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Case Study

Neonatal Cystic Fibrosis. Presentation of a Case and an Overview

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Abstract

Cystic fibrosis is an inherited autosomal recessive disorder that preferentially affects the population of Caucasian origin and is mainly characterized by obstruction and infection of the respiratory tract and digestive problems. The investigations carried out for the location of the gene responsible for this pathology, culminated in the discovery of the encoded protein related to the gradient of chlorine called Cystic Fibrosis Transmembrane Conductance Regulator, (CFTR). The alteration of the protein prevents it from carrying out its transport action and the result of all the mutations detected that alter the function of CFTR is the same: the impossibility of transporting chloride.

We present the case of a newborn who underwent prenatal ultrasonography, pregnancy was associated with polyhydramnios, he was born by eutocic delivery and from his birth presented with abdominal distension, an important amount of biliary fluid obtained by an orogastric tube, and he was diagnosed with of meconium ileus. A postmortem study was performed and the anatomopathological findings were compatible with cystic fibrosis.

Keywords: *Cystic Fibrosis; Meconium Ileus; Bronchial Hypersecretion*

Introduction

Cystic fibrosis is an inherited autosomal recessive disorder that preferentially affects the population of Caucasian origin and is mainly characterized by obstruction and infection of the respiratory tract and digestive problems.

Its incidence varies from 1:3,000 to 1:8,000 live births [1]. The initial histopathological descriptions of cystic fibrosis were made in the sixteenth century, approximately in 1595, by Peter Paaw in Holland, who performed the autopsy on an 11-year-old girl, supposedly bewitched, who had suffered strange symptoms for 8 years; the patient was thin and her pancreas was bulging, cirrhotic, bright white, after cutting and opening it determined that the cause of death was a disease of the pancreas [2].

Presentation of the Clinical Case

We present the case of a newborn, product of Gravida II pregnancy with adequate prenatal control. Last prenatal ultrasound reports polyhydramnios and apparent malformation of the digestive tract. Arrives at 35.3 gestation weeks and presents effective labor with a duration of 5 hrs, born by euthocic delivery, obtaining a newborn male with a weight of 2600 grs, body length 44 cm. head circumference: 33 cm, Apgar: 8/9 (at 5 and 10 minutes of life), S/A 1 (at 10 minutes of life), Capurro: 37 weeks of gestation.

It is assisted with initial resuscitation maneuvers; by abdominal distention, (32 cm of abdominal circumference), an orogastric tube is placed and 30 cc of bile fluid is aspirated from the gastric cavity and it is left there. It is managed with nasal continuous positive airway pressure (nasal CPAP), reporting FC 152X minutes, FR 60X minutes, temperature 37°C and saturation of 92% under handling with oxygen.

After admission to the Neonatal Intensive Care Unit (NICU), he was significant abdominal distention, collateral venous network and decreased peristalsis. 40cc of bile are obtained through an orogastric tube, colon it is performed a colon by enema, diagnosing probable meconium ileus, starting with enemas.

At 24 hrs of life, presents distension and increase the abdominal perimeter of 4 cm, pain on palpation, palpable mass on the right flank, absent peristalsis. During the next four days the management continues with enemas without the presence of stools, the abdominal perimeter is maintained at 37 cm. Intestinal transit is performed, observing passage of the contrast medium to the duodenum and jejunum, without reaching the level of the ileum.

At 6 days of life, an exploratory laparotomy was performed, with a pre-surgical diagnosis of intestinal occlusion, finding dilated bowel loops during surgery, with thick meconium at the level of the distal ileum and colon. Post-surgical diagnosis: meconium ileus. It arrives at the NICU in asystole; it is reversed with maneuvers and 24 hrs. Later it presents irreversible cardiorespiratory arrest.

Anatomopathological findings

Postmortem study was carried out; the main macroscopic findings were the following:

1. Liver (170g vs 100g), green with yellow necrotic areas surrounded by ring of hemorrhagic aspect.
2. Kidneys: left (14.5g vs 23.3g) and right (16g vs 23.3g) with violaceous areas, and hemorrhagic cortical areas.
3. Meconium and purulent peritonitis with adhesions.
4. Hemorrhage of focal intestinal wall.
5. Jejunal type II atresia.
6. Multifocal pulmonary hemorrhage.

