Profile and Factors Determining Outcome in a Cohort of Cystic Fibrosis Patients Seen at the Aga Khan University Hospital, Karachi, Pakistan

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Summary

Cystic fibrosis is the most common potentially lethal autosomal recessive, genetic disease associated with pulmonary and pancreatic insufficiency. It is caused by variations in the CFTR (cystic fibrosis transmembrane regulator) gene. The most common mutation in the CFTR gene designated F508, is found in only 33 per cent of CF patients in Pakistan. The variability in presentation and clinical severity of disease may be a function of genotypic-phenotypic factors. Our aim was to attempt to define the disease in this region and to lay the ground work for future mutational analysis. This study was a retrospective chart review was conducted to identify cystic fibrosis patients seen at the Aga Khan University Hospital over a 10-year period. Our study identified 56 patients diagnosed by a pilocarpine iontophoresis sweat test. A chart review was then done to look at the various clinical profiles. 58.3 per cent of our patients presented in the first 6 months of life supporting the hypothesis that CF may be a severe disease in Asians with an earlier age of presentation. Most of the patients (80.6 per cent) presented with pulmonary problems while 83.9 per cent had failure to thrive. The most frequently isolated pathogen was Pseudomonas aeruginosa in 87.5 per cent of the patients tested. 70 per cent of the patients died in the first year of life. The clinical parameters studied suggest a severe form of CF in Pakistani patients and provides a foundation for future studies to define genotype/phenotype correlations of the specific mutations involved in Pakistani CF patients.

Introduction

Cystic fibrosis is an inherited disease affecting epithelial cells with predominantly pulmonary and pancreatic failure. The defect lies in the cystic fibrosis conductance regulatory protein (CFTR) that leads to sodium chloride secretion and hence the secretion of water. Many of the manifestations of cystic fibrosis are therefore due to a lack of luminal hydration of macromolecules. Inherited as an autosomal recessive trait, it has been considered uncommon in Asian and Middle Eastern countries. The incidence of cystic fibrosis is Pakistan is still unknown. While variability in presentation and clinical severity of disease may be a function of genotypic-phenotypic factors there have been few reports defining the disease in this region. As a step in attempting to identify the disease in Pakistan, we reviewed cystic fibrosis cases seen at the Aga Khan University Hospital at Karachi, Pakistan.

Methods

A retrospective medical record review was done to include cystic fibrosis patients seen at the Aga Khan University Hospital over a period of 16 years from 1987–2003. Patients up to the age of 15 years with positive sweat tests were included in the study. A diagnosis of cystic fibrosis was made using the iontophores pilocarpine sweat test, using a minimum of 70 g of sweat. A positive test was defined as a sweat chloride secretion of greater than 40 mmol/l. Equivocal test results were repeated. Patients with a history of meconium ileus were considered to have cystic fibrosis and were included in the study. Patients who received evaluation for cystic fibrosis had had clinical features of recurrent respiratory problems and failure to thrive. Serum samples from the prospectively identified patients were saved for
gene mutation analysis. The system to screen for mutations in our laboratory is PCR (polymerase chain reaction) -SSCP-Sequencing. Regions in the gene of interest are amplified by PCR and the amplified product is then analyzed through Single Segment Conformation Polymorphism (SSCP).

Results
A total of 56 patients were identified as having cystic fibrosis. Of these patients, 36 (64.3 per cent) were males and 20 (35.7 per cent) were females and 41/56 (73.3 per cent) presented between the ages of 0–6 months. The mean age at presentation was 8.4 months (range of 0–72 months). The age at which the first sweat test was done was documented for 48 patients and in 28/48 (58.3 per cent), sweat tests were done in the first 6 months of life. The test was repeated in nine patients. The interval between the first and second sweat evaluation was at a mean of 45 months (range 2–124 months). There was a history of a consanguinity in 22 patients (39.2 per cent) and in 11, a sibling had been previously diagnosed to have cystic fibrosis. A history of a sibling death was present in 15 patients (26.7 per cent) and 20 patients (35.7 per cent) had siblings who had a history of frequent respiratory tract infections. Seventeen (30.3 per cent) patients had a sibling who suffered from failure to thrive and 11 patients (19.6 per cent) had a sibling with a history of chronic diarrhea.

