Cystic Fibrosis in Bahrain Incidence, Phenotype, and Outcome

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Summary

To identify the incidence and evaluate the causes of high mortality among Bahraini children with cystic fibrosis, we studied retrospectively, 25 patients diagnosed as proven cases of cystic fibrosis at Sulmaniya Medical Center, the main referral center on the island, from January 1978 to December 1995. With extrapolation of the study data to the general population, the incidence of cystic fibrosis in Bahrain is at least one in 5800 and the prevalence is at least 3 in 100,000 population. Consanguineous marriage is documented in 80 per cent of the cases. Cystic fibrosis in Bahraini children is phenotypically severe, this is inferred from early age of presentation (mean of 2 months ± 1 month) and early age of diagnosis (mean 4 ± 1 month), development of pancreatic insufficiency by 1 year of age in all of the study patients, failure to thrive in 96 per cent of the patients, hypoalbuminemia in 48 per cent, meconium ileus in 20 per cent, progressive lung disease in 84 per cent at an early age, and early colonization with Pseudomonas aeruginosa. Age-specific mortality in the first year of life showed dramatic decline from 80 per cent between 1981 and 1985 to 50 per cent from 1986 to 1990, and to 9 per cent from 1991 to 1995. This improvement in survival is believed to be due to increased awareness among medical professionals and improved treatment.

Introduction

Cystic fibrosis (CF) is a multi-organ disease with the cardinal pathogenic feature is a dysfunction of exocrine glands leading to pancreatic insufficiency, recurrent lung disease, and failure to thrive. The mutant gene responsible for cystic fibrosis is located on chromosome no. 7 and was cloned in 1989. It codes for cystic fibrosis transmembrane conductance regulator protein (CFTR). Lack of this protein, which is a chloride channel dependent on cyclic AMP, is believed to lead to defective chloride transport across membranes which causes reduction of water in external secretions and the cascade of pathologic events known to occur in CF.

Cystic fibrosis is the most common inheritable disorder among Caucasians in western countries. Until recently, it was believed that cystic fibrosis does not exist in Bahrain. However in 1985, Khan et al. reported 10 cases of CF in Bahraini children. One of the striking findings in their report was the high mortality rate at an early age. Eight of the 10 reported cases died in the first year of life. In contrast, reports from western countries indicates that the mortality in the first year of life is far lower, being 7.6 per cent among British CF children in 1988. This is considered high in comparison with other western countries where mortality is two to three times lower than in England and Wales, but it is a far cry from our data where mortality in the first year is 80 per cent.

This figure is similar to the mortality of CF cases in the West in the 1940s and 1950s. In addition, the current life expectancy of cystic fibrosis cases in western countries has increased to about 30 years. This has been attributed to earlier diagnosis and better treatment.

This observation of high mortality rate at an early age among CF patients in Bahrain has prompted us to try to find out the cause(s) of the phenomenon. The first hypothesis is that these children have a severe type of cystic fibrosis, this can be inferred from the clinical presentation, progress of the disease, outcome, and type of gene mutation. The type of gene mutation is currently under investigation and so far none of the common known CF mutations are identified. The other hypothesis is that there is a delay in diagnosis and in instituting the appropriate therapy for these patients. To test these hypotheses, a retrospective study was designed to critically review the medical records of all cases of cystic fibrosis diagnosed in Sulmanyia Medical Center since 1978.

Materials and Methods

From January 1978 to December 1995, 30 patients were diagnosed to have cystic fibrosis and were followed in Sulmaniya Medical Center (SMC). Patients were identified through an extensive computer search of Ministry of Health database and department of pediatrics records. Five of these cases were excluded from the analysis because sweat chloride test was either not available or normal. Three of them are siblings of...
documented cases of CF, thus they are included in the calculation of incidence, but excluded from the rest of the analysis due to either lack of or incomplete records. The fourth patient, had failure to thrive, chronic diarrhoea, and chronic lung disease with the isolation of Pseudomonas aeruginosa from deep tracheal aspirate. Sweat chloride test (done twice) and tryptic activity were normal. The fifth excluded patient was a Saudi child diagnosed in Saudi Arabia and admitted to SMC once only during a visit to Bahrain.

