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Clinical, paraclinical, and genetic profile of patients with cystic fibrosis from Colombian Caribbean

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ABSTRACT

Background: Cystic fibrosis (CF) is a serious autosomal recessive disorder. Early diagnosis, comorbidity prevention, and control are cornerstones for a quality life and for improving life expectancy. In Colombian Caribbean, where there is a genetically admixed population, CF is an orphan disease affecting children and adults, and it remains a challenging issue to be addressed carefully. This work describes the genetic, clinical, and paraclinical profiles of CF patients from Cartagena de Indias, Colombia.

Methods: Thirty-six patients were included in the study. The subjects were identified and evaluated through the Regional Program for CF patients. CFTR gene mutations, anthropometric parameters, microbiological infections, and pulmonary function were analyzed. Data on demographic parameters, pharmacological treatments, and comorbidities were reported. Frequency and percentages were established for the categorical variables and mean or median for the quantitative variables. In addition, comparisons were made by sex.

Results: The average age of the patients was 11.9 ± 5.3 years and the median age at diagnosis was 14 months. 55.5% were women and 44.5% were men. The mean values for weight, height, and body mass index were 35 ± 17.6 kg, 139.9 ± 28 cm, and 16.5 ± 2.9 kg/m^2, respectively. The clinical manifestations that occurred more frequently were steatorrhea (65.4%) and recurrent pneumonia (46.2%). Chronic airway infection with *Pseudomonas aeruginosa* was identified in 71.4% of the cases and the p.F508del mutation was found in 47.2% of the subjects.

Conclusion: The current profile of CF patients from the Colombian Caribbean showed some concerning features, such as nutritional status; however, progress in early diagnosis and clinical follow-up could contribute to improve the general conditions of patients. It is necessary to continue efforts to increase the life expectancy and quality of life of the patients.

1. Introduction

Cystic fibrosis (CF) is a common autosomal recessive disease within populations of European ancestry, with a frequency of 1/2000–3500 newborns [1]. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, located at

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7q31.2. Mutations in this gene usually cause alterations in ionic transmembrane transportation, resulting in viscous epithelial secretions that accumulate in the airway and gastrointestinal tracts. Typically, viscous secretions are successively colonized by opportunistic microorganisms, mainly *Pseudomonas aeruginosa*, leading to life-threatening pulmonary and nutritional deterioration [2,3].

Currently, more than 2000 disease-related mutations have been registered in the Cystic Fibrosis Genetic Analysis Consortium, classified into six classes depending on their effects on *CFTR* expression and protein function. Class I, II, and III variants are known as minimal function variants because they demonstrate little or no CFTR function, and they are therefore usually associated with more severe disease, while class IV, V, and VI variants are related to milder phenotypes, since CFTR is expressed in the cell membrane with residual activity [3,4].

Initially, CF was cataloged as a pediatric disease, linked to a shortened life expectancy and poor quality of life due to recurrent pulmonary and multi-systemic complications; however, this landscape has dramatically changed in the last four decades. In most high-income countries with European ancestry, multidisciplinary efforts have led to improvements in genetic counseling, early diagnosis protocols, and clinical approaches. Consequently, comorbidity severity has reduced, while life span has progressively increased. In fact, by 2005, more than 35% of CF patients were found to be over 18 years of age. In the United States, survival increased from mid-teens in the 1970s to a span of 36–50 years [1].

In populations with African, Asian, and admixed ancestry, CF occurs less frequently; therefore, investments in research and attention have been modest (with some notable exceptions). In Latin America, since genetic heterogeneity is a widespread pattern, CF prevalence is highly population-specific, with frequencies as high as 1/4000 in Chile, 1/5000 in Cuba, 1/7576 in Brazil, 1/9600 in Uruguay, and 1/11252 in Ecuador [5–9]. In Colombia, a total of 3145 patients with CF were estimated, with a frequency of 78 cases per year, according to the data obtained from other countries and the National Administrative Department of Statistics (DANE, *Departamento Administrativo Nacional de Estadísticas*) [10].

