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Cystic Fibrosis In Jordan : Clinical And Genetic Aspects

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Objective: To describe the demographic characteristics, phenotype, genotype, microbiological data, treatment and outcome among Jordanian children with cystic fibrosis .

Design : A prospective Cohort Study .

Setting: Princess Rahma Teaching Hosptial (PRTH).

Methods: All patients with cystic fibrosis seen between 1995 and 2000 inclusive (n=72). Clinical and laboratory data were collected on these patients.

Results: There were 37 males and 35 females in the study group. The mean age of all patients was 4.5 years; the mean age at presentation was 21.2 months; the mean age at diagnosis was 30.7 months and the mean delay of CF diagnosis was 9 months. Pancreatic exocrine insufficiency was documented in 94% of cases. Twenty (27%) children died, most below the age of 1 year. Pseudomonas aeruginosa was isolated in 30% of cases. Therapeutic measures were suboptimal in the majority of cases.

Consanguineous marriage was present in 70% of cases. Genetic screening of the study population revealed 20 different Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations with Delta F508 mutation accounting only for 6.3%.

Conclusion: There is a wide variability in the phenotype and genotype of patients with cystic fibrosis. Jordanian CF patients have a severe clinical course of disease with genetic and environmental factors may be contributory.

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Cystic Fibrosis is a complex metabolic disorder characterized by dysfunction of the exocrine glands, including sweat glands, the pancreas, and mucous glands of the respiratory, gastrointestinal and reproductive tracts. It is the most common lethal genetic disease among the Caucasian populations[1]. The incidence of CF varies considerably in different parts of the world and among different ethnic groups. The generally accepted incidence of CF in the United States is 1 in 2000 - 2500 in Caucasian populations[1]. The incidence of CF among Arab populations is estimated to range from extremely rare to as common as among Caucasian population[2,3].

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The gene associated with CF was cloned and sequenced in 1989 and is called Cystic Fibrosis Transmembrane Conductance Regulator and assigned to the long arm of chromosome 7. The first CF mutation described is known as Delta F508, this is the most common mutation in Northern European derived populations including the United States and accounts for 70-75% of CF chromosomes[4,5]. The most reliable diagnostic test for CF is the quantitative analysis of sweat electrolytes after collection of sweat by pilocarpine iontophoresis method of Gibson & Cooke[6].

The spectrum of clinical manifestations in CF is broad because of the extent and severity of involvement of the various organ systems, the type of gene mutation, and the age at clinical manifestation. The most characteristic clinical findings include: elevated sweat electrolytes, pancreatic exocrine insufficiency, chronic bronchopulmonary infections, focal biliary cirrhosis and intestinal abnormalities. Because of the marked heterogeneity among individuals affected by CF, prognosis is highly variable, depending on the extent and severity of involvement of various organ systems, and the type and severity of complications.

This article reviews the clinical and laboratory data collected at time of diagnosis and follow-up of all patients with CF. Their demographic characteristics, phenotype, genotype, microbiological data, treatment and outcome of patients with CF are documented.

METHODS

All patients with CF who had been seen and followed at Princess Rahma Teaching Hospital between 1995 and 2000 inclusive. Seventy two cases were diagnosed by the attending pediatrician. The diagnosis of CF was confirmed by typical clinical features with sweat sodium and chloride values greater than 60 mmol/L. All sweat tests were performed by the same person in the same laboratory.

Data were collected on all patients by the author at time of diagnosis and follow-up and were incorporated into a computerized data base (Epi 6 software). The following information was collected: sex, place and date of birth, age at presentation, age at diagnosis, mode of presentation, family history of CF, consangunity of parents, sweat chloride test results, sputum culture results, pancreatic enzyme replacement, use of chest physiotherapy and bronchodilators, use of antibiotics, use of non-steroidal anti-inflammatory medications, use of multivitamins, complications, ethnic origin and mortality data. The respiratory microbiology data were derived from sputum cultures obtained by deep tracheal aspirate. Organisms were identified in accordance with the standards of the American Society for Microbiology, the National Committee for Clinical Laboratory Standards or both[7,8]. The mutations in the CFTR gene among the study group was determined by using a multiplex heteroduplex shift analysis followed by direct sequencing on blood taken from 72 children and 42 parents. The screened region included promoter, all exons with flanking intron sequence as well as the T-tract. The genetic analysis was conducted at the laboratory department of the hospital for sick children, Toronto, Canada .

The annual number of registered live births between 1995 to 2000 was obtained from the Jordan vital statistics[9,10]. The total number of registered live births in Northern Jordan during the study period was 200,000, of which 67 were born with CF. The other 5 were born before the start of the study. Therefore, the estimated incidence of CF during the study period would approximately be 1 in 3000.

RESULTS

Seventy two children with CF were seen between January 1995 and December 2000. They were followed for a mean duration of 55 (range 6-72) months. Forty-four children (61%) were followed for 6 years. All cases were Jordanians born in Northern Jordan. There were 37 (51.4%) males and 35(48.6%) females. The mean age at presentation was 21.2 months (range 1-90 months), the mean age at diagnosis was 30.7 months (range 3-96 months) and the mean delay of CF diagnosis was 9 months. Consanguinity was present in 50 (70%) of cases and parents were first-or second degree cousins in 42(58%). Family history of CF was confirmed in 30 (41%) cases.

