

# Cystic Fibrosis

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## SUMMARY

Cystic fibrosis (CF) is a multisystemic autosomal recessive disease caused by a defect in the expression of CFTR protein, i.e. chloride channel present in the apical membrane of respiratory, digestive, reproductive and sweat glands epithelium. It primarily occurs in the Caucasians, while being considerably or exceptionally rare in persons of other races. Absence, deficit or structural and functional abnormalities of CFTR protein lead to mucosal hyperconcentration in the respiratory, digestive and reproductive systems and malabsorption of chloride and sodium in the sweat glands. Thus, the clinical features of patients' with CF are predominated by respiratory, digestive and reproductive disorders, as well as the tendency to dehydration in the condition of increased sweating. Beside genotype variations, the degree of disease manifestation is also essentially influenced by various exogenous factors, such as the frequency and severity of respiratory infections, the level of aero-pollution, quality of immunoprophylaxis, patients' nutritional condition and other. Chloride concentration of over 60 mmol/L in sweat, a high level of immunoreactive chymotrypsinogen in blood and the verification of homozygous mutation of CFTR gene are the basic methods in the diagnostics of the disease. CF belongs to the group of severe and complex chronic diseases, and therefore requires multidisciplinary therapeutic approach. Owing to the improvement of healthcare provision, most patients with CF now survive into adulthood. In addition, their quality of life is also considerably improved.

**Keywords:** cystic fibrosis; chloride channels; diagnostics; treatment

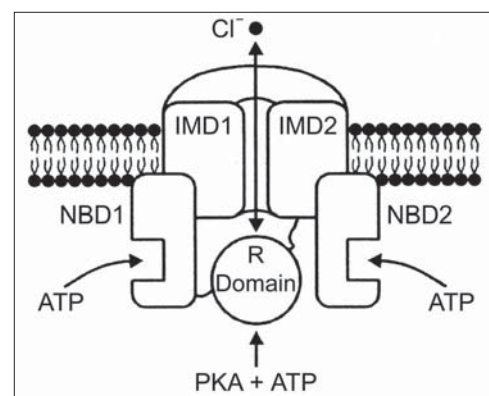
## INTRODUCTION

Cystic fibrosis (CF) or mucoviscidosis is a multisystemic autosomal recessive disease caused by a defect in the expression of chloride channels (cystic fibrosis transmembrane conductance regulator – CFTR protein) present at the apical membrane of the respiratory, digestive, reproductive and sweat epithelium [1]. It primarily occurs in the population of the European origin (1:2000-3200), while in the population groups of other continents it is 3-4 times rarer [2-7]. The frequency of heterozygous carriers of the pathologic gene in the Caucasians rates 1:25-30 [5, 8, 9]. Although involving most complex and severely ill patients, their prognosis today, owing to the improvement of healthcare insurance, is far better than it used to be [4-7, 10-13].

## CFTR PROTEIN

In the basis of the disease is the defect of the CFTR gene which provides the synthesis of the CFTR protein responsible for the transport of chloride ion at the cell membrane level [14]. The CFTR gene was cloned by Riordan et al. in 1989 [15]. It is located on the long arm of the chromosome 7 (7q31.2). Its length is 250 kilobases and contains 27 exons. Owing to this knowledge, up-to-date DNA analysis represents a precious method in the prenatal and postnatal diagnostics of the disease, as well as in the disclosure of its heterogeneous carriers [4, 9, 16, 17].

CFTR protein is a cAMP-dependent ion channel located at the apical membrane of the respiratory, digestive, reproductive and sweat epithelium [18]. It consists of 1480 amino acids distributed by a certain order into five basic polypeptide segments – two intramembranous, two nucleotide-binding and one regulatory (Figure 1). The intramembranous segments (IMD1 and IMD2) form a channel for the passage of chloride ion, nucleotide-binding (NBD1 and NBD2) which, in bondage with ATP, provides energy for the CFTR protein functioning, while the regulatory segment (R), after activation (phosphorylation) mediated by the specific cAMP-dependent protein-kinase A or C, triggers the process of the separation of CFTR protein intramembranous segments and opening of the chloride channel [1, 19, 20].



