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Cystic Fibrosis Patients Evaluation in the Last Decades in a Referral Center, Tehran-Iran

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Abstract

Background

Cystic fibrosis (CF) is the most prevalent lethal chronic genetic and multivariate disease, widespread in Iranian population. The aim of this study was to evaluate the condition of patients with CF from various dimensions in the last decades in Iran.

Materials and Methods

In this cross-sectional study the data were collected from disease registry database of CF patients in Pediatric Respiratory Disease Research Center in Masih Daneshvari, Tehran, Iran. The patients were divided into female and male. The data were collected based on province, birthplace province, marital status, and degree of education, parental consanguinity ratio, age, and age of onset of symptoms, age of onset of diagnosis and body mass index (BMI).

Results

Majority of patients (n=169, 59.3%) were male, born in Tehran province (n=81, 28.4%), and live in Tehran province (n=102, 35.8%). Majority of parents (61.1%, n=174) had consanguineous relation and the rest (n=94, 33%) did not have any consanguineous relation. Results show that mean of age, age of diagnosis, mean for expression of first symptoms and mean of time interval between the onset of symptoms and the diagnosis of the disease were 14.52, 2.51, 6.57, and 4.07 years, respectively. Results showed that high percentage of patients (n=191, 67%) had lower BMI (<18.50), and low percentage (n=3, 1.1%) showed higher BMI (>25). Correlation coefficient also showed positive relation between start age of symptoms and diagnosis age of disease.

Conclusion

In Iran, CF is a multisystem disease and age for its expression is different. Since mean for time interval between the onset of symptoms and the diagnosis of the disease is 4.07 years, it could be recommended to perform the phenotypic and genotypic test at birth.

Key Words: Children, Cystic fibrosis, Growth pattern, Iran, Symptoms.

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1- INTRODUCTION

Cystic fibrosis (CF) is the most prevalent lethal chronic genetic and multivariate disease which is accompanied with clinical changes (1, 2). It is caused due to mutation in the gene responsible for coding cystic fibrosis transmembrane conductance regulator (CFTR). This disease is one of the most lethal multisystem disorders and the most prevalent autosomal recessive mortal hereditary disorder in Caucasians (3, 4). There are differences in the populations, ethnics and countries in terms of distribution and mutation status (5, 6). In Caucasian, one out of every 3,500 new born children suffers from the disease and one out of 30 of them has severe mutation for CFTR gene. The disease symptoms vary in the different individuals. Some individuals are faced with serious problems from birth, but some others have mild degrees which are not expressed up to adolescent and youth periods.

Patients sometimes show low symptoms but symptoms increase with the passing of time. Constipation is one of the first symptoms that parents are faced with. This action causes repeated infections and lung damage. It also prevents pancrease enzymes from entering intestine. As a result, the intestine cannot completely absorb protein and fat which leads to continuous diarrhea. Intestinal obstruction may occur in newborn babies. Excessive gas or acute constipation may cause abominal pain. Increased mucus provides environment for bacterial growth and also lung infection in patients. The patients are faced with problems for enzyme production and food digestion. Primary symptoms include disorders in weight gain despite appropriate nutrition, lung infections and respiratory disorders (7, 8). The disease is the most prevalent genetic disease which is accompanied with decreased pulmonary function and malabsorption disorder in nutrition status (9). CF creates the obstruction disorders in the different ductus (10, 11). Since CF is a multisystem genetic disease, the patients with CF are often faced with vitamin and mineral deficiency including A, D, E, selenium, zinc and copper due to digestive disorders and nutrient absorption (12), and/or mortality due to electrolyte disorders (13). Bone mineral density is known as one of the main phenomena in patients with CF (14). CF is known as a hereditary disease which limits lifespan and influences on different organs. Respiratory disease is still a factor for mortality related with CF (15). Different procedures have been used for diagnosis of disease. Sweat test has been used to detect the CF in children. The levels of sodium and chloride are assessed by using special electrodes inserted into sweat. Infants with CF have high levels of salt (2, 16).

