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FUNCTIONAL STATE OF THE HEPATOBILIARY SYSTEM IN CHILDREN WITH CYSTIC FIBROSIS

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Abstract

Cystic fibrosis (CF), or cystofibrosis of the pancreas (pancreas), is a hereditary disease in which there is a secretion defect characteristic of all epithelial cells of the body, primarily for chloride ions with a secondary decrease in the total volume of secretion. The most common mutation of the CFTR gene (cysticfibrosistransmembraneconductanceregulator) is the deletion of trinucleotides by the 10th exon, resulting in the cpotereostat of kaphenylalanine in the 508th position of the protein molecule (F508). About 45% of all CF patients in the world are homozygotes for the F508del mutation. The genetic polymorphism of the disease causes a phenotypic diversity of CF from severe to erased forms [17]. Cystic fibrosis is one of the most common among the representatives of the Europosomal race of autosomal recessive hereditary diseases. The disease is characterized by the pathology of the exocrine glands of vital organs and systems and usually has a severe course and an unfavorable prognosis. Cystic fibrosis is an important medical and social problem associated with early disability, the need for constant treatment and active dispensary observation, as well as the need for early diagnosis. [21]. An important role in the pathogenesis of the disease is given to the defeat of the digestive system and, above all, the pancreas and liver. In recent decades, the life expectancy of patients with cystic fibrosis has increased, and therefore the frequency of involvement of the hepatobiliary system in the pathological process increases, ranging from 20 to 80%. [22]. The clinical picture of cystic fibrosis is dominated by

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bronchopulmonary changes, determining the course and prognosis of the disease in more than 90% of patients. However, the defeat of the digestive system, primarily the pancreas and liver, significantly affects both the condition of patients and their quality of life. Disorders of the exocrine function of the pancreas are found in almost all patients and manifest themselves already in the neonatal period, but more attention is paid to the correction of bronchopulmonary processes. It should be emphasized that the defeat of the digestive system, in turn, significantly affects both the condition of patients and their quality of life. [23].

Andto study the state of the hepatobiliary system in cystic fibrosis in young children.

Materials and Methods

We examined 29 children with cystic fibrosis, aged 2 months to 3 years, who are on inpatient treatment in the gastroenterology department of the RSNPMCP. Indicators of physical development were assessed according to the standards of physical development of children recommended by WHO in 2006 [7].

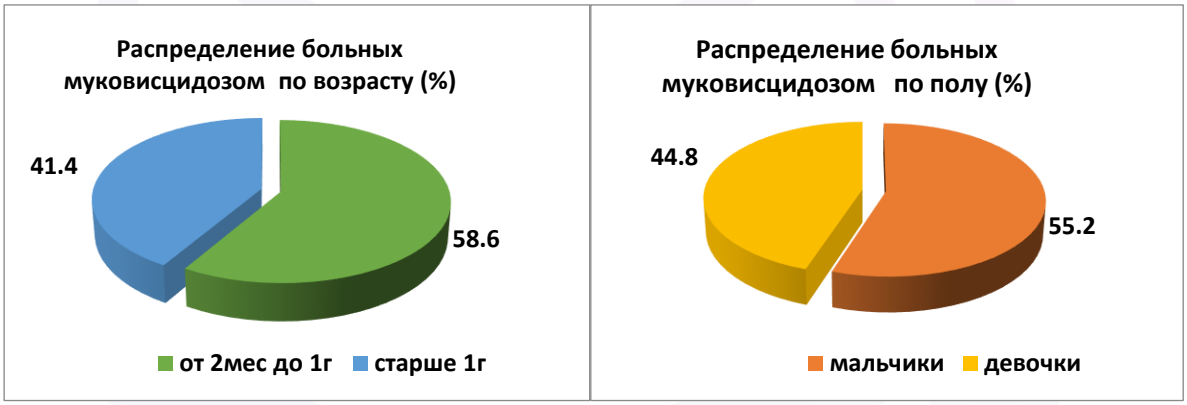

Figure 1 - Distribution of patients with cystic fibrosis by sex and age, in %

As can be seen from Figure 2, boys were 1.2 times more likely to meet, and the number of patients under the age of 1 year was recorded 1.4 times more compared to children over the age of 1 year.

