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LIST OF MAIN ADVANCES IN THE CONTEXT OF CYSTIC FIBROSIS: SYSTEMATIC REVIEW

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ABSTRACT: Cystic fibrosis is a genetic, chronic, progressive and lethal disease, which can be previously diagnosed by the heel prick test. To analyze the main aspects of mucoviscidosis in terms of historical, epidemiological, genetic, pathogenic, clinical features, diagnosis and treatment. This is a systematic review in accordance with the PRISMA statement. The search was carried out in the MEDLINE, SciELO, SCOPUS and LILACS databases. The research was carried out independently by two researchers. Original articles were selected that addressed the object of study and published in Portuguese and English, and 38 articles were selected for qualitative analysis. Great advances were noted in the respective aspects already mentioned above, mainly in the focus on the quality of life and survival of patients, since in the last 80 years notable achievements have been obtained in terms of multidisciplinary treatment. It is concluded that it is essential to carry out new studies, especially in the long term, in order to increase survival and perhaps find a cure for this pathology.
Keywords: Cystic Fibrosis, advances, Survival.

INTRODUCTION

The present research to be discussed aims at a bibliographic survey through the theorization of scientific articles on cystic fibrosis (CF). Mediated by the authors of the present work, this survey has a theoretical nature, which seeks a specific and defined systematization about the disease. Mucoviscidosis or cystic fibrosis is an autosomal recessive genetic disease, with an incidence of 1: 2,500 live births in Caucasian populations (ALVES et al, 2007). Its presentation in the classic clinical form is that of chronic obstructive pulmonary disease, exocrine pancreatic dysfunction

and sweat chloride levels above 60 mEq/L (SPENCE, 2005).

For the purposes of understanding, cystic fibrosis in Brazil has an estimated incidence for the southern region, which is the territory closest to the Central European Caucasian population, while for other regions it decreases to about 1:10,000 live births (RASKIN et al., 1993).

For proof purposes, no other disease has mobilized family members in such an organized way, to the point of forming parent associations on the European continent, in the Americas and also in Brazil. This confirms that such measures play a key role in the evolution of patients with CF (RIBEIRO; OLIVEIRA; RIBEIRO, 2002).

The objective of this work was to carry out a bibliographical review of the cystic fibrosis pathology in terms of aspects: historical, epidemiological, genetic, pathogenic, clinical picture, diagnosis and form of treatment.

DEVELOPMENT

METHODOLOGY

This is a systematic review on the topic of cystic fibrosis, whose object of analysis is the scientific production indexed in the following electronic databases: MEDLINE, SciELO, SCOPUS and LILACS. The analysis was performed in accordance with the methodological recommendations of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for systematic review papers.

The search for articles took place between September and November 2019, using the following descriptors: "cystic fibrosis, pathophysiology of cystic fibrosis, symptoms of mucoviscidosis and cystic fibrosis". In the aforementioned databases, the following filters were applied: article and available text.

Initially, 1,257 articles were found. Then, the scientific documents were selected for inclusion in the study through the evaluation of titles and abstracts, independently by two researchers, in order to comply with the following inclusion criteria: articles closely related to the theme and publication available in English and Portuguese. Thus, all those who did not meet the pre-established criteria were excluded.

After evaluating the titles and abstracts, 256 works were selected, of which, after applying the eligibility criteria, 56 articles were included. 18 papers were excluded from the review due to unavailability of the online version.

Finally, after the critical analysis of the 38 selected scientific documents, carried out by two researchers independently, the articles were analyzed and categorized as follows: type of study, sample size, place of publication, type of population studied, objectives of the work and main findings.

RESULTS AND DISCUSSION

Cystic fibrosis is a genetic disease, with chronic, progressive and fatal development, resulting from a defect in the transmembrane regulatory protein (CHAVES; CUNHA, 2012; PIZZIGNACCO; MELLO; LIMA, 2010; BARNIL, et al., 2017). In the last 80 years, CF has emerged from a scenario that had it as unknown for recognition, being one of the most relevant hereditary, potentially lethal diseases. This context is related to the study of molecular biology in genetics and CF gene sequencing, leading to knowledge of the biochemical mechanisms responsible for the pathophysiology of the disease (LYCZAK; CANNON; PIER, 2002). The main historical moments of mucoviscidosis are shown in table 1.

