

## INSIGHTS INTO CLINICO-MORPHOLOGICAL FEATURES AND MANAGEMENT OF CYSTIC FIBROSIS

Mioara-Florentina Trandafirescu<sup>1</sup>, Angela Moloce<sup>2</sup>, Carmen Ungureanu<sup>1</sup>, Raluca Vasile<sup>3</sup>, Maria Magdalena Leon<sup>4\*</sup>, Alexandra Maștaleru<sup>4</sup>, Elena Cojocar<sup>1</sup>

“Grigore T Popa” University of Medicine and Pharmacy – Iasi

<sup>1</sup>Department of Morphofunctional Sciences I

<sup>2</sup>Cardiology resident doctor

<sup>3</sup>Psychiatry specialist doctor

<sup>4</sup>Department of Medical Specialties I

\*Corresponding author: E-mail: [leon\\_mariamagdalena@yahoo.com](mailto:leon_mariamagdalena@yahoo.com)

**ABSTRACT:** Mucoviscidosis/ cystic fibrosis represents a potentially fatal disease, characterized by heterogeneous clinical features, mainly pulmonary, digestive, cardiac, but other systems may be involved. In recent years, there were constant concerns to identify the pathogenic disease mechanism. The molecular genetics techniques revealed in 1989 that cystic fibrosis comes from the defects of a single gene that decodes the cystic fibrosis transmembrane receptor (CFTR), a chloride channel that is distributed on a large scale in the membrane surfaces. CFTR is expressed by the airways epithelium, paranasal sinuses, pancreas, bowel, biliary tract, vas deferens and sweat glands epithelia. Abnormalities in CFTR function cause pulmonary infections and bronchiectasis, leading to a respiratory insufficiency, pancreatic insufficiency and malabsorption, episodic intestinal obstructions, liver disease and male infertility. At the moment, a symptomatic treatment is available as respiratory physiotherapy, antibiotic therapy, nebulization with mucolytics and bronchodilators, administration of protease inhibitors for pulmonary symptoms, administration of pancreatic enzymes substitutes and vitamins for pancreatic insufficiency. Though the survival rate of patients with cystic fibrosis has known important improvements in the last years, this disease remains a redoubtable adversary not only for the patient, but also for his family. Furthermore, the extremely complex physiological, biochemical and genetic profiles remains of maximum interest for the actual medical research.

**Keywords:** cystic fibrosis, genetic profile, pulmonary symptoms, gastrointestinal symptoms

### Introduction

Mucoviscidosis/ cystic fibrosis constitutes a genuine model of potentially lethal disease, showing an extraordinary clinical polymorphism, with apparently heterogeneous manifestations, like chronic bronchopneumopathy, pancreatic and liver sclerosis, myocardial fibrosis and necrosis, some organ atresia. Although the survival rate of patients with cystic fibrosis has known important improvements in the last years, this disease remains a redoubtable opponent not only for the patient, but also for his family [1]. Moreover, the extremely complex physiological, biochemical and genetic profiles remain of maximum interest for the actual medical research.

In this context, it is not random the fact that 28 years ago, in 1989, the research group coordinated by Lapche Tsui and Jack Ruordan, from the Children Hospital in Toronto, together with Francis Collins from the Medical Institute Howard Huges, University of Michigan, have identified the cystic fibrosis gene, discovery that represents one of the most important achievements of the human genetics [2]. The identification of this gene opened essential exploring pathways in knowledge of disease, in a deeper approach and even the idea of genic therapy solution for one of the most difficult pathology and public health problem [3].

Initial data about cystic fibrosis can be found in the middle Ages German folklore, when people were talking about some *bewitched* children that died young; they had a

salted taste of the skin. Scientific information about the disease starts in 1905, when Landsteiner connects for the first time the meconium ileus and pancreatic damage. In the next years, many authors described the disease symptoms, without bundling them into a characteristically syndrome [4]. In 1936, Fanconi and collaborators described a congenital pancreatic cystic fibrosis, associated with bronchiectasis, distinguishing it from celiac disease, and considering that this is a very rare disease and with a lethalevolution [5]. However, cystic fibrosis was not recognized as a distinct disease until 1938, when Dorothy Anderson and his school, named the disease „pancreas cystic fibrosis”. Actually, only in 1945 Farber reveals a general affection of the exocrine glands, expressed by an abnormal mucus secretion and introduces the concept of „mucoviscidosis”, marking thus a new stage in the disease knowledge. In the same period, Glanzmann defines the disease "dysphoria *entero-broncho-pancreatica congenita familiaris*", highlighting the resonances of this mucus pathology, and Bodian proposes the term of „mucosis" [6].

