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Original Article

Genetic and Clinical Demographics of Adult Cystic Fibrosis Patients in a Middle Eastern Population

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Abstract

OBJECTIVE: Cystic fibrosis (CF) is the commonest life-limiting inherited illness in the Caucasian population but is uncommon in the Middle East, and so the genotypes and clinical course of disease in this population is not well known.

MATERIAL AND METHODS: In this retrospective observational study, we collected and reviewed the data on CF mutations, body mass index (BMI), lung function, microbiology, and the demographics in adult CF patients in the United Arab Emirates (UAE).

RESULTS: Data was reviewed for 39 adult CF patients. The median age of adult CF patients presenting to our clinic was 25 years (interquartile range (IQR) 22-31), the median BMI was 19 (IQR 17-22), and the median percentage predicted forced expiratory volume at 1 second (FEV1) was 49.5% (IQR 38.5-62.5). S549R was the commonest mutation (n = 11, 28%) followed by ΔF508 (n = 9, 23%). Only 5 (13%) out of 39 patients were heterozygote for CF mutations which reflects the high level of consanguinity in the region. Twelve (30%) patients were diagnosed after the age of 16, and in total, 19 (48%) were diagnosed after the age of 10. Thirty-two (82%) of patients are pseudomonas colonized, and 31% had 3 or more exacerbations in the last 12 months.

CONCLUSION: The CF mutation patterns in the UAE are different from western populations with low ΔF508 prevalence, with the presence of rare mutations more specific to this region and a high rate of homozygosity. Late diagnosis, high pseudomonas colonization rate, and exacerbation frequency remain a problem in this region and lead to poor long-term outcomes.

KEYWORDS: Cystic fibrosis, bronchiectasis, clinical epidemiology, rare lung diseases, pediatric lung disease
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INTRODUCTION

Cystic fibrosis (CF) is the commonest inherited life-limiting illness among the Caucasian population[1] and is caused by mutations in the gene of CF transmembrane conductance regulator protein, located on the long arm of chromosome 7. The commonest known disease-causing mutation is ΔF508 which is reported in around 89% of patients in the United Kingdom (UK).[2] CF is thought to be an uncommon disease in the Middle East and the first case report of CF in this region was published in 1958 in a Lebanese child[3] while the first reported case in UAE was in 1991.[4] The estimated incidence of CF in UAE is thought to be around 1 in 15 000 live births.[5] Unlike the western populations with well-established disease databases providing accurate incidence and prevalence data, the incidence estimates in the Middle East are deduced mostly from published case reports and hence are likely to be less accurate.

CF is a multisystem disease, with the most common cause of mortality being progressive bronchiectasis leading to chronic respiratory failure.[6] CF survival has continued to improve in the western countries[7] due to improvement in care provision and the advent of new treatment modalities, resulting in there being more adult CF patients than children. Although survival in middle eastern patients also seems to have improved, it has lagged significantly as compared to western nations; hence the adult CF patients in this region remain a minority. There have been few publications looking at the genetic and clinical parameters of CF patients in the UAE, and no published data on adult patients in this region is available. This lack of genetic and clinical demographic data makes it difficult to make long-term decisions about CF service development and clinical care. Moreover, the genetic mutations common in middle eastern patients are often different from the common mutations in the Caucasian populations and can vary significantly even within the various gulf countries.[8] In this study, we present the CF mutation patterns and clinical parameters in the indigenous UAE adult population.

MATERIAL AND METHODS

This retrospective study was conducted at our adult pulmonary medicine department; the CF clinic here was established in 2015 and looks after almost all indigenous adult CF patients in the UAE. Approval from the local research ethics committee was obtained. All adult patients with the diagnosis of CF who attended our service between April 2015 and June 2019 were included in the study. The CF mutations testing was done by using a 97-mutation panel (Cystic Fibrosis Profile, 97 Mutations,

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CF*plus*®) initially, followed by full gene sequencing if the initial panel was negative and was carried out by Labcorp USA. Data were collected from the patient's electronic medical records, and it included the results of CF mutation testing, forced expiratory volume at 1 second (FEV1), body mass index (BMI), exacerbation frequency in the last 1 year, sputum microbiology, and extra-pulmonary manifestations. To account for the variability in FEV1 and BMI due to exacerbations, only the best-recorded values in the last 12 months were gathered for these 2 parameters. We also collected quality of life data using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Teen/Adult version, with 50 items divided into 12 domains (respiratory symptoms, physical functioning, treatment burden, social functioning, emotional functioning, eating problems, body image, digestive symptoms, role functioning, vitality, weight, and health perceptions) that was designed for patients aged ≥ 14 years. Only the responses recorded within the last 12 months were included in the study.