**Figure 1.** Schematic presentation of CFTR protein

IMD – intramembranous domains; NBD – nucleotide-binding domain; R – regulatory (domain); PKA – cAMP-dependent protein kinase (according to ref. 19)

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Thus, CFRT protein function is carried out in the manner that, under the influence of corresponding stimuli, it opens enabling transmembranous diffusion of chloride ions into the direction of electrochemical gradient, which is of key significance in the activity of secretory processes in the respiratory, digestive and reproductive system, as well as in the reabsorption of chloride and sodium in the sweat glands [21]. Contrary to respiratory, digestive and reproductive system, where both secretory and reabsorptive processes evolve simultaneously and in balance, in the sweat glands distal tubules only reabsorptive processes take place [18, 22]. Chloride secretion is followed by the paracellular transport of sodium and water, while the mechanisms of their reabsorption or absorption are reversed, i.e. chloride ions and water molecules follow sodium transmembranous (transcellular) transport [22]. Beside the exclusively reabsorptive characteristic, the difference in the epithelium of the sweat glands distal segment, in relation to the respiratory, digestive and reproductive epithelium, is that the transport of both sodium and chloride evolve transcellularly [22].

### PATHOGENETIC BASIS OF THE DISEASE

Phenotype expression of the CFTR gene in CF is followed by the absence, insufficient amount or structural and functional defect of the CFTR protein [18, 23]. Up-to-now over 1500 genetic mutations have been discovered that are responsible for the occurrence of this disease [16]. In 70-80% of patients CFTR gene mutation has been registered, followed by phenylalanine deletion at the position 508 ( $\Delta F508$ ), with 50% in homozygous condition and 25-30% in the combination with some other genetic abnormalities [5, 24, 25].

Due to the defect in CFRT protein function, patients with CF develop hyperconcentration of mucus in the respiratory, digestive and reproductive system, as well as malabsorption of chloride and sodium in the sweat glands [18]. In the first case it is related to the insufficiency of the intraluminal efflux of chloride, and in the second of the inability of its reabsorption. Therefore, the clinical features of patients with CF are predominated by respiratory and digestive disorders, as well as a marked tendency of dehydration in the state of increased sweating [26, 27]. The classical form of the disease is characterized by rather typical clinical features already evident during the first months after birth or somewhat later so that in 97-98% of cases it is diagnosed before age 18 years, with about 70% until completed second year (Figure 2) [4, 28]. The dependence of phenotype on the genotype is evident, but not also absolute [28]. Regarding the question of exocrine pancreatic insufficiency, it has been confirmed, which is not the case with the respiratory, hepatobiliary and intestinal component of the disease [29]. Thus, for example, in the homozygous  $\Delta F508$  mutation ( $\Delta F508/\Delta F508$ ) exocrine pancreatic insufficiency is almost regularly present, while in the combination R111H and 3849+10kbC $\rightarrow$ T mutation it is preserved [16, 29, 30]. On the other side, the combi-

nation  $\Delta F508$  and non- $\Delta F508$  gives exocrine pancreatic insufficiency in 72% cases, and two non- $\Delta F508$  mutations in only 36% [30]. Also, in some mutations, among which 3849+10kbC $\rightarrow$ T, chloride concentration in sweat is normal [16]. Beside genotype, in the phenotype expression of CF essential participation is also displayed by various exogenous factors, such as the frequency and severity of respiratory infections, level of aero-pollution, quality of vaccinal protection, patients' nutritive status and other [29, 31, 32, 33]. It is understood that the level of disease manifestation is also essentially conditioned by the patient's age.

### CLINICAL FEATURES

Defect in the secretion of chloride, sodium and water followed by the formation of hyperviscous mucus at the level of respiratory, digestive and reproductive systems represents a key problem in patients with CF, while the insufficiency in the reabsorption of these ions at the level of sweat glands is of secondary significance [4, 5, 8, 16, 34].



Figure 2. A 12-year-old boy with classical cystic fibrosis

Respiratory problems are present in over 90% of patients with CF [5]. They are usually manifested already in the first months after birth featuring pertussis-like cough, repeated episodes of bronchiolitis or obstructive bronchitis. Due to difficulties with elimination of hyperviscous secretions and pulmonary hypoventilation, the disease is associated with the development of recurrent bronchopneumonia and pulmonary atelectasis that are sometimes also additionally complicated by a pulmonary abscess and pneumothorax. Recurrent otitis is often seen, followed by conductive deafness and in older children by purulent sinusitis and nasal polyps. The most frequent causes of infective complications in CF are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Burkholderia cepacia* [5, 8, 16, 35]. In the later phase of the disease there is the development of bronchiectasis and progressive pulmonary fibrosis with emphysema and pulmonary hypertension. At this point there is usually the presence of club fingers as well. About 90% of patients with CF die due to cardiorespiratory failure [5, 36].

Exocrine pancreatic insufficiency occurs in about 85% of children with CF [6, 16]. It develops as the result of pancreatic drainage tubes obstruction and secondary atrophy of acinar tissue. Due to the lack of pancreatic enzymes, which play the major role in the digestive process, there is the development of the malabsorption of nutritive substances with global malnutrition. The child's appetite is often preserved, and sometimes even increased. Stools are more frequent, abundant, fatty and putrid. In more severe cases of the disease, particularly in children of the youngest age, a prolapse of the rectal mucosa can be also seen [37]. It is important to point out the fact that, owing to the compensatory effect of breast milk lipase and amylase, malabsorption syndrome in infants on optimum natural nutrition can be mild, and even unnoticeable [38].