EPIDEMIOLOGY

One in every 25 people in the population carries the defective CF gene, but it is only

1905	Landsteiner exposed meconium ileus relating it to exocrine pancreatic deficiency
1935	Fanconi reported patients with clinical features of celiac disease, but with exocrine pancreatic insufficiency related to pulmonary pathology
1938	Dorothy Andersen described the clinical, anatomical, pathological, and epidemiological features of cystic fibrosis
1950	Farber coined the term *mucoviscidosis*
1953	Di Sant'Agnese found that CF patients had increased levels of salt in their sweat
1955	In the United States, the *Cystic Fibrosis Foundation*
1958	Gibson and Cooke developed pilocarpine iontophoresis (sweat test) as a method of diagnosing CF
1964	Was inaugurated on *International Cystic Fibrosis (Mucoviscidosis)Association* ICF(M)A
1968	Shwachman and Holsclaw reported blockage of the vas deferens and seminiferous tubes, thus underpinning the infertility present in most men with CF.
1983	Paul Quinton and his team set out to discover the basilar defect in chloride ion secretion
1985	Group of researchers located the CF gene, which was cloned and sequenced by the same set of scientists in 1989
1990 -2017	Search for early diagnosis and treatments that aim to promote a better quality of life for the patient.

Table 1: Historical moments of cystic fibrosis.

Source: adapted from AGNESE et al., 1953; SUPER, 1992; RIBEIRO; OLIVEIRA; RIBEIRO, 2002; LYCZAK; CANNON; Pier, 2002.

expressed when a child inherits the defective Cystic Fibrosis Transmembrane Conductance (CFTR) gene from both parents (COLLINS et al., 1999). This fact is consistent with a frequency observed by Alves (2007), in which approximately 1 in every 2,500 live births are carriers of the pathology. According to data from the World Health Organization (W.H.O.), In 2009, the prevalence of CF in Brazil was 1 case in every 6,902 individuals, so that the state of Rio Grande do Sul has the highest incidence, 1 case in every 1,587 births alive (RASKIN, 2001).

In 1938, when cystic fibrosis was identified and described for the first time, survival was very low, children barely reaching the age of five. It was considered a childhood disease, with more than 75% of affected children dying in the first year of life (BERNARDI et al., 2013). Advances in diagnosis and therapeutic methodologies have increased the life expectancy of patients with cystic fibrosis. According to Reis et al (2000), the dense majority of authors encourage survival around 25 to 30 years, so that to achieve this survival, a diagnosis as early as possible is necessary, along with this, support is extremely important. multi-professional.

GENETICS

The gene that encodes the onset of CF is located on the long arm of chromosome 7, at the q31 locus, encoding a protein called Transmembrane Conductance Regulator in Cystic Fibrosis, consisting of 1,480 amino acids, which is responsible for transporting chlorine in the apical membrane of exocrine epithelial cells, thus regulating and participating in the transport of electrolytes through cell membranes (GOMIDE et al., 2007).

More than 1,500 different mutations have already been found in this gene (WAGENER; A HEADLEY, 2003). However, the most frequent of them occurs through a deletion of three base pairs, resulting in the loss of an amino acid (phenylalanine) at position 508 (DF508) of the CFTR protein (BIAZOTTI et al., 2015). According to Alvarez et al. (2004), in their study, 81% of cystic fibrosis patients monitored at UNICAMP had the DF508 mutation.

