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Research Article

Characterization of Patients with Cystic Fibrosis Diagnosed by Means of Chlorides in Sweat in the Period January 2010 - July 2015

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Abstract

Background and Objectives: Cystic Fibrosis (CF) is a genetic autosomal recessive disease characterized by dysfunction of the exocrine glands secretion. The incidence in the caucasian population is 1 in 3,500 live births, 1 in 9,000 and 1 in 17,000 Asians in the black population. Given these statistics, in Honduras we expect to find an incidence of 20 - 23 cases per year Cystic Fibrosis; but there is no review or study on this subject, so it seems important and indispensable to the casuistry of our region and the country therefore the aim of our research is to characterize the epidemiology, clinical and therapeutic genetics of patients diagnosed with Cystic Fibrosis through positive test Sweat Chloride.

Patients and Methods: Medical records were reviewed and an instrument with questions on epidemiological, clinical, therapeutic and genetic patients diagnosed with cystic fibrosis through sweat chloride in the period January 2010 - June 2015 was applied.

Results: Five patients diagnosed with cystic fibrosis occur through sweat chloride test from January 2010 to June 2015. The age at diagnosis ranged newly born to 5 years; Four were female; 2 with antecedents relatives to the disease. At the onset of the disease 3 had respiratory and digestive symptoms. In relation to weight/height for Z score at diagnosis we are found in 4 patients $p < 1$ and in relation to height/age at diagnosis 4 were found at the $p < -3$. In 3 sputum culture it was held in the totaled *Pseudomonas aeruginosa* was reported. Among the studies for the diagnosis of cystic fibrosis to all the patients underwent the sweat chloride, 3 patients and one study genetic neonatal screening. Regarding the therapeutic management of patients diagnosed with cystic fibrosis all of them nebulized hypertonic saline indicated 7%, nebulized beta-2-agonists, systemic antibiotics and enzyme supplements and fat-soluble vitamins. Filed mutation in the CFTR gene was 2 (67%) patients, DELTA.f 508.

Conclusions: Cystic fibrosis is a disease still largely unknown. Health personnel and the general population does not know the consequences that actually produces still a very disabling disease in its evolution, both in the lungs and digestive; also we observed as cystic fibrosis is increasing its impact globally and in regions of Latin America since have improved dissemination of its existence and diagnostic methods so that the Government of Honduras through the Ministry of Health should implement neonatal screening since early diagnosis would help the patient while providing the opportunity to test realized sweat chloride hospital and free in older patients with a high clinical suspicion of this disease.

Keywords: *Characterization; Cystic Fibrosis; Chlorides; Sweat*

Introduction

Cystic fibrosis (CF) is an important pediatric problem due to the high and premature mortality that characterizes it, the poor quality of life that it generates in patients and the absence of a curative treatment [1]. The first descriptions of CF were made by Fanconi, in 1936, and by Andersen, in 1938. In 1959, Gibson and Cook published the determination of electrolytes in sweat by the iontophoresis method with pilocarpine [2]. Only in the 1980s was it discovered that the fundamental defect is due to the failure of cellular chlorine secretion

[3]. CF is due to mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) 1, located on chromosome 7q31.2 [4]. To date, more than 1,400 mutations and 200 variables have been discovered and different polymorphisms causing the disease, and its prevalence varies widely according to the ethnic group and the geographical area being studied [5].

The F508 is the most common mutation, with an average global frequency of 66%, but with notable ethnic differences ranging from 28% in Asia to 70% in Northern Europeans [6].

In the lung, the airways are the initial site of compromise, with abnormal mucociliary clearance, recurrent infections, and bronchiectasis that leads to progressive lung dysfunction and respiratory failure. In the pancreas, obstruction of the ducts leads to atrophy and the need for pancreatic enzyme replacement in approximately 85% of patients [7].

CFTR dysfunction can be documented by:

1. Increase in the concentration of chlorine in sweat.
2. Identification of the mutation causing the disease in each CFTR gene.
3. Demonstration of an abnormal transport of ions in the nasal epithelium [8].