The most frequent mode of presentation was with pulmonary disease in 45 patients (80.4 per cent). In nine patients (16.1 per cent) a history of meconium ileus was present while in two there was a history of an intestinal volvulus. There were only two patients who had evidence of portal hypertension at presentation. On clinical examination, however, 15 (26.7 per cent) had hepatomegaly at initial examination. A large number of patients, 33 (58.9 per cent) had diarrhea and 47 (83.9 per cent) had failure to thrive. Fecal fat testing was documented in nine (16 per cent) and pancreatic supplementation provided to 18 (32.1 per cent) patients. Anemia was frequent and 21 (37.5 per cent) had required blood transfusions. Blood cultures were positive in 20 patients and Staphylococcus was the most frequently isolated pathogen from blood specimens. Pseudomonas was the predominant isolate from tracheal cultures in 14/16 (87.5 per cent) patients tested. The mean duration of hospitalization was 11 days (range 0–45 days). It was not possible to comment on the number of hospitalizations as most patients had been admitted elsewhere as well. While prophylactic antibiotics were used in 34 patients, antibiotic nebulizations were used in only six patients. Albuterol nebulizations and steroids were used in 39 (69 per cent) and 32 (57 per cent) patients respectively. Of the 56 patients seen, 25 (44.6 per cent) were lost to follow-up and 10 died. Four of these 10 patients (40 per cent) died of pulmonary complications, two died of sepsis and in four patients the cause of death was not documented. Three of the 10 patients who died had meconium ileus at birth. Seven of the 10 patients (70 per cent) died in the first year of life. The minimum period of follow up was one year.

On logistical regression analysis, none of the variables tested, age, age at first presentation, failure to thrive, pneumonia, were significant risk factors determining mortality.

Gene mutation analysis for ΔF508 was done for 15 patients with CF and indicated a frequency of 60 per cent. However only 33 per cent of the patients were homozygous for the mutation, which is significantly lower than that reported for Caucasian patients.

Discussion
Although cystic fibrosis is a common disorder in the Caucasian population it is considered less prevalent in other races. The incidence and predominant genetic mutations in the Pakistani population remain unknown and till recently, cystic fibrosis was not considered to be a Pakistani disease. The disease has been reported in many Arab countries with an incidence of 1/5800 live births in Bahrain and 1/2560 in Jordan. Goodchild, et al. estimated an incidence of 1/10000 for cystic fibrosis in Asian populations.

Our study identified 56 patients diagnosed to have cystic fibrosis over a 16 year period. These patients were those who presented to the Aga Khan University Hospital, a tertiary care facility that caters to private patients. We feel the numbers therefore probably represent only a small fraction of CF patients in the city of Karachi.

It has been speculated that cystic fibrosis may be more severe in Asian patients. An early age at presentation with an earlier onset of disease symptoms in our patients would support this hypothesis. Seventy six percent of our patients (42/56) presented in the first 6 months of life and 58 per cent (28/56) were diagnosed by this age. Reports from western countries have also demonstrated that almost 70 per cent of CF patients are diagnosed by one year of age. It would therefore seem that in the majority of our patients, diagnosis of the disease was not delayed.

