Clinical Presentation, Genotype and Microbiological Data among Cystic Fibrosis Children at King Hussein Medical Center

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ABSTRACT

Objective: To describe the clinical presentations, genotype, microbiological data among children with cystic fibrosis treated at King Hussein Medical Center.

Methods: A retrospective review of all the medical records of children (80) already diagnosed with Cystic fibrosis was conducted during the period 2002-2008 at King Hussein Medical Center. Clinical data collected included: age at presentation and diagnosis, clinical manifestation, delay in diagnosis, and family history. Laboratory tests that were done included: complete blood count, kidney and liver function tests, sweat chloride and genetic testing. PCR testing was performed for 36 mutations of cystic fibrosis. Those with borderline sweat chloride reading or atypical presentation were excluded.

Results: The study group consisted of 46 (57%) males and 34 (43%) females with classic cystic fibrosis. Age ranged from one month to 16 years of age with a median of eight months. Most of the patients presented between one and six months of age (35%) with the majority being in neonatal period (24%). Only 13% presented after the age of two years. Most common presentation was recurrent wheezy chest (28%), while the least common was direct hyperbilirubinemia (2%). A delay in diagnosis more than six months was seen in 18 patients (26%). Twenty-one children (26%) had positive family history of Cystic Fibrosis, while 12 (15%) gave a history of male infertility in the family. Sputum cultures were positive in 24 patients; *Pseudomonas Aureginosa* was the most commonly found (24%). Cystic Fibrosis mutations were found in 25 patients (31%); Delta F508 mutation was the commonest 4%. Three patients died (4%); one with respiratory failure and severe pulmonary hypertension, two with severe fatal sepsis.

Conclusion: There are diverse clinical presentations and genotypic features among our study group. A complete analysis of the DNA mutation would be helpful in knowing the most prevalent mutations in our population.

Key words: Cystic Fibrosis, Genotyping, Microbiological data

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Introduction

Cystic Fibrosis (CF) is the most lethal inherited disease among Caucasians.[1] It is a multisystem disease with a wide spectrum of presentations. [1] The usual presenting signs and symptoms involve recurrent and persistent pulmonary infections, pancreatic insufficiency with elevated sweat chloride readings.[1] Although CF is a clinical diagnosis, genetic testing has great implications especially in atypical or borderline cases.[1] However, we use ready made European–based genetic kits to screen our patients which may not reflect the true genotype

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Table I. Age of presentation in the study group

Age of presentation	Number	%
Newborns	19	24
1-6 months	28	35
7-12months	10	16
13-24 months	18	13
>2 years	10	12

Table II. Clinical presentation among classic CF patients in the study group

Clinical presentation	Number (%)
Recurrent chest symptoms	37 (46)
Chronic diarrhea	11(14)
Anemia, hypoalbuminemia	8(10)
Hypotonic dehydration	8(10)
Poor weight gain	6(8)
Hepatoslenomegaly	5(6)
Meconium ileus	3 (4)
Direct hyperbilirubinemia	2(2)

Table III. Comparison of the genotyping among our center and different Arab countries[4]*

Country	Year	Authors	No of pts	Major mutation
Lebanon	1997	Desdeordes *et al*	20	Δf508 W1282X N1303k
United Arab Emirates	1997	Frossard *et al*	17	S549R Δf508
Kingdom of Saudi Arabia (KSA)	1998	El-Harith *et al*	15	3120+1GA N1303K
KSA	1998	Banjar *et al*	70	Δf508 I1234V, R553X N1303k
KSA	1999	Banjar *et al*	70	H139L, S549R

*Reference 4

unique to our population. More cases of the disease are seen in our region with variable phenotypic and genotypic features.[1,2]

We describe the clinical presentations, genotype, and microbiological data among children with cystic fibrosis at King Hussein Medical Center (KHMC).

Methods

The medical records of the already diagnosed children with classic cystic fibrosis were reviewed. This is a retrospective rewiew of 80 children from January 2002 - January 2008 at KHMC. A specially formulated data sheet by the authors themselves was used. Clinical data collected included: age at presentation and diagnosis, presenting clinical manifestation, delay in diagnosis, and family history. Laboratory tests done included complete blood count, kidney and liver function tests, sweat chloride and genetic testing. Polymerase chain reaction (PCR) testing was performed for 36 mutations of cystic fibrosis.