Advancement in detection and management of CF could identify people from mild to severe (15). It is believed that finger print and palm patterns are indicators for congenital abnormality in CF (17). Detection and fast treatment of pancreatic defect are known to be important for malnutrition and inability to grow in children with CF (13). Early detection of the disease and its cause can benefit from early treatment and prevention of possible side effects (18). Evaluation of distribution and its relation with growth pattern of patients with CF is important to prevent the malnutrition and increase the life expectancy. Genotypic and phenotypic procedures have been suggested to detect the CF disease (19). Infection control and protection of respiratory function is a main key for treatment due to chronic bacterial infections. Therapeutic drugs include antibiotics for prevention of infection (20), bronchodilators for opening respiratory tract, cortones for decreasing inflammation in respiratory system and also pancreatic enzymes for decreasing digestive

disorders. Fat soluble daily vitamin supplements have been recommended for patients. Oxygen therapy may be conducted in hospitalized children or patients with progressed respiratory disease. Chest physiotherapy must be conducted daily in order to discard the mucus. The parents must be informed about exercises and respiratory training. Physiotherapy experts, doctors and nurses can guide parents (21). CF detection and hospitalization of children can cause severe anxiety and stress in parents, especially for mother, this may influence on curing period of children (22). With regard to other studies, it has been shown that CF is more prevalent in Iranian (23). Many studies must be conducted to evaluate the disease, its clinical and molecular pattern in Iranian children. This study aimed to evaluate the status of patients with CF from various dimensions such as: demographic, distribution based on BMI, distribution based on age for expression of first symptoms, distribution based on age of diagnosis, distribution based on start interval to diagnosis of disease, and other factors in the last decades in Iran.

2- MATERIALS AND METHODS

This is a descriptive/analytical cross-sectional study. The data were collected from disease registry database of CF patients in Pediatric Respiratory Disease Research Center of National Research Institute of Tuberculosis and Lung Diseases (NRITLD) in Masih Daneshvari Hospital (the most important educational, research and therapeutic center for respiratory diseases in Iran). The patients were divided into female and male. The data were collected on basis province, birthplace province, married status, and degree of education, parental consanguinity ratio, age, and age of onset of symptoms, age of onset of diagnosis and body mass index (BMI).

2-2. Ethics

The study protocol was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.MED.REC.1395.260). Also, data was reported in general without mentioning the name.

2-3. Statistical analysis

The data were analyzed by SPSS statistical software package, version 23.0 (SPSS Inc, Chicago, IL). The results were reported as the mean and also frequency. Tukey test was used to compare data. Pearson correlation was also used. Chi-Square test was used to evaluate the some variables. A p-value of less than 0.05 was seen as significant.

3- RESULTS

With regard to obtained data, most patients (n=169, 59.3%) were male and 116 individuals (40.70%) were female. The majority of patients live in Tehran province (n=102, 35.8%), and the the fewest live in Hamedan and Northern Khorasan (n=1, 0.4%, **Table.1**). Most of the patients were born in Tehran province (n=81, 28.4%), and the lowest birthplace province (n=2, 0.7%) was observed in Golestan, Hamedan, Bushehr, Northern Khorasan, Kohkiluyeh and Boyer Ahmad, Semnan and Chahar Mahal Bakhtiari provinces. Among patients, birthplace was indeterminate for 3 patients, so that 2 patients were from Afghanistan and 1 patient from Azerbaijan Republic. As results showed, most of the patients (n=261, 91.6%) were single. Among patients, 14 patients (4.9%) were married. Results showed that the highest percentage of patients was illiterate, elementary and high school and only 1 patient was MSc. Most parents (61.1%, n=174) had consanguineous relation and the rest (n=94, 33%) did not have any consanguineous relation. The mean for BMI was 15.72$\pm$ 3.26 with minimum 8.32

and maximum 26.39. Results showed that mean of age was 14.52±8.82 years for patients with minimum 0 and maximum 38 years. The mean for expression of first symptoms was 2.51± 7.72 years with minimum 0 and maximum 21 years. The mean for age of diagnosis was 6.57± 7.89 years, so that minimum age was 0 and maximum was 34 years. In addition, the mean for time interval between the onset of symptoms and the diagnosis of the disease was 4.07± 6.80 years with minimum -10.00 and maximum 34 years (**Table.2**).

Table-1 Frequency distribution of the studied patients on basis of habitat province.