Statistical analysis was performed using Microsoft Excel 2019 for Windows software (with Real Statistics resource pack add-in). Data are expressed as the median and interquartile range (IQR). Normality of distribution was assessed using the Shapiro–Wilk test. Proportions were used as descriptive statistics for categorical variables. Comparisons of values between groups were performed by using Mann–Whitney *U* test for non-normally distributed data, and $P < .05$ was considered statistically significant.

RESULTS

Data was reviewed for 39 adult CF patients (21 males, 18 females). The median age of adult CF patients presenting to our clinic was 25 years (IQR 22-31), the median BMI was 19 (IQR 17-22), and the median percentage predicted FEV1 was 49.5% (IQR 38.5-62.5) (Tables 1 and 2).

Figure 1 shows the mutations that were noted in our cohort. S549R mutation had the highest population frequency with 11 patients (28%) having at least 1 copy of it (10 homozygotes, 1 heterozygote) followed by ΔF508, which was present in 9 (23%) patients (8 homozygotes and 1 heterozygote). 3849+10 kbC>T mutation was also present in 9 patients but with more heterozygotes (5 homozygotes and 4 heterozygotes). We did not find any significant difference in terms of age, BMI, and FEV1 between the ΔF508 and non-ΔF508 mutation carriers (Table 2). Most patients were homozygotes for the CF mutations, and only 6 (15%) out of our 39 patients were heterozygotes.

MAIN POINTS

- The CF is an uncommon disease in the Middle East and the mutation patterns in this population differ considerably from the Caucasian populations.
- Consanguinity leads to higher levels of homozygosity in this region.
- The clinical outcomes, although improving, have lagged significantly compared to developed western countries likely due to late diagnosis, high rates of pseudomonas colonization, and exacerbation rates.

Table 1. Baseline Characteristics of the Study Population

	n
Total	39
Males	21 (54%)
Females	18 (46%)
Comorbidities	
Pancreatic insufficiency	32 (82%)
CFRD	16 (41%)
CFRLD	6 (15%)
CFRBD	16 (41%)
Sinus disease	20 (51%)
ABPA	6 (15%)
Depression	3 (8%)
DIOS	0
Exacerbation frequency, *wp*/year	
0	12 (31%)
1	6 (15%)
2	9 (23%)
	12 (31%)

BMI, body mass index; FEV1, forced expiratory volume in the first second; CFRD, cystic fibrosis-related diabetes; CFRLD, cystic fibrosis-related liver disease; CFRBD, cystic fibrosis-related bone disease; ABPA, allergic bronchopulmonary aspergillosis; DIOS, distal intestinal obstruction syndrome.

Twelve (30%) patients were diagnosed after the age of 16, and in total, 19 (48%) were diagnosed after the age of 10. On review of microbiology results, 32 (82%) patients were found to be pseudomonas colonized, and methicillin-sensitive *Staphylococcus aureus* was the second most common colonizing organism (13 patients—33%) (Figure 2). The average exacerbation rate over the last 12 months was 1.74/patient, with 31% of the patients having 3 or more exacerbations in that period (Table 1).

Among the extra-pulmonary manifestations of the disease, pancreatic insufficiency was the commonest (82% of the patients) followed by symptomatic sinus disease (51%). CF-related diabetes (CFRD) and CF-related bone disease (CFRBD) were both present in 41% of the patients. Depression was reported by only 8%, and there were no cases of distal intestinal obstruction syndrome (DIOS) in our cohort. (Table 1).

Unfortunately, only 11 patients had completed the CFQ-R questionnaire in the last 12 months. The median scores for each domain of the questionnaire are listed in Table 3 in ascending order highlighting the respiratory, physical functioning, and treatment burden as the areas with the highest impact on the quality of life.

DISCUSSION

CF is an uncommon disease in the UAE, and there is a paucity of published data on the demographics of CF patients in the region. In this study, we present the genetic and clinical

Table 2. Clinical Characteristics of ΔF508 Versus Non-ΔF508 Mutation Patients

	All Patients	ΔF508	Non-ΔF508		
	Median (IQR)	Median (IQR)	Median (IQR)	Mann–Whitney *U* test	*P*
Age-years	25 (22-31)	27 (22-30)	26 (22-32)	134	.98
BMI-kg/m^2	19 (17-22)	19.2 (17-20)	20 (17-22)	109	.40
FEV1-% Predicted	49.5 (38.5-62.5)	52.3 (39-56)	47.3 (36-65)	119	.82

BMI, body mass index; FEV1, forced expiratory volume at 1 second.