A sweat chloride test was done twice in each case. The mean ± SD (mmol/L) for all readings was 70.2 ± 9.1 mmol/L (range 59-114mmol/L) . Sputum culture was done in 39(54%) cases. Pseudomonas aeruginosa was isolated in 12 (30%) cases, staphylococcus aureus in 7 (17%) cases, Klebsiella in 3(7%) cases and other organisms in 17(43%) cases. Meconium ileus was present at birth in 10% of all patients with newly diagnosed CF and other intestinal obstruction in 4%. The leading clinical symptoms at presentation were persistent or acute respiratory symptoms in 86%, failure to thrive in 75%, steatorrhea and malabsorption in 60%, liver disease in 9% and meconium ileus in 10% .

During the follow-up period, the rates of complications observed were as follows: failure to thrive in 93%, progressive lung disease in 50%, hypoalbuminemia in 16%, intestinal obstruction in 14%, Nasal polyps in 6%, Pseudo-Bartter Syndrome in 0.5% and liver cirrhosis in 0.1%. Diabetes mellitus, pancreatitis, gall bladder disease , pneumothorax and rectal prolapse were not observed among our patients. There was pancreatic exocrine deficiency in 68 (94%) children based on the quantitative estimate of steatorrhea obtained by steatocrit measurement according to Guarino et al[11].

There were 20 (27%) deaths during the study period, 8 (40%) males and 12 (60%) females. The mean age at death ± SD was 1 year ± 0.31. Seventeen (85%) died below the age of 1 year, 12 (70%) males and 5 (30%) females. The cause of death was respiratory failure due to progressive lung disease and failure to thrive.

Pancreatic enzyme replacement was given in 34 (47%) cases, chest physiotherapy and bronchodilators were used in 8 (11%) cases, multivitamins were used in 55(76%) cases, antibiotic therapy was used in 22(30%) cases and Ibuprofen was given to 9(12%) cases. The home intravenous therapy, oxygen therapy and supplemental feeding were not available to any of the study population.

Genetic screening was conducted on the 72 CF children and 42 parents and revealed 20 different CFTR mutations with Delta F508 mutation accounting only for 6.3%. Among the mutations detected, five were alleles found for the first time (296+9A->T, T338M, T760M, 3679 delA and G1244D).

DISCUSSION

Cystic Fibrosis is believed to be rare among Arabs. The number of newly diagnosed CF cases in Jordan has been increasing over the past several years because of recent availability of reliable sweat chloride testing and interested physicians. A neonatal screening study published in 1992[3] calculated the incidence of CF in Jordan to be 1:2560 live births, compatible with the results from our study and close to that reported in the UK (1:2500) and Australia (1:2488) and higher than that in the white population of the USA (1:3500)[12-14].

The slightly higher proportion of male patients might reflect more deaths in females owing to the observed gender gap in CF mortality. This is in agreement with the results of a recently published study from the USA[14]. The death rate among our patients is still high (27%) though it is less than that reported in a study published sixteen years ago (41.7%)[15]. Most deaths occurred in the first year of life (85%), of which 60% were males. The greater male mortality among infants with CF has been noted previously and may be mediated through viral lower respiratory tract infections, an important cause of mortality in infants with cystic fibrosis[16,17]. It may also reflect the higher male infant mortality rate in the general population[18]. Although debatable, the high mortality rate among our CF population could be due to severe disease in our group, as observed in this study compared to CF patients in the United Arab Emirates, Bahrain and Asian community residing in the United Kingdom[2,19,20].

Consanguineous marriage is a very common practice in Jordan and is recorded in 64% of marriages in Northern Jordan[21]. In this study, consanguineous marriage has been documented in 70% of the study patients, showing once again the impact of consanguineous marriage on the incidence of autosomal recessive disorders. Pancreatic insufficiency was documented in 94% of the study patients, this is in contrast to western reports of pancreatic insufficiency in 85% of CF population[22]. It is well established that CF patients with pancreatic sufficiency maintain better nutritional status and have less pulmonary complications than those with pancreatic insufficiency[23]. Therefore, the development of pancreatic insufficiency in the vast majority of the study patients is an indication of severity of the disease.

Failure to thrive was seen at presentation in 75% of cases. Subsequently, 93% developed failure to thrive and 16% had hypoalbuminemia. Failure to thrive at an early age is a well documented cause of high morbidity and mortality in young infants with Cystic fibrosis[24].

Liver disease diagnosed on basis of hepatomegaly, abnormal transaminase, ultrasonic and histopathological findings was the presenting feature in 9% of our patients. This is

three times the incidence reported in European and North American patients (3%), which might be due to genetic and/or enviromental factors such as malnutrition and the presence of other problems causing liver disease[25].

There are two main limitations to the microbiology data of this study. First, sputum cultures were ordered for sicker patients and secondly, the results were based on only one sputum culture which do not reflect the chronicity of infection. Pseudomonas aeruginosa was the most common pathogen isolated (30%), as early as 6 months of age. Early colonization with Pseudomonas is linked with higher morbidity and mortality[26,27] .

Considerable variations in the frequency of the various mutations exists across population and ethnic groups; Delta F508 represents only about 46% of Southern European, 30% of black, and 30% of Ashkenazic CF chromosomes[28-30]. The surprisingly low incidence of Delta F508 mutation among our patients could be explained based on the founding population and the high mortality among patients carrying this severe mutation resulting in under-representation in the sample population. The large number of different mutations would reflect the ethnic diversity of the Jordanian population and the country's complex history.

CONCLUSION

There is a wide variability in the phenotype and genotype of patients with cystic fibrosis. Jordanian CF patients have a severe clinical course of disease with genetic and environmental factors may be contributory.

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