Study on Cystic Fibrosis Evolution in Children

DIANA-MARIA TRASCA[1], CRISTINA FLORESCU[2]*, VENERA CRISTINA DINESCU[3], ILEANA PUIU[4], SORIN NICOLAE DINESCU[5], DIANA RODICA TUDORASCU[6], VERONICA CALBOREAN[2], CRISTINA ELENA SINGER[4]

[1]University of Medicine and Pharmacy of Craiova, 2nd Department of Medical Specialities, 2 Petru Rares Str., 200349, Craiova, Romania

[2]University of Medicine and Pharmacy of Craiova, Cardiology Department, 2 Petru Rares Str., 200349 Craiova, Romania

[3]University of Medicine and Pharmacy of Craiova, Health Promotion and Occupational Medicine Department, 2 Petru Rares Str., 200349 Craiova, Romania

[4]University of Medicine and Pharmacy of Craiova, Pediatrics Department, 2 Petru Rares Str., 200349 Craiova, Romania

[5]University of Medicine and Pharmacy of Craiova, Epidemiology and Primary Health Care Department, 2 Petru Rares Str., 200349 Craiova, Romania

[6]University of Medicine and Pharmacy of Craiova, Internal Medicine Department, 2 Petru Rares Str., 200349 Craiova, Romania

Cystic fibrosis (CF) or mucoviscidosis, although considered a rare disease, is the most common genetic disease with autosomal recessive transmission of the Caucasian race. The study included 13 children aged between 0 and 18 years diagnosed with CF between 01.01.2000 and 31.12.2018, being recorded, monitored and treated in the Regional Center for CF Craiova from the Pediatrics II Clinic, County Emergency Clinical Hospital Craiova, Romania. For each patient we evaluated the following parameters: the year of CF diagnosis, the age at diagnosis, sex and environment of origin, clinical manifestations at onset, evolution of treatment cases by 2018. Of the 13 children with CF in study, most of them (11) are male. The most common clinical manifestations were the respiratory ones. Genetic tests were performed on all children, highlighting that 6 out of 13 children were homozygous ÄF508 and 2 children had mutations not genetically identified, requiring sequencing.

Keywords: Cystic Fibrosis, children, evolution

Cystic fibrosis (CF) or mucoviscidosis, although considered a rare disease, is the most common genetic disease with autosomal recessive transmission of the Caucasian race. Due to the complexity of the disease and the medical-social problems it raises, the CF is considered internationally an important public health problem. It is a multisystemic affection that interests all the internal organs (lungs, digestive tract, pancreas, liver, kidney, cord, reproductive organs), except for the brain. In the absence of early diagnosis and proper treatment, the chances of survival do not exceed the baby's period. On the contrary, early diagnosis and multidisciplinary management can make a sick person reach the adult age with a good quality of life that will ensure its social independence.

Chronic progressive and potentially lethal the disease is characterized by generalized dysfunction of the exocrine glands, associating two types of fundamental disorders: one that concerns the mucous glands and another affecting the serous glands (in this case of sweat), the primary anomaly linking them to the CF gene [1].

CF is caused by the mutation of both alleles of the FC gene (chromosome 7) resulting in abnormalities in the production of a CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) [2].

The incidence of the disease in the USA is similar (1: 2000-1: 3000 live newborns) to that in Europe (approximately 1: 2500 newborns). In 2006, in Romania, by Order of the Ministry of Health no. 247 of 16 March, the Mucoviscidosis Center of Timisoara was officially named the National Mucoviscidosis Center and seven regional centers (Brasov, Bucharest, Cluj-Napoca, Constanta, Craiova, Iasi, Timisoara) were established. In Romania, the number of CF patients evidenced in 2018 is 515 (390 children and 125 adults) according to CNAS Order no. 932/ 2018.

* email: tohaneanu67@yahoo.com, Phone: +40722389517

Experimental part

The aim of the study

The aim of our study was to perform a retrospective, clinical-evolutionary study in children diagnosed with this rare disease, the cystic fibrosis. It was performed over a long period of time (19 years) because it contained a relatively low number of patients and we tried to cover as many essential aspects regarding the evolution of the disease.