The diagnosis of cystic fibrosis was made on the basis of a typical clinical picture of the disease, an increase in trypsin in the blood, established up to 8 weeks of life and an increase in chlorides in sweat of more than 60 meq / l (according to the Gibson-Cook method).

Assessment of the functional state of the liver was carried out by measuring the levels of transaminases, alkaline phosphatase, bilirubin and its fractions in the blood serum, and ultrasound examination of the liver and gallbladder was

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mandatory for all patients. Ultrasound examination was carried out in the morning on an empty stomach on an ultrasound scanner Toshiba APLIO-500 (Japan) with a convex sensor with a frequency of 3.5 - 12,) MHz in real time in B-mode. The complex of studies included color Dopplerography (CDC), energy Doppler (ED) and pulse-wave Dopplerography. The size, echogenicity, contours, structure of the liver, pancreas, gallbladder, the state of the walls, the nature of the contents were determined. Dopplerography was performed, which included measuring the maximum rate of linear blood flow and the rate of volumetric blood flow in the portal and splenic veins on an empty stomach and 30-40 minutes after a physiological breakfast.

Statistical Data Processing

The obtained data were subjected to statistical processing on a Pentium-5 personal computer using programs developed in the Excel package using a library of statistical functions with the calculation of the arithmetic mean (M), the mean square deviation (σ), the standard error (m), relative values (frequency, %), the Student criterion (t) with the calculation of the probability of error (P).

Differences in average values were considered significant at the significance level $P<0.05$. At the same time, existing guidelines for the statistical processing of clinical and laboratory data were followed.

Results:

The average age of diagnosis was 27.15±5.79 months, which was due to difficulties in the differential diagnosis of the disease and the lack of caution of family doctors in detecting cystic fibrosis.

Weight loss of the child is a sensitive parameter that allows you to assess the severity of nutritional disorders occurring with malabsorption syndrome in children (Table 1). Severe protein-energy deficiency a decrease in MRI of more than -3CO was noted in the vast majority of patients of 89.6%.

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Table 1 - Clinical signs of cystic fibrosis

Signs	Абс n=29	%
MRI-2	3	10,3
MRI -3	15	51,7
MRI-4	11	37,9
Flatulence pronounced	20	68,9
Vomit	12	42,4
Sweating	29	100
Peripheral edema	5	17,2
Enlargement of the liver	12	41,4
Putty fatty stool	29	100
Polyfecals	20	68,9
Osmotic diarrhea	24	82,8
Mixed diarrhea (osmotic + secretory)	5	17,2

As shown in Table 1, severe sweating, oily stools and steatorrhea were characteristic of every child with CF. Vomiting 2-3 times a day, 1-2 hours after eating, was observed in almost every second patient with CF (42.4%). A characteristic and most significant sign of insufficiency of cavitary digestion in the children observed by us was pronounced flatulence - in 68.9% of children. Diarrhea was observed in 24 patients (82.8%), and it is noted that osmotic diarrhea prevailed in the mechanisms of development of diarrhea, which we associate with a pronounced violation of abdominal digestion in children, which was noted by other authors [8].

Characteristic signs for patients with cystic fibrosis were the late discharge of meconium (on the second day after birth) and neonatal cholestasis, which were observed respectively in 21 (72.4%) and 15 (51.7%) children. At the same time, there was no meconial ileus in any case.

Table 2 - Biochemical indicators of liver damage in children with cystic fibrosis

Signs	Abs (%)
Increased ALT	8(27,6%)
AST Enhancement	18(62,1)
Increased total-direct bilirubin	8(27,6%) 12(41,4%)
Reducing fibrinogen levels	5(17,2%),
Lengthening the recalcification time	11(37,0%)
Thrombocytopenia	5(17,2%)

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Violation of the structural integrity of hepatocytes leads to the development of metabolic disorders, and deactivation of liver metabolic products, often accompanied by a violation of protein synthesis and hypocoagulation [11].

