

State of the Gut in Children with Non-Alcoholic Fatty Liver Disease

Annotation

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Abstract: Nonalcoholic fatty liver disease (NAFLD) combines with a variety of liver pathologies, including hepatic steatosis, nonalcoholic steatohepatitis, fibrosis and cirrhosis, and acts as hepatic manifestation of metabolic syndrome. Not only the liver is a target organ in the formation of metabolic syndrome: also exist a possibility of gallbladder, pancreas and biliary tract steatosis. Fatty infiltration of the pancreatobiliary system associates with disturbance of digestive processes that promotes dysbiotic changes and intestinal disorders. Changes in intestinal microbiota, in turn, may induce systemic inflammatory response and promote NAFLD development and progression.

Key words: *nonalcoholic fatty liver disease, hepatic steatosis, pancreatobiliary system, syndrome of excessive bacterial growth, children.*

Introduction Non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome and is closely associated with obesity, insulin resistance and dyslipidemia. Not only the liver becomes a target organ in the case of the formation of a metabolic syndrome: the possibility of developing steatosis of the gallbladder (LM), pancreas (PZ) and biliary tract has been proven [1]. Yen H. Pham et al. [2] demonstrated that fatty infiltration of PA is largely associated with NAFLD and is detected in 19% of overweight children. The accumulation of fat in the PA tissue is an additional factor influencing glucose metabolism, which increases the risk of developing metabolic syndrome and causes the severity of the course of NAFLD [3]. At the same time, microcirculatory disorders due to metabolic changes burden the functional state of the po, worsening its external and intersecretory function, forming a so-called pathological circle [4]. Biliary-pancreatic reflux, which develops against the background of dysfunction of the Oddi sphincter (CO), also contributes to the progression of pathological changes in the pancreas [5]. An increase in the lipid content in the wall of the gastrointestinal tract in patients with NAFLD leads to a violation of its contractile function [6]. For its part, a decrease in bile acid excretion and

relative extracretory insufficiency of po contribute to microbial contamination of the small intestine and the development of excessive bacterial growth syndrome [7]. It was found that in patients with histologically confirmed NAFLD, the permeability of the intestinal barrier is significantly increased due to a violation of intercellular close combinations. Translocation of bacterial products and endotoxins into the portal bloodstream with subsequent activation of innate defense receptors (TLRs, NLRs) and Kupfer cells leads to the production of proinflammatory cytokines (TNF- α , IL-6, etc.), recruitment of immunocytes (macrophages, T-lymphocytes) into hepatic, fatty, muscle tissue and the development of low-level systemic inflammatory response, the consequence of which is the progression of NAFLD [8]. The presence of close anatomical and functional connections between the liver and other digestive organs causes the need for a comprehensive approach to the diagnosis and treatment of pancreatic, biliary and intestinal disorders in children with non-alcoholic fatty liver disease.

Materials and methods. There were 34 children with gastrointestinal pathology under our supervision. Determination of the presence and degree of liver steatosis was carried out using the FibroScan-touch-502 apparatus with the study of the controlled parameter of ultrasonic attenuation (SAR). Ultrasound examination of the abdominal organs was carried out according to a generally accepted technique on a Toshiba Xario device (Japan). The functional state of the biliary tract was assessed using ultrasound with a trial breakfast to determine the contractile function of the LM and the tone of the CO [9]. To characterize the state of the small intestine microbiota (the presence of bacterial overgrowth syndrome — SNDB), a hydrogen breath test with glucose or lactose loading was performed using a gas analyzer Gastro + Gastrolyzer from Bedfont Scientific Ltd (Great Britain). All the examined patients underwent anthropometric studies with the determination of body mass index (BMI) proposed by the international group on obesity [10]. BMI was calculated using the formula: $BMI = \frac{\text{body weight (kg)}}{\text{Height (m)}^2}$ the trophic state was assessed according to WHO recommendations according to the centile tables of BMI values in accordance with age and gender [11]. With a BMI value in the range of 85-95 cents, overweight was diagnosed. When exceeding a BMI of 95 cents, obesity was diagnosed. Waist circumference and hip circumference were measured and the obtained values were compared with the data of the centile tables [12]. In the presence of indications, the studied patients underwent fibroesophagastroduodenoscopy (FEGDS). The serum content of total protein, total bilirubin, alkaline phosphatase, gammaglutamyltranspetidase (GGTP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) was determined using a biochemical analyzer Stat Fax 1904 Plus, Awareness Technology (USA). Statistical analysis of the data obtained was carried out using the Statistica 6.0 application software package. The differences were recognized as significant at $p > 0.05$. The distribution of children into groups occurred according to the data of liver elastography (FibroScan): the control group (S0) consisted of 21 patients without liver steatosis (61.8%), the main group (S+) — 13 patients with liver steatosis (38.2%). The average age of the patients was (11.73 ± 2.89) years. The groups were comparable in age and gender. The criterion for excluding patients from the study was the presence of signs of viral, autoimmune or drug-induced hepatitis.

