of 192 patients died which consisted 17.1% of all the patients. Gender distribution among these dead patients was more significant in males and included 22 patients out of 116 (18.9%). Female mortality only consisted of 11 patients out of 76 patients (14%). Mortality was associated with raised pulmonary artery pressure in 33.3% of cases in our study. The mean age of mortality among these patients was 18.15 year. Figure 1 demonstrates the distribution of mortality in different age groups in male and female patients.

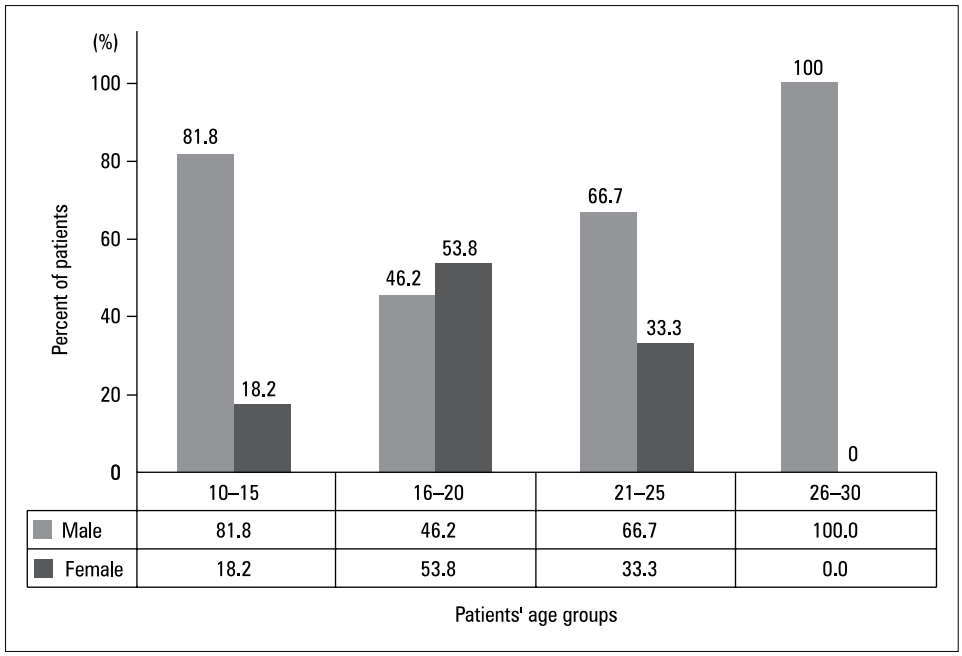

Figure 1. The distribution of mortality among different age groups in male and female patients

Discussion

The main point of this study is to show the various clinical findings and mortality rate of cystic fibrosis patients after 7 years follow-up. Overall, 7 years mortality was 17.1% (33 individuals) in our patients. Previously, cystic fibrosis was invariably assumed to be fatal during early childhood [5]. Today, the average life expectancy is 35 years and therefore cystic fibrosis is no more considered an exclusively pediatric disease [5]. With patients living longer and reaching adult-hood, complications play a major role in the development of complaints which are still a challenge for physicians in both outpatient and acute settings [6].

The median age of diagnosis in our patients was 2.5 year. The median age of diagnosis of cystic fibrosis according to literature is 6 to 8 months. The later age of diagnosis in our patients could be due to later referral time. This may affect the long-term prognosis and outcome.

There was also a male preponderance among the patients evaluated. Considering mortality among these patients, death was significantly much more prevalent in our male patients, approximately twice the female patients. This was in contrast with previous cohorts who were indicative of a worst survival and a lower overall life expectancy in female patients than the males [7, 8]. None of our patients died in the first year of life and even in the first decade of life and this is the result of improved management of cystic fibrosis in recent years. However, no single new therapeutic intervention can be identified as the reason for this improved survival.

Consanguinity is known to be the main cause of genetic disorders and there is a greater risk of occurrence of cystic fibrosis in populations with high levels of consanguineous marriage. The overall rate of consanguineous marriage among Iranians is approximately 38.6% with a range of 30−85% in different provinces. In this study, 67.6% of the patients with cystic fibrosis belonged to consanguineous families [9].

Cystic fibrosis lung is affected in an extraordinary complex manner and cystic fibrosis patients have a unique set of bacterial pathogens that are acquired in an age-dependent manner. According to literature, common pathogens cultured from the respiratory tract of young children with cystic fibrosis which cause endobronchial infections during childhood are *S.aureus* and non-typeable *H.influenzae*. In cystic fibrosis patients, the predominant site of infection with S.aureus, is the oropharynx rather than the anterior nares [10]. Later, as the patient ages, the major organisms which involve the respiratory tract are *P.aeroginosa* and *B.cepacia*. It has been shown that a host enzyme with bactericidal activity, sPLA2-IIA, increase age-dependently in expectorations of patients with cystic fibrosis. These amounts are enough to kill *S.aureus* but only marginally influence the *P.aeroginosa* strains. *P.aeroginosa* isolates from

CF patients are capable to induce sPLA2-IIA expression in bronchial epithelial cells which are known as the major source of the enzyme. Hence, *P.aeroginosa* contributes to *S.aureus* eradication in CF airway [11]. Our results suggested that one species of bacterium could eradicate another one by manipulating the host.

