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Research Article

STEATOHEPATITIS IN OBESITY CHILDREN

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ABSTRACT

Steatohepatitis is hepatic steatosis with inflammation and, in some cases, hepatocyte balloon degeneration and fibrosis [1]. Steatohepatitis is a form of non-alcoholic fatty liver disease (NAFLD), which includes a wide range of conditions: from non-alcoholic steatosis (NAS) - fat deposition in the liver of more than 5% of the parenchymal mass without signs of damage to hepatocytes to non-alcoholic steatohepatitis (NASH), which progresses with development fibrosis, cirrhosis and, in some patients, hepatocellular carcinoma [1]. The prevalence of steatohepatitis in the pediatric population, according to various sources, varies greatly. Thus, the recommendations of the North American Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists (NASPGHAN) indicate that hypertransaminasemia occurs in 29-38% of obese children aged 2-4 years [1]. According to A. Sahota et al. [2], NASH was found in 12% of obese and overweight children. The joint recommendations for the diagnosis, treatment and prevention of obesity in children and adolescents of the Russian Association of Endocrinologists, the Russian Society for the Prevention of Non-Infectious Diseases, and the Association of Pediatric Cardiologists of Russia note that NASH is diagnosed in 12-26% of obese children and adolescents [3]. Obesity and overweight currently affect 25-30% of school-age children [4]. The situation is almost the same for preschool children. The COSI (Childhood Obesity Surveillance Initiative) study, conducted under the WHO program in Moscow in 2017-2018, summing up the dynamics of body weight for the entire preschool period, showed that among children aged 7 years, 27% of boys were overweight and 22% of girls, and obesity - in 10 and 6%, respectively [5]. Another Russian study assessing the physical development of children of middle and school age [6] also demonstrated a significant prevalence of obesity and overweight in this age group in Russian regions. Thus, at 11 years of age, obesity in boys was recorded in 18.6% of cases, in girls - in 9.2%, and excess body weight

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- in 15.4 and 14.3%, respectively. At the age of 15, obesity was detected in 10% of cases among boys, in 3.6% of girls, and overweight in 11.5 and 10.5% of cases, respectively [6]. Based on these data, it can be assumed that the incidence of NASH in the pediatric population varies from 0.5 to 3%. It should be noted that the prevalence of obesity, and with it NAFLD, including NASH, is increasing throughout the world due to modern negative trends in the diet and physical activity of children [7].

KEYWORDS

Population, hepatocytes, non-alcoholic steatosis (NAS), non-alcoholic fatty liver disease (NAFLD).

INTRODUCTION

Pathogenesis

The pathophysiology of molecular abnormalities in NASH is complex and multifactorial. Metabolic imbalances that result in fat deposition in the liver are associated with three mechanisms (see figure) [8]:

an increase in the amount of free fatty acids entering hepatocytes due to increased dietary fat intake or quantitative/qualitative disturbances of the intestinal microbiome;

• an increase in the supply of free fatty acids to hepatocytes from the non-esterified pool, the source of which is white adipose tissue;

• activation of de novo lipogenesis in the liver, the cause of which is associated with excess carbohydrates and/or hyperinsulinemia due to the resistance of adipose tissue to insulin.

Accumulation of triglycerides and free fatty acids in hepatocytes occurs when these processes are not compensated by increased production of very low-density lipoproteins in the liver [8]. It is generally accepted that lipotoxicity is associated with the accumulation in hepatocytes not of triglycerides, but of free fatty acids and their metabolites [8], leading to oxidative stress and subsequent damage to intracellular structures (mitochondria, endoplasmic reticulum). These changes cause a cascade of reactions, including the release of reactive oxygen species, IL-6, -10, -18, TNF-α, IFN-γ by hepatocytes and the recruitment of immune cells (plasmocytes, lymphocytes) [8].

These processes culminate in hepatocyte damage, progressive inflammation, programmed cell death (apoptosis), and fibrotic remodeling of the liver through collagen deposition from activated stellate cells [8].

In recent years, the pathogenesis of NAS and NASH has been linked to changes in the gut microbiota that lead to bacterial translocation, especially of a highly immunoreactive Gram-negative cell wall component called lipopolysaccharide (LPS), into the systemic circulation, which further enhances the inflammatory process by activating macrophages and Kupffer cells.