PATHOGENESIS

Obstruction of the sodium channel leads to a compensatory influx of the ion to maintain electroneutrality, with consequent influx of water, thus forming a thick mucosa characteristic of the pathology. In the classic forms, the mucus becomes progressively thickened over time, so that part of this alteration is due to the CFRT genetic defect, modifying the airway mucosa (REISINHO; GOMES, 2016). In CF, there is a localized immunodeficiency in the upper airways that predisposes to bacterial infections, this whole context is due to CFRT dysfunction, which prevents the secretion of electrolytes and water into the lumen of the respiratory tract, thus, the lysis mechanisms bacteria become harmed (CHAVES et al., 2007).

The clinical expression of the disease is very diverse (PIZZIGNACCO; MELLO; LIMA, 2011). In general, it presents as a multisystemic involvement, characterized by a progressive pulmonary pathology, disease that affects the hepatic system, exocrine pancreatic dysfunction, problems in intestinal capacity, male infertility and high concentration of electrolytes in sweat (DALCIN; SILVA, 2008).

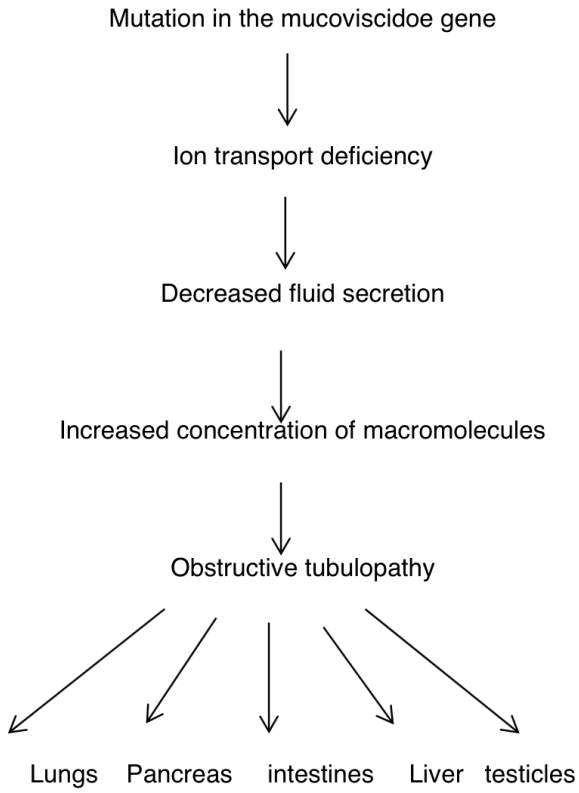

Figure 01 – CF physiopathogenesis.

Source: adapted from RIBEIRO; OLIVEIRA; RIBEIRO, 2002.

PATHOLOGY AND CLINICAL PICTURE

Cystic fibrosis is characterized by a varied clinical picture, such that there is extensive dysfunction of the exocrine glands, thus resulting in a set of manifestations and complications, such as: chronic suppurative bronchitis with malnutrition of the lung parenchyma, malabsorption of nutrients leading to malnutrition, diabetes mellitus and impairment of the male and female reproductive system (FIATES et al., 2001).

The primary pulmonary alterations arise in the lower airways and are characterized by hypertrophy and dilation of the mucous glands. Thus, with the onset of inflammation, inflammatory changes, squamous metaplasia and disruption of the ciliary architecture appear (FEITEN et al., 2016). The manifestation of CF is predominantly

in the bronchial tissue, so that the most common infectious expression is bronchitis. Subsequently, bronchiectasis, rupture of the alveoli and fibrosis appear, which will cause hypoxia, thus altering the vascularization of the lung. Obstructive ventilatory disorders quickly develop, predominantly in the smaller airways (CONTO et al., 2014).

In the pancreas, however, there is an obstruction of the ducts by thickened secretion, thus causing inflammation and fibrosis, interrupting the functioning of the islets of Langerhans until the final stage of the pathology, it is worth noting that this condition - pancreatic insufficiency - develops in a dense part of the carriers of cystic fibrosis. It is worth mentioning that diabetes occurs later and is easier to control than the most common forms of diabetes in children (SALVIANO, 2018). According to Alves et al. (2007), diabetes affects 15-30% of adults with CF and its prevalence tends to increase with the increase in the patient's life expectancy, starting, on average, at twenty years of age.

