Gender Differences in Clinical Presentations of Cystic Fibrosis Patients in Azeri Turkish Population

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Background: Cystic fibrosis (CF) is an autosomal recessive disorder with several clinical presentations. This study was undertaken in the Azeri Turkish population in Iran, to investigate gender differences in the age at onset and diagnosis, age of death, and duration of illness of CF.

Methods: The data of 331 CF patients from 2001 to 2015 was surveyed. Parameters including age, sex, ∆F508 mutation, age at onset, age at diagnosis, age of death and clinical presentations were evaluated for both sexes, using descriptive analysis. The association of gender with these variables was studied using logistic regression, chi-square test and Mann-Whitney U test by SPSS version 18. Odds ratio with a confidence interval of 95% and p≤0.05 was considered statistically significant.

Results: The study included 191 males (57.7%) and 140 females (42.3%), all showing statistically significant difference (p<0.001). Age duration differed between genders. Male and female patients were further under 9 and 4 years, respectively. The occurrence of ∆F508 mutation was 0.51 times more in females than in males. Age, diagnosis and sex were closely associated: males were diagnosed at a significantly later age than females (p=0.05). While this compression performed based on clinical presentations, males with respiratory disease had a later median age at diagnosis than females at lifespan (p=0.001). The risk of infertility in males was approximately two times greater than in females (p=0.02).

Conclusion: These findings indicate gender differences in CF patients. Future studies are needed to establish other differences and evaluate the causes for the gender variations.

Keywords: Cystic Fibrosis; Population; Age at Onset; Iran
Introduction

Cystic fibrosis (CF; OMIM 219700) is the most common lethal autosomal recessive disorder caused by mutations on the cystic trans-membrane conductance regulator (CFTR) gene. It is a multisystem disorder affecting the gastrointestinal, respiratory, hepatobiliary, reproductive systems, and sweat glands. It is observed in 1 in 2,000–3,000 live births in Europe. The incidence of CF in Asians is rare and unknown; however, it is estimated to be 1 in 10,000 in the Middle East (such as Iran, Turkey, and Lebanon). Although numerous mutations in the CFTR gene are a primary cause on the clinical manifestations of CF, recent research has established that various gender, modifier genes, environmental factors, and socioeconomic factors can modify the development and severity of CF.

While gender differences are known to exist due to variations in pathogenesis, mortality, morbidity, and survival, the reasons for such differences between sexes are not fully understood. It has been hypothesized that the nutritional status, social and emotional conditions of patients and their families, physical functions, cultural subjects, hormonal changes, and cultural and ethnic differences explain in part this gender gap. For example, female patients have less eating than males; hide some symptoms such as coughing public, perform less physical activities, and state an overestimation of their own weight. Here, we have summarized the data, which indicates that there is a "CF gender gap" in clinical course.

The retrospective researches, despite some disadvantages, have an important role in depicting the disease. Innovation and non-repetition of these studies are determinate factors. This research has been conducted after searching the electronic databases and literature reviews and finding that no similar study had been undertaken in the region. This study compares numerous parameters between males and females with CF in the Azeri-Turkish population in Iran and surveys the role of a wide range of risk factors in explaining gender-related differences in the age of onset and diagnosis of CF. Ultimately, it could be effective in helping clinicians to manage this disease.

Materials and Methods

This was a cross sectional study (retrospective and prospective) conducted on 331 cases admitted to the Children’s Educational and Treatment Hospital (the most governmental, specialized, and referral hospital in northwestern Iran) of the University of the Medical Sciences and Medical Genetic Laboratory, Tabriz, Iran between March 2001 and February 2015 using the census method, clinic visits, and by phone from the patients or their families. This study was performed on Azeri Turks who are one the largest ethnic groups in Iran.

The diagnosis of CF was according to the typical clinical presentations based on the Guideline for Diagnosis of Cystic Fibrosis (Cystic Fibrosis Foundation Consensus Report) including chronic sinopulmonary disease, gastrointestinal and nutritional abnormalities, salt loss syndromes, and genital abnormalities which manifest as specific symptoms and abnormal sweat chloride values (>60 mEq/L) according to the method of Gibson and Cooke or the identification of mutations in CFTR gene known to cause CF. Patients with incomplete records, incorrect recognition as having CF, and the kappa agreement rate lower than 85% were excluded with the reviewer’s agreement.