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It has been established that changes in the intestinal microbiota in patients with NAFLD are associated with the genes K01470, K01961, K07258 and are manifested by disruption of the pathways of arginine and proline metabolism, fatty acid synthesis and polysaccharide biosynthesis and metabolism [9].

In addition, these three functional genes were associated with significant disturbances in the intestinal microbiome - a decrease in the number of Bacteroides, Bifidobacterium, Ruminococcus and an increase in Prevotella, which shows the possibility of the influence of disturbances in the intestinal flora on changes in lipid metabolism due to differential expression of genes contributing to the pathogenesis of NAFLD, including. h. NASH [9]. Overfeeding of children in infancy leads to excess body weight in the future, which, in turn, can predetermine the development of NAFLD. An experimental study in rats showed that overfeeding rats aged 3-13 weeks caused excess glucocorticoids through activation of the enzyme 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) in the liver, which, in turn, activated de novo hepatic lipogenesis through glucocorticoids. receptors, which led to lipid accumulation in the liver, increased the risk of NAFLD in adulthood [10].

In research, great importance is given to the analysis of genetic predisposition to obesity and NASH. A significant role in the occurrence of NASH belongs to the PNPLA3 gene, encoding the triacylglycerol lipase protein, which is involved in lipid metabolism and promotes the accumulation of lipid molecules in hepatocytes; an association of PNPLA3 polymorphism with increased ALT levels and a more frequent occurrence in obese children of different ages with metabolic syndrome has been established [11]. The TM6SF2 gene, encoding superfamily 2 transmembrane protein 6, promotes the formation of excessive amounts of very low density lipoproteins in hepatocytes, which leads to the accumulation of triglycerides in liver cells [12]. The role of the AKR1D1 gene, encoding steroid 5β-reductase, variants of which increase the accumulation of triglycerides in hepatocytes, insulin sensitivity and glycogen synthesis by increasing de novo lipogenesis and reducing β-oxidation, activating hepatocyte inflammation, has also been noted [13]. There is an association between the MTHFR 677CT gene variant and the level of homocysteine as a component of oxidative stress in patients with NAFLD [14]. Other genes that are important in the development of NASH and progression to steatofibrosis have also been identified [12].

The role of vitamin D in the pathogenesis of NAFLD is being studied. In the work of M. Kong et al. It has been demonstrated that a high-fat diet deficient in vitamin D interferes with the enterohepatic circulation of bile acids, leading to NASH [15]. It has also been shown that vitamin D deficiency can increase adipose tissue dysfunction and, in particular, cause an increase in the production of cytokines (TNF-α, IL-1β, IL-6), which

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contributes to the progression of NAFLD [16]. It was shown that in children with NAFLD, significant liver fibrosis (stage ≥ 2 by ultrasound) was detected in 29% with vitamin D deficiency (serum 25(OH)D concentration - 21-30 ng/ml) and in 17% with normal vitamin levels [17].

Diagnostics

Laboratory diagnostics

Diagnosing NASH in children, as well as NAFLD in general, is not difficult. According to the recommendations of ESPGHAN (2012), the examination and differential diagnosis plan for children with NAFLD should include the following laboratory tests [4]:

- clinical blood test, determination of glycemic levels, fasting insulin, urea, electrolytes, coagulogram;
- analysis of biochemical indicators of liver condition - aspartate aminotransferase (AST), alanine aminotransferase (ALAT), ALT/AST ratio, γ-glutamyl transpeptidase (GGTP), total bilirubin and its fractions;
- lipid profile - cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL);
- oral glucose tolerance test, glycated hemoglobin (HbA1c);
- determination of the HOMA-IR and ISI-gly indices as indicators of insulin resistance;
- assessment of the functional state of the thyroid gland;
- exclusion of Wilson's disease - concentration of ceruloplasmin, copper in the blood serum, urinary copper excretion per day;
- exclusion of cystic fibrosis - sweat test;
- exclusion of celiac disease - antibodies (IgA) to tissue transglutaminase, total IgA;
- other tests in accordance with the medical history - exclusion of viral hepatitis, autoimmune liver diseases (liver autoantibodies), serum immunoglobulins.