We also recorded a decrease in serum fibrinogen levels in 5 (17.2%), as well as a lengthening of the recalcification time in 11 (37.0%) patients with CF.

Cholestasis was characterized by an increase in the serum conjugated fraction of bilirubin, which was recorded in 12 (41.4%) patients with CF.

As indicated in Table 3, an increase in the liver with ultrasound examination of more than 3 cm was detected in 12 (41.4%), which may be due to the duration of the disease.

The most frequent ultrasound finding on the part of the liver was the changes characteristic of steatosis (diffuse increase in the echogenicity of the "granularity" of the parenchyma), which occurred in 23 (79.3%) children with CF. Steatosis, according to various authors, develops in 23–67% of cases, often in association with nutritional status disorders of essential fatty acids, carnitine and choline [24]. Diffuse pationof liver echogenicity was traced in 10 (43.4%), a moderate increase in echogenicity was observed in 13 (44.8%) with CF. There were changes in vascular architectonics in the form of expansion, fuzziness of the vascular pattern in 10 (34.5%) patients. Compaction of the intrahepatic ducts was recorded in almost every third patient 8 (27.6%).

Most children had changes in the gallbladder. The most common pathology of the biliary system in children with CF is an anomaly in the development of the biliary system, which recorded 11 (37.9%) and dyskinetic disorders, which were, hypomotor in nature was observed in every fifth child, and the presence of sediment (sludge) and thickening of the walls of the gallbladder was found in 7 (24.1%) children.

Table 3 - Ultrasound picture of changes in the hepatobiliary system in children with CF

Echosigns	**Abs. (%)**
Enlargement of the liver	12(41,4%)
Increased echogenicity of the liver: **- Diffuse increase in echogenicity** **- Moderate increase in echogenicity**	23(79,3%) 10(43,4%) 13(44,8%)
Fuzziness of the vascular pattern of the liver	10(34,5%)
Compaction of intrahepatic ducts	8(27,6%)
Increase in gallbladder size	6(20,7%)
Thickening of the walls of the gallbladder	4(13,8%)

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Deformation of the gallbladder	11(37,9%)
Biliary sludge	3(10,3%)
Enlargement of the pancreas **-Head** **-Body** **-Tail**	11(37,9%) 4(36,4%) 2(18,2%) 5(45,5%)
Pancreatic shrinkage	2(6,9%)
Increased echogenicity	11(37,9%)
Fibrous changes	15(51,7%)
Hyperechoic inclusions	7(24,1%)
Pancreatic cyst	1(3,4%)
Widening of the Virsung Duct	6(20,7%)

We studied the state of the pancreas by ultrasound, with the help of which it is possible to timely assess the structural changes of the organ at the clinical stage. Thus, we recorded an increase in the pancreas in more than every third patient. An increase in echogenicity was found in 11 (37.9%), the structure of the organ parenchyma in 9 (31.0%) had a fine-grained pattern, in 11 (37.9%) there was a coarse-grained pattern.

The pancreas echogenicity corresponded to the liver in 7 (24.1%) patients with cystic fibrosis, in 15 (51.7%) children fibrous changes were recorded, and hyperechoic inclusions were observed in every fourth patient. Evaluation of the Virsungov duct was carried out by measuring the diameter and an average expansion of 2.2±0.02 was detected. A pancreatic cyst was found in 1 (3.4%) of the patient.

With a Doppler examination of the state of blood flow in the portal vein system in children with a diffuse increase in the echogenicity of the liver, an expansion of the diameter of the portal vein was established on average 6.1 ±0.02. In this group of children, there was a decrease in the rate of linear blood flow by 17.6 cm per second. in children with a moderate increase in the echogenicity of the liver, the diameter of the portal vein averaged 4.6± 0.03. When assessing the postprandial reaction of blood flow through the portal vein in children with signs of a diffuse increase in the echogenicity of the liver, there was no increase in the rate of linear blood flow and the rate of volumetric blood flow by less than 30%. In the group of children with a moderate increase in echogenicity, the increase in the rate of linear and volumetric blood flow was 45%.