The mutations present in the CFTR gene vary significantly between different populations [11]. The most frequently described mutation for the disease is the p.F508del mutation, which is a class II mutation; its frequency depends on geographic and ethnic variations. In Latin America, the frequency reported for this mutation is 46.7% [12]. In Colombia, the frequency reported by some studies is 41.8% [11,12].

In Cartagena de Indias, on the Colombian Caribbean Coast, one of the largest Colombian group of patients with CF has been previously identified [10,13,14]. A record of these patients has been developed by the Foundation for Patients with CF and their Families (YURANIS foundation http://www.fundacionyuranis.entercol.com.), supported by the "Comprehensive Care Program for patients with CF and their families" designed by the UNIMOL research group at the University of Cartagena. Although preliminary reports have been published and marked progression in early diagnosis and treatment has been reached in the last decade [10,13–15], a comprehensive description is still lacking, and most relevant clinical features are little known. Thus, this study was aimed at describing the genetic, clinical, and paraclinical profiles of patients with CF from the Colombian Caribbean population.

2. Materials and methods

2.1. Patients

A descriptive study was performed in 36 patients with a confirmed diagnosis of CF, included in the "Comprehensive Care Program for patients with CF and their families." These patients were enrolled through public and private pediatric consultation services in Cartagena de Indias, Colombia. About 95% patients had clinical features suggestive of CF with positive sweat test results (>60 mM/L). Informed consent was evaluated and approved by the Ethics Committee of the University of Cartagena. Written informed assent or consent was requested from all participants and their parents.

2.2. Clinical profile

Clinical symptoms were documented from medical records after pediatric consultations. Suggestive signs and manifestations were observed during a physical examination. Height was measured using a fixed stadiometer with the patient standing, and weight was measured using a digital scale with the patient wearing light clothing and no shoes. Anthropometric data, including body mass index (BMI), were calculated to determine nutritional status, taking into account the recommendations suggested by the World Health Organization [16]. Finally, the obtained indexes were expressed as Z-Scores for a specific age and gender.

2.3. Paraclinical profile

Sputum samples were collected for microbiological analysis. Pulmonary function was measured by trained physicians using a spirometer (Pneumos 300, H&C SPA, Italy). Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FCV) were obtained in accordance with technical specifications published by the American Thoracic Society and the European Respiratory Society [17]. Procedures were performed on stiff chairs, with no wheels, in rooms with adequate ventilation and stable temperature, and patients were asked to make themselves comfortable before and during the test.

2.4. Mutation analysis

Peripheral venous blood samples were collected. Nucleic acid extraction was performed according to standard procedures using a DNA extraction kit (Wizard ® Genomic DNA Purification Kit, Promega, USA). CFTR gene mutations were determined in collaboration with the Laboratory of Human Genetics of the University Medical Center Hadassah EinKerem (Jerusalem, Israel). Each sample was tested for the following mutations: p.F508del, p.W1282X, p.G542X, p.N1303K, 3849 + 10kbC > T, 1717-1G > A, 405+1G > T, p.S549RT > G, p.W1089X, p.Y1092X, p.G85E, c.4010del4, p.R75X, c.2183AA > G, c.3120+1G > A, c.C225X, EX2del, c.1677delTA, and p.E92X.

2.5. Data analysis

To describe the population, measures of central tendency were used. The averages among populations of men and women were compared using the Student's t-test, and the medians were compared using the Mann-Whitney *U* test. Categorical variables were described as frequencies. Confidence intervals were set at 95% and were considered significant at $p < 0.05$. Statistical analysis of the data was performed using R program 3.1.0.

3. Results

A total of 36 patients were included in the study, of whom 55.5% were women and 44.5% were men. Of the total, 26 had anthropometric and clinical data, with ages ranging from 3 to 20 years. The clinical characteristics of these 26 patients are shown in Table 1.

3.1. Clinical profile

The clinical manifestations that occurred more frequently were steatorrhea and recurrent pneumonia. The frequencies of clinical features are described in Table 2.