Province name	Frequency	%
Alborz	9	3.2
Ardebil	4	1.4
Bushehr	2	0.7
Chahar Mahal Bakhtiari	2	0.7
East Azarbaijan	9	3.2
Esfahan	14	4.9
Fars	18	6.3
Gilan	4	1.4
Golestan	2	0.7
Hamedan	1	0.4
Hormozgan	5	1.8
Kerman	3	1.1
Kermanshah	7	2.5
Khorasan Razavi	2	0.7
Khuzestan	23	8.1
Kohkiluyeh and Boyer Ahmad	2	0.7
Kurdistan	7	2.5
Lorestan	10	3.5
Markazi	4	1.4
Mazandaran	12	4.2
Northern Khorasan	1	0.4
Qazvin	7	2.5
Qom	5	1.8
Semnan	2	0.7
Sistan and Baluchestan	9	3.2
Tehran	102	35.8
Western Azerbaijan	8	2.8
Yazd	6	2.1
Zanjan	5	1.8
Total	285	100.0

Table-2: Descriptive statistics for patients based on age.

Descriptive statistics	Number	Minimum	Maximum	Mean	SD
Age	285	0.00	38	14.52	8.82
Age of onset of symptoms	271	0.00	21.00	2.51	4.72
Age of diagnosis	273	0.00	34.00	6.57	7.89
Time interval between the onset of symptoms and the diagnosis of the disease	269	-10.00	34.00	4.07	6.80
Valid N (listwise)	221	-	-	-	-

SD: Standard deviation.

The data for frequency distribution of BMI in patients with CF in classes of >18.5, 18.5-25 and >25 are reported in **Figure.1**. Results showed that high percentage of patients (n=191, 67%) had lower BMI (<18.50) and low percentage (n=3, 1.1%) showed higher BMI (>25). **Figure.2** shows that age for most patients (n=109, 38.2%) ranged from 10-20 years and the lowest percentage (n=12, 4.2%) had mean age of 30-40 years. The age for expression of first symptoms is shown in **Figure.3**. Most of the patients (n=223, 78.20%) expressed first symptoms at 0-5 years of age. Lower percentage of patients (n=1, 0.4%) showed symptoms at 20-25 years of age.

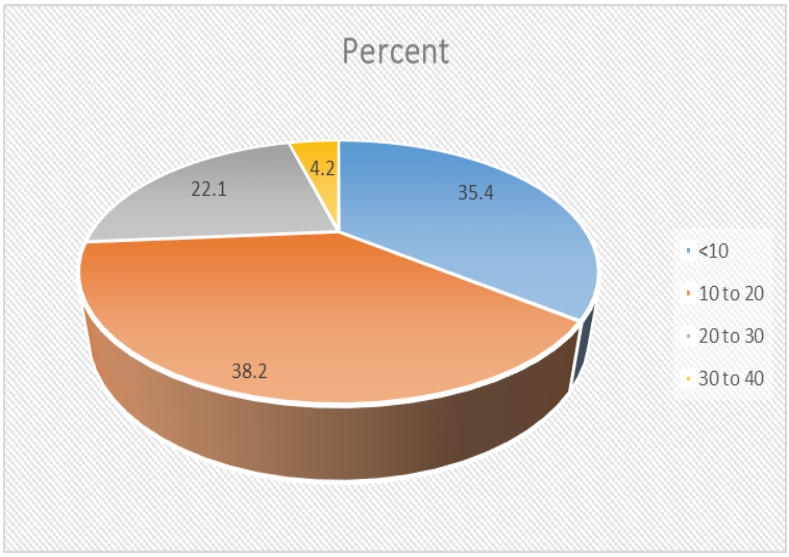

Fig.1: Frequency distribution of the patients based on BMI.

BMI: Body mass index.

