

Cystic fibrosis: Saudi arabia current situation and perspectives

Cystic fibrosis in Saudi Arabia

Shehab Ahmed Alenazi

Department of Pediatrics, Faculty of Medicine, Northern Border University, Arar, Kingdom of Saudi Arabia

Abstract

Cystic fibrosis (CF) is an autosomal recessive disease of the exocrine glands with multiple serious complications. It was reported that the incidence of CF in Saudi Arabia is 1 case in every 4243 of the population in 1986. Around 2000 mutations were listed in the CF Mutation Database, among them only the 32 were considered as common mutations. In Saudi Arabia, 1548 delG is the most common mutation among CF cases. The main problems of CF in Saudi Arabia are the delay in diagnosis, lack of awareness and the economic burden of treatment of CF cases especially with late diagnosis and multiple complications. However, recently, more attention is paid to CF with more specialized diagnosis facilities and more awareness, however further large scale and longitudinal studies should be done to determine Saudi CFTR mutation patterns which could be needed during a screening of CF in Saudi Arabia.

Keywords

Cystic Fibrosis; Saudi Arabia; Cystic Fibrosis Mutations; Pulmonary Infections.

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Corresponding Author: Shehab Ahmed Alenazi, Department of Pediatrics, Faculty of Medicine, Northern Border University, Arar, Kingdom of Saudi Arabia.
T.: 00966555385578 E-Mail: alenazishhabi@gmail.com
ORCID ID: 0000-0002-6231-2785

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease of the exocrine glands that involves multiple organ systems but chiefly results in chronic respiratory infections, pancreatic enzyme insufficiency, and associated complications in untreated patients [1]. Pulmonary involvement occurs in 90% of patients surviving the neonatal period and end-stage lung disease is the principal cause of deaths [2]. Once limited largely to infants and children, the immediate prognosis has changed drastically over the last three decades so recently, the majority of patients survive into adolescence, and nearly 80% live beyond their twentieth birthdays [3].

Cystic fibrosis had been well known in European folklore since the middle ages. It was defined as woe, which was manifested as a child who tastes salty from a kiss on the brow, for he is cursed, and soon must die [4]. Cystic fibrosis was first recognized as a separate disease entity and was distinguished from celiac disease in 1938 in the pancreas during postmortem dissection of malnourished infants and termed as “cystic fibrosis of the pancreas” [5], while the causative gene mutation was first discovered in 1989. Since then, research was expanding to highlight the underlying molecular abnormalities [6].

Epidemiology of CF:

Cystic fibrosis is the most common life-shortening autosomal recessive disease of whites, which affects approximately 1 in 3,500 live births [1,2]. Cystic fibrosis was estimated to affect 60,000 individuals worldwide. It was observed primarily in individuals of European Caucasian descent with an incidence ranging from 1 in 2,000 to 1 in 4,000 [7]. In the United States of America, the number of CF cases registered in CF Foundation Patient Registry had increased from 21000 to 26000 cases between 2000 and 2010. Their median age increased from 14.3 to 16.7 years with adjusted mortality lowered by 1.8% per year and increased median survival of children born with CF to be 37 years for females and 40 years for males. Hence, its lifespans are expected to increase with continuously lowered mortality rates [8].

A more recent study in 2017 compared CF survival between the United States of America and Canada revealed that based on the available data collected from 2009 to 2013, the median age of survival in Canada was 10 years longer than the United States (50.9 vs. 40.6 years, respectively) [9]. Cystic fibrosis is much less common in native African and native Asian populations [7].

In China, there are no definite data about CF statistics and only 38 cases were reported from 1974 until 2018. This under-reporting of cases in China may be due to more difficult diagnosis caused by low awareness, atypical clinical symptoms, and a lack of testing facilities in most hospitals [10].

There is no definite data regarding the prevalence of CF in the Middle East countries including Saudi Arabia [11]. The first Middle East reported case of CF was from Lebanon in 1958 [12] while the first reported case in Saudi Arabia was in 1986 [13]. It was reported that the incidence of CF in Saudi Arabia is one case in every 4243 of the population in 1986 [13]. However, it is roughly estimated that at least 800-1000 cases may have CF in Saudi Arabia. This estimated number is expected to increase in

reality due to high rates of consanguinity [11]. Cases reported from Saudi Arabia are shown in Table 1.