An ulterior step is linked to the sweat electrolytic anomalies, findings that will change the pathogenic disease conception, observing that the glands that do not produce mucus are equally affected. From this point of view, Kessler and Andersen in 1951 remark a particular sensitivity to heat of patients with cystic fibrosis, and in 1953, Di Sant'Agnes and his collaborators demonstrate the electrolytic anomalies in the sweat of affected children. All these data conducted to identification of the pathognomonic diagnosis test for patients that suffer from this disease [3]. Later, scientifically paperworks regarding physiopathological aspects of cystic fibrosis have tried to fundament the nature of the mucus structure alteration and the significance of the sweat perturbations, in the context of a generalized disease and implicit in discovering the anomaly that underlines the disease. The next step is characterized by numerous studies and researches that aim to detect the anomaly

that underlies all the disturbances of the disease [6]. Although numerous data highlighted the autosomal recessive transmission, the unique defect assumed to be genetic has not been identified and demonstrated for a long period of time [4,7].

Symptomatology polymorphism and the complexity of characteristic pathogenic mechanisms of cystic fibrosis have constituted a difficult stage to surmount. The ulterior development of molecular genetics techniques have revealed the intimal pathogenic mechanisms understanding, culminating in 1989 with the detection of the specific loci of the responsible gene, on the long arm of the 7th chromosome and its protein, that intervenes in the physiopathological mechanism at the level of all the exocrine glands [4,8].

Thus, cystic fibrosis originates from a single gene defects that decodes the cystic fibrosis transmembrane receptor (CFTR), a chloride channel that is distributed on a large scale in the membrane surfaces. The airways, paranasal sinuses, pancreas, bowel, biliary tract, vas deferens and sweat glands epithelium express CFTR and depend on it for its normal function. Deficiencies CFTR function cause pulmonary infections and bronchiectasis, leading to respiratory insufficiency, pancreatic insufficiency and malabsorption, episodic intestinal obstructions, liver disease and male infertility [4]. The chloride transport alteration mediated by CFTR induces a marked increase of chloride in sweat, being the most important feature for the final diagnosis of cystic fibrosis. Early physiopathology was difficult to study in newborn children [9].

Therefore, it emerged the perspective of new logical steps in biochemical anomalies correction, through pharmacological methods, as well as the genic therapy intervention [10].

Cystic fibrosis is a disease that is almost constantly diagnosed in the early childhood. The new-born screening has been gradually adopted by all the states. In 2013, The Foundation for Cystic Fibrosis reported

that 62% of all patients are now diagnosed at birth and 72,4% in their first year of life [11].

In Romania, as it was underlined at the First National Congress of Mucoviscidosis (Cystic Fibrosis) with international participation, in Timisoara, 7-9 may 2003, the disease is incompletely diagnosed; there is no clear and real approach evidences close to reality, although constant concern in this direction have existed earlier than in some neighboring countries. The first organized studies regarding cystic fibrosis started in the Pediatric Clinic from Timisoara in 1964-1965, by Professor Eugen Alexandru. The initial research group was later transferred to the II<sup>nd</sup> Pediatric Clinic, in 1974, once this was founded. The research activity was continued, augmented and internationally affirmed by founding in 1987 the Mucoviscidosis Center, in 1992 the Mucoviscidosis Romanian Association and its affiliation to Cystic Fibrosis International Association, inclusive as a voting member in CFW, through the efforts of professor Ioan Popa [12].

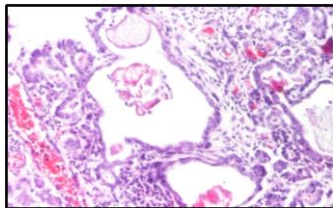
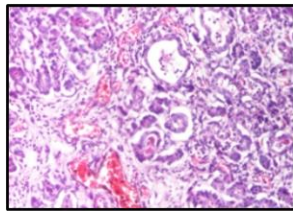
Nowadays, patients with cystic fibrosis benefit from Mucoviscidosis National Program (children and adults), included in the chapter – „National Health Program for intransmissible diseases” – „Diagnosis and treatment National Programme for rare diseases”.

Cystic fibrosis (engl. "*cystic fibrosis*"; franc. "*mucoviscidose*") is considered one of the most frequently autosomal recessive genetic diseases in Caucasian population, with a chronic, progressive and potentially deadly evolution. It is defined as a generalized stress of the exocrine glands, predominantly on the ones that secrete mucus, with clinical consequences: exocrine pancreatic insufficiency, chronic pulmonary disease and increased concentrations of chloride and sodium in sweat [13]. Cystic fibrosis clinical manifestations vary not only between people from different families, but also between people from the same family. In most of the cases, the disease is diagnosed before adolescence, but in some situations, this remains asymptomatic until adult age [13].