Materials and methods

A group of 13 children aged between 0 and 18 years diagnosed with CF between 01.01.2000 and 31.12.2018 was included in the study and was monitored and treated in the Regional Center for CF Craiova at the Pediatrics II Clinic, County Clinical Emergency Hospital Craiova, Romania.

The study was based on the folder containing the medical history of each patient. During these years, all children were periodically admitted for evaluation and treatment according to the National Health Program (NSP) for Mucoviscidosis.

We evaluated the following parameters in each patient: the year of the diagnosis of CF, the age at the onset, the sex and the background, the clinical manifestations at onset, the complications and the evolution of the cases under treatment until 2018. These patients were diagnosed by the sweat test and genetic tests (molecular analysis). The sweat test is the gold standard in CF diagnostics and evaluates the concentration of chlorine and sodium ions in the sweat. Normal electrolyte sweat values are < 40mMol/ L. In children, positive values are > 60 mMol/L, and in adolescents and young adults > 70 mMol/L. Between 40-60 mMol/L are considered equivocal values; the test is repeated and interpreted it in a clinical context.

There were systematically carried out a multitude of paraclinical investigations of the affected systems during the course of the disease.

Results and discussions

Between the years 2000 - 2018, there were 13 children diagnosed and monitorized with CF. According to the year in which they were diagnosed, the following were discovered: in the year 2000 there were 2 children diagnosed and in the years 2003, 2004, 2005, 2007, 2008, 2010, 2011, 2012, 2013, 2015, 2016 there was 1 child diagnosed per year (fig. 1).

The distribution by the place of birth was the following: 7 chidren (53.8%) come from the country side and 6 children (46.2%) come from urban enviroment (fig. 2).

Regarding the sex, the distribution of the pacients was the following: 11 children (84.6%) are male and 2 children (15.4%) are female (fig. 3).

The birth county was: Dolj-6 children (46.1%), Olt- 4 children (30.8%), Valcea- 2 children (15.4%), Gorj- 1 child (7.7%) (fig. 4).

The distribution of the patients by the age range, when the diagnose of the CF was settled, was: newborn - 3 children (23.1%), infant- 7 children (53.8%), scholar- 3 children (23.1%) (fig. 5)

Studying the clinical manifestations since the onset of the affection we found the following aspects: the presence of meconial ileus in 2 children (15.4%); dehydration syndrome with hyponatraemia was present in 2 children (15.4%); recurrent diarrhea and recurrent wheezing occurred in 3 children (23.1%); steatorrhea was present in 2 children (15.4%); triple association: chronic cough, growth retardation, diarrheal stools - 2 children (15.4%). Two children were diagnosed before the onset of clinical manifestations: 1 child diagnosed by testing (sweat test and genetic test), having a first-month diagnosed brother with CF and a child diagnosed with neonatal screening in Italy (table 1).

The time interval from the onset of the disease to the diagnosis was variable: weeks (0-3) for 3 children (23.1%), months (between 2 and 9 months) for 7 children (53.8%), or years (1-3 years) in 3 children (23.1%) (fig. 6).