Major histopathological findings:

1. Trachea and bronchi with hyperplasia of submucosal glands with dilatation of excretory ducts and dense eosinophilic secretion with an intraluminal mucinous appearance (Figure 1).
2. Ascending colon and ileum with extensive eosinophilic intraluminal dense secretion and focal glandular dilation. Myocytolysis and intense plastic peritonitis (Figures 2 and 3).
3. Pancreas with focal ductal dilatation, dense eosinophilic secretion in light of intralobular ducts and acini; interstitial fibrosis (Figure 4 and 5).
4. Liver with portal fibrosis, proliferation of bile ducts with dense eosinophilic intraluminal secretion and portal lymphocytic infiltrate. Extensive multifocal necrosis (Figure 6 and 7).

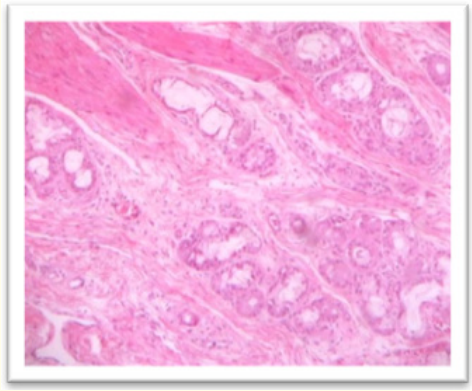

Figure 1: *Trachea and bronchi with hyperplasia of glands submucosal dilatation of excretory ducts and dense eosinophilic secretion and mucinous appearance intraluminal.*

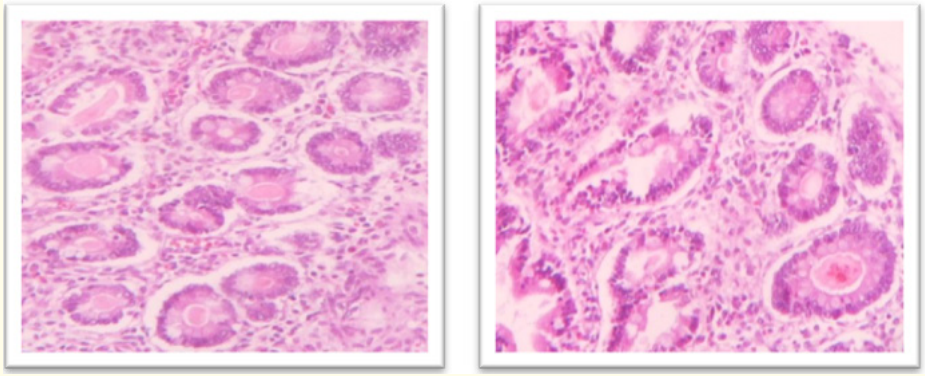

Figure 2 and 3: *Ascending colon and ileum with extensive eosinophilic intraluminal dense secretion and focal glandular dilation. Myocytolysis and intense plastic peritonitis.*

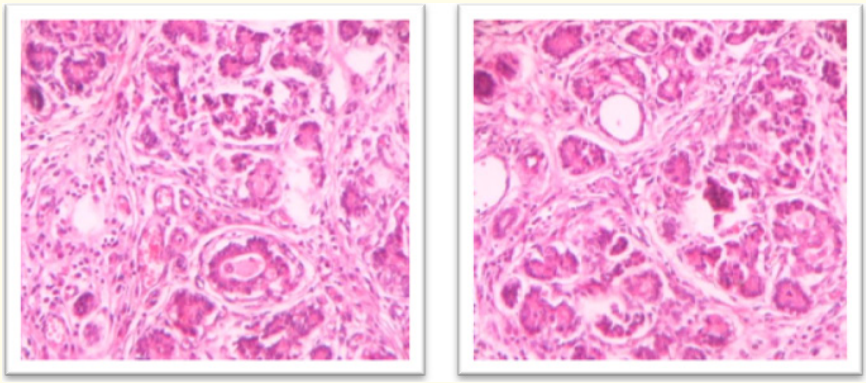

Figure 4 and 5: *Pancreas with focal ductal dilatation, dense eosinophilic secretion in light of intralobular ducts and acini; interstitial fibrosis.*

