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FEATURES OF CLINICAL PRESENTATION AND DIAGNOSIS OF CYSTIC FIBROSIS

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Abstract. Cystic fibrosis is a common hereditary disease caused by a mutation of the *CFTR* gene responsible for the synthesis, preservation of the structure and function of the CFTR protein, manifested primarily by pathology of the gastrointestinal tract and respiratory system. The lack of protein function in cystic fibrosis leads to an increase in the viscosity of the secretion of exocrine glands, obturation of organs and disruption of their functions. As a result, it causes steatorrhea, malabsorption, diabetes mellitus, metabolic disorders, with developmental delay and chronic bronchopulmonary process. This article will consider the main aspects of the clinical course and diagnosis of this disease.

Key words: *cystic fibrosis; diagnostics*

ОСОБЕННОСТИ КЛИНИЧЕСКОЙ КАРТИНЫ И ДИАГНОСТИКИ МУКОВИСЦИДОЗА

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Резюме. Муковисцидоз, или кистозный фиброз, — распространенное наследственное заболевание, обусловленное мутацией гена *CFTR*, ответственного за синтез, сохранение структуры и функции белка CFTR. Муковисцидоз проявляется, в первую очередь, патологией со стороны желудочно-кишечного тракта и дыхательной системы. Недостаток функции белка при данной патологии приводит к повышению вязкости секрета экзокринных желез, обтурации органов и нарушению их функций, как следствие возникают стеаторея, мальабсорбция, сахарный диабет, нарушение метаболизма, задержка физического развития и хронический бронхолегочный процесс. В данной статье будут рассмотрены основные аспекты особенностей клинического течения и диагностики данного заболевания.

Ключевые слова: *муковисцидоз; диагностика*

INTRODUCTION

Cystic fibrosis (CF) — is a widespread hereditary disease caused by mutation in the CFTR gene (cystic fibrosis transmembrane regulator) responsible for the synthesis, conservation and function of protein CFTR. [1, 2]. Recently, pneumonia and malabsorption were the causes of death in children with CF in early childhood and first year of

life. Nowadays, CF changed its classification from "fatal" to chronic disease, with over than 25% of adults in patients with CF in 2019 year. Active research of the CFTR gene, CFTR protein, and its functions has contributed to the development of new possibilities for a personalized approach to the pharmacotherapy for patients with CF aimed at restoring the structure and function of the CFTR protein.

The average age of patients was 13.7±9.7 years, according to the "Register of patients with cystic fibrosis in the Russian Federation" in 2020. The eldest patient in the reporting year was observed in Saint Petersburg. His age was 63.1 years, and the youngest patient was 3 weeks old. The proportion of adult patients (≥18 years of age) was 26.5%. Among the patients with CF, a slight predominance of males was 52.0%, and females were 48.0%. Neonatal screening allowed to diagnose 52.3% of patients [3].

ETIOLOGY AND PATHOGENESIS OF THE DISEASE

Cystic fibrosis has autosomal-recessive inherence; the responsible gene is localized on the long arm of chromosome 7. It codes the membrane-associated protein CFTR, which is a cyclic adenosine monophosphate (cAMF). The cAMPF-controlled chloride movement channel regulates the transport of chlorides, salts, and bicarbonates throw membranes of epithelial cells of respiratory tract, saliva, sweat glands, pancreas, and intestine.

All variations of the CFTR gene's nucleotide sequence fall into one of seven main classes based on the effect of the CFTR protein [4, 5]. Not all polymorphisms of the CFTR gene's nucleotide sequence are categorized, and it is known that a single mutation might disrupt a protein's structure or function in multiple ways.

Mutations of the CFTR gene disrupt not only transport, but also the secretion of chlorine ions. When glandular cells reabsorb more sodium due to the difficulty of their passage throw the cell membrane, the disruption of the lumen's electrical potential occurs. In this causes a change in the electrolyte composition and dehydration of the secretion of the glands of external secretion. As the result, allocated secret becomes excessively thick and viscous. The deficiency of the function of protein in CF leads to the disruption of the chloride channel located on the apical part of cells of the exocrine glands. As the result of such defect, chloroanions are retained in the cell, increasing the absorption of sodium cations and water. Loss of water from the lumen of exocrine glands leads to an increase in the viscosity of secretion, obturation of organs and impairment of functions [6, 7].

