The clinical and laboratory manifestations of Iranian patients with cystic fibrosis

Gholamhossein Fallahi[1], Mehri Najafi[1], Fatemeh Farhmand[1], Fatemeh Bazvand[1]
Maedeh Ahmadi[1], Faezeh Ahmadi[1], Kambiz Eftekhari[1], Ahmad Khodad[1]
Farzaneh Motamed[1], Gholamreza Khatami[1], Asghar Aghamohammadi[1,2], Nima Rezaei[1,2]

[1]Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center, and [2]Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

SUMMARY: Fallahi G, Najafi M, Farhmand F, Bazvand F, Ahmadi M, Ahmadi F, Eftekhari K, Khodad A, Motamed F, Khatami G, Aghamohammadi A, Rezaei N. The clinical and laboratory manifestations of Iranian patients with cystic fibrosis. Turk J Pediatr 2010; 52: 132-138.

Cystic fibrosis (CF) is a hereditary disease, characterized by chronic pulmonary disease, pancreatic insufficiency and abnormal electrolytes in the sweat.

In order to evaluate the clinical manifestations and laboratory findings of Iranian children with CF during a 10-year period, 243 CF patients, with a median age of 5 months, were investigated in this study. The most common manifestations were gastrointestinal disorders and respiratory manifestations. Cough was the most common symptom, followed by malnutrition, diarrhea, respiratory distress, and vomiting. The frequency of these findings after treatment was significantly decreased in comparison with the period before diagnosis. During the mean follow-up of 40.9 months, seven cases died due to severe infections.

Cystic fibrosis as a common genetic disorder should be considered in any child with recurrent gastrointestinal and respiratory manifestations, since delayed diagnosis could lead to severe complications and even death in this group of patients.

Key words: cystic fibrosis, respiratory infection, Iran.

Cystic fibrosis (CF, OMIM#219700) is a hereditary disease of mucus and sweat glands that mainly affects the respiratory and gastrointestinal systems, leading to progressive disability. It could be characterized by chronic pulmonary disease, pancreatic insufficiency and abnormal electrolytes in the sweat[1-3].

Cystic fibrosis is one of the most common autosomal recessive disorders, with an estimated incidence of 1/2,500 to 1/3,900 live births [2,4,5]. CF is caused by mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*, OMIM: *602421) gene, located on the long arm of chromosome 7[1,6]. While the product of *CFTR* is a chloride ion channel, it has an important role in producing sweat and mucus; therefore, this molecular disorder affects chloride ion secretion[7], causing salty sweat and abnormal mucus secretion of several epithelial cells in different organs, especially the lungs, pancreas, liver, intestines, and the airways. This change transforms mucus from the normal function of protecting the cell to sticky and thick mucus causing tissue damage.

Cystic fibrosis can present with different clinical features and severity from patient to patient. Although the reason is unclear, it could be due to type of mutations and other modifier genes[8] and can cause other symptoms in the nature of the disease. The abnormal mucus hinders exhaustion secretion from different organs and leads to a variety of clinical symptoms, including recurrent infections of airways, obstruction of the pancreatic duct causing pancreatic insufficiency, disorder of bile secretion resulting in biliary cirrhosis, and gastrointestinal obstruction like meconium ileus[2].

This study was performed in a main referral center in Iran to evaluate for the first time the clinical manifestations and laboratory findings of patients with CF.

Material and Methods

In order to determine the clinical and laboratory findings of Iranian patients with CF, the consecutive records of 243 patients, who had been referred to the referral gastroenterology departments of the Children's Medical Center Hospital, Tehran, Iran, were reviewed. These data were gathered by interviewing the patients' parents and reviewing the medical documents over a 10-year period (1999-2008).

The diagnosis of CF was made based on increased levels of electrolytes in the sweat, which was confirmed with sweat test twice (3). Molecular analysis was performed in 70 cases, and mutations of the *CFTR* gene were found in all of them[9].

Data analysis was performed using SPSS statistical software package, version 14.0 (SPSS Inc, Chicago, IL). The results were presented as the mean ± standard deviation and also median (minimum-maximum). As for non-parametric data of admission per patient per year, Wilcoxon signed ranks test was used for comparison before and after diagnosis. A p-value of less than 0.05 was considered significant.

Results

Patient Characteristics

Two hundred and forty-three patients with CF (137 male, 106 female), with a median age of 4.5 years (range: 1-20 years) were reviewed in this study (Fig. 1). Among them, 219 cases experienced symptoms by the age of 1 year (90.1%). The median onset age was 3 months (range: <1 week - 11 years). The median age at the time of diagnosis was 5 months (range: 2 weeks - 15 years), with a median diagnostic delay of 1 month (0-146 months). Although 224 cases had been diagnosed within 1 year after onset of the symptoms (92.4%), 9 patients were diagnosed with a delay of more than 4 years (Table I). There was no significant difference in either onset age or diagnosis age between males and females (median onset age of 3 months for both sexes; median diagnosis age of 4.5 months for males and 5.5 months for females). Statistical analysis of these data indicated that the diagnosis has increasingly been made at an earlier age in recent years (R= -0.431, R Square= 0.186, F= 46.992, p<0.001) (Fig. 2).