The treatment includes nebulizations with hypertonic saline at 7% and beta-2-agonists, systemic and inhaled antibiotics, supplementation with fat-soluble vitamins and pancreatic enzymes, anti-inflammatories, corticosteroids and the new ones are the CFTR protein repairing drugs approved by the FDA in July 2015 [9-11].

Objective of the Study

The objective of the present study is to characterize patients with cystic fibrosis diagnosed by chlorides in sweat.

Patients and Methods

In Honduras, the sweat chlorides test was carried out since the year 2,010 at the Pneumology and Allergy Center, located in the city of San Pedro Sula. It is known that there are 22 people diagnosed with this disease, of which 17 are in control in National Cardiopulmonary Institute in the city of Tegucigalpa and the remaining 6 do so with doctors from the Mario Catarino Rivas Hospital (HMCR).

Inclusion criteria: All patients diagnosed with cystic fibrosis by positive test of chlorides in sweat, with clinical manifestations of the disease.

Exclusion criteria: All patients with a patient with doubtful evidence or who through induction do not collect enough sample to perform the test.

One patient refused to participate in the study.

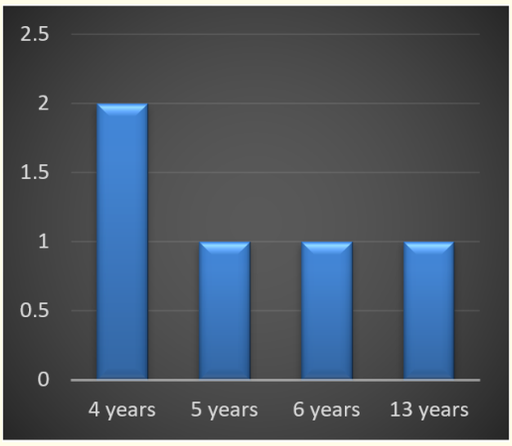
The clinical histories of 5 patients diagnosed with cystic fibrosis during the period from January 2010 to July 2015 were analyzed retrospectively. For this purpose, a clinical record was drawn up showing age, sex, place of origin, family history, nutritional status (evaluating weight/height and height/age), hospitalizations, respiratory and/or digestive symptoms, bacterial colonization, therapeutics and mutation.

Sweat electrolytes were obtained by electro-stimulation with pilocarpine and the type of mutation by means of DNA.

The data were analyzed with frequency, percentages and the tabulation of data was made to the computer.

Results

The age of the patients diagnosed with Cystic Fibrosis was included in the preschool stage in 3 (60%) patients (See graph 1)



Graph 1: *Distribution by age of patients diagnosed with cystic fibrosis by sweat chlorides test during the period January 2010 - June 2015.*

Of the 5 cases of patients studied, 4 (80%) were female and 1 (20%) male.

The city of San Pedro Sula was in 3 (60%) patients the place of prevalent origin.

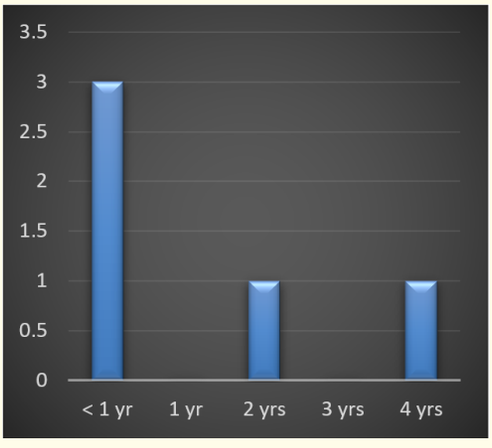
The age at the time of diagnosis in 3 (60%) patients was greater than 1 year of age (See table 1).

Age	
NB	1 (20%)
11 months	1 (20%)
15 months	1 (20%)
3 years	1 (20%)
5 years	1 (20%)

Table 1: *Distribution of patients with Cystic Fibrosis according to age at the time of diagnosis.*

The family history of cystic fibrosis in 2 (40%) of the cases was positive.

