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Unraveling the Mysteries of Cystic Fibrosis: Causes, Symptoms, and Treatment Strategies

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ABSTRACT

In this work we present the most relevant and important data, so that the reader will be able to identify the disease "Cystic Fibrosis", regardless of the fact that in Mexico this disease is not common, thanks to the fact that in Mexico and in the world newborns are screened. In this way the rate of this disease in Mexico and the world was reduced.

In Mexico, there are 350 new cases every year, said the General Director of the National Center for Gender Equity and Reproductive Health, Dr. Ricardo García Cavazos. Thanks to this data, the purpose of this work is to guide readers in the identification of this disease and in this way generate a positive and active influence in the identification of this disease.

This disease is a disease that has its historical antecedents since the year 1595, when with the thought of a spell on a girl during her autopsy, the first clinical data that are characteristic of this disease were given. Being in the 70's where with the passage of time and as new knowledge came to what we know today.

Cystic fibrosis is an inherited multisystem disorder of children and adults, it is the leading cause of severe chronic lung disease in children. Cystic fibrosis occurs most often in white populations in Northern Europe, North America and Australia/New Zealand and is inherited in an autosomal recessive manner.

KEYWORDS: cystic, fibrosis, lung, disease.

ARTICLE DETAILS

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INTRODUCTION

In 1595, the famous professor of anatomy and botany in Leiden, Holland, Peter Pauw (1564-1617), performed an autopsy on an 11-year-old girl who was very thin due to hectic fever and had pericarditis. In the report, the doctor noted: "... the child was supposed to be bewitched ... the child was very thin ... the pancreas was bulging, cirrus and bright white ...".

In a medical book edited in 1606, written by the Spanish professor Alonso, the following paragraph can be read: "...an honorable lady says that she knows bewitched people, if when scratching their foreheads, one notices afterwards a salty taste in the fingers...".

Other ancient stories, similar to the previous ones, where the excess of salt on children's foreheads was inevitably a symptom of spells, charms, magic, demonic possession, etc., were found in many other European countries such as Russia, Poland, Czechoslovakia, Hungary, Romania, Italy, Switzerland, Austria, etc.

It was in 1905 when Karl Landsteiner described the association between thick meconium in a newborn and fibrosis of the pancreas, speculating that both phenomena occur due to an enzyme deficiency. In 1912, Sir Archibald Garrod described families, some of whose children had steatorrhea and died of bronchopneumonia, suggesting a possible recessive mode of inheritance.

In 1936, the Swiss pediatrician Guido Fanconi was the first to use the term cystic fibrosis (CF) to describe the combination of pancreatic insufficiency and chronic lung disease in children(3), but his report was poorly disseminated because it was written in German. In 1938, Dorothy Andersen associated meconium ileus with CF, noting that the histological lesions in the pancreas were identical in both conditions, and described this disorder separately from celiac disease. In the same year, Blackfan & May describe 35

children with atrophy and fibrosis of the pancreas due to thickening of secretions and dilatation of ducts and acini.

In 1943, Sydney Farber recognized CF as a systemic disease, and coined the term "mucoviscidosis". In 1945, Andersen & Hodges study 46 families of their patients and 56 other families from the literature and conclude that CF is inherited in an autosomal recessive manner. In 1953: Paul Di Sant'Agnese assigns diagnostic value to sweat electrolytes. In 1958 Shwachman and Kulczycki published their classic review of experience with 105 patients, the largest report to that date. This paper included a description of their clinical score, which, with some updates, is still used today. In 1959, L. Gibson & R. Cooke described the pilocarpine iontophoresis method of sweat stimulation and collection, which remains the standard to this day.

The 1950s were characterized by the development of centers dedicated to the study and management of CF in Europe and North America. In 1955 the US National CF Research Foundation (later CF Foundation) was created and in 1959 the Canadian CF Foundation, and in 1965 the CF International Association was formed in Paris.

In the 1960s, the outlook for affected children was still terrible as most died in childhood, after years of suffering. It was not until 1976 that Mitchell-Heggs reported the first 45 patients over 12 years of age, from 3 London hospitals. It was not until 1979 that neonatal screening became available using immunoreactive trypsin (IRT). In 1983 Paul Quinton, a CF carrier, published that the chloride impermeability he had demonstrated in sweat glands was the basis for the elevation of electrolytes in the sweat of CF patients. This was considered a decisive step in the understanding of the basic defect.