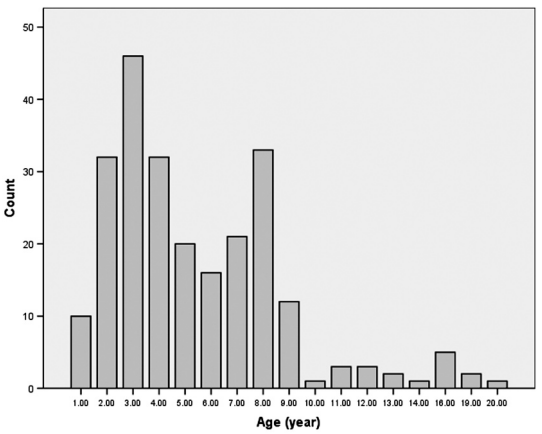

Fig. 1. Age distribution of the CF patients at the time of the study.

Table I. Characteristics of Cystic Fibrosis Patients (n=243)

Male/Female	137/106
Status	
Alive/Dead	236/7
Study age	
mean±SD	5.5±3.5 years
median (range)	4.5 (1-20) years
Onset age	
median (range)	3 months (1 week - 11 years)
Diagnosis age	5 months (2 weeks - 15 years)
median (range)	
Delay in diagnosis	
median (range)	1 month (0-146 months)
Family history	
Consanguinity	
Positive famil	155 (63.8%)
history of disease	38 (16.6%)

Consanguinity and Family History

Consanguineous marriage is defined as two partners having at least one ancestor in common, with the ancestor being no more distant than a great-great grandparent. For descendants who are of the same generation, a consanguineous marriage would be between one person and a third cousin or closer relative.

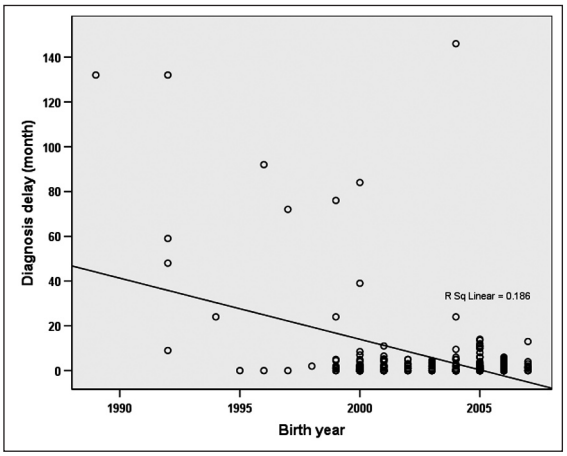

Fig. 2. Association between birth year and diagnosis delay.

In 155 families, parents were consanguineous (63.8%). There was a history of CF and death due to CF complications in the siblings of 38 affected patients (16.6%).

Presenting Features

The most common presenting manifestation of these CF patients was gastrointestinal disorders, seen in 152 patients (62.6%). Respiratory manifestations were the second most common features of the patients (93 patients, 38.3%). The gastrointestinal manifestations of the patients, in descending order of frequency, included malnutrition or failure to thrive (FTT: 65 cases), fatty diarrhea (54 cases), poor feeding (lack of interest in feeding, 30 cases), and vomiting (23 cases). Three patients were presented with ileus meconium and two patients with jaundice. The respiratory manifestations of the patients, in descending order of frequency, included cough (58 patients) and respiratory distress (40 patients). There were some overlapping symptoms in the patients, while some patients were presented with two or more symptoms at the first occasion of disease presentation. Eleven patients were presented with respiratory distress and vomiting; 9 with respiratory distress and diarrhea; and 8 with FTT and respiratory infections. Seven cases were presented with weakness, and 5 with fever and irritation or fever and vomiting. Five patients were presented with edema, and 1 also had FTT and cough in addition to edema.

Clinical Manifestations

During the disease course, gastrointestinal disorders and respiratory manifestations were the most common features. Among them, cough was the most common symptom, which was present in more than half of the patients (126 cases, 51.9%). Malnutrition was the second most common manifestation (99 cases), followed by diarrhea (88 cases), respiratory distress (80 cases), poor feeding (74 cases), and vomiting (57 cases) (Table II). The frequencies of some of these findings after diagnosis and treatment were significantly decreased in comparison with before diagnosis (Table II). Seven cases also experienced edema during the course of the disease. Hepatomegaly was detected in 52 cases (21.4%). One patient had diabetes mellitus.