King Faisal Specialist Hospital, the main referral center for CF cases in Saudi Arabia, reported that 183 cases were diagnosed as CF from 1985 to 2003. They were diagnosed as CF by their typical clinical picture and two consecutive positive sweat tests. Their ages were around 4.3 ± 3.3 years with no significant difference of prevalence between both genders. Their follow-up period ranged from 0.01 to 18 years [14]. Unfortunately, the median survival for CF cases in Saudi Arabia was estimated to be up to 20 years of age [11-15] due to delayed diagnosis caused by low awareness and decreased specialized medical facilities for CF. In addition to poor follow up of the diagnosed cases, delayed diagnosis caused by a lack of parents' awareness.

Table 1. Published reported cases of cystic fibrosis in Saudi Arabia and their reported mutations.

Authors	Year	Number of cases	Reported mutations
Abdullah MA [13]	1986	1	Mutations Not studied
Nazer et al. [15]	1989	13	Mutations Not studied
Nazer and Rahbeeni [16]	1994	36	Mutations Not studied
Al-Mobaireek & Abdullah [17]	1995	10	Mutations Not studied
El-Harith et al. [18]	1997	15	3120p1G/A, N1303K, 1548delG
Banjar et al. [19]	1998	70	F508del, I1234V, N1303K, R553K, 3120p1G/A
Kambouris et al [20]	2000	70	H139L S549R
Banjar [21]	2013	317	1548delG, DF-508, I1234V, 3120+1G→A, 711+1G→A, H139L in 20 [8.5%].

Pathogenesis of CF:

Cystic fibrosis is an autosomal recessive disease caused by abnormalities in the cystic fibrosis transmembrane regulator [CFTR] gene, which encodes for a protein that functions as chloride and bicarbonate channels and also regulates the flow of other ions across the apical surface of epithelial cells [6]. In 1989, the CF locus was localized through linkage analysis to the long arm of human chromosome 7 [22]. Thus far, 1893 CFTR mutations have been identified [23].

Around 2000 mutations are listed in the Cystic Fibrosis Mutation Database [10]. Among them, only the 32 were considered as common mutations and included in the recommended CFTR gene mutation screening panel [24]. The most common mutation is named as p.F508del, which was reported in about 70% of diagnosed Caucasian CF cases [25]. Half of affected individuals of northern European descent are homozygous for the p.F508 mutation, another 25%-30% have one copy of $\Delta F508$ plus another mutation, however, the p.F508del variant is not common among reported Asian CF cases. [10]

CFTR mutations result in abnormalities of cAMP-regulated anion transport across epithelial cells on mucosal surfaces. The failure of chloride and sodium conductance of epithelial cells and associated water transport abnormalities result in viscid

secretions in the respiratory tract, pancreas, GI tract, sweat glands, and other exocrine tissues. Increased viscosity of these secretions makes them difficult to clear and predispose to the colonization of pathogens and repeated infections with excessive neutrophils infiltrates and cytokines secretion [26]. Microbiology studies reveal a fairly typical evolution of pathogens with respiratory viruses, Haemophilus influenzae and Staphylococcus aureus, predominant at an early age. With time, more problematic and resistant pathogens develop, including, Pseudomonas aeruginosa and other gram-negative bacteria e.g. Burkholderia cepacia, Stenotrophomonas maltophilia [27].

Based on molecular and structural defects, CF-causing mutations are classified into five classes [28]. Classes I, II, and III are generally more severe causing "classic CF." While Classes IV and V are usually milder. Also, other genes called modifier genes can affect a person's symptoms and outcome. A sixth class has also been proposed but this class has not been well described yet (Table 2) [29]. Unfortunately, this classification is not correlated well with the clinical findings regarding disease severity and recommended guide counseling [30].

Atypical CF was described as a milder form of the CF caused by mutations of the CFTR gene. These cases usually have 1 severe mutation and 1 less common mutation or abnormality of trinucleotide repeats on their other CFTR gene [31]. Cases with atypical CF might only have dysfunction in a single organ system [32].