In 1989, Lap-Chee Tsui's group identified and cloned the CF gene, located on the long arm of chromosome 7, and named the protein for which it codes as CF transmembrane conductance protein (CFTR), publishing the findings in a memorable issue of the journal Science. Since then, more than 1,600 mutations have been identified, the most frequent being the one called DF508, both in Chile and in the rest of the world. At that time, it was thought that gene therapy for the disease could quickly become available, which to date is still experimental.

In the last 70 years, CF has "mutated" from a poorly understood genetic disorder, usually fatal in infants and children, to a complex multisystem disorder, affecting many children and adults. Survival has allowed the increase of associated conditions: osteoporosis, diabetes mellitus, liver disease, pregnancy, infertility, among others.

The demonstration that early and aggressive treatment improves prognosis makes it necessary to improve early diagnosis (neonatal screening) and to make the greatest efforts in the development of advances, both in conventional therapies (pharmacological, nutritional, etc.) and in the most innovative ones (lung transplantation, gene therapy).

ETIOLOGY

Cystic fibrosis is an inherited multisystem disorder of children and adults, it is the leading cause of severe chronic lung disease in children. CF occurs most often in white populations in Northern Europe, North America and Australia/New Zealand and is inherited in an autosomal recessive manner.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7q31.2 encodes a protein CFTR, consisting of 1,480 amino acids, which is expressed mainly by epithelial cells of the respiratory tract, digestive tract (including bile ducts and pancreas), genitourinary tract and sweat glands.

CFTR is a protein member of the adenosine triphosphate-binding superfamilies. The main function of CFTR is to act as a chloride channel, reabsorbing luminal chloride ions and increasing sodium reabsorption through ENaC (epithelial sodium channel) among other regulatory functions of different ion channels and cellular processes. More than 1.800 mutations related to the disease which are grouped into 6 classes, the most prevalent is Class II in which there is an abnormal folding, processing and circulation of the protein, is the deletion of three nucleotides encoding phenylalanine at amino acid position 508 (F508del), causing the protein does not fold or glucosylation, and is degraded before reaching the cell surface, causing a complete lack of CFTR protein on the apical surface of the cells. This mutation can be found in 70% of CF patients worldwide (Kliegman, 2016, p. 2196).

"A few mutations, such as 3849 + 10kbC→T, are found in patients with normal sweat chloride concentrations" (Kliegman, 2016, p. 2197).

Several patients with gene polymorphisms have few or no clinical manifestations until adolescence or adulthood, where they may present with pancreatitis, sinusitis, diffuse bronchiectasis or male infertility.

Several pangenomic studies have been performed to detect new polymorphisms associated with the severity of pneumopathy where it was detected that the polymorphism in chromosome 11, in the region between APIP (an inhibitor of apoptosis) and EHF (an endothelial transcription factor) are associated with the severity of the disease and may influence the expression of these two genes as well as the expression of other genes found in the PDHX, CD$$ and ELF5 region. In addition, a region on chromosome 20 was found to be related to the severity of pneumopathy as several genes involved in lung defense, polymorphonuclear activity, apoptosis and phagocytosis were found, among these genes are MC3R, CASS4, AURKA) (Kliegman, 2016, p. 2198).(Kliegman, 2016, p. 2198).

EPIDEMIOLOGY

With an incidence of 1 per 2500 live births, cystic fibrosis is the most common fatal genetic disease in Caucasian populations. The carrier frequency in the U.S. is 1 in 20 in Caucasian patients, but is much lower among African

Americans, Asians and Hispanics. Although cystic fibrosis is transmitted in an autosomal recessive manner, recent data indicate that even heterozygous carriers show an increased incidence of pancreatic and respiratory disease compared to the general population. (Robbins, 2015, p. 466)

PATHOGENESIS

In normal duct epithelia, chloride is transported through plasma membrane channels (chloride channels). The major defect in cystic fibrosis is related to an abnormal function of an epithelial chloride channel protein encoded by the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7q31.2. The 1,480 amino acid polypeptide encoded by CFTR has 2 cytoplasmic nucleotide-binding domains (NBD) and a regulatory domain, which contains the phosphorylation sites for protein kinases A and C. The two transmembrane domains form a channel through which chlorine passes.(Robbins, 2015, p. 466).