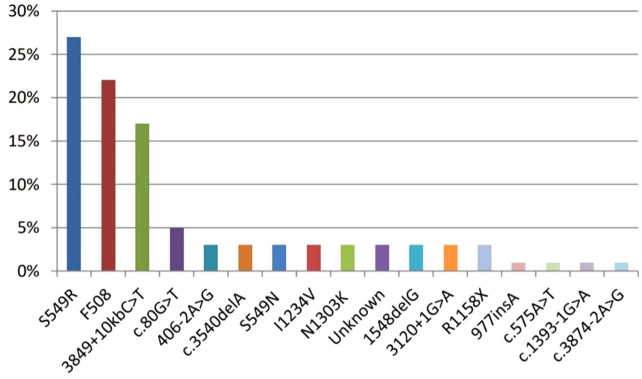

Figure 1. Population frequency of CF mutations.

demographics of adult CF patients in the UAE, and below, we also compare our results to the CF Trust UK data to highlight the differences among the 2 populations.

FEV1 and BMI are important predictors of survival in CF[9] and in our study population, we found these to be significantly lower than expected. To illustrate the point, we compare our results with the data from the UK CF trust's 2018 report.[2] Although our population is younger than the adult UK cohort, the median BMI for our patients was significantly lower (19 vs. 23.1).

Similarly, the percentage predicted FEV1 also was lower in our patients (49.5% vs. 71.1%). We also encountered a higher prevalence of chronic pseudomonas colonization in our patient population (32 patients 82% vs. 41.4% colonization in the adult UK population). Chronic pseudomonas colonization is associated with increased disease severity due to a higher exacerbation frequency and a decline in lung function.[10] About one-third of the patients in our study had 3 or more exacerbations in the last 12 months which is at least partly due to the high pseudomonas colonization rate. Low FEV1 and BMI along with high pseudomonas colonization and exacerbation frequency highlight that the long-term prognosis of our cohort is likely to be worse than comparable patient cohorts in developed countries.

The only previously published data on CF genetics in the UAE was from Frossard et al. in 1998 who reported the genetic mutations of 16 CF patients and observed that all patients of Bedouin origin were homozygote for S549R (9 patients) while the patients of Al Balushi origin (7 patients) were ΔF508 homozygotes.[11] We found a similar trend in our data as S549R was the commonest mutation followed by ΔF508, but we also discovered a significant number of patients with 3849+10 kbC>T mutation and several other less common or rare mutations. The presence of rare mutations and the lower incidence of ΔF508 mutation means that the common genetic mutation panels that test for a smaller number of common mutations are likely to be less useful in diagnosing CF in this region; therefore, if the clinical suspicion for CF is high, then one should have a low threshold for utilizing full

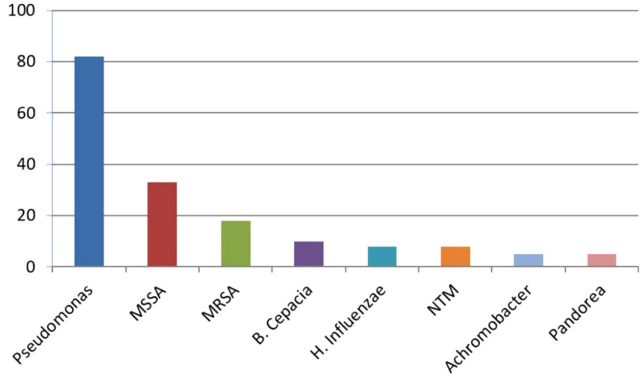

Figure 2. Prevalence of bacterial colonization.

Table 3. CFQ-R Scores of the Study Population

CFQ-R Domains	Median Score (IQR)
Respiratory symptoms	44.4 (36.1-69.5)
Physical functioning	54.2 (41.7-62.5)
Treatment burden	55.6 (50-72.2)
Social functioning	61.1 (52.8-69.5)
Vitality	66.7 (41.7-75)
Role functioning	66.7 (62.5-75)
Weight	66.7 (51.7-71.7)
Emotional functioning	73.3 (43.3-90)
Eating problems	77.8 (66.7-88.9)
Health perceptions	77.8 (44.4-94.4)
Body image	77.8 (55.6-77.8)
Digestive symptoms	88.9 (83.3-100)

gene sequencing. We also found a high level of homozygosity for CF mutations in our cohort, which is likely due to the high level of consanguinity and intertribal marriages.