Hematological Study

Total white blood cell (WBC) counts ranged from normal to markedly elevated numbers in

Table II. Comparisons of Common Clinical Manifestations of Cystic Fibrosis Before and After Diagnosis

Clinical manifestations	Before diagnosis Frequency (%)	After diagnosis Frequency (%)	P-value	OR (95% CI)	Total Frequency (%)
Failure to thrive	85 (34.9%)	14 (5.8%)	<0.0001	8.80 (4.76-16.83)	99 (40.7%)
Diarrhea	70 (28.8%)	18 (7.4%)	<0.0001	5.06 (2.82-9.16)	88 (36.2%)
Vomiting	38 (15.6%)	19 (7.8%)	0.011	2.19 (1.18-4.08)	57 (23.5%)
Cough	73 (30.0%)	53 (21.8%)	0.049	1.54 (1.00-2.37)	126 (51.9%)
Respiratory distress	58 (23.9%)	22 (9.1%)	<0.0001	3.15 (1.80-5.53)	80 (32.9%)

patients with acute infections, with the mean count of 11527±4516 cells/mm^3. Twenty-six patients had thrombocytopenia (platelets <15000 cells/mm^3), while none of them had splenomegaly. Twenty-four patients had severe anemia (hemoglobin <7 g/dl) and 80 patients had mild anemia (hemoglobin: 7-10 g/dl). Although anemia could be due to chronic infection, iron deficiency or vitamin E deficiency, further investigations to show the cause of anemia were unfortunately not performed in this group of patients.

Hepatic and Pancreatic Study

Most patients were asymptomatic at the time of diagnosis and only identified by evidence of hepatomegaly (52 cases) after a routine examination. Such finding was also confirmed by abdominal sonography. Two patients also had jaundice. Eighty patients (33.3%) had hypoalbuminemia (albumin <3.5 g/dl), while only 7 cases developed edema (2.8%). Thirty-two patients had high prothrombin time (PT >13 seconds). Elevated serum levels (more than 2 times the upper limit of normal) of at least two liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase) were detected in 13 cases. One hundred patients with fatty diarrhea also had some evidences of pancreatic exocrine deficiency. All of them had Sudan 3 in stool exam revealing more than 100 fatty droplets; 27 of them had trypsin activity higher than 1/96.

Pulmonary Study

Chest X-ray was taken from the patients, and 93% had hyperaeration of both lungs; radiologic findings in 29% of cases suggested the diagnosis of pneumonia. Pulmonary function tests were not performed in our patients, because most were not old enough to perform such tests.

Treatment

The patients were treated with supplemental therapy (vitamins and minerals). Patients with pancreatic insufficiency and hepatomegaly were treated with Creon and ursodeoxycholic acid, respectively. In the patients suffering from malnutrition, a high-caloric diet with increased macronutrient in addition to vitamin supplements was prescribed. Supplementation with medium-chain triglyceride (MCT) oil and pancreatic enzymes was also prescribed in some patients. Antibiotic prophylaxis (cotrimoxazole) and respiratory physiotherapy were used for patients with pulmonary involvement. In an acute phase of pulmonary involvement, nebulized bronchodilators were also used.

Mortality

Seven cases died (5 females, 2 males) due to severe respiratory distress and sepsis, all before the age of 4 years. The remaining 236 patients were followed-up for a total of 718.9 patient-years (40.9±31.4 months per patient). Six hundred and seventy-four admissions were recorded for all patients; 486 of them belonged to the period before diagnosis, while 188 were recorded after diagnosis ($p<0.001$). Hospital admission of the patients after diagnosis was significantly lower than before diagnosis (0.03 vs. 0.41 admission per patient per month, respectively, $p<0.001$).

Discussion

Cystic fibrosis is a hereditary disease of mucus and sweat glands, with multi-organ involvement that causes different symptoms[1,2]. The majority of diagnoses were based on clinical features of the respiratory and gastrointestinal systems [1,2].

The male to female ratio in our study was 1.29, which does not show any significant difference between sexes. This finding is compatible with previous studies[10-13]. Since CF is transmitted as autosomal recessive inheritance, it is expected that the number of affected males and females would be similar. The consanguinity rate was 68% in our study. Although this rate is much higher than in a previous study in Brazil[14], the high rate of consanguineous marriages in some regions, especially in Middle East countries, could associate with the high rate of diseases with autosomal recessive inheritance[15]. In these countries, where consanguinity is common in marriage, there is an urgent need for public education programs and provision of the facilities for genetic counseling and reproductive risk assessment[15].