The bronchial secretion in the lungs dehydrates, thickens, and interferes with the removal of mucus from the rhinoceros epithelium. Due to this condition, bacterial infections may occur; *Staphylococcus aureus, Pseudomonas aeruginosa*, multi-resistant strains of *Stenotrophomonas maltophilia*, and Burkholderia cepacia are the main pathogens. The spectrum of microorganisms associated with respiratory tract infections in CF continues to expand. The studies of the pulmonary microbiome in this category of patients demonstrate a complex synergy between cultivated and non-cultivated microorganisms [8]. Features of chronic lung infection in patients with cystic fibrosis include the fact that the infection is produced by an association of microorganisms in 2/3 of cases rather than by a monoculture [9].

Chronic respiratory tract infection with pathogenic microorganisms causes morphological changes in the bronchial tree and interstitium of lungs. The typical changes in CF are bronchiectasis and bronchiectasis, focal points of interstitial fibrosis, cystic changes, bullous emphysema, and atelectasis of segments. Chronic pulmonary aspergillosis is a slowly progressive, destructive process in the lungs caused by the mushrooms of Aspergills spp. in previous bronchiectasis. The development of pulmonary aspergillosis in patients with CF is promoted by impaired mucociliary clearance and immune response, as well as prolonged antibacterial and glucocorticosteroid therapy [10, 11].

In the pancreas, there is an early obturation of the conduits with viscous secretion and fibrocystic changes in the parenchyma. Such condition contributes to the autolysis of gland tissue with the formation of typical fibrosis, cavernosa pancreatitis, steatorrhea, malabsorption and associated deficiency of fat-soluble vitamins A, D, E, and K. This causes a delay in physical development. As the result of the defects of the islets of Langerhans, endocrine pancreatic insufficiency develops, which leads to the formation of diabetes mellitus.

Pathological changes in the liver are characterized by obstruction of the intrahepatic ductuses, accompanied by inflammatory infiltration, proliferation of stroma with the formation of micronodular cirrhosis of the livers. Patients have fatty liver disease, gallbladder hypoplasia, often with the formation of gallstones [12].

The World Health Organization (WHO), International Cystic Fibrosis Association, and European Cystic Fibrosis Society currently adopt the following classification:

1. Classical cystic fibrosis with pancreatic insufficient (mixed or pulmonary-intestinal form of the disease), E84.8.
2. Classical cystic fibrosis with pancreatic-sufficient (mainly pulmonary form of the disease), E84.0.
3. Cystic fibrosis unspecified (uncertain diagnosis in positive neonatal screening for cystic fibrosis (CRMS/CFSPID)), E84.9.
4. Diseases associated with the CFTR gene: isolated obstructive azoospermia; chronic pancreatitis; disseminated bronchiectasis.

FEATURES OF CLINICAL PICTURE OF CYSTIC FIBROSIS

The advancement of modern technology has made it feasible to recognize the indicators that suggest cystic fibrosis in prenatal and neonatal periods: the presence of hyperechogenic bowel according to the data of ultrasound (US), the existence of meconium ileus in newborn, prolonged neonatal jaundice, and vitamin K-dependent hemorrhagic conditions.

The clinical picture of cystic fibrosis has some features. Therefore, this pathology can be detected at early age in the form of such manifestations: obsessive cough like whooping cough; often recurring respiratory infections with phenomena of bronchitis and pneumonia; wheezing; shortness of breath; cough with purulent sputum, including outside periods of exacerbation; various lung sounds of different localizations depending on the prevalence of the process.

Meconium ileus is one of the syndromes that can be observed in children with CF from birth. It is characterized by the manifestation of bowel obstruction, which is caused by mechanical causes — accumulation in the lumen of a dense meconium block [13]. Meconium ileus is diagnosed in 15–20% of newborns with cystic fibrosis. The percentage of patients with meconium ileus at birth in the group of children of the first year of life was 22.1%, reflecting its true incidence, according to the Russian Federation's register of patients with cystic fibrosis [14].