Children between one month to 16 years of age were included. Diagnosis of classical CF was based on sweat chloride readings >60 mmol/l on two separate occasions plus classical clinical features suggestive of cystic fibrosis. Those with borderline sweat chloride less than 60 mmol/l or unusual presentations were excluded. Sweat testing was done in our laboratory using the Wescor Macroduct system. Samples for culture were collected each visit either by expectoration for those who can or through deep throat swabs taken by physicians themselves or from bronchial lavage during flexible bronchoscopy. All patients in this study underwent genetic testing for CF mutation using the Ennogenetics, INNO-LiPA, Belgium, which includes 36 mutations. Frequency tables were used to describe the study results.

Results

The medical files of 80 patients were reviewed. There were 46 males and 34 females with a ratio of 1.7:1. Table I represents the age at clinical presentation of the study group. The majority of the patients presented in the first 6 months of life (37%) and in the newborn period (24%). Only 13% of our group showed symptoms after the age of two years.

There were variable clinical presentations: most commonly patients presented with respiratory symptoms (28%), followed by chronic diarrhea (14%). The least common presentation was neonatal cholestasis in 2% as shown in Table II. Delay in diagnosis more than six months was seen in 18 patients (26%)

We look for the gene mutation using the Ennogenetics, INNO-LiPA, Belgium kit. Twenty five

children tested positive: homozygous genes were seen in 11 children, while compound heterozygous mutations were documented in 14 children. The most common was the delta F508 mutation (4%).

Nearly one quarter of our cohort had a positive family history of CF; only 10% of these were found to have positive mutations. The most common mutation found in these families was the heterozygous MN1303 mutation. Consanguinity was seen in 44 cases (55%), 50% of them are 1st or 2nd degree cousins. Family history of male infertility was seen in 16%.

Sputum or deep throat cultures were sent to all patients at each visit: 24 patients had positive results. *P. Aureuginosa* was most commonly seen (24%), followed by *Staphyloccocus areus* (4%), and equal number of *Klebsiella spp* and MRSA 1% each.

We lost three patients. Two infants died upon referral with severe sepsis and severe failure to thrive. While one infant died at the age of eight months with respiratory failure and severe pulmonary hypertension.

Discussion

Cystic Fibrosis is a multisystem disease with variable presentations.[2] Most of the patients were diagnosed during neonatal period in Western countries by screening test. More adults with this disease are seen due to better understanding and advanced care and management all over the world. [2] The clinical manifestations do not vary among ethnic groups though there is variability in the prevalence of gene mutations.[2,3] We therefore highlight the diversity of patients with CF followed at our clinic in KHMC regarding clinical presentations, genotype, and their microbiological data.

Knowledge about CF in Arab countries is evolving but as yet little data is available. It relied initially on the pattern of sporadic case reporting. With the changing knowledge of CF larger case series described in Saudi Arabia and the United Arab of Emirates.[4] This is explained by the growing prosperity in the Gulf region. In Jordan previous studies about CF mostly come from centers from northern Jordan but not performed at a national level. The calculated incidence of CF in Jordan in 1992 was estimated to be 1:2560.[5] The 1st CF case was reported in 1984 but ever since we believe that there is a very rapid increase in the number of recognized new cases.[5] The 1st reported cases in Kuwait were of Jordanian descent.[5]

The majority of our patients presented in infancy (35%); while 24% presented in neonatal period. Neonatal screening program for CF is not routinely adopted in Jordan, and the lack of awareness explains the variable ages of presentation in our cohort. Screening protocols have a great impact on identifying patients with CF at an early age.[6] Those presenting in the newborn period had different presentations: three had meconium ileus, two neonatal cholestasis. The latter two had spontaneous resolution of cholestasis. There is no clear incidence of neonatal jaundice in CF patients; some reported it as high as 68% in infancy. Some studies suggested an association between meconium ileus and neonatal cholestasis, this was not documented in our cohort.[6,7]

Thirteen percent of our cohort presented older than two years of age. Such group may carry milder gene mutations that tend to express the disease later in life.[7] The majority presented with asthma-like picture and responds to bronchial asthma treatment; it is other clinical features as finger clubbing that raise the suspicion for CF.

It was noticed that the clinical manifestations at the time of presentation were similar to that from western countries. The usual presenting signs and symptom involve recurrent and persistent pulmonary infections (46%); chest symptoms are the most troublesome to the family that mandates frequent visits to hospitals. Such chronic symptoms are the alarming ones where physicians warrant further investigations.[8] The least common presentation was direct hyperbilirubinemia as shown in Table II.

Chronic diarrhea was the 2nd most common presenting feature seen in 14% of cases. They usually report bulky greasy stool. More of our patients manifested pancreatic insufficiency as disease progressed (97%) which is higher than what is classically known (85%).[9]This may reflect the probable genetic diversity of the disease in our population compared to the Western one.