In this study, about 90% of the patients experienced symptoms before the age of 1 year. The median onset age and diagnosis age were 3 and 5 months, respectively. Although

more than 80% of the patients were diagnosed before the age of 1 year, and more than 90% of the patients were diagnosed within 1 year after the start of symptoms, 9 patients were diagnosed with a delay of more than 4 years. However, the median delay in diagnosis was 1 month, which is much lower than in previous studies[10,11,13,16,17]. It could indicate the acceptable level of awareness of medical staff in our country about the disease. In the study by Sturgess et al.[16], only 60% of cases were diagnosed within the first year of life and more than 25% were still undiagnosed by the age of 2 years. In another study on 3,795 patients, more than 10% of patients were not diagnosed before the age of 5 years [13]. However, it should be indicated that the different age of diagnosis is dependent on various symptoms, severity of disease, onset age of symptoms, and screening for CF[10]. We did not find any significant difference in onset age and diagnosis age between males and females, which is in contrast with previous studies that indicated females were diagnosed later than males[11,16].

In our study, the most common presenting manifestations were gastrointestinal disorders followed by respiratory manifestations. FTT, fatty diarrhea, and poor feeding were the most common gastrointestinal manifestations. Although meconium ileus is considered as one of the important clinical manifestations of CF, it only occurred in 1% of our patients, which is much lower than in previous studies[18-22]. The study by the Registry of the United States National Cystic Fibrosis Foundation reported an incidence of 16% for meconium ileus in CF patients[22], while this incidence varied between 7% and 20%[18-21]. There are controversies in the role of meconium ileus as a risk factor for developing liver disorder[23-28]. It should be emphasized that as this study is hospital-based, it is possible that some undiagnosed cases with CF died before referral to the hospital.

Although percentages of respiratory signs and symptoms in our study are much lower than in previous studies, reporting the patients from the gastrointestinal department could be a reason for missing some cases with just pulmonary involvement. Moreover, pulmonary function tests are generally performed in the patients over 5 years of age in our center. As noted in the Results section, the median age of the patients was 4.5 years; among them, 90% of cases experienced symptoms by the age of 1 year. The median onset age and diagnosis age of patients were 3 and 5 months, respectively. They were also followed for 40.9±31.4 months per patient. Thus, pulmonary function tests were not performed in many patients, because most were not old enough to be capable of performing such tests; consequently, the pulmonary findings, as very important manifestations of CF, are underestimated in this study. It should also be pointed out that while sputum culture was routinely performed in almost all subjects, which was positive for *Pseudomonas aeruginosa* in several cases, we cannot provide the exact percentages of involvement with this pathogen or other microorganisms because empiric therapy is performed for treatment of pulmonary infections.

Although diabetes is one of the complications of CF, which can occur in about 13% of patients, it is most often diagnosed in the patients older than 30 years[6]. It is also estimated that 50% of patients over 18 years of age have glucose intolerance[29,30]. Only one of our CF patients had diabetes at the age of 15 years. The low rate of diabetes in this study can be explained by the fact that our patients were in the pediatric age group.

More than 40% of our CF patients had anemia, while approximately 10% had severe anemia. Chronic infections could lead to anemia. Some patients presented anemia with the triad of CF including hypoproteinemia, edema and anemia. Anemia is common in CF, which could be due to iron and vitamin E deficiency[31]. The incidence of anemia, hypoproteinemia and edema in infants is approximately 5%[32].

Liver involvement including hepatomegaly occurred in more than 20% of our CF patients, while only 2 cases developed jaundice. Liver disease is one of the rare clinical manifestations of CF in infancy[26,33], with the most common presentation being conjugated hyperbilirubinemia[6]; it usually occurs in adolescence[34], with a prevalence of 41%[27].

The regular treatment regimens for CF patients were supplemental therapy (vitamins and minerals). Respiratory physiotherapy was used for the patients with pulmonary involvement. Use of normal saline or NaCl 3% via nebulizer was prescribed for patients in our center, while

dornase and recombinant human DNAse are not easily available to patients.

In our study, the rate of hospitalization after diagnosis was significantly decreased in comparison with before diagnosis, which could indicate the role of early diagnosis and appropriate treatment in reducing morbidity. During the mean follow-up of 40 months, 7 cases died. The mortality was higher in females than males, which is similar to previous studies[10,13,17,35-43]. It seems that survival of CF patients has increased in recent years [44,45]. Early diagnosis of the patients could be associated with decreased risk of mortality[13]. In fact, delayed diagnosis could lead to severe complications, including malnutrition, potentially accelerated respiratory diseases, and possibly high mortality risk[10,46-53]. While this study provides clinical data of CF patients from the main referral center and some studies have provided molecular analysis of the CF patients[9,54,55], further studies on association of genotype and phenotype of CF are suggested.

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