Regarding nutritional status, 15.4% (n = 4) of patients presented a marked alteration in height, established by a Z-score value of length/height-for-age below −2 SD. Additionally, 15.4% (n = 4) of the population had abnormal BMI values, with 3 patients being under the age of 18 years with a value standard below −2, and one patient being over the age of 18 years, with a BMI value of 14.2 kg/m^2.

Mucolitiques were used by 100% of patients. A total of 80.8% (n = 21) of patients were using pancreatic enzymes, while antibiotics were being utilized by 76.9% of patients (42.2%, nebulized antibiotics). Bronchodilators, inhaled steroids, and vitamin E were also being used by 65.4% (n = 17), 19.2% (n = 5), and 7.7% (n = 2) of patients, respectively.

Among the reported complications in the patients were gastritis, gallstones, hepatobiliary abnormalities, otitis media, diabetes, atelectasis, depression, fatty liver, bronchiectasis, and nasal polyposis.

3.2. Paraclinical profile

In total, 21 patients (80.8%) underwent microbiological studies. In this group, *Pseudomonas aeruginosa* was the most frequently detected microorganism, being present in 71.4% (n = 15) of the individuals, followed by bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, which were both found in 19% (n = 4) of the population, and *Kleibsiella* sp., which was present in 14.3% (n = 3) of the patients. Some patients also presented with less frequent infections by other microorganisms such as *Enterobacter coaclae*, *Branhamella catarrhalis*, *Streptococcus viridans*, and *Escherichia coli*.

Of all patients, 16 underwent respiratory function tests (spirometry), of which 68.8% (n = 11) had FEV_1 >50%, 6.2% (n = 1) had FEV_1 between 50% and 35%, and 25% (n = 4) had FEV_1 below 35%. The overall mean FEV1% was 79% (±28.5).

3.3. Mutations

The mutation that was detected most frequently in the entire study population was p.F508del, found in 47.2% (n = 17) of the

Table 1
Characteristics of patients.

	All n = 26	Male n = 11	Female n = 15	*p-value*
Age (years)	11.9 (±5.3)	10.3 (±5.7)	11.8 (±5.0)	0.3663
Weight (kg)	35 (±17.6)	40.8 (±19,5)	27.1 (±12.9)	0.0414
Height (cm)	139.9 (±28.1)	149.2 (±26.6)	127.3 (±27.5)	0.0552
BMI (kg/m^2)	16.5 (±2.9)	17.1 (±3.3)	15.7 (±2.4)	0.2233
Age at diagnosis (months*)	14 (4.5–51.8)	17 (5.5–48)	7 (5–46.5)	0.5892
FEV1 (%)	71.5 (±28.4)	84.0 (±21.1)	50,7 (±28.0)	0.1113
Sweat test (mM/L)	54.18 (15.4)	60.0 (±0.0)	55.67 (±8.6)	0.2072

BMI: Body Mass Index, mean (±SD), *median (IQR).

Table 2
Clinical features of patients.

Clinical Manifestations	n	%
Gastrointestinal and Nutritional manifestations		
Steatorrhea – malabsorption	17	65.4
Growth failure	9	34.6
Vomiting	3	11.5
Poor appetite	1	3.8
Respiratory manifestations		
Bronchial obstructive syndrome	7	26.9
Recurrent pneumonia	12	46.2
Bronchiectasis	1	3.8
Other symptoms		
Salty-tasting skin	3	11.5
Dextrocardia	1	3.8

population. Of this, 33.3% (n = 12) patients were heterozygous for the mutation with unidentified mutations in the second allele, 5.6% (n = 2) were heterozygous with p.F508del/p.S549R mutations, and 8.3% (n = 3) were homozygous for the mutation. In total, 27.8% (n = 10) of the population had no identifiable mutations, and 25% (n = 9) showed no CF mutations.

