Cystic Fibrosis and Consanguinity in the Saudi Arabian Population

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Abstract: Until relatively recently, cystic fibrosis (CF) was considered to be to be rare in saudiarabia. The prevalence of CF varies considerably in different regions of the country, with the highest rate (37%) being found in the eastern region followed by the central region (28%), western region (22%), southerner region (8%) and finally the northerner region (5%). An association has been suggested between consanguineous marriage and the high incidence of CF. In saudiarabia, marriages between first cousins represents 40 -50% of general population. However, in the last few years the prevalence of CF among saudis has risen. This could be attributed to the omission of CF from the national newborn screening program, low awareness of CF among saudis and a dearth of appropriate genetic counseling services. This study represents a detrailes evidence based report focuses on history of CF among saudis, its epidemiology, complications of the disease and consanguineous marriage in relation to CF.
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Introduction

CF is an autosomal recessive disorder that leads to a shortened lifespan unless it is treated with appropriate medication sufficiently early. It is a disorder that involves severe pulmonary and gastrointestinal manifestations. CF shows considerable heterogeneity and often there are no clinical signs apparent at birth. All the body's exocrine glands are affected by CF, resulting in the production of abnormal mucus. Mucus acts in the body to lubricate and protect the lining of several organs; for example, the lungs and stomach. However, due to the thickness and viscosity of the mucus of CF patients, they are subject to bacterial infections. Bronchiolar obstruction and pulmonary infection eventually lead to damage to the lungs. In addition, the pancreatic ducts in the digestive system are blocked by this viscous mucus, which can lead to hepatic cirrhosis, intestinal obstruction, steatorrhoea, malnutrition, diarrhea, and meconium ileus. This last is often the first indication of CF. Furthermore, CF can be the cause of growth problems and male infertility, which manifest themselves in late childhood or early adulthood[16].

A Brief History of CF in Saudi Arabia

Cystic fibrosis (CF) is often considered to be rare in Saudi Arabia. However, in 1989 thirteen Saudi children were diagnosed as having CF at King Faisal specialist hospital. The diagnosis was made by elevated sweat chloride concentrations (> 60 mmol/1) as well as typical clinical characteristics of the disease. The duration of symptoms prior to diagnosis ranged between one month and five years, with a mean of 23 months. The principal clinical manifestations of CF in the children were abdominal distention, failure to thrive, steatorrhoea, hepatomegaly, rectal prolapse and recurrent respiratory infections, frequently with Pseudomonasaeruginosa. A further eight patients had symptoms and a family history highly indicative of CF[15].

A study carried out between 1985 and 2003 with 183 patients at the King Faisal Specialist Hospital and Research Center, the only center treating cystic fibrosis Saudi Arabia. At the end of study period, 81% of these patients were still alive. The mean age at diagnosis was 3 years, while the mean follow-up period was 4.3 years. The study found that approximately two-thirds of these patients were mildly to moderately malnourished for their age and height. The factors making the greatest contribution to progressive lung disease were found to be the weight to height ratio, albumin levels, high HCT, low MCHC, low MCV, and development of Pseudomonas resistance to antibiotics. The study demonstrated that preventing premature mortality from CF was strongly associated with early diagnosis, appropriate management, and nutritional rehabilitation. Further, it was found that the early onset of multi-drug resistant Pseudomonas also contributed considerably to early mortality[6].

Since the cystic fibrosis transmembrane regulator (CFTR) was cloned in 1989[18], over 750 new mutations have been reported to the Cystic Fibrosis Consortium. In Saudi Arabia, it is reported that 1:4,243 children suffer from CF, although the cystic fibrosis transmembrane conductance regulator (CFTR) is uncommon. DF508, which causes (between 65 and 85% of CF in the Caucasian population has been found to be less common among Saudis. The

prevalence of CF varies considerably in different regions of the country, with the highest rate, 37%, being found in The distribution of CF patients in different Saudi regions are as follows: (37%) from the Eastern region followed by the Central region with, 28%, then western region with 22%, then Southerner region with 8% and northerner region with 5%[4].

Among Saudi population different reports about distribution in CFTR detection showed that: 89% of CFTR alleles, have been identified[9, 13]. F508del constitutes 12% of CFTR mutation. 1548 delG is the most common Saudi CFTR mutation identified (20%). 1548 delG, F508del, I1234V, 3120þ1G > A, H139L, 711þ1G > A, N1303K, S549R, 2043delG, 1507del 9 are the common CFTR mutations of Saudi ethnic origin (80%)[9, 13].

Epidemiology

CF is found in approximately one in every 2,000 to one in every 3,500 children born to Caucasians of European origin. In North America, it occurs in one in every 8,400 births to Hispanics, one in every 89,000 births to Asians, Hawaii Americans while among African-Americans, the rate is one in every 15,000 births [19].

In the Middle East, the rate differs according to ethnic origin and the degree of consanguinity. In the Arab world, consanguinity is estimated to be around 65%, with estimates ranging between 1 in 2,560 and 1 in 15,876. Some of the mutations in the Middle East are also found in a number of other regions in the world. These include F508del, N1303K, W1282X and 3120+1G>A, although this last is more often found in people of African descent and may have spread from African to Arabic populations through mixed marriage[1, 4, 9-11, 13].