We also studied doppler-ray indicators of the splenic vein in order to detect chronic pancreatic insufficiency, which is a more reliable method for assessing the severity of pancreatic lesions in children with cystic fibrosis. The results of

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Doppler studies showed that 16 (55.2%) showed a decrease in the volumetric velocity of blood flow, and 15 (51.7%) had a decrease in linear velocity.

Discussion: Mucoviscidosis is a multisystem disease that develops as a result of the production of high viscosity secretion by the exocrine glands, with the formation of secondary changes mainly in the bronchopulmonary, as well as the digestive and reproductive systems. A clear relationship has been established between the insufficiency of the exocrine function of the pancreas (pancreas) and mutations in the CFTR gene. In CF, the exocrine glands of the respiratory system and the digestive system (pancreas, liver, biliary tract, digestive tract), sweat glands and urogenital tract are involved in the pathological process [11]. Determining for the life of the patient are the nature and degree of damage to the lungs, as well as the digestive system, primarily the pancreas and liver.

The main cause of protein-energy deficiency in CF is exocrine pancreatic insufficiency. This condition leads to impaired absorption of fat, protein, starch and loss of nutrients in the stool, and the violation of fat absorption is accompanied by a deficiency of fat-soluble vitamins and PUFAs of Omega-3 acids. Another cause of malnutrition in CF is inflammation in the bronchopulmonary system, which is accompanied by the formation of pro-inflammatory substances (cytokines) in the blood that inhibit the formation of growth factors, stimulates the breakdown of muscle proteins, and fever and shortness of breath increase energy consumption, these conditions are the direct cause of weight deficiency - malnutrition. Significant digestive disorders are also noted in our observations. Thus, a pronounced weight deficit is established in 89.4%, fatty stools in 100% of observations, and polyfecal - in 68.4% of children. [1, 12]. On the other hand, an excess of viscous substances in the mucous membrane of the small intestine reduces the availability of nutrients for intestinal enzymes, which is a pathogenetic factor leading to protein-energy deficiency in children with CF [13]. Early diagnosis of liver damage in patients with CF is of particular relevance, as a number of authors point to the reversible nature (against the background of treatment) of such changes as fatty hepatosis and cholestasis. However, clinical and laboratory signs of liver damage in CF appear late. [12]. Liver damage in CF in the early stages is usually asymptomatic. Rarely in infancy, cholestasis syndrome, neonatal hepatitis, fat malabsorption, hypotrophy, vitamin K-dependent bleeding disorder can be detected. Most young children with CF develop a picture of cholestasis [11]. We have recorded an increase in the liver in more than every third child. Every second child has fibrotic changes and every

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fourth has hyperechoic inclusions of the liver. The presence of the degree of liver damage can be judged by the activity of increasing serum enzymes, which is a highly sensitive indicator of cytolysis of hepatocytes. Intracellular aminotransferase enzymes (ALT, ASAT) belong to the markers of cytolysis and are organ-specific for the liver, Thus, among the children we examined, every fourth (26.1%) had an increase in ALT and more than half (63.2%) registered an increase in ASAT. Damage to cells involving mitochondria, especially in heart muscle cells, leads to increased elimination of ASAT [14]. Transient increase in ALT and ASAT can also be noted with hypoxemia, frequent antibiotic therapy during bronchopulmonary exacerbation. Increased activity of organ-specific enzymes indicates damage to the liver parenchyma, heart muscle, which allows you to diagnose liver and heart damage [15]. The frequency of lesions of the biliary tract in CF increases with age and varies, according to various sources, from 5 to 40%: there is an increase in mucus production, an increase in bile viscosity, the formation of gallstones; the development of strictures of the biliary tract is possible [5].