The records of all patients were reviewed and the following information was collected: age at presentation, age at diagnosis, sweat chloride test results, tryptic activity, ethnic origin, consanguinity, presentation, complications, deep tracheal aspirate, throat swab, and sputum culture results, use of bronchodilators, use of chest physiotherapy, and the use of appropriate anti-microbial therapy for Pseudomonas aeruginosa and Staphylococcus aureus. The appropriateness of anti-microbial therapy was judged based on the guidelines given in the memorandum of the joint WHO/ICF(M) meeting on therapeutic approaches to cystic fibrosis. The sweat chloride determination is done by using the quantitative pilocarpine iontophoresis method.

The incidence of CF was calculated independently for each year from the ratio of the number of CF cases to the total number of Bahraini live births for each year. The incidence of cystic fibrosis in Bahrain is one case/5800 Bahraini live births, and the prevalence is three cases/100,000 population.

Most cases are residents from northern villages and Sitra, and their ethnic origin is Bahraini except for three cases: two are of Persian and the third of Syrian origin. Eight out of the 25 cases (32 per cent) are from Sitra village, 9/25 cases (36 per cent) are from the northern area villages, and 4/25 cases (16 per cent) are from the middle region. Consanguinity was documented in 20/25 cases (80 per cent). Family history of cystic fibrosis is confirmed in 11/25 (44 per cent), and suspected in 6/25 (24 per cent).

A sweat chloride test was done 2–3 times in each case. The mean ± SD (μmol/l) for the three readings are 95 ± 38, 100 ± 47, and 76 ± 48. At presentation, tryptic activity was 1/100 or below in 75 per cent of the cases. By 1 year of age all the study patients developed pancreatic insufficiency.

Patients presented with the typical manifestations of cystic fibrosis at a mean age of 2 ± 1 months and a range from birth to 5 months. Diagnosis is made for all cases at a mean age of 4 ± 1 months, with a range from birth to 9 months.

Presentation and complications in the 25 cases are shown in Figs 1 and 2, respectively. Deep tracheal aspirate or throat or sputum culture is done in 16/25 cases (64 per cent). Pseudomonas aeruginosa is isolated in 13/16 cases (81 per cent), Klebsiella is isolated in 9/16 cases (56 per cent), Staphylococcus aureus is isolated in 5/16 (31 per cent), and other organisms in 10/16 (62 per cent).

Appropriate anti-pseudomonas therapy is used in 12/13 (92 per cent) cases in whom pseudomonas had been isolated and in three other cases who had no deep tracheal aspirate done, making the total of 15/25 cases (60 per cent) who received appropriate anti-pseudomonas therapy at a mean age of 1 year 8 months and a range of 1 month to 8 years.
Appropriate anti-staphylococcus therapy was used in the five cases with a positive culture and in 23/25 (92 per cent) cases at a mean age of 6 months, and a range of 1 month to 3 years. Pancreatic enzyme replacement was given in 20/23 (91 per cent) cases at an average age of 8 months, there is 4 months lag from the mean age of diagnosis. Predigested, protein hydrolyzed formula was used in 9/25 (36 per cent) cases at a mean age of 5 months. Chest physiotherapy was used in 21/25 (84 per cent) cases. Bronchodilators were used in 16/25 (64 per cent) cases. The cause of death in all deceased patients was respiratory failure due to progressive lung disease and failure to thrive. Age specific mortality in first year of life was 80 per cent from 1981 to 1985, which dropped to 50 per cent from 1986 to 1990, then to 9 per cent from 1991 to 1995. Corresponding infant mortality is shown in Table 1.

Discussion
SMC is the main referral centre on the island; most patients requiring secondary and tertiary care are referred from the 21 health centres which provide primary care. Cases are also referred from private clinics and hospitals. Sweat chloride test is done in SMC only; hence, all cases with suspected cystic fibrosis are referred to this centre.

Despite the fact that the vast majority of children with CF are referred to SMC and the chance of missing a case is small, there is still some concern about biases resulting from selective pattern of referrals which may result in under reporting. Keeping these limitations in mind, we can conclude that the incidence of CF in Bahrain is at least 1/5800 live births and the prevalence is at least 3/100,000 population.