Patients with CF are characteristic of delayed weight gain, frequent abundant steatorrhoea, increased appetite, episodes of rectal prolapse, and stool retention with clinical manifestations of partial or complete bowel obstruction (so-called distal intestinal obstruction syndrome). At an early age, there are also episodes of manifestations of cerebral salt wasting syndrome (hypokalemia, hyponatremia, hypochloremia) in the form of weight loss, regurgitation, vomiting, lethargy, and refusal of food. Insufficient intake of salts with food and water, and also due to loss of electrolytes through the gastrointestinal tract and with sweat fluid, especially in conditions of increased sweating (fever, hot weather), can lead to the development of pseudo-Bartter syndrome (PBS). The syndrome manifests mainly at the first year of life in patients with CF. Because of its potential for fatality, it is regarded as a severe and dangerous complication of cystic fibrosis that, in some situations, a reason to call for emergency medical care. PBS can be the first symptom of CF. The clinical manifestations of this syndrome are varied, from a delay in physical development to an acute condition, occurring with refusal to eat and drink, lethargy, regurgitations, and vomiting—signs of dehydration. This syndrome is frequently confused with adrenogenital syndrome, kidney pathology, and acute intestine infection [8].

One of the manifestations of cystic fibrosis is cystic fibrosis — associated liver disease (CFLD), which includes a variety of nosologies in the form of biliary cirrhosis with or without portal hypertension, persistent elevation of liver enzymes, fibrosis, steatosis, and gallstones disease [15, 16]. Globally, the incidence of hepatobiliary pathology associated with cystic fibrosis is estimated to be 37.9%, with 2.5% of deaths resulting from liver disease decompensation. [17]. Biliary cirrhosis with portal hypertension in the Russian Federation in 2017 was recorded in 4.5% of patients, without portal hypertension in 2.3%, liver cirrhosis (hypertension is unknown) in 0.7% of patients, and liver damage without cirrhosis in 15.9%. In 1.5% of patients, liver damage is the first clinical symptom of CF. That is why it is recommended to include a sweat test in the diagnostic algorithm for cirrhosis of the liver of unclear etiology [15, 16]. Like many other phenotypic manifestations of cystic fibrosis (CF), liver damage depends more on modifying genes outside the *CFTR* locus, not just on the genetic defect and type of mutation of this gene.

Patients with CF often have age-related endocrine insufficiency of the pancreas — cystic fibrosis-related diabetes (CFRD), which is typically asymptomatic and can be undiagnosed for a long time. At the same time, it is known that already 2–4 years before the manifestation of CFDR, indicators of nutritional status and respiratory function deteriorate. The combination of CF and diabetes mellitus has a negative impact on life expectancy [18].

Mostly male patients have reduced fertility. In most cases, the fertility in women with cystic fibrosis is preserved. However, in certain cases it is possible infertility caused by anovulatory cycle and

secondary amenorrhea, due to protein-energy deficiency. The most common cause of decreased fertility in patients with a normal ovulatory cycle is a change in the water and electrolyte composition of cervical mucus due to a large amount of *CFTR* in the cylindrical epithelium of the cervix. As a result, the cervical secretion becomes too viscous, which reduces the ability to fertilize [19, 20].

Osteoporosis, often found in these patients, is always secondary. The causes of its development in CF include chronic microbial-inflammatory processes, low calcium intake, low physical activity, hypoxia and hypercapnia, diabetes mellitus in the context of CF, bone mass deficit, violation of bone microarchitecture due to inadequate acquisition of peak bone mineral density during the period of active growth, and excessive bone loss in adults. Osteoporosis for CF in childhood and adolescents is between 20 and 50% and increases after 18 years of life (50–75%) [21].

Allergic bronchopulmonary aspergillosis (ABPA) in patients with CF is proceeds chronic with periodic exacerbations. The main clinical signs of exacerbation of ABPA are: uncontrolled course of CF, attacks of suffocation, cough with sputum containing brown or black inclusions and mucous block, bronchial obstructive syndrome and/or the occurrence of infiltrates with eosinophilia, chest pain, refractory increase in fever to the use of antibacterial drugs, as well as a decrease in lung function [22].

The duration of pulmonary aspergillosis for more than 3 months may indicate the development of a chronic form of the disease (chronic pulmonary aspergillosis (CPA)). It is manifested by a productive cough, shortness of breath, hemoptysis, a progressive decrease in lung function, as well as intoxication syndrome. CPA is often mistaken for exacerbating CF caused by a bacterial pathogen and prescribes inefficien reserve antibacterial therapy in these cases [10, 11, 22].

