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MODERN ASPECTS OF HEPATOLOGY: LIVER STEATOSIS AND FIBROSIS THROUGH THE PRISM OF COMORBIDITY IN PEDIATRIC PRACTICE

Larysa Strashok, Turchyna Svetlana, Natalia Shevchenko, Zalina Yeloyeva, Olga Belousova, Olha Tsodikova

The relevance of the topic is dictated by the growing prevalence of hepatic steatosis and fibrosis in the pediatric population, which is due to an increase in the number of pathologies of various organs and systems, which may be accompanied by the development of these liver lesions.

The aim of the study: *to analyze the data of modern sources of scientific literature regarding the prevalence and features of the course of pathology of various organs and systems, which is associated with the development of steatosis and liver fibrosis in the pediatric population.*

Materials and methods*. A systematic search of scientific was carried out using Web of Science, Scopus, PubMed, scientific bases with key words: «hepatic steatosis», «hepatic fibrosis», «non-alcoholic fatty liver disease», «comorbid pathology», «children and adolescents».*

Conclusions. *Currently, the number of children and adolescents who are diagnosed with steatosis and/or fibrosis of the liver is increasing in the world. In particular, the formation of this pathology is associated with the presence of metabolic syndrome and is associated with its main components, such as obesity, hypertension, disorders of carbohydrate and lipid metabolism. More and more studies indicate the role of non-alcoholic fatty liver disease, which is based on steatosis, as a comorbid pathology in systemic, cardiovascular, endocrine diseases, gastrointestinal tract pathology, and genetic disorders. Also, a number of drugs with steatogenic and fibrogenic effects on liver tissue have been established, which are widely used in pediatric practice. It is necessary to monitor the structural and functional state of the liver already in childhood and adolescence for adequate treatment of the underlying disease and prevention of the formation of comorbid pathology*

Keywords: *hepatic steatosis, hepatic fibrosis, non-alcoholic fatty liver disease, comorbid pathology, children and adolescents*

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1. Introduction

The liver is the largest parenchymal internal organ that performs vital functions such as secretory, metabolic, hematopoietic, regulation of blood volume, support of the immune system, cleavage of xenobiotic compounds, including many modern drugs [1].

For many years, scientists around the world have considered liver fibrosis as an irreversible process due to the collapse of the liver parenchyma and its replacement with collagen-rich tissue. Today fibrosis is considered as a model of the wound healing response to chronic liver damage. The use of non-invasive diagnostics, assessment of blood biomarkers, non-invasive calculated indices made it possible to identify and monitor the formation of hepatic steatosis and fibrosis, without resorting to the gold standard for studying morphological changes in the liver - biopsy, which is not always possible to apply both in therapeutic and even more so in pediatric practice [2]. Effective therapy for the treatment of hepatic steatosis and fibrosis still does not exist, which determines the urgency of preventing its development [3]. According to the literature, there are three main causes of progressive liver diseases: chronic inflammation followed by fibrosis, hepatic steatosis, and drug lesions [4].

Currently, there is an increase in the number of children in the world who are diagnosed with fatty liver disease (liver steatosis). This is mainly due to the growing epidemic of childhood obesity, which is associated with the development of metabolic syndrome, one of the criteria of which is the formation of steatosis as the initial stage of non-alcoholic fatty liver disease (NAFLD). However, more and more studies appear that indicate that NAFLD may act as a comorbid condition and be associated with the pathology of various organs and systems by general pathogenetic mechanisms: cardiovascular diseases, type 2 diabetes mellitus (T2D), hypothyroidism, gastrointestinal diseases, polycystic ovary syndrome (PCOS), hypogonadism/hypoandrogenism, genetic and metabolic

disorders. A number of drugs have also been established that have steatogenic and fibrogenic potential [5].

The aim of the research was to analyze the data of modern sources of scientific literature regarding the prevalence and features of the course of pathology of various organs and systems, which is associated with the development of steatosis and liver fibrosis in the pediatric population.

2. Materials and methods

A systematic search of scientific sources was carried out in the scientometric databases Web of Science, Scopus, PubMed, as well as in the archives of journals using the following keywords: «hepatic steatosis», «hepatic fibrosis», «non-alcoholic fatty liver disease», «comorbid pathology», «children and adolescents».