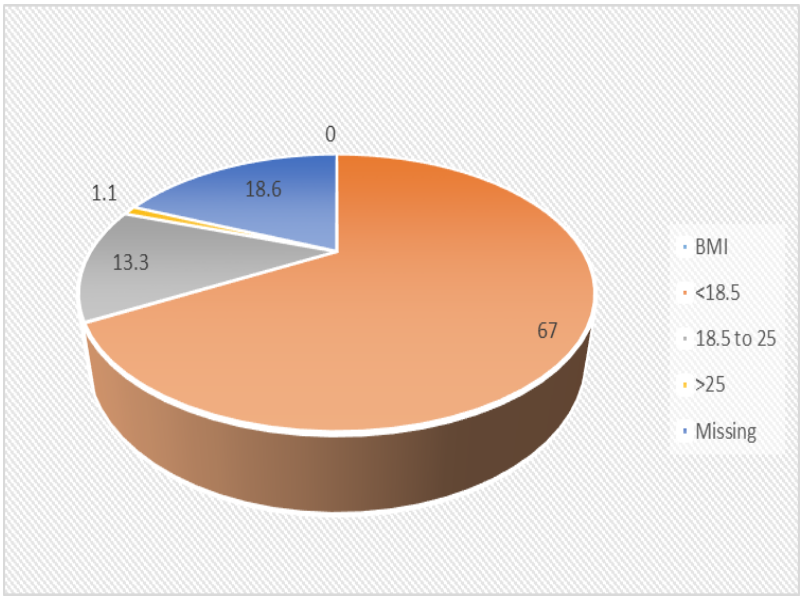

Fig.2: Frequency distribution of the patients based on age.

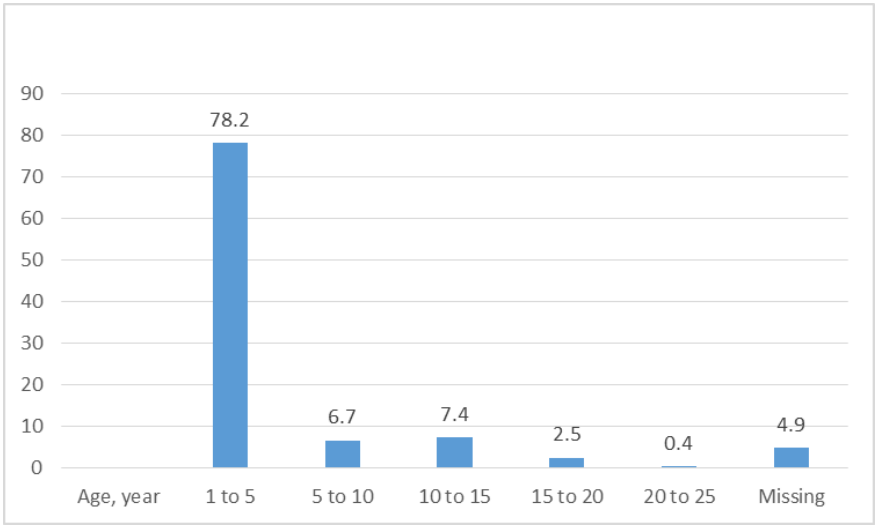

Fig.3: Frequency distribution of the patients based on age for expression of first symptoms.

Table.3 shows age of diagnosis. The disease was diagnosed in 159 patients (55.8%) in < 5 years and low percentage of patients (n=2, 0.7%) was detected in 30 up to 35 years of age. The data for frequency distribution of the patients based on start interval to diagnosis of disease are shown in **Table.4**. Start interval to diagnosis of disease was 68.40% (n=195) in <5 years of age and lowest percentage (n=1, 0.4%) in 30 up to 35 years of age.

Table-3: Frequency distribution of the patients based on age of diagnosis.

Variables	Age of diagnosis, year	Frequency	%
Valid	0-5	159	55.8
	5-10	36	12.6
	10-15	33	11.6
	15-20	25	8.8
	20-25	14	4.9
	25-30	4	1.4
	30-35	2	0.7
	Total	273	95.8
Missing	System	12	4.2
Total		285	100.0

Table-4: Frequency distribution of the patients based on start interval to diagnosis of disease.

