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ORIGINAL ARTICLE

Gastrointestinal manifestations of cystic fibrosis in children

Manifestaciones gastrointestinales en fibrosis quística en una población pediátrica

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What do we know about the subject matter of this study?

Cystic fibrosis of the pancreas is a multisystemic disease, with high morbidity and mortality, whose early diagnosis has considerably improved the management and quality of life in the long term. There is no national information about hepatic and gastrointestinal characteristics in pediatric patients.

What does this study contribute to what is already known?

This is the first description of a national experience of 4 sentinel sites in the Metropolitan Region. The diagnosis took 4 months and 5.8% of the mutations detected were not included in the gene panel used in Chile.

Abstract

Cystic fibrosis (CF) is a multisystemic disease, with high morbidity and mortality, and its early diagnosis improves results. Lung conditions are the main cause of morbidity and mortality and are closely related to nutritional status and survival. There is little national information about the liver and gastrointestinal characteristics in pediatric patients with CF. **Objective**: to describe at a gastrointestinal level, the general, nutritional, and genetic characteristics and the evolution of CF carriers with/without neonatal screening. **Patients and Method**: Retrospective study carried out in 4 public referral hospitals in the Metropolitan Region. The diagnosis of CF confirmed with two positive sweat tests (Gibson and Cooke method) was considered as an inclusion criterion. Those patients with unconfirmed neonatal screening tests through Immunoreactive Trypsinogen (IRT) or with only one positive sweat test were excluded. Sex, age, nutritional status, date of diagnosis,

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clinical presentation at the onset, evolution, and therapies received were recorded as clinical variables, and as laboratory ones, genetic study by means of a diagnostic panel with 36 mutations. The STATA 12 software was used for statistical analysis. **Results**: 127 patients were included. Respiratory manifestations (recurrent obstructive bronchial syndrome and pneumonia) were present in >60% and gastrointestinal ones (mainly malabsorption and malnutrition syndrome) in >80% of patients. On average, diagnostic confirmation took 4 months. The diagnosis guided by IRT was associated with better nutritional outcomes in the evolution of the patient. In 81.1% of the patients, the genetic study was performed. The most frequent mutations were those associated with DF508 (deletion of phenylalanine 508). 5.8% of the patients presented mutations not included in the gene panel used. **Conclusions**: Gastrointestinal CF appears with pancreatic, intestinal, and hepatic pathology throughout life. Malnutrition is a frequently present factor, which worsens the prognosis. The management of gastrointestinal manifestations and malnutrition are relevant to improve the morbidity and mortality of CF patients.

Introduction

Cystic fibrosis (CF) is the most frequent mortal genetic disease in the Caucasian population[1], with an estimated global incidence of 1/2,000 to 1/4,000 live births (LB)[2]. In Chile, the estimated incidence is 1/8,000 to 1/10,000 LB, and approximately 30 new cases are diagnosed each year[3]. Despite being a multisystemic disease with high morbidity and mortality, it has been shown that greater knowledge of its diagnosis and early management improves the prognosis[1,4].

Although pulmonary disorders are the main cause of morbidity and mortality, gastrointestinal complications are very frequent and have a great impact on the quality of life of patients, and there is a close relationship between nutritional status, pulmonary function, and survival[5].

This demonstrates how essential it is to ensure that affected patients are regularly screened, diagnosed, and followed up, maintaining strict and multidisciplinary monitoring throughout the patient's life. Undoubtedly, the role of the pediatric gastroenterologist is relevant, since she/he must routinely check for and manage the manifestations of the digestive system to ensure the best possible nutritional status. For nutritional management, the collaboration of the nutritionist is highly recommended.

Currently, there is no national information about frequency, clinical characteristics, and/or main problems presented by gastrointestinal manifestations in pediatric CF patients. In 2013, a national CF program was implemented in Sentinel Sites, so we consider it of interest to analyze the experience gained. The objective of this study was to describe, at the gastrointestinal level, the general, nutritional, genetic characteristics, and evolution of patients with/without neonatal screening.

Patients and Method

Retrospective descriptive study, based on the information from the databases of four public CF referral hospitals in Santiago. 127 patients were included who are seen at *Hospital San Juan de Dios* (HSJD), *Hospital Roberto del Río* (HRR), *Hospital Exequiel González Cortés* (HEGC), and *Hospital Clínico San Borja Arriarán* (HCSBA), from their admission to the program until October 2018.