CFTR regulates multiple other ion channels and cellular processes, although initially characterized as a conductance channel for chloride, it is now known that CFTR can regulate multiple ion channels and cellular processes, primarily through interactions involving its NBDs. These include rectified chloride extraction channels, rectified potassium insertion channels (Kir6.1), the epithelial sodium channel (ENaC), slit junction channels, and cellular processes involved in ATP transport and mucus secretion. Of these, it appears that the interaction between CFTR and ENaC is the most pathophysiologically important in cystic fibrosis. ENaC is located on the apical surface of exocrine epithelial cells and is responsible for the uptake of sodium from the luminal fluid, so that it becomes hypotonic. ENaC is inhibited by the normally functioning CFTR, therefore in cystic fibrosis ENaC activity is increased, which greatly increases sodium uptake across the apical membrane.

The main function of CFTR in sweat gland ducts is to reabsorb luminal chloride ions and increase sodium reabsorption through ENaC. In sweat ducts a loss of CFTR function reduces sodium chloride reabsorption and results in hypertonic sweat.

In the intestinal and respiratory epithelia, CFTR determines a loss or reduction of chloride secretion into the lumina. Active luminal sodium absorption also increases and these two ionic changes increase passive reabsorption from the lumina, which reduces the amount of water in the superficial fluid layer lining the mucosal cells.

The pathogenesis of respiratory and intestinal complications in this disease seems to be due to an isotonic but low volume superficial fluid layer. In the lungs, this dehydration leads to defective mucociliary action and accumulation of hyperconcentrated viscous secretions, which obstruct the airways and predispose the patient to repeated pulmonary infections.

CFTR is involved in the transport of bicarbonate ions. The function of CFTR in bicarbonate transport is mediated by reciprocal interactions with a family of anion exchangers called SLC26, which are co-expressed on the apical surface together with CFTR. Alkaline fluids are secreted by normal tissues, whereas acidic fluids are secreted by epithelia harboring these CFTR mutant alleles. Reduced luminal pH can lead to increased mucin precipitation and formation of plugs in the ducts, with increased bacterial binding to the mucin plugs. Pancreatic insufficiency, almost always appears when there are CFTR mutations with alterations in bicarbonate conductance.(Robbins, 2015, p. 467).

CFTR GENE MUTATIONS

Class I: defective protein synthesis. It is associated with an absence of CFTR protein on the apical surface of epithelial cells.

Class II: abnormal protein folding, processing and circulation. They determine an alteration in the processing of the protein from the endoplasmic reticulum to the Golgi apparatus, the protein does not fold completely or glycosylates and is degraded before reaching the cell surface, this mutation is a complete lack of CFTR on the apical surface of epithelial cells.

Class III: defective regulation. They prevent CFTR activation because they prevent binding and hydrolysis of ATP, an essential requirement for ion transport, therefore a normal amount of CFTR is found on the apical surface but is not functional.

Class IV: reduced conductance. There is a transmembrane domain of CFTR, which forms the ionic pore for chloride transport. A normal amount of CFTR is found in the apical membrane, but with reduced function.

Class V: reduction of abundance. Affects intron cleavage sites in the CFTR promoter, thereby reducing the amount of normal protein.

Class VI: alterations in the regulation of separate ion channels. Affects the regulatory role of CFTR.(Robbins, 2015, p. 468).

Since cystic fibrosis is an autosomal recessive process, affected individuals carry mutations in both alleles.

Although cystic fibrosis remains one of the best known examples of the axiom, there is increasing evidence that genes other than CFTR modify the frequency and severity of organ-specific manifestations. The severity of pulmonary manifestations in cystic fibrosis is associated with polymorphic variants in several genes, including mannose-binding lectin (MBL2) and transforming growth factor B1 (TGFB1). MBL is a key effector of innate immunity, involved in the opsonization and phagocytosis of microorganisms, and polymorphisms in the MBL2 gene associated with a reduction in circulating protein concentrations determine a triple risk of end-stage lung disease. TGFB is an indirect inhibitor of CFTR function.