Cystic fibrosis in adults can be divided into two groups: patients with a typical form of the disease, who became ill in early childhood and lived to adulthood; and patients with an atypical form, with late manifestation. The first group is characterized by low nutritional status, ongoing, recurrent infection, and an inflammatory process in the lungs with noticeable, long-lasting bronchial wall alterations, the formation massive bronchiolo- and bronchiectasis, widespread pneumofibrosis, and obstructive and bullous emphysema. The respiratory tract of these patients is much more often to be infected with gram-negative microflora: there are cirrhosis changes, pansinusitis, hemoptysis, diabetes mellitus (20%) and other pulmonary and extrapulmonary complications [23].

FEATURES OF DIAGNOSIS OF CYSTIC FIBROSIS

ДThe diagnosis of CF is confirmed if there are one or more characteristic phenotypic manifestations of it in combination with evidence of *CFTR* dysfunction, such as the detection of clinically significant mutations of the *CFTR* gene during genotyping or an increase in the level of chlorides in the secretion of the patient's sweat glands. To address the challenges associated with CF diagnosis, a set of criteria has been established. According to which mandatory for CF is the existence of a distinctive clinical symptom and evidence of any malfunction related to the functioning of the chlorine canal one of the methods proven.

Nowadays, professionals use a number of variations of the CF diagnosis criteria [6, 8].

The most common, national consensus and European Standards-approved diagnostic criteria are used, which call for the patient to comply with two requirements:

1) a positive sweat test result and/or two *CFTR* mutations;
2) neonatal hypertrypsinogenaemia or characteristic clinical manifestations (diffuse bronchiectasis, expulsion from sputum of pathogenic microflora relevant to CF, exocrine pancreatic insufficiency, salt wasting syndrome, obstructive azoospermia) [6, 24].

In the diagnosis of obstructive intestinal obstruction (including meconium ileus) in the neonatal period, attention should be paid to the presence of signs of intrauterine small bowel perforation or transferred intrauterine necrotizing enterocolitis (intrauterine formation of adhesions, peritonitis), and also to the violation of colon obstruction under normal formation of its neural apparatus. Since the disorders mentioned are related to late fetopathies them can be visualized in the third trimester. DNA testing for cystic fibrosis is recommended if the child continues to exhibit intrauterine symptoms of hyperechogenic bowel in order to determine the most prevalent mutations. The infant is susceptible to developing intestinal blockage and meconium ileus after birth.

After birth, diagnosis of intestinal obstruction and complications is necessary in accordance with clinical practice of patients with meconium ileus. A cystic fibrosis specialist consultation, sweat test, and DNA test are required. If the sweat test is not possible, a DNA-test should be performed [24].

A child is diagnosed with pseudo-Bartter syndrome if they have established diagnosis of cystosis fibrosis, the classic clinical presentation, biochemical abnormalities in the blood: hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis [8].

Since many diagnostic criteria overlap with the common symptoms of the underlying disease, diagnosing aspergillosis in patients with cystic fibrosis is hard and frequently delayed. To determine a diagnosis, a complex specialist examination is necessary. According to the consensus of the Cystic Fibrosis Foundation (2003), the diagnostic criteria for ABPA include [25]:

- deterioration of the course of cystic fibrosis: cough with sputum containing mucous tubes, shortness of breath, suffocation attacks, reduction of TLC (lung capacity of the lungs), FEV_1 (the forced expiratory volume in 1 second), acute or persistent deterioration of the condition, not related to other causes;
- total IgE >500 IU/ml;
- presence of specific *Aspergillus* IgE or positive *aspergillus* antigen skin test;
- presents of specific *aspergillus* IgG;
- changes in the X-ray or CT [25–27].