In Saudi Arabia, CF cases report data regarding CFTR mutations detection showed that 89% of CFTR alleles have been identified (Table 1) [18-21]. F508del constitutes 12% of CFTR mutation. 1548 delG is the most common Saudi CFTR mutation identified (20%). 1548 delG, F508del, I1234V, 3120 1G > A, H139L, 711 1G > A, N1303K, S549R, 2043delG, 1507del 9 are the most common CFTR mutations of Saudi ethnic origin (80%) [11]. Screening for the previously mentioned 10 mutations would identify 80% of C.F. alleles

Clinical features of CF:

Cystic fibrosis is characterized by chronic sinopulmonary and

gastrointestinal involvement [33]. Most body organs are involved (Table 3). Mostly the progressive pulmonary disease leads to death in the majority of patients (about 90% of CF mortalities) [2]. Abdominal symptoms (AS) of CF are a hallmark of the multi-organ disease CF. However, the abdominal involvement in CF is insufficiently understood and still receives little scientific attention than the pulmonary manifestations [7]. Pancreatic CF is rare in children. Malnutrition, diarrhea, and abdominal pain are its main clinical manifestations [34].

Table 3. Clinical manifestations of cystic fibrosis [2, 11, 33, 34 ,35]

System	Manifestations
General	Growth failure due to malabsorption and vitamins deficiencies especially A,D,E,K.
Respiratory system	- Nose: Nasal Polyps and sinusitis - Lungs: Bronchitis, bronchiectasis, bronchiolitis, pneumonia, Atelectasis, hemoptysis, pneumothorax, Cor pulmonale, respiratory failure, mucoid impaction in the bronchi.
Cardiovascular	Right ventricular hypertrophy and dilated pulmonary artery
Gastrointestinal	- Gastric: gastro-esophageal reflux - Spleenic: Hypersplenism - Pancreatic: Pancreatitis, Pancreatic insufficiency of both exocrine and endocrinal functions leading to malabsorption, insulin deficiency, asymptomatic hyperglycemia, diabetes mellitus, - Intestinal: Meconium ileus and peritonitis, distal intestinal obstruction syndrome, volvulus, rectal prolapse, appendicitis, intestinal atresia, colonic strictures, inguinal hernia
Hepatobiliary	- Hepatic: elevated aminotransferases, cholestasis, hepatic steatosis, focal biliary cirrhosis, and multilobular cirrhosis with or without portal hypertension hepatic fibrosis and hepatocellular carcinoma - Biliary: micro gallbladder and neonatal obstructive jaundice, cholelithiasis.
Urinary	- Nephrolithiasis, electrolyte abnormalities, and acute kidney injury [AKI]. - Rarer manifestations include progression to chronic kidney disease, amyloidosis, diabetic nephropathy, nephrocalcinosis, diffuse, and nodular glomerulosclerosis and nephrolithiasis
Reproductive	- Delayed puberty, Amenorrhea in females, Absent vas deference and azoospermia in males
Skeletal	- Hypertrophic osteoarthropathy, clubbing, arthritis, and osteoporosis

Diagnosis of CF:

Diagnosis is based on a panel of screening test, clinical and laboratory data which are shown in Table 4. Late diagnosis is a limiting factor for proper treatment in the majority of cases due to minimal early manifestations which mimic other diseases. Lack of training and awareness among healthcare physicians are among other important issues in the delayed diagnosis. Additionally, a limited number of CF-specialized testing centers in the Middle East and Saudi Arabia is another crucial cause for delay in diagnosis. Sweat test remains the standard test for diagnosis [36].

Management of patients with cystic fibrosis:

A problem in the treatment of CF patients is that very mild cases can also rapidly deteriorate after viral infections or due to other unrecognized factors, implying that once the diagnosis has been made, the preparedness to treat mild symptoms is important. Monthly check-up for CF cases is recommended. It is also well recognized that a center should be organized as a team consisting of a doctor, nurse, physiotherapist, dietician,

Table 2. Classes of Cystic fibrosis causing mutation[11,26]

	Effect on CFTR Protein	Examples
Class I	These mutations prevent CFTR protein production and may cause complete absence of CFTR protein as they form premature stop codons.	Arg553X, Gly542X, Trp1282X
Class II	In this class, an insufficient amount of CFTR reaches the apical cell surface leading to inadequate transport	Phe508del [the commonest], 32,33 [Gly85Glu, Arg560Thr, Ile507del, Asn1303Lys]
Class III	Structurally Normal CFTR protein formation with disturbed function causing disturbed gate opening [gating mutations].	Gly551Asp [the commonest class III mutation]
Class IV	Structurally normal CFTR with impaired conductance capacity	Arg117His and Arg347Pro
Class V	A reduced amount of intact CFTR proteins with decreased function due to the paucity of protein at the cellular surface but each individual protein exhibits normal function.	Intron mutations, which affect splicing and reduce CFTR synthesis.
Class VI	Increased turnover due to a shortened CFTR protein half-life due to formation of unstable proteins.	Missense mutations [eg, 432delITC]