3.4. Clinical-molecular correlation

The correlation between clinical condition and genotype of the patients could be evaluated only in patients who had complete records of medical history (n = 18). Patients who presented with the p.F508del mutation showed more severe clinical symptoms of the disease, earlier presentation of symptoms, and changes in the lungs and pancreas. Moreover, those who did not have mutations in this condition presented only one or two symptoms related to the disease.

4. Discussion

In this study, the clinical, paraclinical, and genetic profiles of patients with CF from Colombian Caribbean were described. In addition, data on demographic and anthropometric parameters, microbiological infections, functional tests, pharmacological treatments, and comorbidities were reported, bringing a wide perspective on the regional status of this disease.

The median age at diagnosis was 14 months, and the average age of diagnosis for patients was 28.4 months, which is similar to what was reported among black and white patients in the United States in 1994 (average 25.2-and 32.4-months, respectively) [18], higher than that reported in the United States and Canada between 1986 and 2013 (median 7 months for both countries) [19], slightly different from that reported in European countries, where the average age of diagnosis is approximately 12 months, and detections occur from the first month of life [20], and in contrast with Asian countries where diagnostic ages range from 42 to 120 months [21–23]. Although the mean was not essentially similar to that described in European regions, where early detection strategies are often used, this result differs from reports in national studies in which the age at diagnosis was over 44 months [10]. Regarding this variation, it is important to consider the influences that some regional organizations have exerted against this disease, which has allowed for early recognition by the medical community. It is important to note that the first diagnosis was made in some CF patients guided by the UNIMOL group. It was made in patients aged ≥7 years, indicating a considerable improvement in the recognition of the condition and visualization of the interdisciplinary work between different groups of pneumologist, parents of patients, social security services, and pharmaceutical industries, which has contributed to better care and disease control. Moreover, a possible interpretation is that many of the patients presented a severe clinical profile since the beginning of their disease, which allowed for a faster approach for the diagnosis of the condition.

The mean age in this study was 11.9 years, ranging between 2 and 20 years, and 15.4% (n = 4) of the population was over 18 years, which matches with the reported average of 12.0 years, ranging between 2 and 25 years, with only 14.8% of patients over 18 years old [10]. These observations differ from those reported in Latin America and the United States, where survival ranges were 0–79 and 0–74 years, respectively [24]. However, although in the present study, no patients were over 20 years of age, it could be expected that due to advancements in disease diagnosis and treatment, many of these patients would reach a much higher life expectancy in the future, as has been seen internationally, bringing with it the need to promote a medical community specializing in the management of adult patients with CF in the country [24].

With regard to nutritional status, we observed that 15.4% (n = 4) of patients showed alterations in height, a finding that would suggest a chronic nutritional compromise in these patients [25]. Furthermore, 15.4% of patients also showed abnormalities in BMI, wherein one of the patients over 18 years was under severe thinness classification according to the WHO guidelines [26]. Among the factors commonly associated with these findings are the presence of chronic lung disease steatorrhea-malabsorption, which has not been treated properly, meconium ileus, recurrent infections, vomiting, poor appetite, protein and nutrient loss in sputum, socioeconomic status, and quite possibly psychological stress, which are signs and symptoms present in some of the individuals in this study [10]. These data are consistent with those reported by other authors, as these symptoms usually predominate in these types of patients [21]. Findings about gastrointestinal alterations were consistent with the classical CF phenotype [21], indicating a high frequency of

steatorrhea and alterations in growth, followed by other less common symptoms such as vomiting and poor appetite [27].

Of the total population, 21 patients underwent microbiological studies. *P. aeruginosa* infection was detected in 71.4% of patients, followed by infections caused by *S. aureus* and *S. pneumoniae,* with a frequency of 19%. In this regard, Cox et al. also reported high frequency of infections caused by microorganisms such as *P. aeruginosa* (73%) and *S. aureus* (65%), and low frequency of infections caused by other microorganisms [28]. However, Bonadia et al. reported frequencies of 50% for both *P. aeruginosa* and *S. aureus* [2]. As shown in the analysis of sputum cultures reported nationally, *S. aureus* was reported as the most frequent infection-causing microorganism, present in 57% of the population, while the reported frequency for *P. aeruginosa* was 39.8%. Studies in patients with CF in the city of Cartagena found certain findings regarding the relationship between hematological profile and the presence of anemia and infection by *P. aeruginosa* [29]; in our study, this type of correlation could not be performed because no data as available on hematologic profile.