When diagnosing liver cirrhosis in people with cystic fibrosis, it is important to consider the existence of the following symptoms: increased alanine aminotransferase, aspartate transferase and gamma-glutamyl transferase for more than 6 months with the exception of other causes [28, 29]; palpatory increase in the size of liver and spleen [29]; prolonged prothrombin (thromboplastin) time in the blood or in the plasma [29, 30]; a characteristic ultrasound (heterogeneous echogenicity of parenchyma, severity, rounded borders hepatic, growth of connective tissue in the gate of the liver), finding of a significant amount of free fluid in the abdominal cavity, which indicates ascites [31, 32]; depletion of venous blood flow and discovered portal vein hypertension formation indicators through hepatic duplex ultrasound scanning (DUS); the presence of cirrhosis or fibrosis-related symptoms as determined by indirect liver elastometry research, with signs of fibrosis severity determined by morphological classification METAVIR (Meta-Analysis of Histological Data in Viral Hepatitis); identifying of stomach and esophageal varices while performing an esophagogastroduodenoscopy (EGD). In clinical practice, the severity and degree of compensation of liver cirrhosis associated with CF is determined by the Child-Pugh score [34].

The presence of early morning hyperglycemia (fasting blood glucose ≥7.0 mmol/l), "diabetic" blood glucose levels in the standard glucose tolerance test (fasting blood glucose <7,0 mmol/l and fasting blood glucose level after 2 hours in the oral glucose tolerance test ≥11,1 mmol/l), or postprandial hyperglycemia — which is determined by continuous monitoring of glycose in the absence of symptoms — are the diagnostic criteria for diabetes related to cystic fibrosis [35].

Patients with cystic fibrosis (CF) can be diagnosed with osteoporosis through laboratory methods of investigation, clinical picture evaluation, and bone density scanning.

The diagnosis of osteoporosis in cystic fibrosis (CF) is established when there are one or more vertebral body compression fractures that are not connected to a high-energy injury or a localized disease that results in a change in MBD or when there is a history of fracture and MBD by z-criterion ≤–2 SD (standard deviations) [36].

In the Russian Federation, neonatal screening for cystic fibrosis is done on all newborns to diagnose the condition. Early diagnosis and prompt treatment initiation lower the risk of serious complications, enhance physical development, decelerate the rate of lung function loss, and minimize the need for hospital stays [6, 8, 24]. There are three required steps in the screening protocol: immunoreactive trypsin (IRT) test and sweat test. The first step involves measuring the amount of IRT in a dried drop of blood from newborns (4–5 days for full-term, 7–8 days for premature). Administer blood is carried out in accordance with Order No. 185 of 22th of March 2006 "On mass screening of newborn children for hereditary diseases". In the second step, if the IRT threshold level (cut-off >99.5 centile) is exceeded a retest is conducted on the 21–28th day of life. In the third step, in the event of a positive re-test, a sweat test is conducted. In the fourth step, with the sweat test's borderline outcome, additional testing techniques, such as DNA analysis and measuring the intestinal potential difference. When a sweat test is positive, it is considered a positive screening result, and the patient is sent to the cystic fibrosis center (or the profile unit). All children with meconium ileus require a sweat test because of the possibility of a false-negative result, regardless of the level of IRT. The first two months of life are the best time to diagnose and begin monitoring a patient identified by the neonatal screening program [8, 24].

The sweat test is the "gold standard" for the diagnosis of cystic fibrosis. It takes at least two positive results to establish a diagnosis. It is possible to conduct the sweat test on a child who weighs at least 2 kg and is 48 hours old [6, 8, 24].

There are two types of sweat test methods used in the Russian Federation.

1. The classical direct method of determining the electrolyte composition of sweat (chlorine or sodium) by the method of pilocarpine electrophoresis by Gibson and Cooke (1959). The norm is up to 30 mmol/l, the borderline significance is 30–59 mmol/ll, the positive result is 60 mmol/l and above (with a hose of sweat of at least 100 mg). If the chloride content exceeds 150 mmol/l, it should be questioned [6–8].
2. Sweat sample collection was first used in the mass screening of newborns. Sweat analysis with specialized equipment was widely used to help determine the conductivity of perspiration. This correlates with the measurement of the chloride content and enables the measurement of 3–10 µl of sweat to yield a sufficient result. For the purpose of assessing conductivity, a positive result for cystic fibrosis is defined as an indicator that is greater than 80 mmol/l; the borderline significance is 50–80 mmol/l; normal — up to 50 mmol / l. When conductivity exceeds 170 mmol/l, it is cause to be questioned. The time to collect sweat should not exceed 30 min, the minimum permissible amount of sweat is 75–100 mg (15 µl in the Macroduct collector), the rate of sweating should be at least 1 g/m^2 per minute [24]. It is necessary to thoroughly cleanse the patient's skin beforehand [8].