Pseudomonas was more frequently cultured from the sputum of the older patients in our study (28% in patients less than 5 yr old vs. 44% in patients older than 5 yr old). In a study performed in 2011–2012 nearly half of the cystic fibrosis patients were diagnosed by *P.aeroginosa* [12]. *P.aeroginosa* is considered to be the most significant pathogen in these patients also because of its association with worsening of the pulmonary status. In our previous study performed in 2009–2010, *P.aeroginosa* was one of the main risk factors of patients' death [13]. Its eradication is really difficult despite intensive antibiotic treatments. The co-existence of multiple phenotypes of *P.aeroginosa* with highly resistance to any antimicrobial treatment is one of its most striking characteristics in chronic lung involvement in cystic fibrosis. This was strongly consistent with our findings in these patients. As most of them with positive pseudomonas sputum cultures were infected with resistant strains to two or even more antimicrobial agents such as cefepime, ceftazidime, amikacin and gentamicin. Colistin was the antimicrobial agent with the least degree of resistance in our study, may be due to the fact that it has been much less available than the above mentioned agents.

Aspergillus fumigatus is another pathogen with an important role in cystic fibrosis lung disease and is frequently isolated from cystic fibrosis patients. This role is not exclusively in the context of ABPA. In our study 8.8% of our patients had positive sputum cultures with Aspergillus. It has been shown that cystic fibrosis patients with colonization of this fungus experience more frequent hospitalizations, with more prominent radiological abnormalities and a lower lung capacity than others without colonization [14]. Chest radiographs in patients with cystic fibrosis usually reveal degrees of hyperinflation, dilated bronchi with thickened walls as well as well-defined areas of air-space opacification or nodules due to mucoid impaction, atelectasis, cavities and hilar lymphadenopathies. Pneumothorax is also frequently seen and can be recurrent. While the radiologic evaluation of our cystic fibrosis patients revealed hyperinflation in 98% of patients, bronchiectasis in 96.5% of the patients, consolidation in 83.3% of patients and collapse atelectasis in 81.3% of them which are similar to our earlier studies [15, 16], colonization with aspergillus associated with hyperinflation, bronchiectasis, consolidation and atelectasis were reported as 5.9%, 9.1%, 6.3% and 13.3%, respectively.

Candida infections are not rated as a priority by cystic fibrosis patients and may simply reflect contamination of the sputum but airway colonization with Candida albicans has been associated with a greater rate of FEV_1 decline and hospital-treated exacerbations in cystic fibrosis [17, 18]. In our study, Candida cultures were classified based on FEV_1 of patients which 28.6% of candida culture positive had $FEV_1 > 80\%$ and 71.4% had $FEV_1 < 80\%$. This could be an issue for further studies.

The prevalence of rhinosinusitis in the cystic fibrosis patients reaches 100% [19]. Cystic fibrosis patients have a high susceptibility for a sinus disease. This may be related to altered properties of their mucous secretions, leading to impaired mucociliary clearance. It has been suggested that the CFTR mutation responsible for cystic fibrosis might be a predisposing factor for sinus disease, by demonstrating an increased occurrence of CFTR mutations in the general population with chronic rhinosinusitis. In our study 100% of the patients were suffering from chronic sinus disease which significantly influenced their quality of life.

According to literature, pulmonary artery pressure is raised in adults and correlates well with pulmonary disease severity and survival [20]. However, FEV_1 and PaO_2, have been suggested as stronger predictors of death in these patients [20]. In our study, 60% of patients had normal pulmonary artery pressure and a raised pulmonary artery pressure was seen in 40% of them. Raised pulmonary artery pressure was associated with mortality in 33.3% of cases in our study. However, most of the mortality associated with cystic fibrosis results from progressive lung disease. Patients with respiratory disease may experience a steady decline in lung function, with eventual development of cor pulmonale, respiratory failure and death. In a Canadian cohort modifiable risk factors such as malnutrition and pulmonary exacerbations are associated with an increased risk of death [21].

Although failure to thrive is a hallmark of the disease but surprisingly 10.5% of our patients did not show any growth failure. This may be explained by mutations with less severe forms of presentation of the disease. To evaluate

the disease severity, scoring systems such as "Shwachman-Kulczycki score system" are available [22]. It also underscores this fact that higher socioeconomic status of the family with better provision of nutritional supplements may greatly influence the growth of the child.

Children who already have a lung disease such as cystic fibrosis and asthma are at greater risk for health problems when they are exposed to tobacco smoke [23]. Research has shown these children have a greater decline in lung function and their disease worsens or progresses more than those who are not exposed. Lung damage from second-hand smoke exposure can happen silently even if the child does not seem to have any symptoms. Children with cystic fibrosis exposed to second-hand smoke not only are confronted with diminished growth and increased air-trapping, but also have MRSA isolated from their respiratory cultures more frequently [24]. We evaluated our patients with second-hand smoke exposure for MRSA and we found that 18.8% of these patients had positive sputum cultures for MRSA.

Conclusion

The clinical outcome of cystic fibrosis is variable in different countries. This may reflect environmental influences on expression of one single genetic disorder. However, the role of early diagnosis in long-term outcomes of the disease cannot be ignored. The final goal in patients with cystic fibrosis is to take steps toward better clinical outcomes and to achieve a near normal life.

Conflict of interest

The authors declare no conflict of interest.

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