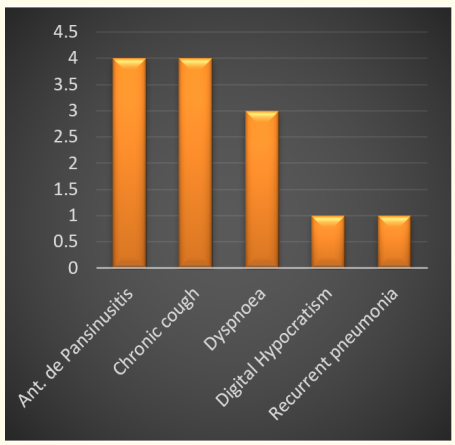
The time between the first symptoms and the time of diagnosis was less than 1 year in 3 (60%) patients diagnosed with cystic fibrosis (See graph 2).



Graph 2: *Distribution according to the time of onset of symptoms and diagnosis of patients diagnosed with cystic fibrosis by chlorides in sweat during the period January 2010 - June 2015.*

The clinical presentation in 3 (60%) patients was mixed, 1 (20%) patient was pulmonary and 1 (20%) patient was digestive.

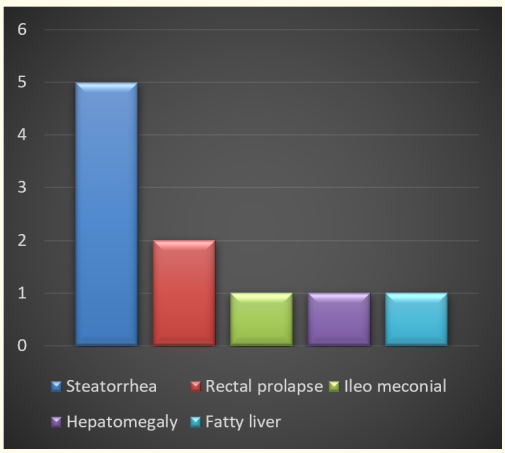
The presented pulmonary clinical manifestations were 4 (80%) patients with chronic cough and antecedents of pansinusitis, 3 (60%) patients with dyspnea and 1 (20%) patient with digital clubbing and recurrent pneumonia (See graph 3).



Graph 3: *Distribution according to pulmonary clinical manifestations in patients diagnosed with Cystic Fibrosis by Chloride Sweat test during the period January 2010 - June 2015.*

In the X-rays of the thorax performed in 3 (60%) patients a persistent interstitial image was observed and in 2 (40%) patients data of air trapping.

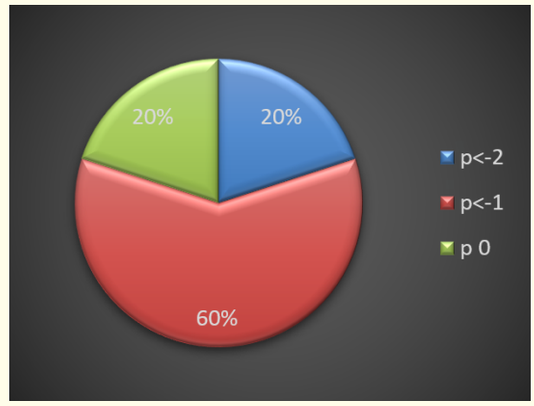
The digestive clinical manifestations found were steatorrhea and chronic malnutrition in all patients, in 3 (60%) patients growth retardation, 2 (40%) patients with rectal prolapse and 1 (20%) patient with meconium ileus (See graph 4).



Graph 4: *Digestive clinical manifestations of patients diagnosed with cystic fibrosis by chlorides in sweat during the period of January 2015 - June 2015.*

Bacterial colonization was reported in 3 (60%) patients, which in their totality was by bacillus gram negative (*Pseudomonas aeruginosa*).

The BMI at the time of diagnosis in 3 (60%) patients was in the p < -1 in Z score and only 1 (20%) at the time of diagnosis was in p0 in aforementioned score (See graph 5).