Variables	Age, year	Frequency	%
Valid	<1	4	1.4
	1-5	195	68.4
	5-10	26	9.1
	10-15	18	6.3
	15-20	14	4.9
	20-25	9	3.2
	25-30	2	0.7
	30-35	1	0.4
	Total	269	94.4
Missing	System	16	5.6
Total		285	100.0

Our results for comparison of mean of start age of disease symptoms based on consanguinity of the parents are presented in **Table.5**. There was significant difference among individuals, so that patients with consanguineous parents were significantly higher (1.77± 3.98) in comparison to those patients with non-consanguineous parents (3.75±5.73) (P<0.05). Comparison mean of start age of disease and diagnosis age of disease based on BMI is shown in **Table. 6**; as results show, mean of start age of disease and diagnosis age of disease based on BMI has been accepted (P<0.05).

Table-5: The comparison of mean of start age of disease symptoms based on consanguinity of the parents.

Parameter	Consanguinity	Number	Mean	Std. Deviation	P-value
Start age of disease symptoms	Consanguineous	168	1.77	3.98	0.00
	Non-consanguineous	90	3.75	5.73	

Table-6: Comparison of mean and analysis of variance of start age of disease and ddiagnosis age of disease based on BMI.

ANOVA					
	Groups	Degrees of freedom	Mean Square	F	Sig.
Start age of disease	Between Groups	2	203.945	9.642	0.000
	Within Groups	220	21.152	-	-
	Total	222	-	-	-
Diagnosis age, year	Between Groups	2	917.912	17.198	0.000
	Within Groups	220	53.373	-	-
	Total	222	-	-	-

BMI: Body mass index.

Concerning Table.7, there is a significant relation between start age of symptoms and diagnosis age of disease. Correlation coefficient shows positive relation between start age of symptoms and diagnosis age of disease. As Figure.4 shows, there is positive correlation between start age of symptoms and diagnosis age of disease with correlation coefficient of 0.267. With regard to Table.8, there is significant relation between province residing in with diagnosis age of disease (P<0.05).

Table-7: Relation between start age of symptoms and diagnosis age of disease.

Start age of symptoms		
Diagnosis age of disease	Pearson Correlation	0.517*
	P-value	0.000
	Number	269

*Correlation is significant at the 0.01 level (2-tailed).

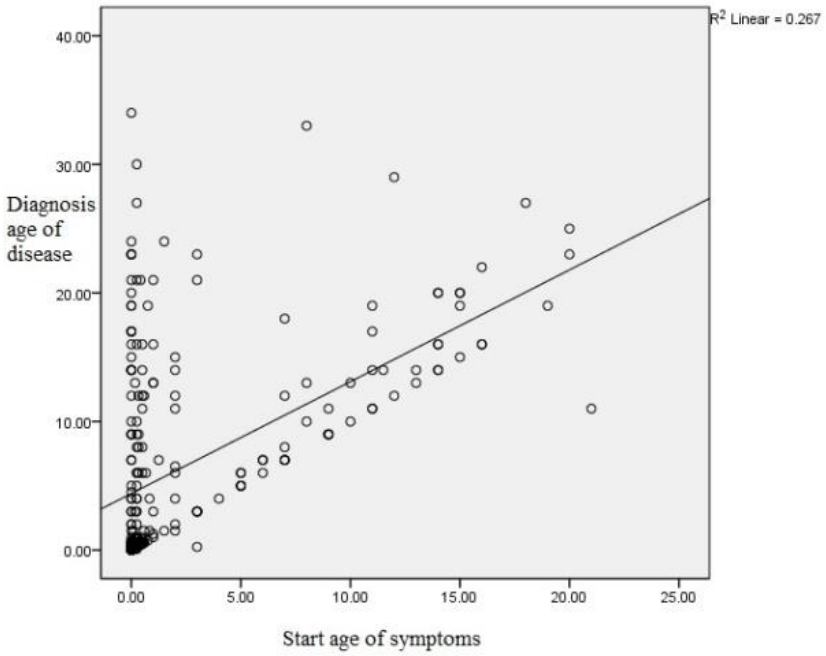

Fig.4: Correlation between start age of symptoms and diagnosis age of disease.

Table-8: Relation between province residing in with diagnosis age of disease.

	Value	Degrees of freedom	Diagnosis age of disease. Sig. (2-sided)
Chi-Square	1533.655[a]	1316	0.000
Likelihood Ratio	592.930	1316	1.000
N of Valid Cases	273	-	-
a. 1389 cells (99.8%) have expected count less than 5. The minimum expected count is .00.			