Those clinical manifestations that differed from Western countries included: earlier P. *Aureuginosa* colonization, and hypochloremic dehydration (Pseudo Barter Syndrome) PBS (10%). Theses patients usually present with recurrent hypotonic dehydration, more commonly during hot weather periods.[10] Worldwide PSB is reported to occur as high as 18%.[10] Predisposing factors include: infancy, severe pulmonary involvement, severe pancreatic insufficiency and profuse sweating.[10,11] Such presentation leads to miss diagnosis and delay in diagnosis where patients would be followed up at the nephrology clinic before they are referred for appropriate diagnosis.[11] Countries in our region usually report this recurrent symptom more

frequently. Turkey reported a high frequency of episodes in children during hot months of the year where eight children over a period of 15 days had similar episodes, one child died.[12] In Saudi Arabia, nearly 50% of the children during a seven year period presented with PSB.[13]

Sputum cultures were positive in 24 patients in our study. *P. Aureuginosa* was most commonly seen (24%). We noticed an early colonization in our patients; while most of the patients in UK have chronic P. *Aureuginosa* infection by their late teens.[14] Our contrasting result may be partly explained by the fact that many patients receive several courses of systemic antibiotics before they are referred for further investigation and diagnosis. Lack of neonatal screening programs might also contribute to the delay in diagnosis and thus early colonization with microorganisms. Another factor might be cross infection and the presence of an older sibling with CF and *P. Aureuginosa* colonization.

Syndrome of anemia and hypoproteinemia is a well recognized association in infancy.[15] Male genders, breast-milk feeding, and the presence of severe CFTR mutations are predisposing factors.[15] Such cases usually improve with proper nutritional support and treatment. It is reported in 10% of our cohort; mostly they presented in infancy and started as failure to gain weight.

CF is an autosomal recessive inherited disease thus should be seen more in consanguineous marriages.[16] The high consanguinity rate among most of the Arab population must be the contributing factor for the evolving CF seen in our region.[17] Twenty six percent of our cohort had a positive family history of CF, consanguinity was seen in 44 cases (55%). A study from northern Jordan showed that consanguinity reached up to 70% of the study group.[17] In Bahrain consanguinity among CF members was as high as 80%.[4,18] In addition we had 11 siblings followed at our clinic; which reflects the burden on these families as well as the lack of proper genetic counseling clinics. A positive family history of infertility was found in 15 % of cases. Certain mutations are reported to be associated with male infertility and obstructive azospermia.[18] Many of the infertile males are not diagnosed with CF.[18,19]

There are more than 1000 known gene mutations.[19] We test for only 36 mutations and only 31% of our study group having one of these CF mutations. This is relatively low which may indicate that still we have novel mutations that are unique to our populations. Delta F508 the most common gene mutation responsible for CF in western countries was seen only in (24%) of our cohort. This mutation is also most commonly seen in most Arab studies, which might not be genuinely true as limited mutation analysis studies are conducted in the Arab world.[20] Kambouris *et al.* from Saudi Arabia identified 8 novel mutations in 61 Arab families.[20] Some of the mutations are found in both populations as demonstrated in Table III. Yet it is probably not appropriate to conclude that a panel of 11 common mutations account for 70% of all Arab CF chromosomes; as still many novel mutations are being reported every now and then as occurs from Lebanon.[21] This may reflect the presence of several communities within the Lebanese population.[21] It is probably advisable to do whole DNA sequencing as this would identify the most common mutations in our population that can aid in diagnosis especially in atypical cases of CF.

Three of our patients died during the follow-up period. Two of them died with severe fatal sepsis in infancy during their hospitalization upon initial referral for further evaluation. Another infant died with severe pulmonary hypertension and respiratory failure at the age of 8 months. Algeria had a higher mortality rate (42%) that occurred at an early age (mean: 4 years) compared to other countries.[22] Worldwide mortality in CF is related more to the respiratory complications, it varies between countries.[23,24] The life expectancy for CF patients has improved over the years with the expected median currently to be 50 years with optimal medical care.[24]

Conclusion

There are diverse clinical presentations and genotypic features among our study group. A complete analysis of the DNA mutation would be helpful in knowing the most common mutations in our population.

Recommendations

1. A complete analysis of the DNA mutation would be helpful to know the most common mutations in our population. This may help us to formulate our kit of the common mutations specific for our population and possibly to introduce neonatal screen program at a national level
2. A specialized cystic fibrosis clinic and center is needed and can offer better care and long term results to patients and their families.

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