Results and discussion. The analysis of anthropometric data revealed that all patients in the main group were obese or overweight (Fig. 1). Almost half (47.6%) of patients in the control group were obese, 6 patients (28.6%) were overweight, 5 patients (23.8%) were normal weight (Fig. 1). Complaints abdominal pain was detected in 73.5% of the examined patients. More often, patients complained of pain in the epigastric and umbilical regions without significant differences in the frequency of symptoms between the groups (Fig. 2). Complaints of painful sensations with

localization in the right and left hypochondria probably bothered patients from the groups with steatosis more often, which may be evidence of involvement in the pathological process of the biliary tract and po. The correlation analysis revealed that the presence of pain in the left hypochondrium correlated with an excess of waist circumference > 95 percentile ($r = 0.552$, $p < 0.05$), the presence of pain in the right hypochondrium — with the level of ALT ($r = 0.422$, $p < 0.05$) and AST ($r = 0.437$, $p < 0.05$), which indicates the connection of the pathology of the pancreatic system in these patients with liver steatosis and metabolic disorders. The most common combined pathology of the digestive organs in the examined patients were chronic gastritis/gastroduodenitis and functional disorders of the biliary tract (FRBT) (Fig. 3). Intestinal pathology in the form of irritable bowel syndrome (IBS) and SNDB was probably more common in the group of children with liver steatosis. Changes in the state of the microflora of the small intestine were observed in 27.6% of the examined patients. The frequency of SNDB detection in the group of patients with hepatic steatosis was higher and amounted to 33.3%. The analysis of objective data revealed that pain prevailed in all examined children during palpation of the abdomen with localization in the epigastric region, behind the bowel and in the right hypochondrium (Table 1). Soreness during palpation of the abdomen along the course of the intestine was probably more common in groups of patients with liver steatosis. Liver enlargement was observed in a third of patients in the main group. Splenomegaly was not detected in any of the examined patients. The analysis of biochemical hepatogram indicators revealed differences in ALT and AST levels, but the significance of the differences did not reach a sufficient level (Table 2).

Table 1

Characteristics of the data of objective examination of patients

Soreness during palpation	Groups					
	S ₀ , n = 21		S ₊ , n = 13		Total, n = 34	
	n	%	n	%	N	%
in the right hypochondrium	8	38,1	5	38,5	13	38,2
in the epigastrium	16	76,2	10	76,9	26	76,5
behind the course of the intestine	7	33,3	9	69,2*	16	47,1
Hepatomegaly	2	9,5	5	38,5*	7	20,6

Note. * - The significance of the differences between the indicators compared to the S₀ group at $p < 0.05$ according to the Mann -Whitney U-test