3. Research results and discussion

NAFLD includes a spectrum of histological changes in the liver that are not associated with alcohol consumption: from simple steatosis (presence of fat in more than 5 % of the hepatocytes) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD is closely related to a number of metabolic risk factors; therefore, it is considered a hepatic manifestation of metabolic syndrome, which is based on obesity, impaired carbohydrate and lipid metabolism, hypertension, and other pathology. It is believed that in obesity, especially visceral obesity, with the participation of insulin resistance, the supply of free fatty acids (FFA) from adipose tissue increases and the rate of their oxidation in mitochondria decreases. This leads to esterification of FFA, excessive accumulation of triglycerides and very low density lipoprotein cholesterol in hepatocytes, which forms steatosis. Further, factors such as mitochondrial dysfunction, oxidative stress and activation of proinflammatory cytokines lead to the development of steatohepatitis. In addition to the above mechanisms, the number of studies has recently increased, which indicate that other links are involved in the pathogenesis of the development of NAFLD, such as the influence of the intestinal microbiota, chronic low-intensity inflammation, genetic factors, etc. [6].

The prevalence of NAFLD in the pediatric population has increased 2.7 times since the late 1980s, which is primarily associated with the growing obesity epidemic. In favour of the association of these two pathologies is evidenced by the fact that NAFLD is noted at the level of 9.6 % among children with normal weight and 38 % among children with obesity in the United States [5]. In a systematic review prepared by Anderson et al. it was reported that 7.6 % of children without obesity and 34.2 % of children with the disease had NAFLD [7], similar trends were noted in a study conducted at the State Institution "Institute of Children's Health and adolescents of the National Academy of Medical Sciences of Ukraine" [8]. It is also noted that the prevalence of NAFLD depends on the region of residence and ethnicity [7].

Studies are accumulating that highlight the links between the individual components of metabolic syndrome, namely insulin resistance, dyslipidemia, abdominal obesity, and NAFLD in pediatric practice. In a review prepared by Prokopowicz et al. it was found that obese children with NAFLD had significantly higher indicators of waist volume, total cholesterol and triglycerides, insulin compared with obese children without NAFLD. At the same time, metabolic syndrome was diagnosed reliably more often in children with NAFLD compared with those who did not have pathological changes in the organ – 40.8 % and 22.8 %, respectively [9]. It was found that adolescents with metabolic syndrome had signs of atherogenic dyslipidemia, as well as statistically significantly higher values of body mass index and degree of abdominal obesity than adolescents without signs of metabolic syndrome [10]. Pacifico et al. demonstrated that children and adolescents with a high value of such an indicator of dyslipidemia as the ratio of triglycerides/high-density lipoprotein cholesterol have an increased risk of insulin resistance and an association with NAFLD [11]. Thus, the available data indicate that NAFLD is closely related to the main components of metabolic syndrome already in childhood and adolescence.

NAFLD may be associated with the development of cardiovascular disorders already in childhood. Recent studies have established a close relationship between NAFLD and indicators that characterize the development of atherosclerosis. An increase in the thickness of the intima-media complex of the carotid arteries was recorded in children with NAFLD compared with children without this pathology [12, 13]. Modern research data indicate that NAFLD may be a risk factor for structural and functional disorders of the heart. Pacifico et al. noted that in the group of children with NAFLD, an increase in the thickness of the interventricular septum was diagnosed, as well as impaired systolic and diastolic function of the left ventricle. It was found that with the deterioration of the histological picture of the liver in children, more severe disturbances in the work of the heart were noted [14].

It is known that steatosis and steatohepatitis are among the most frequent extraintestinal complications of inflammatory bowel disease (IBD) in adults, but their prevalence among the pediatric population with this pathology is poorly understood. Cohen et al. revealed that 6 % of children with IBD had NAFLD. The formation of hepatic steatosis in IBD is associated with long-term persistent inflammation and metabolic disorders on the one hand and the use of corticosteroids and methotrexate in the treatment of the disease on the other [15].

Research is underway aimed at studying endocrine pathology associated with NAFLD. The active participation of the liver in glucose metabolism explains its close relationship with the pathophysiology of diabetes mellitus. Recent studies show that the prevalence of prediabetes and T2DM is significantly higher in overweight or obese children with NAFLD. In their study, Pacifico et al. reported a higher prevalence of prediabetes in overweight and obese children who had NAFLD [16]. Bedogni et al. found that impaired glucose tolerance or T2DM is diagnosed more than 3 times more often in children aged 8-18 years with obesity and NAFLD, namely in 25 %, compared with 8 % of obese children without NAFLD [17]. Xanthakos et al. studied the prevalence of T2DM in obese adolescents who underwent bariatric surgery, depending on the stage of NAFLD. It was found that in patients without NAFLD, the prevalence of

T2DM was 6.6 % and increased to 8.8 % with steatosis and up to 66.7 % with NASH [18]. It should be noted that establishing causal relationships in the NAFLD/T2DM pair is a difficult task, since there is a so-called "vicious circle". On the one hand, NAFLD can serve as a risk factor for the development of T2DM, since it is characterized by an increase in insulin resistance in the liver and other tissues, which leads to impaired glucose metabolism. On the other hand, insulin resistance is observed in T2DM, which leads to an increase in the delivery of FFA to the liver, increased de novo lipogenesis and, as a consequence, the accumulation of fat in hepatocytes, which may precede the development of NAFLD.