Data on sex, age, date of diagnosis, clinical presentation at the onset, genetic study, evolution, and therapies received were recorded. The data were compiled in an Excel spreadsheet and analyzed anonymously. The information obtained was used exclusively for the purposes proposed in this research.

The protocol was approved by the ethics committees of the participating hospitals before data collection. When additional information was required and/or the clinical record was used, patients signed an informed consent form.

The inclusion criterion was that the patient had a diagnosis of CF confirmed by two positive sweat tests (Gibson Cooke method)[6]. Patients with unconfirmed neonatal screening tests by Immunoreactive Trypsinogen (IRT) or those with only one positive sweat test were excluded.

The analysis of nutritional status in patients under 6 years of age was performed by Weight/Age, Height/Age, and Weight/Height[7,8], considering the following working definitions: *Eutrophy* in children under 1 year of age as W/A between + 1 and - 1 standard deviations (SD), between 1 and 6 years of age as W/H between +1 and -1 SD and children over 6 years of age as BMI/age between + 1 and - 1 SD; *Risk of Undernutrition* is considered as W/A between -1 and -2 SD in children under 1 year, W/H between - 1 and - 2 SD in children between 1 and 6 years and in children older than 6 years a BMI/

age between -1 and - 2 SD; *Undernutrition* is defined by W/A less than - 2 SD in children under 1 year and W/H less than - 2 SD in children between 1 and 6 years and in children older than 6 years a BMI less than - 2 SD; *Overweight* is defined by W/H between + 1 and + 2 SD up to 6 years of age and in children older than 6 years a BMI/age between + 1 and + 2 SD; and *Obesity* defined as W/H greater than + 2 SD up to 6 years of age and BMI/age greater than + 2 SD in those older than 6 years.

The genetic study was performed at the *Centro de Genética Humana, Facultad de Medicina Clínica Alemana-Universidad del Desarrollo* (diagnostic panel with 36 mutations INNO-LiPA CFTR19 and INNO-LiPACFTR17 + Tn Update, Fujirebio, Europe). The STATA 12 software was used for statistical analysis.

Results

General characteristics

Between 2013-2018, information was collected from 127 patients, 61.4% (n = 78) were male. The patients were identified, diagnosed, and treated in different health care centers, which led to variation in the expression of certain results in the data analyzed. This was a limitation of this work, which was managed by unifying the criteria as far as possible, always respecting the original data, without deducing other expressions of results from the information available.

In 16/127 cases, the diagnostic suspicion was made by positive IRT at birth. The mean age at clinical onset was 1.74 years (95% CI 1.41 - 2.68; range neonate-10 years). From clinical suspicion, definitive diagnosis took 3.96 months on average, with an average age at diagnosis of 2.07 years (95% CI 1.43 - 2.63 years; range neonate-5 years).

Onset

The most frequent clinical presentation was respiratory infections and nutritional deterioration. Recurrent obstructive lung disease (OLD) (3 or more in the first year of life) and recurrent pneumonia (2 or more per year) accounted for more than 60% of the respiratory symptoms. Among the gastrointestinal manifestations, malabsorption syndrome (diarrhea/steatorrhea) with undernutrition was present in more than 80% of patients. Table 1 summarizes the clinical manifestations present at the onset.

Nutritional Status

At the time of diagnosis (coinciding with admission to the referral center), 47% of the patients presented undernutrition or were at risk of undernutrition, 5% were overweight, 3% were obese, and 45% were eutrophic.

Genetic Study

Genetic testing was performed in 103/127 patients (81.1%). There were several reasons for not performing this test in the remaining patients, most frequently due to the high cost of this test (18.9%). Among the 103 patients who underwent the study, 5.8% did not present genetic mutations of those included in the gene panel used in Chile. The most frequent mutations were the DeltaF508 heterozygosity (deletion of phenylalanine at 508 position) associated with a mutation not included in the panel (DF508/?), DF508 heterozygosity (DF508/other mutation), and the DF508 homozygosity (DF508/DF508). Table 2 details the most frequent mutations.

Follow-up and evolution

At the time of this study, the patients evaluated had an average follow-up of 8.2 years (range 3.7 months - 19.9 years) and an average age of 10.3 years (range 5.5 months - 23.5 years). Patients presented different gastrointestinal manifestations during their follow-up, most frequently pancreatic insufficiency (measured by fecal elastase-1 determination), hypertransaminasemia (defined as one or two times above the high normal value according to the laboratory), and constipation (Table 3). 15% of the patients required or had required enteral feeding with gastrostomy/ileostomy at some time during their evolution.