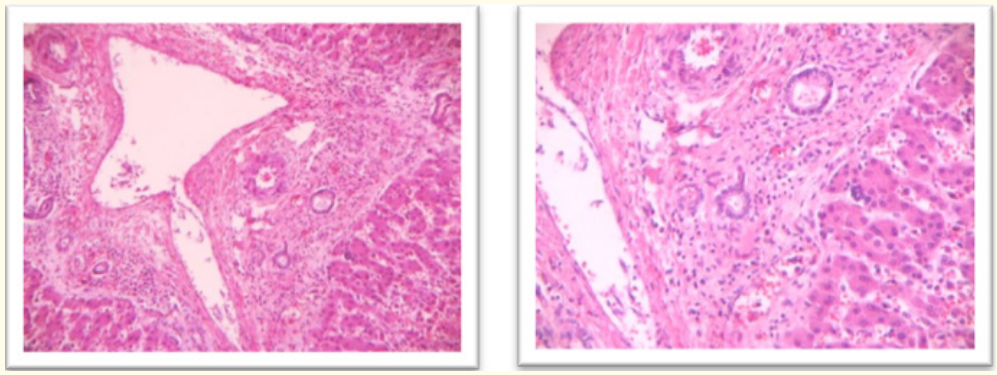

Figure 6 and 7: *Liver with portal fibrosis, proliferation of bile ducts with dense eosinophilic intraluminal secretion and portal lymphocytic infiltrate. Extensive multifocal necrosis.*

Final diagnoses:

1. Main diseases: Atresia of jejunum type II with meconium and plastic peritonitis.
2. Predisposing cause: Cystic fibrosis (microscopic changes in the pancreas, respiratory tract, liver and digestive tract).
3. Secondary diagnoses: Plastic peritonitis; microscopic manifestations of shock: myocytolysis in the digestive tract, pulmonary microatelectasis, liver with multifocal necrosis, renal cortical necrosis and multifocal hemorrhage.
4. Cause of death: Shock.

Discussion

Etiology and pathogenesis

A gene responsible for cystic fibrosis was identified by a group of researchers led by Lap-Chee Tsui and John R Riordan [14], of the Hospital for Sick Children, in Toronto and by Francis S. Collins, at the University of Michigan. The protein encoded by this gene and related to the chlorine gradient was named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), located on chromosome 7q 31.2 [2].

The absence or functional defect of the protein produces effects on the hydration of epithelial ducts, and also predisposes to greater bacterial adherence [3].

The result of all mutations detected that alter the function of CFTR is the same: the impossibility of transporting chloride. This explains the natural history of the disease in the sweat glands, respiratory system, pancreas, male genital system and hepatobiliary system.

Regardless of the mutation in the CFTR gene, each patient has the following abnormalities to varying degrees:

a) An abnormal concentration of ions in the secretions of the serous glands, manifested by an increase in the concentration of chlorine and sodium in the sweat.

b) An increase in the viscosity of secretions of mucus-secreting glands, associated with obstruction and secondary loss of glandular function.

c) An increase in susceptibility to chronic endobronchial colonization by specific groups of bacteria (*Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, Burkholderia cepacia*).

To date, six classes of mutations have been described.

Mutations I-III are the most common and are usually associated with pancreatic insufficiency. In Mexico, 46 different mutations that affect 77% of cystic fibrosis chromosomes have been identified.

Preimplantation diagnosis

The objective of this diagnosis is to determine the genetic characteristics of the embryo from a single cell obtained by embryo biopsy, without affecting the viability of the embryo. Therefore, PGD requires obtaining embryos by *in vitro* fertilization, analysis of a cell of each embryo and finally the selection of those who do not have the disease for its implantation [2].

Prenatal diagnosis: Analyzing the DNA of chorionic villi cells or amniotic fluid. It is done if the parents are carriers or if there is a brother with CF.

Neonatal screening: Based on the fact that serum levels of trypsin in patients with pancreatic insufficiency can be up to eight times normal, trypsin, trypsinogen or trypsin 1-antitrypsin complex can be studied, the first study is performed between the first and fifth day of life, if it is positive it is repeated between the second and the eighth week, if it is kept high, the Gibson and Cooke test and genetic study are done [5].

Clinical picture

Most cases of cystic fibrosis are presented with the classic triad:

a) Chronic progressive obstructive pulmonary disease with added infection

b) Exocrine pancreatic insufficiency;

c) Elevation in Cl and Na levels in sweat [4].

Affected patients will rarely manifest respiratory symptoms during the period of newborns, although those under 6 months of age may show tachypnea, wheezing, increased respiratory work, overdistension of the chest and atelectasis [6].