Graph 5: *Distribution according to BMI (Z score) at the time of diagnosis in patients with cystic fibrosis during the period January 2010 - June 2015.*

In relation to weight/height by Z score at diagnosis 4 (80%) patients were found in p < -1 and 1 (20%) patients in p < -2.

In relation to Height/Age at the time of diagnosis 4 (80%) were found in the p < -3 and 1 (20%) patient in the p < -2 with respect to the Z score.

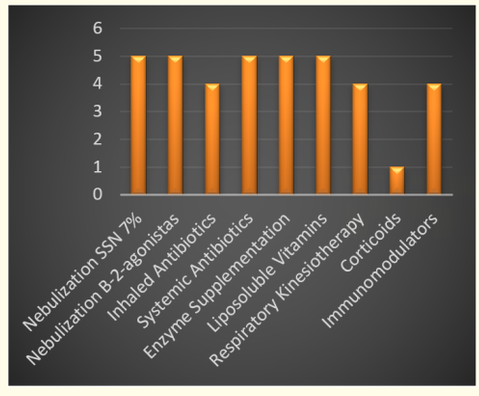
The studies carried out with the suspicion of Cystic Fibrosis were X-Ray thorax and arterial oxygen saturation in all the patients of the investigation, and a patient underwent TAC Thorax, pulmonary function and alveolar bronchial lavage.

Among the studies carried out for the diagnosis of cystic fibrosis, all of the patients underwent chlorides in sweat, 3 (60%) patients underwent a genetic study and 1 (20%) neonatal screening (See table 2).

Realized Study	
Amniotic liquid DNA	0 (0%)
Neonatal sieve	1 (20%)
Electrolytes in Sweat	5 (100%)
Genetic Study	3 (60%)

Table 2: *Distribution of patients according to studies performed for the diagnosis of cystic fibrosis.*

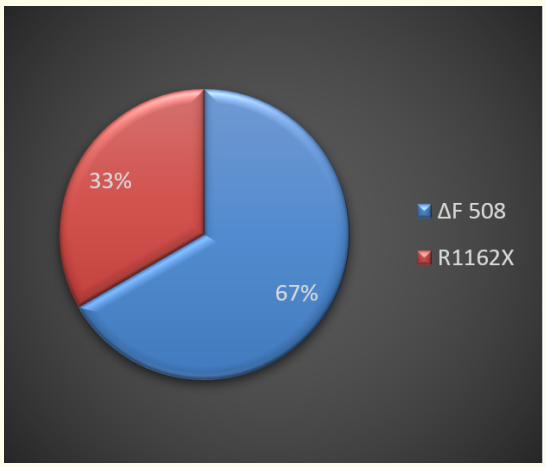
Regarding the therapeutic management of patients diagnosed with cystic fibrosis in all of them, nebulizations were indicated with 7% hypertonic saline, nebulizations with beta-2-agonists, systemic antibiotics and enzyme and fat-soluble vitamins supplementation; 4 (80%) patients were managed with inhaled antibiotics, respiratory kinesiotherapy and immunomodulators; and 1 (20%) patient had the indication of corticosteroids (See graph 6).



Graph 6: *Distribution according to therapeutics used in patients diagnosed with cystic fibrosis by chlorides in sweat during the period January 2010 - June 2015.*

The number of hospitalizations reported since the diagnosis of the disease was two in 2 (40%) patients, one in 1 (20%) patient and none in 2 (40%) patients.

The mutation presented in the CFTR gene was in 2 (67%) patients ΔF 508 (See graph 7).



Graph 7: *Distribution according to genetic mutation in patients with cystic fibrosis diagnosed by chloride test in sweat during the period January 2010 - June 2015.*

Discussion

Cystic fibrosis is the major cause of chronic lung disease in children. it may also be responsible for most of the exocrine pancreatic insufficiencies in the first years of life and is often also associated with limitations in growth.