In 10-20% of neonates with CF, particularly those with the  $\Delta F508/\Delta F508$  genotype, meconium ileus is seen, sometimes associated with prenatal intestinal perforation and peritonitis [5, 16]. Episodes of bowel obstruction due to the thickened mucus, intussusception and intestinal volvulus are not rare even later [5, 6, 37]. There is also a possibility of mucous impaction of the appendix with subcutaneous appendicitis and periappendicular abscess [16, 37].

Chronic pancreatitis is a rare complication of CF seen in patients with the  $\Delta F508/\Delta F508$  genotype and a relatively preserved acinar tissue [16, 39]. Insulin-dependent diabetes mellitus caused by scarring destruction of the Langerhans islets occurs in 1% of patients up to completed five years, and in 12% among those aged 13-19 years [11, 12, 40].

Cholestasis is found in 20-30% of patients, and is mainly of milder degree [5, 16]. Liver steatosis occurs in 15-30%, focal biliary cirrhosis in 10%, and multilobular biliary cirrhosis and portal hypertension in only 2-5% of patients with CF [5, 16]. Cholelithiasis is considerably more frequent in relation to the general population and mainly occurs in the second decade of life or later [16, 37]. In 40% of patients with CF a dysfunctional or micro vesica fellea can be seen [27]. Although being independent of genotype,

liver changes are often associated with meconium ileus and exocrine pancreatic insufficiency [16].

The consequence of exocrine pancreatic insufficiency and/or cholestasis, as a part of CF there is also the development of other manifestations, such as osteopenia and osteoporosis, hypoproteinemic oedema and discharges into free body cavities, hemorrhagic diathesis due to the deficit of vitamin K-dependent coagulation factors (II, VII, IX and X), peripheral neuropathy and haemolytic anaemia caused by vitamin E deficiency and other [5, 16, 41]. Due to the associated deficit of proteins and minerals, rachitis is rare [16]. Because of chronic cough, malnutrition and abdominal distension, a significant number of CF patients has inguinal hernia, while 25% present with gastroesophageal reflux, among whom half of them have also gastroesophageal reflux disease [16, 37].

As aforementioned, chloride malabsorption in the sweat glands does not feature so drastic clinical manifestations. Pathological concentration of chloride in sweat (>60 mmol/L) is disclosed in about 98-99% of patients with CF [4]. Chloride is eliminated with sodium and potassium, so that such patients, under the condition of increased sweating, show a tendency to hyponatremic dehydration, hypokalemia and metabolic alkalosis [8, 10, 43]. Secondary hyperaldosteronism induced by hypovolemia and hyponatremia have essential participation in the development of hypokalemia and metabolic alkalosis. Hypokalemia is also contributed by metabolic alkalosis, which does not only shift potassium into the cell, but also favours its renal loss [44].

## DIAGNOSIS

Determination of chloride concentration in sweat (sweat test) is the first procedure in the diagnostics of CF. Chloride level in sweat of over 60 mmol/L is considered pathological and below 40 mmol/L normal, while 40-60 mmol/L is border-line [5, 6, 16]. The sweat test does not have a diagnostic value in neonates aged below the first seven days or of body weight less than 3000 gr, and neither in patients with oedema or eczema [6, 16]. When analyzing sweat test findings it should be kept in mind that border-line or slightly increased chloride rates in sweat can be also found in other pathological conditions, such as untreated adrenal insufficiency, ectodermal dysplasia, glycogenosis type 1, hereditary nephrogenic diabetes insipidus, hypothyreosis, hyperparathyroidism, mucopolysaccharidosis, fucosoidosis and severe malnutrition [16, 45]. Also, sweat test findings can be false in pyrexia, dehydration, high table salt consumption and during diuretic therapy.

Today DNA analysis represents a modern method in the diagnostics of CF. However, most laboratories can detect only most frequent mutations, so that genetic verification of rare variants of the disease are likely to go unnoticed [16].

Others tests of diagnostic valued include a high level of immunoreactive serum trypsinogen, which is widely used within the framework of neonatal screening on CF, then a low level of pancreatic enzymes in the duodenal juice,



high content of fat in stool, pathological pancreozymin-secretion test, low fecal elastase level, increased potential difference at the level of the nasal epithelium and other [6, 16, 34].