In 10 - 20% of patients, meconium ileus may be the first manifestation of the disease. It is produced by the impaction of dehydrated meconium in the terminal ileum, with a picture of intestinal obstruction. It can be suspected before delivery by ultrasound or present at birth with progressive abdominal distension, bilious vomiting and lack or delay in the elimination of meconium, in the first 24 to 48 hours of life. Abdominal radiography usually shows dilated bowel loops, with areas of air mixed with dehydrated meconium [7].

Pathological anatomy

The macroscopic findings are limited and suggestive only of cystic fibrosis. Histopathological findings are variable and incipient in newborns with main affection to mucous glands, becoming more evident with the progression of the disease.

We list below the most representative:

a. Pancreas: 93% of cases have histopathological changes. Before 40 weeks it may look normal or with decreased acinar radio relative to the connective tissue; at six weeks of age, the changes are more evident, the acinar volume decreases and can reach up to 25% less at 5 months of age. Luminal material is identified in acini and ducts, eosinophilic, corresponding to mucinous secretion, positive to PAS staining (periodic acid Schiff) and occasionally also contains calcium.

b. Gastrointestinal tract: In newborns, meconium ileus (15% to 20%) and intestinal atresia (ileum and/or jejunum) have been associated as an initial pathological finding of cystic fibrosis in 15 to 25% of cases of cystic fibrosis. Histopathologically: in the stomach, small intestine, colon and cecal appendix the suggestive changes are: dilated glands with eosinophilic intraluminal secretion; in the small intestine: hyperplasia of goblet cells and Brunner's glands and when associated with stenosis or intestinal atresia: mucosal atrophy, fibrosis, ischemia and transmural reparative changes; Meconium peritonitis found in 33% to 50% of patients with cystic fibrosis due to intrauterine intestinal perforation [8,9].

c. **Liver and biliary tract:** In the liver, 60% of patients present clinical and morphological manifestations such as focal biliary cirrhosis manifested by proliferation of dilated bile ducts with intraluminal eosinophilic material and areas of irregular portal fibrosis and infiltration of lymphocytes.

d. **Respiratory tract:** The main morphological manifestations are: hyperplasia of bronchial submucosal glands with thick intraluminal mucus, bronchiectasis, atelectasis, pneumonia, bronchial obstruction due to mucus and inflammatory cells that expand the airways and extending to the lung parenchyma [10,11].

Treatment

There are 5 basic pillars of the treatment of this disease: 1) treat the infection, inflammation and repair the mucociliary clearance; 2) Maintain a good state of nutrition; 3) Treat insufficiency of the exocrine pancreas; 4) Respiratory physiotherapy; 5) Detection and early treatment of associated diseases: diabetes, liver disease and osteopenia

The most frequently isolated germ in sputum of patients with CF is P. aeruginosa, which colonizes approximately 60% of patients [12].

There is great interest in the use of aerosolized antibiotics, the potential benefits of using antibiotics via aerosol include; the direct deposit in the endobronchial site of the infection, less toxicity, better cost-benefit ratio and a better quality of life [6].

An evidence-based study by the American CF Association recommends the use of inhaled alpha dornase (Pulmozymes) which is a recombinant deoxyribonuclease that acts as a mucolytic by degrading DNA [4].

The increased energy expenditure in the patient with CF is due to pancreatic insufficiency, nutrient malabsorption and inflammation. An adequate diet promotes protein synthesis. Lately, the use of Kalydeco, (Ivacaftor), which works as an enhancer, has been authorized, allowing the channel to transport more chlorine. It is particularly useful for the G551D mutation, which represents only 4% of the mutations in the United States [13].

Prognosis

The prognosis is marked in particular by the commitment of respiratory function. Patients without pancreatic insufficiency have a better long-term prognosis [7].

To the increase of the survival, the advances in the digestive therapy and antibiotic have contributed decisively, being translated by an improvement of the nutritional state and diminution of the respiratory infections. Another important point that has influenced the increase in survival has been the creation and organization of the multidisciplinary CF units made up of gastroenterologists, pneumologists, nutritionists, physiotherapists, psychologists, social workers, microbiologists and expert radiologists.

Conclusions

Cystic fibrosis is a hereditary disorder that is characterized by producing viscous mucous secretions in all the exocrine glands of the organism associated with increased concentrations of electrolytes in the eccrine glands. Meconium ileus should always force us to rule out pathologies such as cystic fibrosis.

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