The following could be the cause of the sweat test's border results: individual characteristics in people without cystic fibrosis, especially in adults; improper preparation for the test; carrying soft mutations in cystic fibrosis [24]. It is advised to employ various techniques for determining sweat chloride levels in this situation: carrying out repeated research, performing advanced DNA analysis (gene sequencing), extended clinical laboratory tests, and instrumental examination (coprological examination, determining the pancreatic elastase-1 stool test, the biochemical analysis of electrolytes of blood, sputum or swab culture from the posterior wall of the throat, chest X-ray, sinus X-ray, spermogram), the procedure to identify variations in nasal potentials or measuring the electrical current in the intestinal biopsy and finding a function violation in the chlorine canal.

It may be suggested that patients who exhibit suspicions of cystic fibrosis undergo an additional test for intestinal current measurement, particularly in cases that are questionable (at the boundary values of the sweat test, with unexpressed symptoms, and/or with incomplete classical manifestations of the disease) [6–8].

For the following indications, a genetic molecular testing to identify *CFTR* gene mutations is advised: newborns with positive IRT and positive or limit values of the sweat test, meconium ileus; people with limit value of sweat test; patients with clinical manifestations of classical or monosymptomatic CF; in *CFTR*-associated diseases (pancreatitis, congenital bilateral absence of the vas deferens / obstructive azoospermia); relatives of patients with CF (to media status determination as desired); women after the birth of the first child with cystic fibrosis, as well as during subsequent pregnancies in the presence of a child with cystic fibrosis; intrauterine child in 10–12 weeks of gestation with suspicion of CF (siblings with CF) or exposure of hyperechogenic bowel during ultrasound examination; to gamete donors and embryos in vitro fertilization programs (IVF), intrauterine insemination; when there are no limitations or contraindications, married couples with high genetic risk cystic fibrosis (CF) who want to undergo IVF (preimplantation genetic testing) on CF to prevent the birth of a child with CF [8, 24].

The Consensus guidelines and the regularly updated databases should be taken into consideration when evaluating the clinical significance of the genetic variants that have been detected.

The molecular genetic testing strategy for cystic fibrosis involves multiple phases.

1. The first stage involves searching for the most prevalent mutation variants in the population that the subject is a member of [8].
2. In the second phase, an advanced search for more rare variants is carried out using Sanger sequencing or High Performance Genomic Sequencing (MPS/NGS). The analysis includes the study of the entire CFTR gene encoding sequence (27 exons), exon-intron compound areas, 5′- and 3′-noncoding regions (up to 200–300 nucleotides), as well as the deep introne areas where the variants with established pathogenicity are found.
3. The third stage is when minor alterations in the gene sequence can be found using standard scanning techniques, such as sequencing: nucleotide replacement, small deletion or insertion. These methods are not effective in detecting modifications that involve multiple exons or introns. It is advised to use the following technologies: MLPA (multiplex-ligation dependent probe amplification) or QF-PCR (fluorescent quantitative multiplex PCR) [24, 37].

The European Consensus on CF states that in 98% of cases, a pathogenic variant can be identified through a thorough molecular analysis of the

CFTR gene. This could be because of the following: the methods employed precluded the examination of the gene's regions containing pathogenic genetic variants, the phenomenon of uniparental disomy, or the CF phenocopy [24].

OTHER LABORATORY TESTS FOR CYSTIC FIBROSIS DIAGNOSTIC AND MONITORING OF PATIENTS WITH CYSTIC FIBROSIS

All CF patient must undergo a blood test to determine their level of inflammation, track how their medication is affecting these markers, and participate in a complex nutritional status evaluation [8, 38]. Also, it is advised that all CF patients have a urinalysis performed during primary diagnosis and dynamic observation in order to identify kidney damage early on.

It is advised that laboratory testing be done on all patients who have CF suspicion or who are confirmed to have the disease in order to assess the degree of pancreatic insufficiency (measurement of the pancreatic elastase-1 stool test), the degree of correction of the pancreatic insufficiency, and the stool test with the measurement of neutral fat in stool [6, 8, 24].