CF in the UAE is often diagnosed late, with many patients presenting in adulthood with established severe respiratory failure. Late diagnosis of CF is not unusual even in the developed western countries with well-established CF care networks, and according to the UK data report, 8.5% of the patients in the registry were diagnosed aged 16 or over.[2] In a retrospective review of the University of Colorado, the adult CF clinic database showed that the late diagnosis in their cohort represented a unique patient population with significantly better FEV1 and lower prevalence of ΔF508 homozygosity, CFRD, and pseudomonas colonization rates compared to the patients diagnosed earlier in life.[12] Hence, the late diagnosis group in this study was a population of patients with a milder or non-classical form of CF. Unfortunately, we found that the experience of late diagnosis of CF in the UAE is not the same, as patients diagnosed in adulthood or adolescence have classical CF with advanced lung disease. The low disease incidence leading to lack of awareness of the disease among the population and the care providers, presence of rare mutations in the population, scarcity of centers with adequate diagnostic facilities all contribute to the late diagnosis in this region, leading to missed opportunities in preserving lung function and quality of life. The late diagnosis problem highlights the pressing need for the development and implementation of a neonatal screening program in the country. Neonatal screening involves the measurement of immunoreactive trypsinogen in blood, and if positive, then move on to genetic testing for common CF mutations. In UK neonatal screening guidelines, the initial mutation testing panel recommended includes ΔF508, G551D, G542X, and 621+1G>T.[13] The mutation data presented in our study shows that using the UK CF screening protocols in UAE will miss most of the CF patients in UAE as the ΔF508 is not the commonest mutation here and the other 3 mutations included in the initial genetic testing panel are not reported in this region at all. We hope that our study will help in choosing more region-specific mutation testing to be included in any future guidelines for neonatal screening. The true incidence of the disease is probably underestimated in the UAE, likely due to all the factors discussed above that lead to late diagnosis. Also, it is possible that some patients with severe illness may be dying without establishing the diagnosis while others with non-classical/mild CF may not get diagnosed till very late in adult life.

The prevalence of common CF-related comorbidities such as pancreatic insufficiency, CFRD, CF-related liver disease (CFRLD), and CFRBD in our study seems to be similar to the western populations. Perhaps the 2 notable differences in terms of comorbidities were the low levels of depression and DIOS. There were no cases of DIOS in our CF population which could be due to low ΔF508 prevalence. This lower prevalence of gastrointestinal symptoms was also reflected in the CFQ-R scores, with a high median score for the digestive symptom domain. Depression was reported by only 8%, which is probably a gross underrepresentation of the problem as patients often fail to report or admit to such symptoms due to the stigma associated with the psychiatric disease. We also find that reluctance to talk about psychological issues is also partly responsible for the lower number of patients agreeing to return the CFQ-R questionnaires. Although a lower number of patients completed the CFQ-R, it is unsurprising that the respiratory symptoms seem to have the highest impact on the quality of life closely followed by the physical disability and the treatment burden.

Although it is useful to try and define the demographics of CF in the UAE, the retrospective observational nature of our study introduces certain limitations, out of which perhaps the most important is survivorship bias. Our study population includes only adults; hence it is possible that some patients with mutations associated with severe disease phenotypes may have died before transitioning to adult care, leaving a higher proportion of patients with mutations with milder disease phenotypes. Such a bias could result in the under-representation of class I and II mutations, including ΔF508. Since the pediatric CF population in the country is significantly larger, it would be useful to include all the CF patients in any future analysis to reduce the risk of bias and to improve the data accuracy. The development of a national or regional CF registry will be of paramount importance in conducting future epidemiological studies.

In conclusion, CF is an uncommon and under-recognized disease in the UAE and among the adult patients, the prognosis seems to be significantly worse due to lower FEV1 and BMI as compared to their counterparts in the UK. This has been the largest cohort analysis of the CF patients in the country and also highlights other important observations. First, the CF mutation patterns in the UAE are different from western populations with low ΔF508 prevalence, presence of rare mutations more specific to this region, and a high rate of homozygosis due to consanguinity. Late diagnosis remains

a problem in the region and, along with high pseudomonas colonization rate and exacerbation frequency, lead to poor long-term outcomes.

Ethics Committee Approval: This study was approved by the Cleveland Clinic Abu Dhabi research ethics committee on 26 June 2018, (Protocol no. A-2018-024).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Supervision – I.S.,S.S., A.S.W.; Design – I.S.,S.S., M.H.U., Z.Z., M.A.; Resources – I.S., Z.Z., A.S.W.; Materials – I.S., A.S.W., M.H.U., S.S., M.A.; Data Collection and/or Processing – M.H.U., Z.Z., S.S.; Analysis and/or Interpretation – I.S., A.S.W., S.S., M.A.; Literature Search – Z.Z., M.H.U.; Writing Manuscript – I.S., S.S., A.S.W.; Critical Review – A.S.W., M.A., Z.Z.

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