The currently recommended test for screening for steatohepatitis is the determination of ALT activity [1, 18]. NASH is more often found in children with ALT ≥ 80 U/L compared with children with enzyme activity < 80 U/L (41% and 21%, respectively). If the ALT level is > 80 U/L for ≥ 3 months, clinical data should be assessed, since such an increase in enzyme activity may indicate existing hepatocyte damage [18]. In the absence of risk factors for the development of NAFLD (excessive weight gain, type 2 diabetes mellitus, obstructive sleep apnea), ALT activity is recommended to be tested every 2-3 years [1]. In the presence of these risk factors, it is recommended to repeat the ALT test in blood serum [1], the frequency of repeat testing is not defined in international recommendations, the issue is resolved individually. A number of studies have shown that overexpression of HIF-2a (hypoxia-inducible factor) [19], visfatin [20, 21], increased concentrations of C-reactive protein, apolipoprotein A1, haptoglobin and α2-macroglobulin [22], fibroblast growth factor 21 [23], adiponectin and adiponectin receptor 2 [24] are

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associated with the progression of NAFLD, suppression of fatty acid β-oxidation and induction of lipogenesis in the liver [19]. In addition, the above factors have pronounced lipotoxicity and trigger a cycle of progressive damage to hepatocyte organelles, leading to their apoptosis and aseptic inflammation [25]. Inflammation of adipose tissue and intestinal dysbiosis provide substrates for the formation of reactive oxygen species that enhance inflammation [25]. And finally, progression from simple steatosis to NASH provides an imbalance between pro-inflammatory (TNFα-, resistin, IL-6) and anti-inflammatory (adiponectin) cytokines with the dominant effects of the former [26].

Histological examination

Liver biopsy is a test for the diagnosis and differential diagnosis of steatosis and steatohepatitis and exclusion of other diseases, recommended by ESPGHAN and called the reference test in consensus [4]. Histological signs of NASH are the presence of hepatocytes with fatty macrovesicles and a nucleus displaced towards the membrane, changes in hepatocytes like balloon degeneration, mixed inflammation in the liver lobules [4]. Also, when studying liver biopsies, perisinusoidal-pericellular fibrosis along with megamitochondria, acidophilic bodies and glycogenated nuclei may be noted, but are not required for the morphological diagnosis of NASH. Liver biopsy cannot be widely used due to its invasiveness and the risk of complications in both adults and children. There are no specific recommendations for selecting children for this study in international guidelines; in fact, it is indicated for all patients with NASH. The high cost (according to our estimates, in Russia - 12,000-20,000 rubles) of this diagnostic method is also a problem [1].

Instrumental visualization

In the instrumental diagnosis of NAFLD, ESPGHAN (2012) recommends the use of ultrasonography, computed tomography, magnetic resonance imaging, and liver fibroscanning [4], which are also appropriate for NASH, primarily to identify fibrosis of the liver tissue that occurs along with inflammation.

Ultrasound diagnostics (ultrasound) is a method of qualitative assessment of the condition of liver tissue, available in most medical institutions. The sensitivity of ultrasound for detecting liver changes in NAFLD is 60-96%, specificity is 84-100% [4]. There is no doubt that the results of ultrasound diagnostics depend on the apparatus and the skills of the doctor performing the examination. However, this method is fast enough to diagnose liver damage - the duration of the study is about 20 minutes. The threshold for detecting changes in the liver parenchyma by ultrasound in patients with NAFLD is the presence of fatty infiltration of ≥ 20% of hepatocytes [4]. To assess the degree of NAFLD, an ultrasound fatty liver index has been proposed - a new scoring system in the range of 2-8 points, based on such indicators as the intensity of ultrasound signals of the liver relative to the kidneys, weakening of the

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ultrasound signal in the retroperitoneal space, unclear visualization of blood vessels, difficulty in visualization gallbladder walls, diaphragm, detection of focal changes in the liver [27]. In a study by H.K. Liu et al. An ultrasound fatty liver index score ≥ 6 was a predictor of steatohepatitis in children with NAFLD, and the authors proposed using this score to predict steatohepatitis in children with NAFLD without requiring liver biopsy [28].

Computed tomography (CT) allows one to assess the presence and degree of fatty infiltration of the liver, i.e. conduct a qualitative and quantitative analysis of the condition of the liver tissue. The sensitivity of CT for detecting liver changes in NAFLD is 82%, specificity is 100% [4]. Moreover, CT makes it possible to identify steatosis with fatty infiltration of more than 30% of hepatocytes [4]. CT scanning is available and performed quite quickly - it takes no more than 5 minutes to obtain the result. However, it should be emphasized that this method is associated with ionizing radiation, which limits its use in children.