All patients with CF (or with suspicion of CF) are shown sputum analysis (induced sputum or tracheal aspirate). In exceptional situations (for infants), oropharyngeal swab and/or bronchoalveolar lavage (BAL) to identify the pathogen/pathogens and determine the sensitivity of the secreted microflora [6–8, 24].

The study is conducted during the primary diagnosis and dynamic observation processes, including therapy efficiency monitoring at least once every three months, based on indications — preferably more frequently. To assess the efficacy of eradication in the initial seeding of *P. aeruginosa* and other multidrug-resistant gram-negative microflora, a control study is also conducted 10–14 days following an antimicrobial therapy.

Sending a monthly microbiological examination is advised in cases of chronic multidrug-resistant gram-negative microflora in CF patients to assess the effectiveness of pathogen eradication therapy. To send kids under five years old for a deep throat saliva test to diagnose their microbiological flora. Prioritizing sputum analysis is advised for adults and children older than 5–6 years old.

Laboratory tests should be considered to diagnose allergic bronchopulmonary aspergillosis: the total IgE test (IgE), *Aspergillus fumigatus* specific IgE and IgG antibodies. The same tests are recommended in case of suspicion of CPA and the determination of galactomannan (metabolite *Aspergillus fumigatus*) in the blood (definition of fungal metabolites) [6, 8, 10, 24, 25].

Patients with CF with suspicion of ABPA are shown the *aspergillus* antigen skin test to exclude/confirm mycogenic sensitization [25].

All patients with CF are recommended to conduct a biochemical blood test (protein total, albumin, determination of the activity of Aspartate aminotransferase, alanine amino transferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, study of the level of cholesterol, triglycerides, sodium, potassium, chlorides, total bilirubin, free and albumin-bound bilirubin, C-reactive protein in blood) annually, according to indications — more often. The purpose of the study is to track chronic inflammation, pancreatic function, electrolyte metabolism, and liver health based on indicators [8, 38].

Patients with CF should have tests for acid-base blood, potassium, and sodium to rule out PBS and to keep track of PBS therapy [8, 30].

It is advised that all patients with cirrhosis of the liver and a primary diagnosis of cystic fibrosis undergo a coagulogram, a reference study of the hemostasis system, 1 every 3 to 6 months in order to track the function of their livers, synthesis of proteins, and timely prevention of hemorrhagic complications [24].

For the purpose of tracking the pancreatic endocrine system, all patients with CF should have a blood glucose assessment once every 6 months. As a screening for the timely diagnosis of CFRD, it is recommended to consider performing a glucose tolerance test with a glucose load of 1.75 g/kg (no more than 75 g; control points — on an empty stomach, after 60 min, after 120 min) for all children over 10 years of age (as indicated — earlier) annually during the period of clinical stability. The use of glycated hemoglobin (HbA1c) as a screening test is not required because there is not enough information available to patients with CF about these indications [35].

For the complex diagnosis of osteoporosis and the diagnostic of kidney pathology, patients with CF are recommended to determine the level of total and ionized calcium, phosphate in blood, serum blood creatinine and creatinine clearance (calculated according to the Cockcroft-Gault formula), alkaline phosphatase [8].

For all male patients with CF who are 15 years of age or older, spermogram and molecular genetics testing (which, if not done previously, analyzes mutations in the *CFTR* gene) in order to ascertain the prognosis and strategies for resolving

the issue of reproduction. All male patients with cystic fibrosis (CF) who are 15 years of age or older should have testing for total testosterone and steroid-binding proteins in their blood serum to rule out hypogonadism [39, 40].

For patients with CF or suspected CF, chest organ computed tomography (CT) and X-ray are advised in order to assess the type and degree of lung tissue damage [6, 8, 24].

X-rays can reveal such signs as deformation and enhancement of the pulmonary pattern, pneumofibrosis, peribronchial cuffing, consolidation (atelectasis), bronchiectasis, pleural bullae, manifestations of bronchial obstruction (local emphysema, increased retrosternal airspace, flattening of the diaphragm), bronchial wall thickening, mucus plugs, and kyphosis. In the past, X-rays were more frequently used in different centers that care for patients with CF, including foreign ones, for dynamic observation; a number of centers used CT. [24]. Now the main method of diagnosis of changes in the lungs in CF.