There was a history of co-sanguinity in 39.2 per cent of our patients which is in contrast to that of Al Mahroos, et al. who reported an incidence of 80 per cent co-sanguinity in their study on CF in a middle eastern population. Most of our patients presented with pulmonary symptoms (80.6 per cent), (58.9 per cent) had diarrhea and (83.9 per cent) had failure to thrive at the time of diagnosis. Meconium
ileus which has previously been associated with a poor outcome was present in 16 per cent of our patients and is similar to figures reported in other studies.8

Various parameters have been used to study the prevalence of liver disease in CF. In previous studies the prevalence of overt liver disease indicated by the presence of an enlarged liver or spleen (or both) was 4.2 per cent.13 In our study 26.7 per cent of the patients were documented to have hepatomegaly on examination at initial presentation. There were only two patients (3.5 per cent) with evidence of portal hypertension amongst those studied at the time of presentation. This value is comparable to those quoted in other studies with prevalence rates of 2–37 per cent for liver disease.16–19 There are a number of reasons for this wide variation in prevalence including the fact that the criteria used for the diagnosis of liver disease have varied widely in the published literature.20

Factors that may be responsible for a more severe disease course in Asian patients may include frequency of infections and poor nutritional status. The most frequently isolated pathogen from tracheal aspirates was Pseudomonas aeruginosa in 87.5 per cent of the patients tested. Bowler, et al found that this pathogen was grown at a significantly earlier age in Asian patients and that it may adversely affect outcome.11 Other respiratory pathogens isolated included Acinetobacter, Staphylococcus aureus and Candida. Probably contributing to an adverse outcome was inadequate medical support. Pulmonary function testing was not possible and most patients included in the study had significant pulmonary disease requiring frequent hospitalization and therapy with bronchodilators and steroids.

There was inadequate nutritional management and testing for exocrine pancreatic function and pancreatic enzyme supplements were infrequently used. As a result almost 83.9 per cent of the patients had failure to thrive.

Of the patients followed, 32 per cent died with a significant number (70 per cent) dying in the first year of life. These numbers are similar to those reported from studies from Bahrain.8 Forty per cent of these deaths were due to pulmonary complications.

The test used in Pakistan for the identification of these cystic fibrosis patients was the quantitative pilocarpine iontophoresis test that utilized 70 g of sweat. A positive value was defined as sweat chloride concentration of greater than 40 mmol/l. Although the ΔF508 mutation accounts for almost 70 per cent of cystic fibrosis worldwide,21 33 per cent CF patients are homozygous for the mutation in Pakistan.22 The predominant mutations in the remaining Pakistani CF patients is yet unknown. In a similar study from India 46 per cent of CF patients were homozygous for the ΔF508 mutation.23–25

Greater than 1300 sequence alterations in the CF gene have so far been identified worldwide. The frequency of each mutation in a given population varies according to the geographical location and ethnic origin. Phenotype-genotype analyses suggest that the severity of clinical manifestations may depend on the mutation involved.26 Frossard, et al have extensively studied CF in Middle Eastern populations. They studied the genotype-phenotype correlations in six CF patients carrying the (–102T > A + S549R (T > G)) complex allele and in 16 patients with the S549R mutation alone and found that the former complex allele was associated with a better prognosis than S549R alone.27 S549N (G > A) homozygosity previously reported for a Pakistani family has also been associated with significant disease.28 Five other novel mutations Y569D, Q98X, 296+12(T > C), 1161delC and 621+2(T > C) have also been identified in Pakistani patients.29

Our study serves to elucidate that cystic fibrosis previously misdiagnosed as asthma and tuberculosis, exists in Pakistani children and initial descriptive statistics show that most parameters are similar to those reported from other Middle Eastern countries. However, patients included in the study had suboptimal follow up and care, partly attributed to the unavailability of sophisticated diagnostic services and therapeutic modalities. The mortality and morbidity are hence affected by these factors.

We conclude that a stronger and more structured system of diagnosis and management are required for the effective management of this disease. We have initiated several programs to improve awareness about CF in Pakistan and have an ongoing project to identify the common mutations in Pakistani patients and to study their phenotypic/genotypic correlations. We hope that the identification of Pakistani mutations will allow for the development of screening tools for the diagnosis of CF. We will also be undertaking population studies to determine the frequency of CF in Pakistan.

References