Role of Ultrasound

During follow-up, an abdominal ultrasound was performed in most of the patients (93%) and 42.3% showed abnormalities. The most common ultrasound findings were the presence of hepatic steatosis (14.2%), signs of chronic liver disease (8.7%), and portal hypertension (6.3%). Patients with signs of chronic liver disease on abdominal ultrasound were on average 11.1 years old (range 6-17 years).

Effect of neonatal screening by Immunoreactive Trypsinogen (IRT).

Given that neonatal screening by IRT has been performed since 2013 in some centers in our country, we analyzed separately the 38 patients with CF born since that year. Of these, 16 (42.1%) were diagnosed through screening by IRT and then confirmed, and in 22 (57.9%) the diagnosis was based on clinical suspicion. The frequency of gastrointestinal complications did not show significant differences between the two groups ($p > 0.05$). The nutritional status at the time of diagnosis and the last available checkup was analyzed; although the follow-up times were variable, it was ob-

Table 1. Clinical manifestations present at the onset of disease in 127 patients with cystic fibrosis.

Manifestations	N (%)
Gastrointestinal tract and others	
Poor weight gain	44 (34.7%)
Undernutrition	33 (26%)
Malabsorption syndrome	24 (18.9%)
Anemia	23 (18.1%)
Hypoalbuminemia	17 (13.4%)
Diarrhea	16 (12.6%)
Meconium ileus	12 (9.5%)
Edema	11 (8.7%)
Intestinal obstruction	9 (7.0%)
Cholestatic jaundice	8 (6.3%)
Dehydration (hypochloraemic hyponatraemic alkalosis)	7 (5.5%)
Rectal prolapse	3 (2.4%)
Constipation	2 (1.6%)
Meconium peritonitis	1 (0.8%)
Respiratory	
Recurrent obstructive lung disease	57 (44.9%)
Recurrent pneumonia	27 (21.3%)
Asthma	9 (7.0%)
Atelectasis	4 (3.2%)
Sinusitis	2 (1.6%)
Nasal polyps	1 (0.8%)

Table 2. Genetic testing in patients with cystic fibrosis.

Genes	N (%)
F508/?	
Not studied	24 (23.3%)
F508/Other mutation	18 (17.5%)
F508/F508	16 (15.5%)
G542X	7 (6.7%)
3849 + 10 Kb C > T	5 (4.8%)
R553X	4 (3.8%)
R334W	4 (3.8%)
c.3120 + 1G > A	3 (2.9%)
R1162X	3 (2.9%)

Table 3. Follow-up and evolution in 127 patients with cystic fibrosis.

Manifestations	N (%)
Pancreatic insufficiency	95 (74.8%)
Hypertransaminasemia	41 (32.3%)
Constipation	35 (27.6%)
Gastrostomy/Ileostomy	19 (15.0%)
Hepatic steatosis	18 (14.2%)
Chronic liver damage	11 (8.7%)
Gastroesophageal reflux	10 (7.9%)
Type 1 Diabetes Mellitus	9 (7.1%)
Portal hypertension	8 (6.3%)
Cholelithiasis	6 (4.7%)
Rectal prolapse	6 (4.7%)
Gastritis	5 (3.9%)
SIBO	5 (3.9%)
Pancreatitis	4 (3.1%)
Appendicitis	3 (2.4%)
Hepatitis	3 (2.4%)
DIOS	2 (1.6%)
Intestinal invagination	2 (1.6%)

SIBO: Small Intestinal Bacterial Overgrowth syndrome.
DIOS: Distal Intestinal Obstruction Syndrome.

served that the group screened early (screening by IRT), achieved a significant change in the current nutritional status, eutrophic patients went from 18% to 55%; and undernourished patients or at risk of undernutrition from 82% to 36%. This change did not occur in the group identified later through clinical suspicion (Figure 1).

Mortality

Up to 2018, 4/127 patients died (3.14%). The mean age at death was 14.5 years (range 9-19 years). Regarding the end-stage clinical presentation, 2 patients had chronic OLD and the other 2 had anemia, edema, hypoalbuminemia, and undernutrition. Only 2 of them have had the genetic study performed and the other 2 patients did not due to its high cost. One of the deceased patients had DF508 heterozygosity and the other DF508 homozygosity. It is noteworthy that the patient with the earlier installation of gastrostomy had longer survival.