4- DISCUSSION

Most of the patients (n=169, 59.3%), were male and 116 individuals (40.70%) were female. Previous studies have refuted the gender gap observation in CF (24-27). However, studies have shown mechanisms for the gender difference in CF and reported on the role of female sex hormones. For example, estrogen has been shown to be a hormone that reduces air surface liquid on bronchial epithelial cells through modulation in ion channels on airway epithelium and thus female patients with CF have greater disadvantage than males by increasing mucus viscosity. Estrogen has also been shown to increase the conversion of *P. aeruginosa* from a nonmucoid to mucoid form in CF, that is the more drug resistant and pathogenic form (24-27). In the present study, gender difference was not significant (59.3 vs. 40.70). It confirms that sexuality cannot have significant effect on prevalence of CF. Results also showed that birthplace and habitat province were Tehran which could be attributed to the major population in Tehran. Most patients (n=261, 91.6%), were single and 14 patients (4.9%) were married. It could be argued that patients with CF have lower tendency for marriage. The husbands of patients with CF could not tolerate it and most marriages resulted in divorce. In addition, the majority of these patients did not have sufficient education degree. It could be because most patients cannot continue their education due to disease and its disorders. As mentioned, most of the parents (61.1%, n=174) had consanguineous relation and

the rest (n=94, 33%) did not have any consanguineous relation. It has been accepted that family relationships are to be calculated as greater risk for disease and intervention is recommended for family therapy (28). CF is known as a significant heterogeneity disease, but there are no clinical signs apparent at birth. Most of the previous studies have shown a relation between CF and parental consanguinity, so that populations in which consanguineous marriage was common had considerable rate for inherited CF. Khan et al. (29) showed that of the eight proven cases of CF in Bahrain between 1979 and 1984, five were in children born from consanguineous parents. Al Arrayed and Abdulla (30) found that 20 of the 27 CF patients had consanguineous parents and a family history of CF. In Jordan, Kakish (31) also showed that consanguinity was a factor in 50 of the children with CF of the 72 patients studied. Consanguineous relation can have significant effect on CF prevalence. The mean of age, age at diagnosis, mean for expression of first symptoms and mean for time interval between the onset of symptoms and the diagnosis of the disease were 14.52, 2.51, 6.57 and 4.07 years, respectively. Based on the 2013 European CF society report, the mean age for patients with CF in 27 European countries was 18.4 years, and the patients over 18 years old were 50.9% of the total (32). In Iranian population, Aghamohammadi et al. (33) showed the people with CF patients over 18-years-old were only 5.5%. There was a 4.07 year time interval between the onset of symptoms and the diagnosis of the disease that is a considerable delay. In another study in Southwestern Iran, a study showed a 1 to 2-year delay between the first clinical presentation and the diagnosis of CF and also showed that delayed diagnosis caused progressive disease and irreversible changes (34). Most patients were detected at low age (0-5 years of age). As mentioned, the majority of individuals are faced with serious problems from birth, but some others have mild degrees which do not appear until adolescent and youth periods. Patients sometimes show low symptoms but symptoms increase with the passing of item. Results show that most patients had lower BMI and very few of the patients (n=3, 1.1%) showed higher BMI (>25). BMI is criteria to show body size (kg/m^2). Studies have not shown relation between CF and body composition (35, 36) and/or shown a direct relation between adiposity and lung activity (37). Some studies in individuals with CF have shown a preferential decrease of fat-free mass, that is related with indexes of disease severity, such as reduced lung function, raised pulmonary exacerbations, and inflammation (38-40). It seems that lung disorders in patients with CF decrease BMI and our results confirm such claim.

5- CONCLUSION

In conclusion, the disease has various symptoms which are expressed in has various symptoms and its symptoms the different ages. There was a 4.07 year time interval between the onset of symptoms and the diagnosis of the disease. With regard to early diagnosis and its treatments, it is essential to perform the screening tests and phenotypic and genotypic tests at birth in order to minimize the time interval and malnutrition and increase life expectancy. Regarding consanguinity of the parents, genetic consultations before marriage and prevention of family marriage have been recommended.

6- CONFLICT OF INTEREST: None.

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