Data had included sex, age, age at onset, age at diagnosis, AF508 mutation, outcome, cause of mortality, death age, duration of illness, and clinical presentations were extracted onto the extraction table. The age of onset referring to the age at which patients develops first experiences as symptoms of a disease or disorder with calculating the difference between the date of birth and onset of the first symptoms. The age of diagnosis referring to the age at which clinicians recognized disease for the first time first with calculating the difference between the date of birth and diagnosis of disease. The outcome variable was considered as living and deceased patients died because of chronic sinopulmonary disease, gastrointestinal and nutritional abnormalities, and salt loss syndromes.

Mean, standard deviation, median, interquartile range, frequency, percentage, mode, ratio, maximum, and minimum were calculated using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Logistic regression analyses, chi-square test, independent-samples t test and Mann-Whitney U test were used for comparison between these parameters and gender. The normalizing of the data distribution was evaluated using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. An odds ratio (OR) with a 95% confidence interval, and a p<0.05 indicated statistical significance. Ethical aspects were considered while approving the proposal by the Ethics Committee of the university (No. 5/4/1775) and obtaining permission from patients or their parents. Participation in this study was voluntary and subject information was kept secret even from the data analyzers.

Results

Three hundred thirty-one cases were evaluated during the 14-year period. The demographic characteristics of the patients are represented in Table 1 and Figure 1. Most patients were males with a significant difference (p<0.001).

Based on the Kolmogorov-Smirnov test and Shapiro-Wilk for age at onset and diagnosis (p<0.001), median was preferred to the mean because of non-normal distribution and associations between ages and genders were tested by a logis-
Table 1. Demographic variables of CF patients

| Variable                        | Male     | Female   | p-value | OR     | 95% CI   |
|--------------------------------|----------|----------|---------|--------|----------|
| No. (%)                        | 191 (57.7) | 140 (42.3) | <0.001  | -      | -        |
| Age at onset                    |          |          |         |        |          |
| Mean                            | 1.19     | 0.58     | -       | -      | -        |
| Median (IQR)                    | 0.16 (0.003–31) | 0.16 (0.003–17) | 0.12   | 0.93   | 0.84–1.02 |
| Age at diagnosis                |          |          |         |        |          |
| Mean                            | 2.58     | 1.32     | -       | -      | -        |
| Median (IQR)                    | 0.50 (0.003–50) | 0.33 (0.2–27.29) | 0.05   | 0.94   | 0.89–0.1 |
| Deceased patients               | 51 (26.7) | 35 (25)  | 0.4     | 1.09   | 0.66–1.80 |
| Living patients                 | 140 (73.3) | 105 (75) |         |        |          |
| Age (living patients)           |          |          |         |        |          |
| Mean                            | 7.16     | 6.18     | 0.06    | 0.94   | 0.88–1   |
| Median (IQR)                    | 5.06 (0.42–50) | 4.40 (0.62–31.2) |         |        |          |
| Age (deceased patients)         |          |          |         |        |          |
| Mean                            | 2.43     | 1.22     | 0.2     | 0.92   | 0.81–1.05 |
| Median (IQR)                    | 0.56 (7 days–30 years) | 0.36 (0.02–11.6 years) | 0.2    | 0.92   | 0.81–1.164 |
| Cause of mortality              |          |          |         |        |          |
| C: 23 (45.1)                    | C: 15 (42.9) | 0.4     | -       | -      | -        |
| G: 23 (45.1)                    | G: 19 (54.3) |         | -       | -      | -        |
| S: 5 (9.8)                      | S: 1 (29) |          | -       | -      | -        |
| Duration of illness             |          |          |         |        |          |
| Mean                            | 3.62     | 3.31     | 0.9     | 0.48   | 0.96–1.07 |
| Median (IQR)                    | 2.5 (7 days–18.4 years) | 2.33 (7 days–30 years) | 0.3    | 0.88   | 0.67–1.164 |
| Positive for genetic testing, n (%) | 112 (58.6) | 85 (60.7) | 0.3     | 0.88   | 0.67–1.164 |
| Positive for ∆F508, n (%)        | 12 (6.3) | 29 (20.7) | <0.001  | 0.25   | 0.12–0.52 |
| Infertility, n (%)              | 7 (3.7)  | 0 (0)    | 0.02    | 1.76   | 1.60–1.93 |

Values are presented as mean, median (IQR), or number (%). All age has been shown based on year and rest data based on number (%). Variables were considered for male/female. Age for CF patients alive and rest ages for alive and dead CF patients have been considered. CF: cystic fibrosis; OR: odds ratio; CI: confidence interval; IQR: interquartile range; C: chronic sinopulmonary disease; G: gastrointestinal and nutritional abnormalities; S: salt loss syndromes.