Desgeorges et al. (1997) conducted a study in the Lebanon, finding 10 different mutations, with DF508 occurring in only 34% of the group, and the W1282X mutations being the second most common[8].

Khan and Mohammad (1985) conducted a review of patients diagnosed with CF in Bahrain between 1979 and 1984. They reviewed eight proven cases of CF (6 females, 2 males), aged from 42 days to 5 months[14]. Also in Bahrain, Al-Mahroos (1998) carried out research to identify the incidence and evaluate the causes of high mortality among Bahraini children with CF. Over an Twenty-five children with a mean age of two months were diagnosed with CF in an 18-year period (January 1978 to December 1995). Thus, the incidence of CF in Bahrain is estimated to be 1:5,800 live births, while the prevalence is 3:100,000 individuals[2].

Dawson and Frossard (1999) studied 17 unrelated families with children affected with CF in the United Arab Emirates. Around 15 to 20% of the children were found to have developed hyponatremia, despite their parents having been advised to increase the children's intake of salt. Dawson and Frossard (1999) suggested that the presentation of hyponatremia in patients could be attributed to the high temperatures in summer and recommended that cystic fibrosis be considered in babies and young children presenting with hyponatremia[7].

Rajab et al. (2005) conducted research in Oman to estimate the prevalence of autosomal recessive diseases, using a hospital-based register for the years 1993 to 2002. They found that 32 patients were diagnosed with CF in this period, with an observed incidence of 1 in 15,000 births[17]. In saudiarabia the incidence of cystic fibrosis was reported to be 1 in 4243[15] which raise awareness to initiate national screening program to detect and treat all affected baby with CF.

Complications in Cystic Fibrosis

CF can lead to a number of complications, among which are the following:

Bleeding in the lungs:

CF sufferers may develop hemoptysis, or bleeding in the lungs. This typically causes patients to cough up blood in their sputum. If this happens, patients should visit their doctor immediately.

Cirrhosis:

CF patients have viscous secretions in the digestive tract which may obstruct the tube that carries bile from the liver and gallbladder into the small intestine, thus resulting incirrhosis (inflammation and scarring) of the liver.

Diabetes:

The viscous secretions in the digestive tract may obstruct the tubes near the pancreas. As the pancreas produces insulin, which regulates the blood sugar level, there is a risk of CF patients developing diabetes. Indeed, it is estimated that 20% of CF patients develop diabetes.

Heart failure:

The lower right chamber of the heart may eventually fail due to the effects of CF. Heart failure brought on in this way is usually fatal.

Lung infections:

In CF patients, the viscous mucus in the airways is an ideal environment for the growth of micro-organisms such as bacteria. Thus, CF patients are prone to frequent lung infections, such as bronchitis, bronchiectasis, and pneumonia, which may be fatal.

Nutritional deficiencies:

The majority of CF patients have nutritional deficiencies, which may result in weight loss and short stature, particularly in children. These deficiencies are due to the viscous secretions in the digestive tract of CF patients preventing pancreatic enzymes, which are necessary for the digestion of proteins and fats, from reaching the intestine. The viscous secretions also act

to prevent the absorption of certain vitamins, particularly vitamins A, D, E, and K.

Respiratory failure:

Respiratory failure results when the body cannot supply the muscles and tissues with sufficient oxygen. CF sufferers are at risk of respiratory failure, for which the only treatment is a lung transplant.

Cystic Fibrosis and Consanguineous Marriage

High rates of consanguineous marriage lead to the development of inbred groups subject to a number of inherited diseases. Hence, in children of a consanguineous marriage, the expression of recessive genes from ancestors can lead to significant health disorders. Higher rates of congenital malformation, as well as neonatal and post-neonatal mortalities have been reported in the children of consanguineous parents in comparison with those with non-consanguineous parents.

The majority of previous studies on the link between CF and parental consanguinity found that populations in which consanguineous marriage was common practice have a considerably higher rate of inherited CF. For instance, In Khan and Mohammad's(1985) study found that of the eight proven cases of CF in Bahrain between 1979 and 1984, five were in children born to consanguineous parents. Similarly, again in the context of Bahrain Al Arrayed and Abdulla (1996) found that 20 of the 27 CF patients had consanguineous parents and a family history of CF, while Al-Mahroos found this to be the case for 11 out of the 25 CF patients he studied[3]. In Jordan, Kakish (2001) concluded that consanguinity was a factor in 50 of the children with CF of the 72 he studied and that in 30 of these cases, there was a family history of CF[12].

In Saudi Arabia, several study showed that autosomal recessive and other major genetic disorders occurs due high rate of consanguineous marriages, and the rate of consanguineous marriages in these studies were above 50%[20]. However, this practice has a negative effect in that there is a high prevalence of autosomal recessive disorders among the children of consanguineous unions, as well as higher morbidity and mortality rates. Banjar (2003) found that in total of 190 CF patients were diagnosed at King Faisal Specialist Hospital which is the only only hospital in the country offering treatment for CF patients 88% of CF patients were found to have consanguineous parents[5].