As is known, GGTP is a marker of cholestasis, the risk of liver fibrosis, an increase in GGTP is associated with dyslipidemia and insulin resistance [14]. The level of gammaglutamyltranspeptidase in our study was probably higher in patients with hepatic steatosis, but it did not exceed the generally accepted normative indicators. It was found that the level of GGTP correlated with the index of SAR ($r = 0.533$, $p < 0.05$), ALT ($r = 0.631$, $p < 0.05$), AST ($r = 0.609$, $p < 0.05$). The ALT level also revealed a correlation with the SAR index ($r = 0.470$, $p < 0.05$). Signs of impaired absorption of starch and neutral fat according to the coprogram were significantly more often observed in groups of patients with liver steatosis, which may indicate the development of concomitant exocrine pancreatic insufficiency in them. However, given the prevalence of concomitant intestinal pathology, it cannot be excluded that disorders in the coprological study associated with the acceleration of intestinal transit, therefore, determining the level of fecal elastase in these patients should be considered optimal for assessing the exocrine

function of the pancreas. Type 2 steatorrhea was probably more common in patients with liver steatosis, which may indicate a violation of biliary function. A comparative analysis of sonographic data revealed a probable increase in the volume of LC in the group of patients with steatosis compared with the group of patients without it. Changes in echogenicity and granularity of PO were found in patients with liver steatosis. The size of the head and body of the pancreas were probably higher in the main group. It should be noted that 7 patients (20.58%) had signs of biliary sludge without probable differences in the detection frequency between the groups ($p > 0.05$). When assessing the contractile function of the gallbladder, it was found that 52.9% of patients (18 people) had hypokinesia of the gallbladder, 47.1% (16) had normokinesia. In the group of patients with steatosis, more than half of the patients (53.8%) had signs of gallbladder hypokinesia. When determining the tone of the CO, it was found that a third of the patients had hypotension of the sphincter of Oddi. 5 patients (14.7%) met the criteria for pancreatic CO disorder, 2 patients (5.9%) had a biliary CO disorder. FEGDS was performed in 88.2% of the subjects (30 people). During FGDS, signs of catarrhal gastropathy with erythema of the antral mucosa were most often encountered, regardless of the presence of steatosis. It was revealed that in the group of patients with steatosis, when examining the duodenum, a symptom of "semolina" was observed: in the most edematous areas

Table 2

Characteristics of biochemical hepatogram indicators in the studied groups

Indicator	Groups	
	S0, n = 21	S+, n = 13
	M ± m	M ± m
Total bilirubin, mmol/l	10,58 ± 3,00	9,22 ± 3,10
Total protein, g/l	73,95 ± 3,83	74,77 ± 4,92
Alkaline phosphatase, Units/l	246,20 ± 81,71	214,48 ± 94,44
GGTP, Units/l	15,09 ± 5,37	19,90 ± 6,75*
ALT, Units/l	17,07 ± 3,93	28,38 ± 9,82
AST, Units/l	14,99 ± 4,22	22,83 ± 11,72

Note. * — Significance of differences between indicators at $p < 0.05$ according to the Mann - Whitney U—test

multiple whitish grains with a diameter of up to 1 mm protruding above the surface were detected (45.5% of patients in the main group versus 10.5% in the control group, $p < 0.05$), which may be a sign of PO damage. Thus, liver steatosis in overweight and obese children is characterized by the presence of concomitant structural and functional changes in the pancreatobiliary system and intestines. Timely correction of functional biliary and pancreatic disorders, restoration of the state of the small intestinal microbiota should be considered as factors that will prevent the progression of NAFLD in children.

Conclusions

1. Children with non-alcoholic fatty liver disease have symptoms of damage not only to the liver, but also to the biliary tract and pancreas.
2. Lesions of the biliary tract in patients with NAFLD are more often manifested in the form of hypotension of the Oddi sphincter and hypokinesia of the gallbladder.
3. In children who have hepatic steatosis, there are significantly more signs of pancreatic dysfunction (dyspeptic syndrome, signs of external secretory insufficiency) against the background of an increase in the size and changes in the echogenicity of the pancreas.

4. Changes in the functional state of the pancreas in children with NAFLD are associated with the presence of a functional disorder of the Oddi sphincter and pancreatic steatosis.
5. Lesions of the pancreatobiliary zone in patients with liver steatosis are accompanied by intestinal pathology in the form of excessive bacterial growth syndrome and irritable bowel syndrome

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