Figure 1. Age distribution is shown among cystic fibrosis (CF) patients alive in males and females.
There were 86 deceased patients (25.9%) and 245 living patients (74.1%) at the time of the study. Of the 245 living CF patients, 202 (82.4%) were less than the age of 9 years, and 77 (89.5%) of the 85 deceased CF patients, had died younger than the age of 4 years.

Age distribution in males differed from females. Among females and males, patients alive were mostly under the age of 4 and 9 years and had died under the age of 9 and 15 years, respectively (Table 2, Figure 1).

In the application of the Kolmogorov-Smirnov test and Shapiro-Wilk, age was assumed as non-normal distribution (p<0.001), consequently, median age for living patients was 4.76 years (0.4–50 years); and median and mode age at death were 0.48 years (7 days–30 years) and 2 months, respectively. Association between age for living patients and age at death with genders were not significant, respectively (p=0.2 and p=0.1). The cause of mortality was reviewed between sexes and this difference was not statistically significant. These variables and their associations with sexes are represented in Table 1.

Three hundred and thirty-one patients with CF, the median duration of illness was 2.46 years (7 days–30 years). Difference between two population medians (a non-parametric approach) was not significant (p=0.9); however, this value was somewhat higher in males than females.

The genetic characteristics of the two genders are represented in Table 1. There was no significant difference between gender and a positive genetic test with significant difference between gender and a positive genetic test for ∆F508. Females had a 49% greater likelihood of having the ∆F508 genotype than males.

Based on clinical presentations (at the time of onset, at the time of diagnosis, and over the lifespan), there was a notice-

Table 2. Age distribution among cystic fibrosis patients

| Variable     | Male Living patients | Male Deceased patients | Female Living patients | Female Deceased patients |
|--------------|----------------------|------------------------|------------------------|-------------------------|
| Age group, yr | 140 (73.3)           | 51 (26.7)              | 105 (75)               | 34 (25)                 |
| 0–4          | 68 (47.9)            | 45 (88.2)              | 64 (60.4)              | 33 (92.4)               |
| 5–9          | 46 (33.5)            | 3 (5.9)                | 23 (22)                | 2 (5.7)                 |
| 10–14        | 14 (10)              | 0 (0)                  | 10 (10.4)              | 0 (0)                   |
| Higher (≥15) | 12 (8.6)             | 3 (5.9)                | 8 (6.6)                | 1 (2.9)                 |

Values are presented as number (%).
For living cystic fibrosis patients, age at for the study and deceased patients, age at death has been considered.

Table 3. Comparison of age at onset and diagnosis based on clinical presentations between sexes

| Clinical presentations at time onset | Clinical presentations at time diagnosis | Clinical presentations at lifespan |
|-------------------------------------|----------------------------------------|----------------------------------|
| R p-value | G p-value | R p-value | G p-value | R p-value | G p-value | R p-value | G p-value |
| Age at onset | Male | 0.17 | 0.8 | 0.17 | 0.5 | 0.17 | 0.9 | 0.17 | 0.6 | 0.17 | 0.1 | 0.17 | 0.9 |
| Female | 0.17 | 0.09 | 0.17 | 0.11 | 0.17 | 0.15 |
| Age at diagnosis | Male | 0.5 | 0.1 | 0.44 | 0.2 | 0.5 | 0.3 | 0.44 | 0.1 | 0.58 | 0.001 | 0.48 | 0.2 |
| Female | 0.33 | 0.33 | 0.39 | 0.33 | 0.33 | 0.33 |

Data have been shown for R and G based on median years.
R: respiratory symptoms; G: gastrointestinal symptoms.
able difference in the age at diagnosis with respiratory symptoms over the lifespan and males presented their illness with delayed periods than females. This difference was not statistically significant at the rest materials with narrow disparities that have been represented (Table 3).

Discussion

CF is often considered to be a problem that patients suffer from several serious complications of their disease throughout their lifetime. The aim of this study was to evaluate gender differences in a number of parameters in CF patients in the Azeri-Turkish population as follows:

The results of this study show that, sex ratio is approximately 2.15 (male:female) with a significant difference. This ratio was similar to the results of Jackson et al. who reported that amongst 601 patients, 328 were males and 273 were females. Corey et al. reported that, out of 499 patients from Boston and 538 patients from Toronto, percentage of male/female was 57/43 and 58/42, respectively with no significant differences. This gender difference may be related to cultural matters, an intrinsic ethnic difference or religious issues.