In the liver, there may be jaundice due to obstruction of the biliary canaliculi, in older patients there may be eseatosis and focal biliary cirrhosis. In this same situation, the patient with mucoviscidosis may have clinical symptoms of cholecystitis and cholelithiasis caused by mucus impaction (MAUCH et al., 2016).

DIAGNOSIS

There are several reasons for the physician to suspect CF, but the diagnosis is made by the pediatrician, which is carried out by carrying out neonatal screening, using the dosage of immunoreactive trypsin, which is recommended by the Ministry of Health. It is worth noting that this test detects trypsin, which is altered in patients with CF (SILVA FILHO et al., 2003). The standard exam for sweat testing is necessary, which consists of stimulating the production of sweat, so that the concentration of Na+ and Cl- ions can be verified (MOTA et al., 2015). According to Mattar et al. (2010), the sweat test has a very accurate confidence in diagnosing cystic fibrosis.

The diagnosis of mucoviscidosis is also based on clinical findings – in view of its sovereignty –, by means of common manifestations with pulmonary, gastrointestinal and case reports on the pathology in the family (ROSA et al., 2008).

It is extremely important to point out that cystic fibrosis has a spectrum of manifestations that varies widely, so that there may be cases of intrauterine death, even asymptomatic patients who are discovered by more complex tests such as DNA mutation analysis (ARAÚJO et al, 2008).

In Brazil, the diagnosis ranges from 1.6 to 9.6 years old (LUDWIG NETO, 2009). In the work carried out by Andrade et al. (2001), with 52 patients at the Hospital das Clinas de Porto Alegre (HCPA) the mean age at diagnosis was 2.95 ± 3.11. In studies carried out in Florianópolis at the Hospital Infantil Juana de Gusmão by Fiantes et al. (2001), 54.5% of CF patients were diagnosed before the first year of life. In the research by Rozov et al. (2013), 152 patients with mucoviscidosis were followed up in a clinical study on the quality of life of CF patients, thus finding an average diagnosis of 9.3 years. Alvares et al. (2004), in their study, analyzing 104 CF patients over a period of 10 years, found an average of 2.4 years of age at diagnosis. In the research by Ziegler et al. (2007), the median of diagnosis was 10 years, in adolescent patients at HCPA. Thus, according to the studies, it is observed that the diagnosis of cystic fibrosis occurs in a certain way in childhood, but the time interval for this diagnosis is quite expressive.

TREATMENT

In summary, it can be said that, despite the relevant advances regarding the knowledge of the disease and the quality of life of patients with cystic fibrosis, there is still no specific treatment for CF, which may be related to its multisystemic and chronic nature (SANTOS et al., 2004). It is worth remembering that this pathology requires a multidisciplinary team, so that the monitoring of cystic fibrosis patients in specialized clinics increases survival and improves well-being (BREDEMEIER; GOMES, 2007; CABIZUCA et al., 2010).

FINAL CONSIDERATIONS

The present study described above tried to clearly and concisely objectify the respective points about cystic fibrosis and its aggravating factors. In view of this, such a survey that had been carried out, sought to address the various areas of this subject with regard to its clinical and pathophysiological implications.

The respective results raised demonstrate a margin of parallelism in the face of the concepts addressed about cystic fibrosis, which consists of a disease of genetic predominance, which affects countless people around the world. Therefore, the academic content exposed in this work reaffirms that there is still much to know about this genetic disease, although studies are causing exponential knowledge about this purpose of understanding.

The researchers showed relevant interest in this review, although some journals have caused significant problems of understanding and textual prospecting, given that this disease is still in the phase of proper knowledge of the scientific and academic scope of medical schools spread throughout the world.

Finally, it is worth emphasizing that the measures taken regarding this bibliographical review on cystic fibrosis are allied to academic and social perspectives and that preserve human resources in general, given that the survey carried out sought to cohesively synthesize the relevance of this issue for the entire political and social sphere.

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