To clarify the method for reducing radiation exposure with repeated control of the inflammation process, patients with CF are recommended to perform magnetic resonance imaging (MRI) of the chest organs. Up to 7 years in conditions of conscious sedation, after free-breathing [41].

It is recommended to perform CT of the paranasal sinuses (PC) (cone beam or multislice) or MRI of the PC in the initial assessment of the pathological process in the paranasal sinuses and in preparation for each rhinosurgery [41]. Children are not recommended to perform CT paranasal sinuses without clinical indications (for the purpose of dynamic observation). This significantly increases the total radiation exposure (due to the need for periodic chest CT scans).

In cases of suspicion of CF and in patients with CF, it is recommended to examine the function of external respiration. The spirometry is done on average every 3 months (study of unprovoked respiratory volumes and flows, if necessary; additional study of breathing volumes with the use of drugs). Body plethysmography is performed annually, on indications and on average, in order to determine the dynamic control of pulmonary function and the reversibility of airway obstruction in its presence (in the absence of age or other contraindications) [6, 8, 24]. An external respiratory function study (spirometry) is possible in children from 5 to 6 years of age if the patient can perform a forced exhalation maneuver. For children under five, the study's diagnostic value is lower. Spirometry allows an indirect assessment of lung capacities. The body plethysmography is carried out to more accurately evaluate the lung capacities according to indications.

Pulse oximetry and/or blood gas analysis should be performed at each hospitalization for all patients with CF suspicions and all CF patients, depending on the indications (exacerbation of the chronic bronchopulmonary process, presence of respiratory failure, needing oxygen therapy) —more often [8]. All patients with suspicion of CF and patients with CF are recommended to perform abdominal ultrasounds and liver ultrasounds. To detect changes typical of the disease and their dynamics, special attention should be given to the pancreatic structure in order to ascertain the type of liver blood flow. It is also recommended to perform liver elastometry in all patients with CF to assess the severity of fibrosis on the METAVIR scale [8, 24].

All male patients aged over 15 years with CF should undergo a urological/andrological examination with an ultrasound of the genitals to detect structural and morphological changes.

Regular periodic doppler echocardiography (measurement of the pulmonary arteriovenous pressure) is recommended in patients with CF, as with this pathology, especially with widespread damage. The development of pulmonary hypertension and the formation of pulmonary heart is possible [8].

It is recommended to perform an electrocardiography of patients with CF in PBS to monitor the effect of electrolyte disorders on heart activity. Also, before starting therapy with proton pump inhibitors, drugs against nontuberculous mycobacterial infections (NTMs), with prolonged use of azithromycin for other indications, against the background of high-doses of selective Beta 2-adrenergic agonists (2 weeks) therapy to evaluate the *Q–T* interval [30].

When a CF patient needs a BAL microbiological examination in addition, tracheobronchoscopy is advised. This method is used for the purpose of rehabilitation, should conservative therapy prove ineffective in an effort to rectify lung lobe atelectasis [6, 8, 10].

Nasal endoscopy in patients with CF is recommended for indications: if necessary, assessment of the severity of chronic rhinosinusitis, degree of nasal polyps, clarification of indications for surgical treatment on the nose, evaluation of the results of endoscopic endonasal surgical interventions.

EGD (esophagogastroduodenoscopy) is recommended for all patients with CF with cirrhosis of the liver to monitor esophageal varices — 1 time every 6–12 months. If you suspect erosive-ulcera-

tive lesions, inflammatory diseases of the stomach and esophageal mucosa, or gastroesophageal reflux disease [8].

Sigmoidoscopy with biopsy is advised in order to assess the variation in intestinal potential for patients suspected of having CF.

CONCLUSION

Patients with cystic fibrosis require active dispensary observation and clinical monitoring. Improving the prognosis for this disease is closely related to an early and adequate diagnosis. So, it is crucial to consider not only the patient's objective state but also information regarding the clinical picture, diagnosis, and course of treatment. Multidisciplinary care and collaborative patient observation by experts with diverse backgrounds are essential in the treatment for CF in patients, because the illness requires complex therapy and damages numerous organs and systems.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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