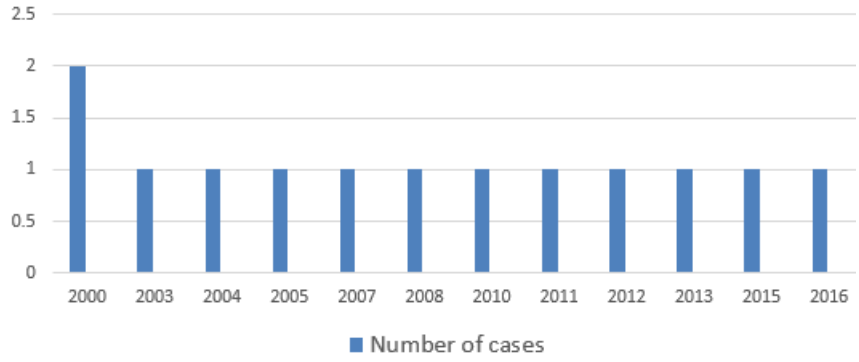

Fig.1. Distribution of CF cases by year of diagnosis

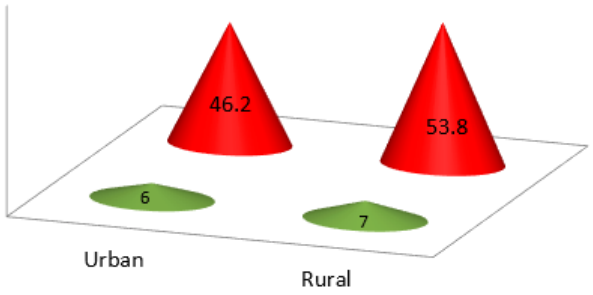

Fig. 2. Distribution of CF children by origin

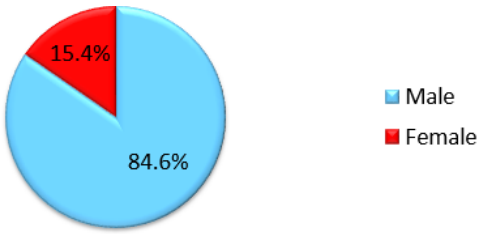

Fig. 3. Distribution by sex of children with CF

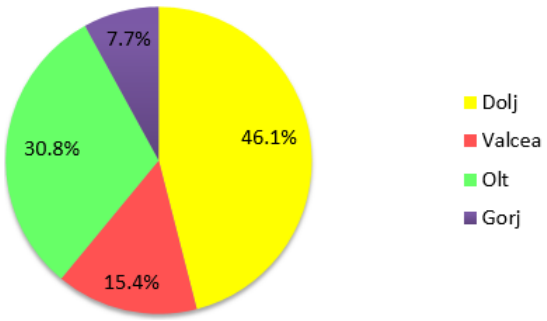

Fig. 4. District distribution of CF children

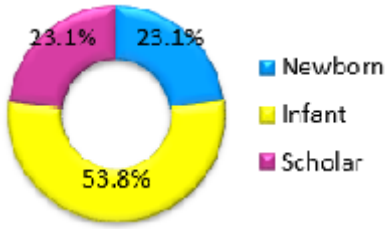

Fig. 5. Distribution by age group to diagnosis of FC

Table 1

CLINICAL MANIFESTATIONS ON THE ONSET OF THE AFFECTION

Clinical manifestations	Number	Percent
Meconial ileus	2	15.4
Dehydration syndrome with hyponatraemia	2	15.4
Recurrent diarrhea and wheezing	3	23.1
Chronic cough, growth retardation, diarrheal stools	2	15.4
Steatorrhea	2	15.4
Neonatal screening Italy	1	7.7
Child diagnosed by sweat test and genetic test (having a first-month diagnosed brother with CF)	1	7.7

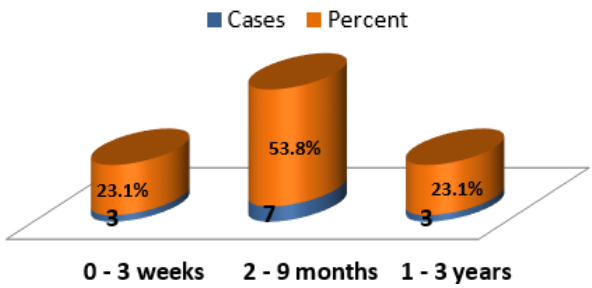

Fig. 6. The time interval from onset of the disease to diagnosis

Depending on the health unit in which the diagnosis was established, we found that: in the Regional Center for CF Craiova we diagnosed 6 children (46.2%), in Bucharest - 3 children (23.1%), in Timisoara - 2 children (15.4%), in Cluj-Napoca - 1 child (7.7%), in Italy - 1 child (7.7%) (fig. 7).

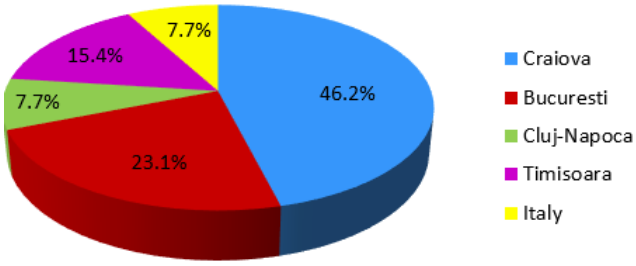

Fig. 7. Distribution of CF cases according to the unit in which the diagnosis was established

The analysis of the heredocolateral antecedents in children diagnosed with CF showed the following: two brothers diagnosed with CF, one at birth (male) and his sister at the age of 7; the two brothers still have a 14-year-old sister, untested by the sweat test or genetic test because of the parents' refusal. Another child with CF had a deceased brother at the age of 4 months with severe respiratory manifestations. Another child with CF has a deceased brother at birth (the mother cannot tell the diagnosis of death). In 3 children with CF, the brothers were tested (two by amniocentesis and one by genetic test) and the results were negative. Three children with CF are only children in their families. For the other children there were not performed on brothers the test of the sweat (parental refusal) or the genetic tests due to parental refusal or high costs.