Patients with CF usually present with progressive changes in lung function. Currently, the best available predictor of survival is FEV_1 [30]. In this study, 16 patients presented a record of spirometry, of which 68.6% had an FEV_1 above 50%, considered as a mild obstruction of the airway, while 6.3% had an FEV_1 between 35% and 50%, that is, a moderate obstruction, and the remaining 25% had an FEV_1<35%, that is, a severe obstruction in the airway [31]. Vásquez et al. reported in their study a mild, moderate, and severe obstruction of airway in 23.1%, 25%, and 19.2% of patients, respectively [10]. This suggests that much of our population was found in a considerably good range, despite the fact that a certain percentage presented nutritional alterations, which is associated with low FEV_1 and FVC values [14]. Therefore, knowing the value of parameters such as FEV_1 is essential for CF patients. Some researchers have described that patients with CF and an FEV_1<30% of its predicted value have an expected 50% 2-year mortality, considering this value (FEV_1 <30%) as an oft-quoted benchmark for lung transplantation [30]. Fortunately, in this study, a small percentage was in this condition. However, it is important to continue monitoring this parameter because of the ease of variation that can occur during the course of the disease.

Drugs used for the population match those generally described for the treatment of diseases worldwide. Dornase alfa was used as a mucolytic agent in 100% of patients. Recombinant human deoxyribonuclease (rhDNase, dornase alfa, Pulmozyme) has been shown to improve lung function, reduce sputum viscosity, and the number of pulmonary exacerbations in patients with severe disease [32]. Of the patients, 76.9% used antibiotics, of which 46.2% used nebulized antibiotics, which are usually recommended when the eradication of chronic infection with *P. aeruginosa* and represent a part of standard therapy. Treatment with inhaled bronchodilators has been used as standard therapy in CF. However, in spite of not being able to determine their effectiveness, some authors suggest that short- and long-term action of beta-2 agonists can have a beneficial effect in patients in the short and long term, with a demonstrated bronchodilator response or bronchial hyperactivity [32]. Moreover, corticosteroids have no benefits in terms of lung function or sputum inflammatory markers [32]. In this study, 65.4% of CF patients received inhaled bronchodilators, and 19.2% received management with inhaled corticosteroids.

Of the total population, 80.8% (n = 21) of patients received treatment with digestive enzymes, which is consistent with the evidence supporting its routine use. Treatment with pancreatic enzymes in patients with pancreatic insufficiency is associated with an increase in the coefficient of fat absorption, a reduction in bowel movement frequency, an improvement in the consistency of feces, and weight gain [27,32]. In some studies, it has been reported that a high oxidative stress in the lungs of CF patients theoretically justified the supplementation with A and E vitamins, due to its antioxidant effects, and its important role in the immune response, for which the use of these supplements is recommended for the management of the disease [32]. In this study, more than half of the population (65.4%) used vitamin E to manage the disease. High doses of ursodeoxycholic acid seem to exert a hepatoprotective effect by increasing the transport of hydrophilic bile acids that accumulate in the cholestatic liver, stimulating bile flow; however, there is no conclusive evidence regarding its use, except in cases of cholestasis-fibrosis-cirrhosis sequence [32]. In this study, the use of ursodeoxycholic acid was not reported in any patient.

The most frequently observed mutation was p.F508del, which was present in 47.2% (n = 17) of the population. These data agree with those observed in several countries worldwide, where p.F508del also represents the most frequently described mutation, showing heterogeneous values among different places, such as 26% in Algeria, 56% in Tunisia, and 88% in Denmark [33,34]. In Latin America, a study conducted in 10 countries including Colombia reported an average frequency of 46.69%, with values ranging from 22.91% in Costa Rica to 59.15% in Argentina [12]. Nationally, some authors report frequencies between 41.8 and 54.5% [10,11], which is similar to the observations reported in this study.