Pharmacological Management

44.8% of patients (n = 57) received PPI/H2, 37.7% ursodeoxycholic acid (n = 48), and 28.3% polyethylene glycol 3350 (n = 36) at some point in their evolution.

Discussion

This is the first national descriptive study on gastrointestinal manifestations in pediatric patients with CF. Although not all CF patients in the Metropolitan Region were included, it was possible to analyze a high

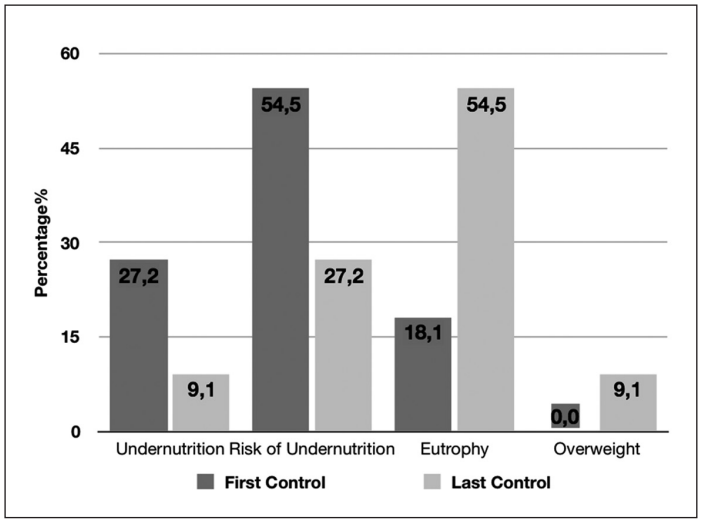

Figure 1. Nutritional evolution in patients with cystic fibrosis screened early by neonatal IRT.

percentage, since those registered in four of the most important referral centers in the country were included.

The average age at the onset of clinical symptoms suggestive of CF was in the older infant period (1.7 years), with about 4 months of delay to reach diagnostic confirmation. This is significantly later than reported in other countries. According to the latest Cystic Fibrosis Foundation Patient Registry, from 2003 to 2018, the median age of diagnosis dropped from 6 months to 3 months of life[9]. It is worth mentioning that universal neonatal screening has been used in the USA since 2010[10]. According to data from the Cystic Fibrosis Foundation Patient Registry Annual Data Report, 2018, in 2003, only 11.9% of CF patients were detected through neonatal screening while in 2018 this figure reached 61.5%, thus corroborating the decrease in the age of diagnosis[9].

In our series of 127 patients, screening by IRT was incorporated in 2013, and so far, only 12.5% of patients were diagnosed through this methodology. In Chile, there is no universal screening for CF. Pilot plans have been in place since 2013, with screening by IRT in newborns in sentinel sites. The protocol is being implemented and results are expected soon[11].

There is evidence showing that individuals diagnosed before the onset of symptoms have a better pulmonary function and nutritional status in later stages[12], which emphasizes the importance of early diagnosis and patient follow-up for survival. In this study, early screening of patients resulted in a significant improvement in the long-term nutritional status, which was not observed in patients without an early diagnosis. Unfortunately, the limited number of cases available for analysis did not allow us to analyze the age variable in greater detail.

Most of the patients had an onset clinical presentation with respiratory (44.9% OLD) and/or gastrointestinal manifestations (18.9% diarrhea/steatorrhea and low weight gain), but what is most striking is that more than half of the patients (60.7%) had undernutrition (poor weight gain or severe acute malnutrition), which strongly suggests that the diagnosis could be earlier. It is interesting to compare our results with series from other countries.

7.8% of patients presented the classic triad described in infants (anemia, hypoalbuminemia, and edema), somewhat higher than the 5% described by Nielsen et al. in 1982[13]. In international series, meconium ileus is described in 10-20%[14] and we found it in 9.5% of patients, which is within the low range described; however, as the average age at diagnosis in our patients was 1.74 years, the history of meconium ileus may not have been recorded. We have no explanation for the high percentage of patients with cholestatic jaundice (6.3%) in our series, compared with the 1-2% described in other studies[15].