In 2018, the distribution by age group of the 13 children is as follows: age group 1-3 years: 2 children (15.4%), age group 3-6 years: 3 children (23.1%), in the age group 6-12 years: 4 children (30.8%), 12-18 age group: 4 children (30.8%) (fig. 8).

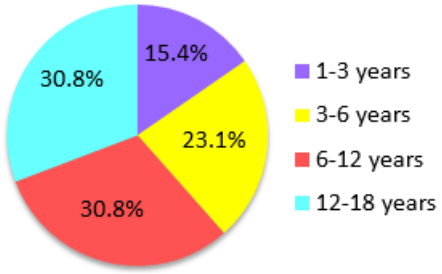

Fig. 8. Distribution by age group of children with CF in 2018

The clinical assessment of these children in 2018 revealed: severe weight hypotrophy (G<5TH percentile) in 11 children (84.7%), chest deformities in 11 children (84.7%), digital hypokratism in 5 children (38.5%), ventilator dysfunction in 5 children (38.5%), bronchiectasis in 4 children (30.8%), dental caries/bone dystrophy in 4 children (30.8%), nasal polyposis in 1 child (7.7%) (table 2).

Table 2

CLINICAL MANIFESTATIONS IN 2018 AT CHILDREN DIAGNOSED WITH CF

Clinical manifestations	Number	Percent
Severe weight hypotrophy (G<P5)	11	84.7
Chest deformities	11	84.7
Digital hypokratism	5	38.5
Ventilator dysfunction	5	38.5
Bronchiectasis	4	30.8
Dental caries/bone dystrophy	4	30.8
Nasal polyposis	1	7.7

Table 3

RESULTS OF BACTERIOLOGICAL EXAMINATION IN CF PATIENTS

Lung infection	Number	Percent	Bacterial colonization	Number	Percent
Pseudomonas aeruginosa	2	15.4	Staphylococcus aureus	2	15.4
MRSA+Pseudomonas aeruginosa	1	7.7	MRSA	1	7.7
MRSA+ candida spp	2	15.4	Pseudomonas aeruginosa+MRSA	1	7.7
MRSA	1	7.7			
Total	6	46.2	Total	4	30.8

Table 4

RESULTS OBTAINED FROM THE SWEAT TEST

Number of pacient	Value (mMol/L)
1	89
2	108
3	110
4	111
5	113
6	116
7	119
8	121
9	125
10	128
11	129
12	131
13	134
The mean value	**118**
Ranging	**89-134**

Bacteriological examinations (sputum examination and hypopharyngeal exudate) showed 6 children (46.2%) with lung infection: Pseudomonas aeruginosa in 2 children, Staphylococcus aureus resistant to methicillin (MRSA) + Pseudomonas aeruginosa in 1 child, MRSA + candida spp at 2 children, MRSA per 1 child; in 4 children (30.8%), bacterial colonization (persistence of positive cultures after one month of treatment) was with: Staphylococcus aureus in 2 children, MRSA in one child, MRSA + Pseudomonas aeruginosa in one child (table 3).

The sweat test was performed on all children diagnosed with CF. The mean value of electrolyte in sweat in patients with CF was 118 mMol/L (ranging from 89 to 134 mMol/L) (table 4).

Analyzing the genetic tests performed in all children with CF, we found the presence of ÄF508 homozygous in 6 children, ΔF508 + N1303K in 2 children, G85E + N1303K per 1 child, ΔF508 + G85E in 1 child, ÄF508 + 333-394delTT la 1 child. In 2 children with disease-specific

clinical manifestations and elevated sweat test, the genetic tests are unclear, requiring sequencing (complex genetic DNA analysis methods) (fig. 9).