Magnetic resonance imaging (MRI) also allows qualitative and quantitative assessment of fatty infiltration of the liver. The method is widely available, but still relatively expensive [4]. Liver density assessment occurs in T1 mode. The sensitivity of the method for detecting liver changes in NAFLD is 100%, specificity is 90.4% [4]. An MRI requires 10-15 minutes. However, MRI has a number of contraindications: the presence of metal elements in the patient's body, as well as excess body weight, for which the positioning table is not designed. It should be noted that assessment using MRI is possible with fatty infiltration of the liver of the 1st degree - 5-30% of hepatocytes [4].

1H-MR spectroscopy - magnetic resonance spectroscopy - a method that allows you to qualitatively and quantitatively assess the condition of the liver parenchyma. The method is highly expensive (from 5,000 to 15,000 rubles). The study is carried out in T2 mode - fat-saturated spectroscopy, measuring the area at the peak of lipid resonance. The sensitivity of the method is 87-100%, diagnostic accuracy is 80-85% [4].

Liver elastography allows you to evaluate fatty infiltration of the liver and detect fibrous changes. The method is based on measuring the density of liver tissue through shear wave propagation. The sensitivity of the method for cases of NAFLD is 81-85%, specificity is 74-78% [4]. The duration of liver elastography is no more than 20 minutes. The test is non-invasive, fast, reproducible [15]. Despite its advantages, this method is not widely used in medical institutions due to a shortage of appropriate equipment and is not included in Russian standards for examining children. Y.D. Kwon et al., examining children with obesity (including NAS and NASH) found fibrosis (liver stiffness > 5.5 kPa) in 30 (51%) of 59 children, while in the group of children without obesity there were cases of fibrosis were not found. The liver stiffness indicator correlated with the activity of AST (r = 0.525), ALT (r = 0.594), insulin

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resistance (HOMA-IR, r = 0.400) and the AST-to-platelet ratio index (r = 0.480) [29].

Calculation indices

Currently, to assess the presence and histological activity of fibrosis, inflammation, steatosis and other processes in NAFLD and NASH, calculated indices are used that take into account the values of biochemical parameters and minimal anamnestic data. These indices have demonstrated their information content and ease of use, but their disadvantage is their high cost (11,000-20,000 rubles). We also note that it was not possible to find information on the diagnostic accuracy of these tests (sensitivity, specificity). The NAS scale (NAFLD activity score, NAFLD activity scale) is proposed for semi-quantitative assessment of steatosis (in %), lobular inflammation, balloon degeneration, and the stage of fibrosis. Thus, the severity and stage of NAFLD is characterized [4, 30]. For each item on the scale there is a score from 0 to 2 points. A total score of ≥ 5 points allows a diagnosis of NASH [4, 31].

The FibroMax test takes into account the values of 10 biochemical blood test indicators: ALT, AST, GGTP, total bilirubin, α2-macroglobulin, apolipoprotein A1, haptoglobin, total cholesterol, triglycerides, glucose. Mathematical algorithms (5 in total) based on the values of these indicators determine such characteristics of the liver condition as:

severity of fibrosis with staging (F0-F4) in accordance with the international METAVIR system (FibroTest);

• activity of necrotic and inflammatory processes with determination of degree (A0-A3) - also in accordance with the METAVIR system (ActiTest);

• presence and severity of liver steatosis (SteatoTest);

• presence of alcoholic steatohepatitis in alcohol abusers (EshTest);

• the presence of NASH in patients with excess body weight, insulin resistance, hyperlipidemia, as well as in patients with diabetes mellitus (Nash-Test, from the English NASH - non-alcoholic steatohepatitis) [31].

A shortened version of the FibroMax test called FibroTest is also carried out, when only 2 calculation algorithms are used based on the results of mathematical processing of 6 biochemical blood parameters: α2-macroglobulin, haptoglobin, apolipoprotein A1, GGTP, total bilirubin, ALT. In this case, the assessment is given only on two scales - the severity of liver fibrosis and the activity of the necroinflammatory process in the liver.