Table 4. Diagnostic methods for cystic fibrosis [11, 33, 36,37,38]

	Method	Comment
Screening 21,22	An increase in immunoreactive trypsin in serum was found to have high specificity and sensitivity for CF screening	After 10 years of age most studies show very little difference to un-screened patients
Laboratory	Sweat test: After Pilocarpine stimulation sweat should be collected over 30 minutes. A sweat chloride concentration of > 60 mmol/L confirms the diagnosis of CF in patients with suggestive clinical symptoms. The sweat test can be carried from the 3rd week of life on, provided the infant weighs more than 3 kg, is normally hydrated and without significant illness. The conductivity sweat test: The skin of the forearm is cleaned, then sweat is stimulated using electrodes with pilocarpine gel disks. Sweat collection lasted for 30 min by macroduct collector and a minimum amount of 15 µl was required. Then Sweat-Chek analyzer device can measure the conductivity of the sample and converted the measured values into sodium chloride molarity unit equivalents. Molecular genetic studies for CFTR mutations: Commercial assays are available that screen for a panel of about 30 popular CF related mutations. In the case of borderline sweat test in a patient with symptoms compatible with atypical CF, extensive mutation screening of both CFTR genes may be required to support this diagnosis. CFTR Bioassay: transepithelial nasal potential difference. This method measures the epithelial ion fluxes or their resultant voltage potential at the mucosal surface.	Sweat test data may be unreliable due to some technical mistakes in sweat collection, performance, biological variation in sodium chloride levels, sample transportation problems, and human personal errors and instrument calibration problems. It is a simpler sweat test method that eliminates the weighing and dilution steps and also reduces the risk of sample evaporation. It yields a high degree of diagnostic accuracy and it showed good agreement with sweat chloride -Genetic studies require experience and training of technicians and scientist especially with the extending newly discovered CF phenotypes with expected more problems in the genetic data interpretations. It is available in a very limited specialized center. Hence it is not commonly used especially in the developing poor countries
Clinical	Suggestive clinical data include failure to thrive and recurrent chest infections in an infant or children. Also newly born meconium ileus with vomiting and not passing stools is highly suggestive. Additionally, recurrent or persistent cough (Mostly triggered by a viral infection such as Respiratory syncytial virus).	Early manifestations are mild and non-specific and most cases are misdiagnosed
Non specific investigations	Chest x ray, Lung function tests, A sputum culture, Abdominal imaging, Insulin assay studies	The non-specific investigations are based on the clinical data

social worker, psychologist, secretary, and technical assistant for sweat tests [38]. The management lines of cases with CF are shown in table [5]. The most attention has been given to the treatment of airway symptoms since pulmonary disease is responsible for 95% of the mortality from CF. Although all strategies rely on a combination of mucus – dissolving agents, passive or active physical activities and antibiotics, success varies greatly between centers and countries [2].

According to King Faisal Specialist hospital guideline, published by Banjar (2003) [14], sputum or nasopharyngeal aspirate cultures are taken routinely from all cases of CF on initial diagnosis and at every follow-up visit. Prophylactic broad-spectrum antibiotics are prescribed for the first 1 to 2 years if cases show tachypnea, wheezing and excessive sputum as recommended

Table 5. Treatment modalities of cystic fibrosis [11, 35, 38-46]