In this study, there was a significant difference between gender and age at diagnosis; males had a considerably delayed diagnosis compared to females. Jackson et al. observed that males had a later median age at diagnosis (4.4 months) than females, although there was no statistical difference. In another study, the mean age of diagnosis was 18.6 months in males, while it was 22.6 months in females. We observed variations in the results of different studies which may be because females reported problems more frequently and earlier due to being more sensitive or lower in body strength in our region. Previous studies have shown that females might be more sensitive or weaker than men, consequently presenting more problems. In addition, malnutrition and a tendency towards respiratory infection in females, hormonal changes, a decline in physical activity and emotional functioning in female patients; and different emotions of mothers to female sex could be additional factors causing an earlier presentation.

In current study, mean, median age, duration illness, age for living patients and the age of death were slightly predominant in males than females with no significant difference; in contrast an increasing risk for the ∆F508 mutation in females. Therefore females died younger or were diagnosed earlier than males. One study found that females die earlier than males particularly in the age group of 1–20 years. When the mean age of current study was compared with results of other studies, it was found to be lower because of economic problems, unavailability of advanced diagnostic techniques and novel drugs; and the lack of coherent registry centers. Corey et al. reported the mean age 15.9±0.6 years and 15.2±8.3 years for CF patients in Boston and Toronto, respectively. Some studies have reported a longer median lifespan for males with no significant differences between sexes. This difference may be due to a higher mortality rate, poor pulmonary function, a tendency towards respiratory infection, and malnutrition in females than in males. Olesen et al. over a study in the Scandinavian patients found a higher incidence of Pseudomonas aeruginosa among the female patients, resulting in the increasing of mortality rate, more days of hospitalization for females than males. Also, Sweeney and Ratjen and Davis were observed an increasing of mortality rate and a decreasing of the median survival age in CF females than males, significantly because of reduced pulmonary function, and decline of weight for height. Some studies established that the homozygous ∆F508 mutation, which results in the display of symptoms at an earlier age, is more predominant in females than in males.

In addition to, males presented respiratory symptoms over the lifespan with a later median age at diagnosis than females. This difference was not significant for gastrointestinal and nutritional symptoms. Our findings were similar to those in a study had been conducted in the Republic of Ireland where males with gastrointestinal and respiratory symptoms were diagnosed 6.8 and 20.4 months later than females, respectively. In the U.K., female patients with gastrointestinal symptoms were diagnosed later, while in the United States, male patients with gastrointestinal symptoms were detected later. Malnutrition, decline in physical activity, a decline in pulmonary function, and consequently the tendency to earlier colonisation with Pseudomonas aeruginosa as well as more reporting of respiratory symptoms in females were important factors. Therefore, respiratory symptoms appear earlier in females. However, reasons for this gender gap are still unclear and it is necessary to perform additional investigations in large populations.

There were several limitations in our study. The primary weakness of this study was a retrospective study with lesser precision although it does encourage future prospective research. The performing of investigation on specialist group reduces the ability to generalization of the study results. Data were limited to Children’s Hospital and the Medical Genetic Laboratory in Tabriz between 2001 and 2015. It is possible that CF patients were not referred to these centers, or were diagnosed without registry.

The strength of this study was the adequate sample size considering the low incidence of CF in this region and its being conducted over a long period of time. Data was approved by two reviewers and were collected from educational, therapeutic and referral centers. This study was conducted at the Liver and Gastrointestinal Disease Research Centre of the University of Medical Sciences and in a population with a unique religion, ethnic origin, and culture, which could be a basis for the performance of comparative studies.
This study indicates associations between gender and ΔF508 mutation, age at diagnosis, and clinical presentation in our CF population. We found that this disease is more common in children younger than the age of nine years and more deaths were observed in those under the age of 4 years of age. Also, males were affected more than females. In contrast, ΔF508 mutation was detected in females than males. Age distribution differed between genders so that mortality and age distribution were observed at younger ages in females than in males. Disease was diagnosed later in males than in females, particularly with respiratory symptoms. The mortality rate, death age and duration of illness were somewhat further in males than males. The present study demonstrated differences between genders and the need for adequate care for females with this condition. With regard to the higher frequency of the disease and the delay in diagnosis, it is necessary to have a low threshold for requesting diagnostic tests in males. Finally, additional research should be directed toward identification and evaluation of other gender differences in CF.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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