This incidence is two times less than other populations with high CF incidence such as the United Kingdom, where the incidence is 1/2475 populations, and USA where the incidence is 1/3500 live white births, but more than the incidence among Afro-Americans where the incidence is 1/17000. Although, CF has been reported in many Arab countries such as Lebanon, Iraq, Jordan, Syria, Kuwait, Saudi Arabia, and United Arab Emirates, the exact incidence of CF is still unknown. A recent neonatal screening study from

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**Table 1**

*The incidence and age specific mortality in CF cases*

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<tr>
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<tbody>
<tr>
<td>Mean number of</td>
<td>8428.4</td>
<td>9818.6</td>
<td>10034.8</td>
</tr>
<tr>
<td>registered Bahraini live births</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of CF cases</td>
<td>9</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>(mean/year)</td>
<td>(1.8)</td>
<td>(1.2)</td>
<td>(2.2)</td>
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<tr>
<td>Incidence of CF</td>
<td>1/4682</td>
<td>1/8181</td>
<td>1/4561</td>
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<tr>
<td>cases</td>
<td></td>
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<tr>
<td>Age specific mortality in first yr of life for CF</td>
<td>80%</td>
<td>50%</td>
<td>9%</td>
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<tr>
<td>Mean infant mortality rate in Bahrain/1000 live births</td>
<td>22.5</td>
<td>20.7</td>
<td>20</td>
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Jordan has reported an incidence of 1/2560 live birth, this is similar to the incidence in many countries in the West. This is contrary to the long held belief that CF is a rare disease in Jordan. This emphasizes the need for neonatal screening studies throughout the region to identify the true incidence of CF and the type(s) of genetic mutations.

Consanguineous marriage is a common practice in Bahrain and is recorded in 39 per cent (23 per cent first cousins) of marriages in Bahrain. In this study, consanguineous marriage has been documented in 80 per cent of the study patients. This is double the rate among the general population, showing once again the impact of consanguineous marriage on the incidence of autosomal recessive disorders.

High mortality in CF can be the result of a phenotypically and genotypically severe disease or delay to diagnosis and inadequate or inappropriate therapy. Severity of CF can be inferred from several clinical observations: (1) age of presentation and diagnosis, the earlier the more severe; (2) development of pancreatic insufficiency at an early age; (3) occurrence of meconium ileus; (4) early progression of the pulmonary disease and early colonization with pseudomonas.

In this study, the clinical indicators of disease severity are reflected in several observations. First, an early age of presentation at a mean age of 2 ± 1 months, and by 5 months of age all of the patients presented with one or more symptoms of CF. Age of diagnosis did not lag behind significantly, it was done at a mean age of 4 ± 1 months, and by 9 months of age all of the study patients were diagnosed as definite cases of CF. This is a very early age of presentation and diagnosis. In 1990, in the USA, the mean age of CF diagnosis was 2.9 years, 70 per cent only were diagnosed by 1 year of age while in this study all were diagnosed by 9 months of age. In another USA study, the mean delay of CF diagnosis was 16 ± 31 months for whites and 34 ± 40 months for blacks. Therefore, we cannot attribute poor outcome in Bahraini CF patients to delay in diagnosis. Some reports indicated that poor outcome of CF patients in the 'developing countries' is due to the frequent diarrheal and respiratory infections. This certainly cannot be applied to Bahraini children who live in an area where the incidence of infectious diarrhea is low. This is supported by the fact that 84 per cent of all patients were diagnosed as definite cases of CF. This is a very early age of presentation and diagnosis. In 1990, in the USA, the mean age of CF diagnosis was 2.9 years, 70 per cent only were diagnosed by 1 year of age while in this study all were diagnosed by 9 months of age. In another USA study, the mean delay of CF diagnosis was 16 ± 31 months for whites and 34 ± 40 months for blacks.

In conclusion, CF is not a rare disease in Bahrain. Bahraini CF patients have a phenotypically severe disease which is characterized by an early age of presentation at a mean age of 2 ± 1 months. Although the mean age of diagnosis was 4 ± 1 months, all of the patients presented with one or more symptoms of CF at an early age. However, the most likely explanation to the reduction in mortality is the improved living standards and medical care for the population of Bahrain in general. However, infant mortality which is a major indicator of the health status of the nation's children did not show such a sharp decline. Infant mortality was 22.5, 20.7, and 20 per 1000 live births for the three study stages, respectively.

Thus, the most likely explanation to the reduction of mortality in this group of patients is increased awareness among medical professionals about CF and better management of cases.

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presentation, severe lung disease with early Pseudomonas colonization, pancreatic insufficiency in first year of life in all patients, and failure to thrive at an early age in the vast majority. In addition, improved management has contributed to significant reduction in mortality during infancy. Whether this improvement in survival in the first year of life would be associated with substantial improvement in long-term outcome and quality of life remains to be seen. Finally, there is a need for identification of the true incidence and the type of genetic mutation(s) of cystic fibrosis in the region.

References