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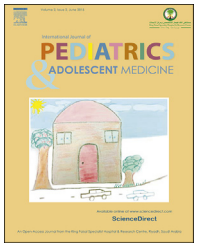

REVIEW ARTICLE

The road for survival improvement of cystic fibrosis patients in Arab countries

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Abstract Cystic fibrosis (CF) is a lethal, monogenic disorder that affects multiple organ systems of the body. The incidence has been described before in the Middle East to be 1 in 2000 to 1 in 5800 live births, and the median survival was estimated to be from 10 to 20 years of age.

The present article attempts to revisit various facets of this disease and specifically highlights the most important lacunae that exist in treating CF. In addition, it also tries to emphasize the steps in improving the median survival of patients with CF, in these countries.

1. Introduction

Cystic fibrosis (CF) is a lethal, monogenic disorder that affects multiple organ systems of the body [1]. As per a Cystic Fibrosis Foundation annual report, 60,000 to 70,000 people across the world suffer from CF [2]. However, this estimate is based on the data available from the existing registries in developed countries (primarily the United States, Europe, and Australia).

Symptoms in patients with CF include accumulation of thick mucus, recurrent lung infections, persistent cough at times associated with phlegm with or without hemoptysis, wheezing, poor growth/weight gain (in spite of a good appetite), frequent greasy, bulky stools or difficulty in bowel movements, and electrolyte imbalance particularly in countries with warm weather [3,4]. The estimated frequency of CF per live birth in Caucasians is believed to be 1 in 2000—2500 children. Determining the precise magnitude of prevalence of CF in South East Asian and Middle East countries remains elusive. Though the prevalence of CF has been estimated to fall in the range of 1 in 30,000 to 1 in 50,000, incidence of the disease has been reported in the range of 1 in 2000 to 1 in 5800 live births (4—13). Based

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFRD, cystic fibrosis related diabetes; FEV_1, forced expiratory volume in 1 second; *P. aeruginosa*, *Pseudomonas aeruginosa*.

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Table 1 Milestones of cystic fibrosis discovery in the Arab countries.

Year (reference)	Country	Comment
1958 [5]	Lebanon	First CF in Arabs
1977 [6]	Iraq	First report
1981 [7]	Kuwait	After death 2:1056, 1/3500 birth/year
1984 [8]	Jordan	A pilot study (post-mortem)
1985 [9]	Bahrain	19 incidence 1:5800, 80% consanguineous marriages
1986 [10]	Saudi Arabia	First case report
1991 [11]	UAE	First report
2001 [12]	Qatar	In a large Bedouin family

on this, research suggests that these regions may harbor a very large proportion of CF patients in the world [13]. As per a recent report on extrapolated CF prevalence rates, it is projected that 34,357 patients in India and 41,898 patients in China may have CF [13]. The high prevalence of CF in these countries may be accountable due to the large population (>1 billion) of these countries. These prevalence extrapolations for CF are only rough estimates derived by applying the prevalence rates from the United States (or a similar country) to the population of other countries, and therefore may not reflect the actual prevalence of CF [13].

Similarly, determining the precise magnitude of the prevalence of CF in the Middle East countries remains difficult. Though the prevalence of CF has been estimated to fall in the range of 1 in 2500—5000. Based on this, It is projected that with a population of 27 million in Saudi Arabia (14), and around 18 live birth/1000, at least 800—1000 cases may have CF (Table 1) [4—19]. These prevalence extrapolations for CF are only rough estimates and could be increased due to consanquinity (50% in the general population and 85% in CF families) [4—19], and therefore may magnify the actual prevalence of CF (Table 1) [5—19].

The median survival in some Arab countries was estimated to be from 10 to 20 years of age [4—19] for many reasons such as: Delayed diagnosis due to decreased awareness of the variable presentation of the disease. Unavailabity of diagnostic tool such as quantitative sweat chloride test (e.g in the city of Jeddah, Saudi Arabia, with 5 million dwellers, only two centers with proper sweat chloride measurement's tool) [4—14]. Delayed institution of treatment due to delayed referral to a specialized CF center [4—19]. Early pseudomonas colonization at 3 years compared to 7 years in the western countries [4—16]. Poor compliance to treatment and chest physiotherapy, poor distribution of CF specialized centers, Delayed nutritional rehabilitation [4,16].

Even after more than 7 decades since CF is known, there are many aspects of the disease which still remain enigmatic [20]. The present review attempts to revisit various facets of this disease and specifically highlights the most important lacunae that exist in treating CF. Further, it aims to emphasize the precarious consequences, if this disease is ignored or left untreated. Therefore early diagnosis of the disease is the important first step towards improved care. In addition, this review also captures the steps toward improvement of median survival in Arab countries.

2. Pathophysiology of CF

Patients with CF inherit a defective gene in each chromosome (i.e. 2 defective copies) that encodes the protein "CF transmembrane conductance regulator" (CFTR). The CFTR gene, which is located on chromosome 7, spans ~250 kB in length, and translates into a protein of 1480 amino acids. The protein is a mucosal surface chloride channel present at the epithelial junctions and submucosal glands, and its dysregulation/failure in anion transport causes the disease manifestations [21—23].

Approximately 1800 known mutations have been identified for CF gene, which gives rise to disease phenotypes [2]. Increasing attempts have been made to classify the known mutations. Six different classes of mutations are described based on the fate of the CFTR protein (Table 2 and Fig. 1). These reported gene defects lead to altered protein synthesis such that there is insufficient, adequately active CFTR at the cell surface. This causes the body to secrete unusually thick and sticky mucus (Fig. 2).

The thick mucus clogs the lungs (pulmonary manifestation) leading to a vicious cycle of infection, inflammation, and lung tissue destruction, ultimately leading to life-threatening lung infections [21,22]. The secreted mucus also clogs the pancreatic ducts, thereby obstructing the flow of bile digestive enzymes (which help in digestion and absorption of the food, especially of fats) to the small intestine. This leads to multitudes of disease conditions such as pancreatic insufficiency, gall stones, cysts, and chronic digestive problems (maldigestion and malabsorption) [23—29]. In patients with CF, epithelial anion transport fails, causing functional disruption in a number of organs besides the airways, including the digestive system, exocrine pancreas, gall bladder, reproductive tracts, and the sweat ducts [21,23]. The types of complications in patients with CF largely depend on the degree and the type of CFTR mutation.

Diagnosis: CF is typically diagnosed based on typical clinical signs and symptoms and confirmed with high sweat chloride test >60 mmol/liter and or CFTR detection of 2 pathogenic mutations [1—3]. Reports from a retrospective study showed that diagnosis of CF in Saudi Arabia was done based on the typical clinical symptoms and high sweat chloride test [29]. In the past, newborn screening for meconium albumin using the BM test strip was used in Jordan to identify CF cases that were subsequently confirmed using the sweat chloride test [30].

The most common CFTR described in the United States and Europe is F508del, which constitutes 50%—85% of the CF population (Table 2), whereas those described in the Middle East were different due to consanguinity (Tables 3 and 4) [26—36].

F508del presents in small numbers 10—20% in the Gulf area, compared to 30—50 in North African countries [26—36]. Novel mutations characterized most Arab