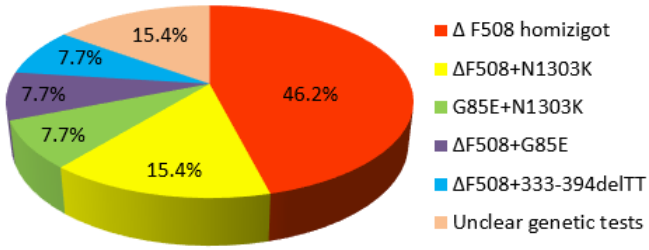

Fig. 9. Results obtained in the genetic tests

Paradoxically, this very severe disease is known as the disease of the 65 roses. This name belongs to a boy who listened to his mother talking on the phone about his illness, in English the pronunciation for Cystic Fibrosis is similar to that for the sixty-five roses [3].

In 70% of patients, the diagnosis is established before the age of 1 year. However, there are cases where the diagnosis is confirmed only after the age of 10 years. In our study, most cases were diagnosed in the newborn and infant, 3, respectively 7 cases of the total 13. Most cases were males (11 out of 13 cases).

After the genetic defect of the gene involved was detected in 1989, more than 1500 different mutations have been described so far [4].

Most of these mutations are rare. 20 mutations occur with a frequency greater than 1%. The most common mutation worldwide is characterized by the deletion of phenylalanine at position 508 (ÄF508 - Phe 508del) is found in approximately 30-80% of patients with CF, depending on the affected ethnic group [5].

In our study, the mutant ÄF508 homozygote was found in 6 out of 13 children. In two children there were genetically undetected mutations, requiring sequencing that was not yet done due to the high costs.

CF varies in severity according to CFTR mutation and environmental factors. The clinical picture is complex, being a polymorphism of signs and symptoms. Classically, the clinical picture is dominated by the triad: respiratory, digestive and deficiency symptoms [6, 7].

The pulmonary infections are the main element in terms of clinical outcome of the patient [8].

In our study the respiratory manifestations present at the onset of 6 children persisted in evolution, they became severe and occurred in time to four other children. The child diagnosed with ileus meconial developed severe respiratory manifestations, and her sister, diagnosed at age 7 (with the same genetic mutation), showed less severe respiratory manifestations. Also, the patient diagnosed with CF by neonatal screening showed lung damage after the age of 3 years. Of the 13 CF children, 5 currently have ventilation dysfunction and 4 bronchiectasis secondary to bronchopulmonary chronical injury.

The main pathogens responsible for the respiratory infection in children with CF are: Pseudomonas aeruginosa and Staphylococcus aureus [9-11]. The same germs were also isolated in our study in CF children, with staphylococcus being predominantly MRSA.

Severe weight hypotrophy (G <5TH percentile) was found in most children (11/13) with CF in the study, particularly due to the persistence of chronic lung injury. Severe weight loss is associated with severe forms of disease [12].

Chronic diarrhea present at onset at 4 children improved with the time under the NSP treatment of CF. At present, the life expectancy and the quality of life of the patients with CF have significantly improved due to the knowledge of the pathophysiological mechanism of the disease and to the modern therapeutic approaches.

The treatment of the disease is complex and has the following objectives: to improve the clearance of the mucous secretion, to control the infection, to maintain nutrition, to treat the complications, the psychological support of the patient and family [13-16].

The Gene Therapy - the identification and cloning of the CF gene and the description of the protein it encodes, CFTR, opened the way to curative therapy by transferring a normal copy of the gene to the affected cells; the current research is focused on the respiratory epithelium [17-43].

Lung transplantation is a complex, high-risk therapy, but having the potential to save the lives of CF patients in advanced stages [19, 20].

Conclusions

Of the 13 children found in the Regional Center for Cystic Fibrosis Craiova, the majority (11) are male.

In our study, the interval from the onset of the disease to the diagnosis was between 2 and 9 months in more than half of the cases.

Most of the CF cases were diagnosed during the 0-1 year period (10/13).

The most common clinical manifestations were the respiratory disorders that over time led to severe weight hypotrophy, chest deformities, ventilation dysfunction and digital hypocratism.

The average sweat electrolyte values were 118 mMol/L.

The genetic tests were performed on all the children, highlighting that 6 out of 13 children were homozygous ÄF508, and 2 children had mutations not genetically identified, requiring sequencing.

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