In our analysis stands out that 81.1% of the patients had the genetic study available. The most frequent mutation was DF508 (65%), which agrees with previous Chilean studies that reported 22%[16], 30%[17,18], and 45%[19]. The most prevalent form was heterozygous DF508, associated with mutations not detected in the national panel. This is also in agreement with international data describing this mutation in 66 to 70% of cases, depending on the ethnic origins of the group studied[20]. In the USA, the Cystic Fibrosis Foundation Patient Registry (2018), described the DF508 mutation of at least one copy as the most frequent (84.7%), while the homozygous form has a lower frequency (44.2%)[9]. In our series, the hetero- and homozygous forms appear with lower frequencies (65% and 15.5%, respectively). The second frequency of the mutations found was G542X (6.7%), a figure similar to that described in the USA (4.6%)[9].

These similarities and differences between studies highlight the ethnic differences in the various populations. Unfortunately, because we are working with anonymous data from the national registry, we do not have other patient data available that would allow us to hypothesize further. It seems necessary to expand the genetic study in the country in order to better understand our national reality and to provide appropriate genetic counseling and specific therapies according to the needs of each patient.

The most frequent complication observed was pancreatic insufficiency (74.8%). In animal studies, it has been seen that damage can begin *in utero* as early as 17 weeks of gestation[21] and is described in 80-90% of pa-

tients with CF, 60% present in the neonatal period, and 90% within the first year of life[22]. In our series, this percentage was lower; however, it should be considered that only fecal elastase-1 of less than 200mcg was considered as pancreatic insufficiency. Of the 95 patients with this diagnosis, 15 did not have a fecal elastase test, but they did present clinical symptoms of malabsorption with steatorrhea and poor weight gain. The rest of the patients (80/95) had fecal elastase values less than 200mcg. It is recommended that fecal elastase-1 levels be monitored every 3 months in children under 1 year of age and annually after 1 year of life[23].

The prevalence of liver disease associated with CF varies widely according to studies, ranging from 2% to 68% in children and adolescents, depending on whether the diagnosis is based on clinical (hepatosplenomegaly), biochemical (elevated transaminases), or ultrasound criteria[24]. In post-mortem studies, hepatobiliary involvement has been described in up to 42% of cases. In our study, 32.3% presented elevated transaminases and 14.2% hepatic steatosis on ultrasound, which is similar to that reported by other authors[26,27,28]. We found cholelithiasis in fewer patients than described in other studies (4.7% vs 15%[29]), which could be influenced by the younger age of our patients.

Our results show that 8.7% of patients had chronic liver damage and 8.7% had portal hypertension. These patients were on average 11.1 years old (range 6-17 years), which makes it difficult to compare with larger series of CF patients, where 90% of patients presented with cirrhosis and portal hypertension at 18 years of age, with a mean age at diagnosis of 10 years[29]. In any case, our results support what is described in the literature regarding the need to perform an annual abdominal ultrasound in an early check for liver damage[30].

The use of ursodeoxycholic acid in CF liver disease would help reduce the viscosity of bile acid, preventing clogging and thus inflammation, in addition to its cytoprotective properties[31]. Even so, its use is controversial, and, to date, there is little and poor evidence of its real effectiveness[32]. Its use can be considered for 2 to 3 months in cases of cholestasis (conjugated bilirubin higher than 1mg/dL), with a dose of 10-20mg/kg/day in two doses[33]. In our study, 37.7% (n = 48) of the patients used ursodeoxycholic acid at some time, either for cholestasis, hypertransaminasemia, or chronic liver damage.

Regarding survival, the international literature clearly shows that this has increased over time, with average survival over 47 years in the USA[34] and more than 50 years in Europe[35]. An increase in survival in Chilean patients has also been described, from 12 years (average age at death) in 1999 to 18 years in 2008[36]. In 2012, another Chilean study describes CF patients who have reached adulthood, two-thirds of them over 20 years of age[37]. In our group, the average age of the deceased was 14.5 years. This shows that CF is a difficult pathology to manage, and that, in our country, much remains to be done.

In conclusion, gastrointestinal manifestations in patients with CF are an important cause of morbidity and mortality, and in our series, their frequency was similar to that reported in the literature.

Evidence shows that early diagnosis and intervention improves prognosis, which means that universal implementation of neonatal screening is a national imperative. The genetic study could not be performed in almost 20% of patients, mainly due to economic reasons. The positive genetic results show differences with international studies. There is a need to include the expanded genetic panel in the national basic basket that evaluates CF patients.

Regarding gastrointestinal aspects, patients with CF should undergo routinely strict clinical, laboratory, and ultrasound follow-up in order to check for early complications and thus try to improve their survival and quality of life.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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