## TREATMENT

Respiratory complaints represent the most severe problem in the therapy of CF [5, 6, 16, 46, 47]. Pulmonary ventilation is improved with adequate hydration of the patient, mucolytics, bronchodilators and anti-inflammatory drugs. Kinesytherapy and other forms of respiratory rehabilitation can be also useful. In infective complications antibiotics are indicated, and in cardiorespiratory failure diuretics, cardiotonics and oxygenotherapy.

Enzymic deficit compensation and adequate diet form the basis of the therapy of pancreatic exocrine insufficiency [5, 6, 16, 48, 49]. Correction of malnutrition improves the general condition, anti-infective resistance and respiratory function of the patient. Due to a reduced level of nutritive substances usage and increased metabolic requirements, the patient's food must be easily digestible and up to 20-50% richer in proteins and calories in relation to healthy children of identical body weight. Breast-feeding is of special significance in the first year after birth, and even after that period. Infants on artificial feeding, and particularly if malnourished, are indicated for milk formulas based on protein hydrolysate and a partial substitution of long-chain with easily digestible and highly usable medium-chain triglycerides. By additional intake of medium-chain instead of long-chain triglycerides later caloric needs are also covered to a considerable level. The optimum of essential fatty acids, linoleic and alpha-linolenic, is achieved by the daily nutritional addition of corn or sunflower oil in the quantity of 1 ml/kg. Liposoluble vitamins also require additional intake, while the needs in hydrosoluble vitamins and minerals are not essentially different from that of healthy children. Pancreatic enzyme preparations protected by an acid-resistant protector are administered with each meal. Their addition is also necessary for exclusively breastfed infants, as well as to those consuming infant formula

based on protein hydrolysate. For a successful correction of severe malnutrition, it is necessary to apply elementary and sometimes also parenteral nutrition [6, 37, 46].

Due to the tendency of dehydration, patients with CF require additional consumption of table salt [16, 48, 49]. This must be specially taken into account in the conditions of increased sweating, such as in the summer period and pyrexia. The correction of hypovolemia, hyponatremia, hypokalemia and hypochloremic metabolic alkalosis in expressed hyponatremic dehydration is achieved by intravenous application of 10-20 ml/kg 0.9% NaCl in bolus or during 15-30 minutes [49].

Certain disclosed complications in CF, such as intestinal obstruction or perforation, nasal polyposis and other, require surgical treatment. Lung transplantation, performed in the condition of terminal respiratory failure, yields modest results today [5].

## PROGNOSIS

Owing to modern therapeutic possibilities, as well as to the prevention of complications, particularly those which additionally endanger the respiratory system, the prognosis of CF is increasingly better from year to year [13, 50]. According to the US data, the average survival of patients with CF was 10.6 years in 1966, 20 years in 1981, and 32 years in 1998. [5].

## CONCLUSION

CF represents a relatively rare multisystemic autosomal recessive disease. Beside genotype, the outcome of the disease is essentially influenced by numerous additional factors, such as the quality of respiratory complications prevention and treatment, the level of aero-pollution, nutritional status of the patient and other. Although, in most cases, this is a severe and potentially highly lethal disease, owing to the advancement of healthcare and team-work treatment, life perspective of such patients has been evidently improved over the last years.

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## Цистична фиброза

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### КРАТАК САДРЖАЈ

Цистична фиброза је мултисистемско аутозомно рецесивно обољење изазвано поремећајем у експресији протеина *CFTR*, тј. хлорног канала који се налази на апикалној мембрани респираторног, дигестивног, репродуктивног и знојног епитела. Превасходно се јавља код припадника беле расе, док је код особа других раса знатно ређа или изузетно ретка. Услед изостанка протеина *CFTR* или његовог структурног и функционалног поремећаја долази до хиперконцентрације мукуса у респираторном, дигестивном и репродуктивном систему и поремећене апсорпције хлора и натријума у знојним жлездама. Отуда у клиничкој слици болесника с цистичном фиброзом доминирају сметње у респираторним, дигестивним и репродуктивним органима, као и склоност дехидратацији у стању појачаног знојења. Поред

генотипских варијација, важан утицај на степен испољавања болести имају и различити егзогени фактори, као што су учесталост и тежина инфекција респираторног тракта, ниво аерозагађења, квалитет имунопрофилактике, стање исхранености болесника и други. Концентрација хлора у зноју већа од 60 mmol/l, висок ниво имунореактивног химотрипсина у крви и потврда хомозиготне мутације у *CFTR* гену основне су методе у дијагностиковању болести. Цистична фиброза припада групи тешких и комплексних хроничних обољења, те изискује мултидисциплинарни терапијски приступ. Захваљујући унапређењу здравствене заштите, већина болесника са цистичном фиброзом данас доживи одрасло доба, а значајно им је побољшан и квалитет живота. **Кључне речи:** цистична фиброза; хлорни канал; дијагностика; лечење

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