Strategy	Treatment modalities
Gene therapy	- Gene delivery with aerosolized adenovirus vector: will not give the targeted results as the adenovirus receptors are deficient on the apical side of the epithelial cells.
Potentiators	- They prolong the channels' opening time with more chloride transference. For examples, Ivacaftor had been shown to be effective in cases with G551D mutations.
Correctors	- They facilitate the movement of mutant F508 CFTR((primarily class II mutations) out of the endoplasmic reticulum to the apical plasma membranes of epithelial cells. For example: Lumacaftor (VX-809), in patients with F508del-CFTR.
Symptomatic	- Antibiotic strategies: Chronic P. aeruginosa infection is treated with: combinations of a beta-lactam (ceftazidime) and an aminoglycoside (tobramycin). Methicillin resistant S. Aureus (MRSA) is treated with: Linezolid or Rifampicin with Fucidin, Trimethoprim or Doxycycline. - Bronchodilators: Inhaled b2-adrenergic bronchodilators - Anti-inflammatory drugs Inhaled corticosteroids. Anti-inflammatory Ibuprofen, and Macrolides such as azithromycin. - Oxygen therapy: Oxygen therapy is recommended at night or continuously. - Immunostimulants Alpha-1-antitrypsin supplementation and Vitamin D regulates both adaptive and innate immune systems. - Lung transplantation: Indicated is FEV1 of < 30% of the predicted values. - Others for air way clearance: postural drainage, hest physical therapy and mucoactive drugs. - Vitamin supplementation Extra supplementation of fat soluble vitamins, antioxidants (vitamin E and β-carotene),and vitamin A. - Diet modification: High fat diet (fat contributes 40-45% of the energy) with the polyunsaturated fatty acids should contribute 10-15 of the energy intake. - Pancreatic supplement therapy: Desiccated Porcine pancreatic extracts are available and other new supplementations, from bacterial lipases and recombinant human bile salt- stimulated lipase, are being studied in clinical trials.

by Weaver et al. (1994) [42] and McCaffery et al. (1999), [43] such as amoxicillin, cephalexin monohydrate, or trimethoprim/sulfamethoxazole (Bactrim). After 2 years of prophylaxis, antimicrobials are given during acute attacks and selected according to the bacterial cultures. Resistant infections are admitted for therapy for further evaluation and treated with intravenous third-generation cephalosporin and an aminoglycoside according to their culture and sensitivity results [44-45]. For pancreatic insufficiency pancreatic enzymes are given, according to Cystic Fibrosis Foundation recommendations [46], in combination with supplementation of fat-soluble vitamins (A, D, E, and K).

Cystic fibrosis current situation in Saudi Arabia:

All over the kingdom and over the last 3 decades, a lot of articles and case reports were published about CF in Saudi Arabia. The number of reported cases was increasing in the successive publications. This means that CF came to the focus of the healthcare services plans and staff. However, more efforts are required especially more cases are expected with the very high rates of consanguinity all over the kingdom.

The main problem in CF in Saudi Arabia is the delay in diagnosis. Most cases start with mild symptoms and their proper diagnosis mostly is overlooked. This problem is multifactorial. Firstly, a lack of awareness of the healthcare staff is a major limiting obstacle in the way of early diagnosis. Additionally, a limited number of specialized centers for CF diagnosis is another problem. These centers should be properly distributed all over the kingdom and should be equipped with the required

facilities and properly trained staff for the genetic diagnostic workup.

The second problem is a lack of public awareness of the disease. This leads to a lack of adherence to the long-life follow-up visits, which are crucial in improvement of the disease complications and increasing the median survival of the diagnosed cases. Also, this incomppliance of the patients and their families may be due to the limited number of the specialized centers. Hence lots of time, money, and efforts are spent in the long follow-up programs. Also, the outcomes of cases are mostly not satisfactory for patients and their families with terminal cases that mostly thought to be not-treatable and hopeless in cases of CF. This concept makes them desperate to continue the follow-up program.

The third important issue is related to the economic burden of treatment of CF cases especially with late diagnosis and especially to continuously deteriorated lung function and prolonged colonization of resistant pathogenic microbial stains. Specific gene therapy potentiators and correctors are highly expensive and only available for big specialized centers. All Saudi people are covered by the umbrella of the government insurance and all services for CF cases are unpaid, but this should not force us to ignore that CF cases survival is strongly affected by social factors and mortalities are more common among cases of the low social class [47].

Mortality among cases of CF in Saudi Arabia is a multi-factorial issue. Delayed diagnosis and delayed onset of nutritional replacement were suggested to play a major role. Also, resistant pseudomonas and methicillin-resistant staph aureus MRSA infections are related to early deaths. Additionally, high hematocrit with low red blood cells indices was shown to be related to CF poor prognosis and mortalities [14].

Finally, the extending publications from Saudi Arabia in the era of CF are promising, however further large scale and longitudinal studies should be done to determine Saudi CFTR mutation patterns which could be needed during screening of CF in Saudi Arabia. Internationally, more researches should be conducted to investigate the long-term effects of the emerging novel CF genetic and functional treatment modalities.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the

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