Given the demographic patterns of our country where more girls are born than boys, the involvement of cystic fibrosis in women was found in 80% of our casuistry, unlike other studies conducted in Latin America, such as in Cuba where an incidence was found. of 60% in men [1] and in Costa Rica where there was no significant difference between sex [7].

The most frequent mutation in the population is delta F 508. Its frequency is variable according to the population although average values have been reported between 48-50% in Spain; 66% in Cuba; 47.8% in Mexico; 60.9% in Argentina; 35.4% in Brazil [12]; in our study a frequency of 67% was found.

Cystic fibrosis is an autosomal recessive genetic disease, whose form of presentation varies, especially in dependence on age, with predominance of the digestive in children and the respiratory in adults [4] in our study the most common clinical presentation was the mixed form in 60% of the patients evidencing that the respiratory tract and pulmonary complications is something that we also observe in pediatrics dominating in 80% the clinical picture mainly dyspnea, chronic cough and the antecedent of pansinusitis.

Hyperinflation is an early finding, and can be detected by simple radiography, and this was observed in all of our patients and this method is still used although the Tomography is more sensitive to detect progression of lung disease, but it is more expensive and exposes to more radiation.

Pseudomonas aeruginosa is the most relevant pathogen in CF, several studies that analyze the immune response have documented that it appears earlier than previously suspected: positive antibodies have been evidenced at 15 months of age while cultures of via the lower area they become positive at 23 months [13], so it should not be considered exclusive of adult patients and this is reflected in our study since 60% of the patients presented this colonization.

The interval before the first symptoms can be variable, but usually begins in the early stages of life. The mean age at the time of diagnosis in our study was 3.5 years, which compared to that reported in the CCF (Cystic Fibrosis Foundation) in 2003, which was 6 months

[14] shows a significant delay in the diagnosis, since 40% of the patients presented symptoms for more than two years before reaching the diagnosis of cystic fibrosis, being able to suppose that the neonatal screening, the education to the health professionals about the signs and symptoms of the disease and the opportune access to the diagnostic methods are the actions that in other countries have contributed to the realization of an early diagnosis and that in our country the current diagnosis continues being carried out basically by clinical suspicion.

In 10 to 20% of patients, meconium ileus may be the first manifestation of the disease [14], as we found in our study, in addition to rectal prolapse was an increased finding since the international literature reports it with a prevalence of up to 20% [15] so we should consider it when making differential diagnoses.

Growth retardation is frequent and occurs due to a combination of factors; the arrest or lack of progress in the weight curve should alert the doctor and we suspect cystic fibrosis [16] as we observed in relation to size/age where our patients were below $p < -3$ by 80% at the time to make the diagnosis. Without nutritional support, many CF patients do not seem to meet their requirements; and always the relation size/age will be the most affected since the child is in growth rate until reaching puberty unlike the adult [17].

Therapeutics currently used for the treatment of cystic fibrosis in Honduras is similar to those described internationally, varying that up to the year of this study, inhaled tobramycin is not yet available, instead using the amino glucoside vials in nebulized form; immunomodulators such as azithromycin provide a modest benefit to children with CF, especially when they are colonized by *P. aeruginosa* [18] and although the FDA approved the use of the combination of Lumacaftor with ivacaftor (Orkambi), for patients with CF homozygous for the DF508 mutation at or above the age of 12 years [11] this is not available in our country.

Conclusion

In conclusion, cystic fibrosis is still a largely unknown pathology. The health personnel and the general population do not know the consequences that really produce being a very disabling disease in its evolution, both at the pulmonary and digestive levels, being able to adopt very effective preventive measures if its symptoms and clinical signs are known. At the same time, we observed that cystic fibrosis is increasing its incidence worldwide and in Latin American regions, given that the dissemination of its existence and diagnostic methods have been improved, which is why the Government of Honduras through the Ministry of Health should to implement neonatal screening since it would help early diagnosis of many genetic diseases; and at least provide the patient with the opportunity to undergo sweat chloride tests in a hospital-free manner in older patients with high clinical suspicion of this disease.

Conflict of Interests

The authors state that during the planning and execution of this research work, there was no conflict of interest.

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