Therapy

Lifestyle change

Currently, the main treatments for children with NASH, as with other forms of NAFLD, are a low-calorie diet and physical activity aimed at correcting overweight or obesity. Lifestyle modification with dietary changes and increased physical activity is recommended as first-line therapy for all children with NAFLD/NASH [1]. Limiting the consumption of sugary drinks is also indicated [1]. In accordance with NASPGHAN recommendations, it is necessary to increase children's

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physical activity to moderate or vigorous intensity and limit time spent on gadgets to 2 hours per day. [1]. The Russian Association of Endocrinologists advises following similar recommendations when treating obese children [3]. Special Russian recommendations for the treatment of children with NAFLD and NASH have not been developed.

Drug treatment

It is important to emphasize from the outset that NASPGHAN (2017) [1] does not recommend the use of any medications or dietary supplements for the treatment of patients with NAFLD/NASH. In experimental studies on mice with NAFLD, it was shown that metformin relieves hepatomegaly, steatosis and abnormal aminotransferase activity [32], which was confirmed by the results of some clinical studies [33]. However, subsequent more rigorous clinical studies did not reveal a reduction in histological changes in the liver in patients with NAFLD during metformin therapy. [34].

According to the results of a randomized, double-blind, placebo-controlled study, treatment with high doses (28-35 mg/kg per day) of ursodeoxycholic acid (UDCA) for 12 months reduces aminotransferase activity and the concentration of serum markers of fibrosis in adult patients with histologically confirmed NASH [35]. A Russian observational study noted that after treatment with UDCA at a dose of 12-15 mg/kg, normalization of liver enzyme activity was achieved in 96% of children with NASH [36]. A randomized controlled trial found that treatment with UDCA and vitamin E for 2 years reduced the activity of AST and ALT and the severity of hepatic steatosis in patients with NASH [37]. In experimental studies on animal models, in addition, it was shown that UDCA drugs have, among other things, antifibrotic and antiapoptotic effects [38]. According to the instructions for the use of UDCA drugs approved by the Russian Ministry of Health, they are indicated, incl. and patients with NASH and do not have any contraindications for children, which means they can be used in children at a dose of 10-15 mg/kg per day for 6-12 months or more. However, the effectiveness and safety of UDCA in children with NAFLD/NASH have not yet been studied in high-quality clinical studies.

In the official instructions of the State Register of Medicines of the Russian Federation, some preparations of essential phospholipids or their combination with other components of hepatoprotective action indicate fatty degeneration and liver degeneration, and contraindications include children under 3 or up to 12 years of age. Therefore, their use in the treatment of NASH in children of the appropriate age is possible. However, it should be noted that high-quality controlled studies of the effectiveness and safety of essential phospholipids for steatohepatitis and liver steatosis in children have not been conducted. There is data on the use of various nutritional supplements in the treatment of patients with steatosis and steatohepatitis. A randomized study

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in children showed the effectiveness of a combination of ascorbic acid + vitamin E / ω3-polyunsaturated fatty acids [39], in randomized double-blind placebo-controlled studies in adults - δ-tocotrienol [40], in children - the probiotic Lactobacillus rhamnosus GG [41] , synbiotics [42]. The effectiveness of Lactobacillus rhamnosus GG was also confirmed in a Russian observational study involving children [43]. The use of ω3-polyunsaturated fatty acids in children also led to relief of the manifestations of NASH, which is described in detail in a literature review by S. Spahis et al. [44]. The use of these dietary supplements reduced ALT activity, body mass index and/or the number of hepatocytes involved in fatty infiltration to varying degrees.

CONCLUSION

NASH, like other forms of NAFLD, is a common pathology of childhood, which is associated with a steady increase in the number of children with overweight and obesity in the population. Unfortunately, due to current dietary trends and a sedentary lifestyle, a decrease in the incidence of NAFLD cannot be expected in the near future. The exact causes and pathogenetic mechanisms of progression of steatohepatosis to steatohepatitis are not completely clear. However, there is no doubt that recurrent or persistent necrotic and inflammatory changes in the liver will eventually lead to fibrosis. Detection of liver damage in children with overweight or obesity should become an additional motivating factor for parents, the child himself, pediatricians and other specialists to intensify efforts to change the patient's lifestyle. This is the main and effective method of treating NASH and NAFLD in general, and the administration of hepatoprotectors and antioxidants in long courses serves as an addition that can slow down the progression of the pathological process in the liver.

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