The symptomatology fluctuates with age. Thus, 10% of the affected new born children have meconium ileus – concretely an intestinal occlusion because of a thick meconium. The implication of two major systems, respiratory and digestive, under the form of repetitive respiratory infections and some specific signs of malabsorption syndrome is evident [14]. The involvement of respiratory system prevails, due to bronchiole obstruction with thick and viscous mucus, which favors multiplication and growth of microorganisms, with the appearance of recurrent respiratory infections. Digestive system involvement is reflected in 85% of patients by a pancreatic exocrine insufficiency, affecting the production of enzymes, obstruction of the pancreatic duct and thus lipoprotein malabsorption [4]. The level of pancreatic insufficiency is a marker of the phenotype severity. It is difficult to realize an inventory and a status of the clinical signs, although lung and gastrointestinal manifestations prevail. But with the introduction of screening tests for cystic fibrosis in newborns, an increasing proportion of children are diagnosed before symptoms appear [15].

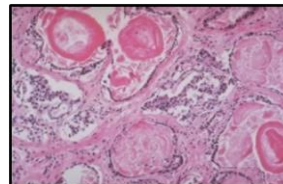
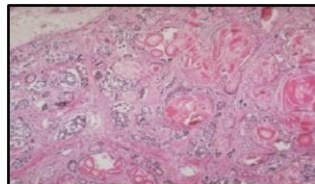
From the physiopathological point of view, sweat gland abnormality leads to an excess of sodium chloride that is secreted along with the sweat, and this salt loss is usually responsible for acute dehydration, in case the patient is exposed to heat. The disease implies other organs, especially those of reproductive system and liver. The injury of the deferent duct with obstructive azoospermia makes 98% of the affected mento be sterile. The hepatic involvement begins like a hepatomegaly in 30% of cases and in 9% of cases like a hepatic insufficiency, caused by the intrahepatic and extrahepatic biliary duct obstruction through a pancreatic compression. This subsequently leads to the appearance of liver cirrhosis [12]. Regarding prognosis, if the disease is not treated, the median survival rate is 3 to 5 years [16].

From histopathological point of view, the consequence for the damaged transport conditions in cystic fibrosis is represented by secretion of a specific viscous, and adherent to the epithelium mucus in various organs. The obstruction of the excretory ducts causes atrophy, fibrosis and parenchymal destruction [9,17]. For example, first prenatal changes at the pancreas level can be observed at 18-20 weeks of intrauterine pregnancy, by an accumulation of an eosinophilic material and secretory duct dilatation. On the microscope it can be visualized the enlargement of ducts and acini. In children with mucoviscidosis and even in the newborn it can be seen the interstitial fibrosis, with the increase of secretions in ducts and acini. The pancreatic lesions differ considering the disease severity and the patient's age [9, 18]. Therefore, in patients with a longer history of the disease, the pancreas has small dimensions, an increased consistency, with fats that are found in large quantities, with multiple cysts and small and large pancreatic ducts obstructed by viscous secretions (fig.1-2).



**dilation, exocrine atrophy, microcysts, HEx40/100**

**Fig.1. Pancreas-duct**



**Fig. 2. Pancreas –intraluminal eosinophilic concretions; large/small lumen ectasia with mucus in lumen, HEx100/40**

Although we could not talk about an effective treatment against cystic fibrosis for a long period of time, an appropriate diagnosis and symptomatic treatment have made it possible to increase the average survival rate to 25-30 years [3, 19]. A symptomatic treatment is available as respiratory physiotherapy, antibiotic therapy, nebulization with mucolytics and bronchodilators, administration of protease inhibitors for pulmonary symptoms, administration of pancreatic enzymes substitutes and vitamins for pancreatic insufficiency [20]. In severe stages, a triple transplant (heart-lung-liver) appears to have promising results, but the main obstacle is the availability of organ donors [21]. Among the latest therapeutic advances of cystic fibrosis stand gene therapy, but also other promising strategies are in study and have as an objective the compensation of the production and/or of the malfunctioning of the protein that depends on the mutation type of CFTR gene (cystic fibrosis transmembrane receptor) [22].

### Conclusion

While in the past it was considered that cystic fibrosis / mucoviscidosis is a disease of the lungs and digestive tract, characteristic of small children, recently this became a complex multisystemic disease that affects also adults. The cystic fibrosis management remains up to date and extremely important for researchers in the medical field, and also for clinicians.

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