CLINICAL CORRELATION

Classic cystic fibrosis tends to present a multitude of manifestations. Pancreatic abnormalities will be present in 85 to 90% of cases. In less severe cases, there may only be mucus accumulations in the small ducts, with some dilatation of the exocrine glands. In more advanced cases, usually seen in older children or adolescents, the ducts are totally plugged, causing atrophy of the exocrine glands and progressive fibrosis. The total loss of pancreatic exocrine secretions will lead to fat malabsorption, above all, which will develop a deficiency of fat-soluble vitamins, resulting in vitamin A, D, or K avitaminosis. Hypoproteinemia will also be seen, which can be severe enough to cause generalized edema. Persistent diarrhea may result in rectal prolapse in up to 10% of children with cystic fibrosis. Such manifestations of malabsorption appear around the first year of life. This will contribute to squamous cell metaplasia of the epithelial lining of the pancreatic ducts, which may exacerbate the lesion, caused by thickened muscle secretion. Thick, viscous plugs of mucus may be found in the intestine of children, sometimes causing intestinal obstruction, known as meconium ileus. Pulmonary changes are the most serious complications of this disease. These changes arise from obstruction of the airways by viscous mucous secretions from the submucosal glands; the bronchioles are usually distended with thick mucus, associated with marked hyperplasia and hypertrophy of the mucous-secreting cells. Superinfections lead to chronic bronchitis and bronchiectasis. Lung abscesses commonly develop, mainly due to S. aureus, H. influenzae and P. aeruginosa, which are the organisms most commonly responsible for such infections. The frequency of infection may be increased by Burkholderia cepacia. This opportunistic bacterium is associated with cepacia syndrome. The liver involves, by the same basic pattern. The biliary canaliculi are plugged by mucinous material, accompanied by ductular proliferation and portal inflammation. Hepatic steatosis is commonly found in liver biopsies. Eventually, cirrhosis will develop, resulting in diffuse hepatic nodularity. This is found in less than 10% of patients. Azoospermia and infertility is found in 95% of affected male patients who survive to adulthood. There is bilateral absence of the vas deferens,(Robbins, 2015, p. 469-470).

LABORATORY FINDINGS

"The diagnosis of CF has been based on a positive quantitative sweat test (Cl- ≥60 mEq/l) combined with one or more of the following.

data: typical chronic obstructive pulmonary disease, chronic obstructive pulmonary insufficiency

documented exocrine pancreatic disease and positive family history" (Kliegman, 2016, p. 2202). This is due to very high chloride increases compared to individuals without cystic fibrosis. The gold standard for the diagnosis of cystic fibrosis is sequencing of the CFTR gene.

"Neonatal screening is another very important tool that is done in the first days of life to verify that there are no obvious clinical manifestations, such as growth retardation and chronic cough" (Kliegman, 2016, p. 2202).

For neonatal screening, most of the algorithms used in this test combine immunoreactive trypsinogen results and a limited study of DNA in dried blood samples on reagent paper; all positive screening tests should be followed by confirmatory sweat analysis. This screening has a sensitivity of ≈95%. "Neonatal diagnosis can prevent early nutritional deficiencies and improve long-term growth, as well as of cognitive function" (Kliegman, 2016, p. 2204).

CONCLUSION

Cystic fibrosis, although not very common, it is important for physicians to be competent enough to detect probable cystic fibrosis early on. If the common manifestations of cystic fibrosis are known, for example, the meconium of ileus, that a mother reports that her child has a salty taste, or that the majority of patients will present pancreatic abnormalities, etc., it would not be difficult for the physician to assume that it is this pathology. Since it is a disease that is hereditary, and also progressive, it can be difficult to identify if you do not have the necessary equipment or studies, and eventually, if it is not identified in time, and the proper treatment is not given, it can have a variety of complications in different important organs and systems, such as the pancreas or in the lungs. So it is important to perform a test such as the neonatal screening test on the newborn, or, in case the patient is suspected of having CF, the sweat test to rule out such pathology. In the event that these tests give a positive result and the diagnosis of cystic fibrosis is confirmed, it is of utmost importance to provide timely treatment and management to improve the patient's quality of life, and to achieve minimal repercussions in the future. Also, as these diseases can easily go unnoticed, it is necessary that the general population is educated about it, especially if people have or had a family member with cystic fibrosis.

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