Among patients who had a clinical record of their condition (n = 18), the clinical features were relatively more complex in patients with p.F508del mutation, who were diagnosed as young as 3 months old (n = 3), an age comparable to that in European countries, where strategies for early detection are often used for diagnosis [2,10]. These results agree with those of some studies linking the discovery of these mutations in a more tortuous course of the disease [2]. This suggests that the implementation of strategies that promote the beginning of neonatal screening and specific identification of this mutation in those affected may bring about an improvement in the quality of life for patients, who we might prevent from starting this type of clinical course and who could be treated with more effective therapies based on their genotype, which could, as a latter measure, be cost-effective [3,10].

The frequency of the p.S549R mutation found in this study was 5.6%. This variant is commonly described with relatively high frequencies in Middle Eastern countries, where values up to 77.3% have been recorded [35–38]. In contrast, low values (0.14%) have been reported in countries such as Ecuador, Brazil, and Argentina [12,33,37,39]. In fact, previous studies have not found this mutation in Chilean patients [40]. In Colombia, Keyeux et al. found a national rate of 2.2% in the Andean Region, 2.9% in Antioquia, and 3.9% in Bogotá [11]. In contrast, that study did not report this particular mutation in patients from the Caribbean region [11]. Therefore, this study is the first to report p.S549R mutation in the Colombian Caribbean population. This finding might be related to recent Lebanese migrations that occurred between 1880 and 1920 [41]. In fact, Middle Eastern descendants represent the fourth most common

ancestry group among this population [42], suggesting that this mutation could be introduced through Barranquilla and Cartagena harbors and spread through the northern Colombian region.

This study has several limitations in data collection, as there is no government/public register. Although private initiatives led by the YURANIS foundation (a non-profit organization where most members are CF patients and parents) have been largely successful, clinical specialized data were found to be barely standardized. To overcome this scenario, patients were encouraged to participate in this study in order to complete data; however, a complete response was difficult to obtain mainly because this group has developed some apathy for medical interventions, which is typical in patients with chronic diseases. In this sense, some data were collected during domiciliary visits using portable equipment. It is known that parents and older patients, as well as professional staff, provide psychological and social support to other patients; however, records of this activity were not available.

Despite these difficulties, the current status of CF patients in Colombian Caribbean suggests that life expectancy and quality are on their way to a significant improvement. In addition, recent application of a national law for orphan diseases attention (Law 1392 of 2010 of the Congress of the Republic of Colombia.) is expected to increase public interest in programs as those developed by the YURANIS foundation and supported by the University of Cartagena. Although routine genetic screening for CF is still lacking, early diagnosis based on clinical manifestations has been mostly achieved; thus, preventing premature *P. aeruginosa* colonization and nutritional status deterioration seems to be the most challenging issue in the near future. Finally, it is necessary to mention that these patients and their families faced the recent COVID-19 pandemic, which increased the levels of anxiety and worries in the relatives of patients with CF in the world due to the fact that viral respiratory tract infections are generally more severe in CF patients than in the rest of the population [43].

5. Conclusion

The current profile of CF patients from Colombian Caribbean showed some concerning features; however, it seems that progress in early diagnosis and clinical follow-up has contributed to improving general conditions. Since local pediatricians are aware of CF manifestations and frequency, an increase in life expectancy and quality is expected in the mid-term.

Author contribution statement

Dacia Malambo-García: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Claudio Gómez-Alegría: Conceived and designed the experiments; analyzed and interpreted the data.

Javier Baena-Del Valle: Performed the experiments; Analyzed and interpreted the data.

Maria Ruiz-Díaz, Eder Cano-Pérez: Analyzed and interpreted the data.

Doris Gómez-Camargo: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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