Cystic Fibrosis Control Program

The detection of CF carriers and genetic counseling to avoid further transmission of the disorder are crucial to any attempt to control the disorder. In particular, carrier detection for anyone who has a family member affected by CF should be provided. Pre-implantation (PGD) can assist CF carriers to have children who are not affected by the disorder. However PGD is an expensive procedure and are thus beyond the means of most people. However, this barrier could be overcome if the government covered some or all of the costs of the procedure for those who could not afford this.

Further, community education and raising awareness about CF among general public and medical professionals are important measures in the control of CF. Among the ways in which these measures can be implemented are giving schoolchildren information about the disorder, and use of the media for the wider diffusion of information on CF, as well as arranging workshops, conferences and symposia on CF.

Moreover, support groups could be established for the CF patients and their families.. Such groups could meet regularly to discuss issues involved in coping with CF and to offer both patients and their families with advice and counseling. In addition, bulletins or newsletters on various issues relevant to CF could be issued for CF patients and their families.

Control of Cystic Fibrosis and Current Challenges in Saudi Arabia

In Saudi Arabia, physical and mental disability and other health issues place great social and economic demands on the country. In addition, increased mortality rates among those with a disability and other serious health problems are a great cause for concern to the Saudi government. For these reasons, the Saudi government has focused on implementing a screening program for 16 genetic diseases for all the born babies born in the country. However, among the major challenges faced in this implementation have been the dearth of diagnostic methods, as well as ways of preventing and treating and the genetic diseases most prevalent in Saudi Arabia.

In April 2003, the Prince Salman Center for Disability Research (now the King Salman Center for Disability Research) entered into partnership with the Ministry of Health and King Faisal Specialist Hospital to establish a newborn screening program in a number of hospitals affiliated to the Ministry of Health, in particular, maternity and pediatric hospitals. At the end of December 2010, the second phase of this partnership was launched to establish newborn screening programs in the remainder of the Ministry of Health hospitals with maternity and pediatric wards. Less than one year later, On Nov 2011 the screening program was accredited as a national program, with responsibility for its management transferred to the Ministry of Health and three laboratories for diagnosis established. The program aims to offer treatment for affected babies.

The national newborn screening program was set up in 2003 with the aim of contributing to the

prevention of disability resulting from the following sixteen diseases which are widespread in Saudi Arabia: Phenylketonuria; Maple Syrup Urine (MSUD), Arginosuccinase Deficiency (ASD); Citrullinemia (ASAS); HMG Co-A Lyase Deficiency (HMG-CoA-LD); Isovaleric Acidemia (IVA); Methylmalonic Acidemia (MMA), Propionic Acidemia (PA); Beta-Ketothiolase Deficiency (BKT); Glutaric Acidemia type-1 (GA1); Medium-chain acyl-CoA dehydrogenase Deficiency (MCAD); 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC); Galactosemia; Congenital Adrenal Hyperplasia (CAH); Congenital Hyperthyroidism (CH), and; Biotinidase Deficiency. It is highly recommended that screening for CF in newborn babies be added to this list.

Currently, CF is not included in the program. All babies with CF in all military hospitals and government Health Ministry hospitals in Saudi Arabia are transferred to King Faisal Specialist Hospital in Riyadh, which is the only hospital in the country offering treatment for CF patients.

The attitude of Saudi couples in relation to reproductive decisions remains perhaps the main obstacle to the prevention of the transmission of genetic disorders. In the knowledge that they are carriers of a genetic disease, many couples nonetheless decide to get married and have children. This attitude can be changed in time through better community education. In addition, it is recommended that detection of adult carriers be undertaken in members of families in which CF is present and that if these adults are found to be carriers of CF, they should not be issued with a marriage certificate but be referred to a regional genetic counseling clinic.

Furthermore, awareness of the public of potential outcome of consanguineous marriage is currently low and efforts must be made to raise it. It is vital that experts in the field should make great efforts to find an effective solution to reduce the number of consanguineous marriages in Saudi Arabia and in particular, marriages between first cousins, in order to reduce the risk of children being affected by autosomal recessive disorders such as CF.

Conclusion

In saudiarabia, CF is a relatively widespread autosomal recessively inherited blood disorder. Numerous studies show a strong association between consanguineous marriage and CF and that the high rate of prevalence of and mortality from CF in saudiarabia can be, at least in part, attributed to such marriages. The establishment of a screening program for all newborn babies in the country and the provision by the Saudi government of genetic counseling services at various health care centers indicate that in the near future CF is likely to be included among the sixteen diseases already screened for in saudiarabia. Moreover, there is greater awareness of the necessity of detecting adult carriers in families where one or more members are affected with CF in order to avoid transmission of the diseases to the following generation. In saudiarabia, there is a strong tradition of consanguineous marriages, and indeed, these account for up to half of all marriages in the country. There is an urgent need to raise greater awareness among Saudis of the risks of consanguineous marriages in terms of passing on genetic diseases to the issue of such marriages.

Conflict of Interests

None

Funding

None.

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