It has long been recognized that patients with CF can also develop gallbladder abnormalities [5,16]. This may include a reduced gallbladder or lack thereof, dysfunction, symptomatic gallstone disease, and even malignancy. Gallstones are quite often detected in patients with CF. Given the frequent development of steatorrhea and malabsorption in CF, it was originally assumed that these patients would have cholesterol stones, CF stones. since fecal loss of bile acids can lead to compensatory lithogenic activity of bile with the subsequent formation of cholesterol stones. However, patients with CF were more likely to have black pigmented stones. In addition, detailed studies have shown that bile in patients with CF is not oversaturated with cholesterol, as originally assumed. Indeed, black pigment stones are the result of abnormal acidification of bile, and a mechanistic defect is created by the absence of CFTR in the biliary epithelium itself. In addition, stasis of bile due to hypokinesia of the gallbladder and bile strictures can serve as a focus for further stone formation. [16].

The defeat of the biliary tract, according to ultrasound, was noted in 82.7% of patients with CF. Thethickness and compaction of the gallbladder wall, indicating an inflammatory process. The most common pathology of the biliary system in children with CF is an anomaly in the development of the biliary system, which recorded 11 (37.9%) and dyskinetic disorders that were, hypomotor in nature was observed in every fifth child, and the presence of sediment (sludge) and

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thickening of the walls of the gallbladder were found in 7 (24.1%) children. In addition, stasis of bile due to hypokinesia of the gallbladder and bile strictures can serve as a focus for further stone formation. [16].

Pathological changes in the pancreatic tissue are secondary, are a consequence of mechanical blockage of the excretory ducts with a thick secret. Disorders of enzymatic function are found in all patients and manifest themselves already in the neonatal period. Normal absorption of nutrients is disturbed, stool disorders occur due to changes in the motility of the gastrointestinal tract and putrefactive processes in its lumen [13].

Difficulty in the outflow of viscous secretion leads to its stagnation with subsequent expansion of the excretory ducts of the glands, atrophy of glandular tissue, progressive fibrosis [11,12].

The introduction of highly informative technologies, including Doppler techniques, makes it possible to assess not only the state of the hepatobiliary system in patients with cystic fibrosis, but also the state of blood flow in the vessels of the portal system. This contributes to the development of additional criteria for the diagnosis and control of the course of this pathology [25].

Thus, the defeat of the digestive organs in cystic fibrosis is characterized by polymorphism. Cystic fibrosis is characterized by pathology of the exocrine glands of vital organs and systems and usually has a severe course and an unfavorable prognosis. However, damage to the digestive system, primarily the pancreas and liver, significantly affects both the condition of patients and their quality of life. According to foreign authors, complications from the hepatobiliary system become the second (after pulmonary complications) cause of death of patients with cystic fibrosis [3].

Weight loss and delayed physical development are common complications of cystic fibrosis that can be exacerbated by the development of liver disease due to increased fat malabsorption and decreased protein synthesis by the affected liver [18,20].

A comprehensive ultrasound assessment of the state of the organs of the hepatobiliary system, spleen, as well as blood flow through the vessels of the portal system allows to clarify the severity of fibrosis, the presence of early diagnosis of cirrhosis of the liver and to identify the initial signs of portal hypertension. Doppler parameters with an assessment of the pre- and postprandial reaction of blood flow through the vessels of the portal system can be used as additional criteria for diagnosing the severity of cystic fibrosis and the

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functional state of the hepatobiliary system in this pathology. Traditional ultrasound of the pancreas allows you to diagnose up to 69.0% of cases, and a comprehensive study with Dopplerography is 93.0%. Timely diagnosis and therapy of liver pathology in this disease can prevent the development of such terrible complications as hypersplenism, bleeding from varicose veins of the esophagus, liver failure, increase the duration and improve the quality of life of patients with cystic fibrosis.

Due to the fact that the hepatobiliary system is affected in almost all children with cystic fibrosis, all of them, regardless of the severity and duration of the disease, it is necessary to regularly conduct a complete clinical and laboratory examination, including a clinical examination with mandatory anthropometry, a complete blood count, a biochemical blood test with a proteinogram, a coagulogram, an ultrasound examination of the abdominal organs, a Doppler examination of the vessels of the hepatobiliary system, fibroesophagogastroduodenoscopy.

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