Another endocrine pathology that is often associated with hepatic steatosis is thyroid dysfunction. Thyroid hormones are metabolized in the liver and play an important role in the regulation of basal metabolism. Hypothyroidism is characterized by a decrease in the function of the thyroid gland, which can lead to a decrease in the utilization of lipids in the liver, their further accumulation and serve as an impetus for the development of steatosis. In a recently published meta-analysis on the association of NAFLD with thyroid function, it was noted that, regardless of age, an increased level of thyroid-stimulating hormone was significantly associated with a higher risk of NAFLD, and its further increase was recorded as the disease progressed [19].

In modern literature, there is an increased interest in the issue of the association of NAFLD and such diseases of the reproductive system as PCOS and hypoandrogenism/hypogonadism. PCOS is one of the most common gynecological conditions and is characterized by hyperandrogenism, menstrual dysfunction, impaired production of female sex hormones, and cystic changes in the ovaries. It is believed that insulin resistance and hyperinsulinemia associated with obesity underlie the increased production of androgens by the ovaries, which creates a steatogenic and proapoptotic background and increases the predisposition of girls and women with PCOS to the development of NAFLD. In turn, liver damage can affect androgen metabolism and, as a result, aggravate hormonal disorders in PCOS patients [20].

Adolescents with PCOS are often characterized by metabolic syndrome, insulin resistance, and impaired glucose tolerance. In a study by Ayonrinde et al. NAFLD was diagnosed reliably more often in girls with PCOS compared with those who did not have this pathology, which amounted to 37.5 % and 15.1 %, respectively. It was also found that combined pathology of the liver and reproductive system were characterized by more pronounced obesity, higher levels of androgens and markers of inflammation, compared with adolescents with NAFLD without PCOS [21]. Carreau et al. obtained similar results: prevalence of NAFLD was noted at the level of 50 % and 13 % in adolescent girls with PCOS and without PCOS, respectively [22].

In recent years, there is more and more evidence that testosterone deficiency is associated with an increased risk of developing certain components of metabolic syndrome, including obesity and NAFLD. Obesity plays an important role in the development of hypogonadism due to complex interactions between gonadal hormones, excess aromatase activity of adipose tissue, the production of various hormones by adipocytes, as well as markers of inflammation, which leads to a decrease in testosterone production. Low testosterone levels in young men are characterized by delayed puberty, short stature, decreased bone and muscle mass, increased cardiovascular risk, depression, etc. [23].

A recent retrospective study showed a significantly higher prevalence of NAFLD in young men with hypogonadism compared with healthy men – 34.9 % and 4.4 %, respectively, as well as a positive effect of testosterone supplementation on reducing fat and liver enzyme levels in several studies [24]. The prevalence of hypoandrogenism or hypogonadism in adolescents and young people with obesity ranges from 30 to 60 % depending on various criteria used to diagnose obesity [23].

In our studies, conducted at the State Institution "Institute for the Protection of Children and Adolescents Health of the National Academy of Medical Sciences of Ukraine", a factorial model of the formation of liver steatosis in young men with hypoandrogenism was developed, which is based on atherogenic changes in lipid status, androgen deficiency, the presence of insulin resistance, activation of cytological processes in the liver and formation of oxidative stress by reducing the effectiveness of antioxidant protection [25].

It is known that there is a group of genetic and metabolic disorders that can be accompanied by the development of hepatic steatosis, while their first clinical signs are most often manifested in childhood. These include: urea cycle disorders, citrin deficiency, glycogenosis, hereditary fructose intolerance, congenital disorders of glycosylation, cholesteryl ester storage disease, abetalipoproteinemia/ hypobetalipoproteinemia, Wilson's disease, cystic fibrosis, Down syndrome, Shereshevsky-Turner syndrome [5].

Taking various medications can cause liver damage, including the development of steatosis and more severe stages of NAFLD. Based on the histological picture, steatosis is characterized as macrovesicular (a large fat droplet displaces the nucleus to the periphery of the hepatocyte), microvesicular (an accumulation of many small lipid droplets that do not displace the nucleus) or mixed. The list of drugs, the use of which is associated with the development of macrovesicular steatosis, includes: methotrexate, glucocorticoids, estrogens, nitrofurantoin, antihypertensive drugs, for example, metoprolol, nonsteroidal anti-inflammatory drugs (ibuprofen, indomethacin and sulindac), and chemotherapeutic agents (5-fluorophenoroid). Microsteatosis is associated with the intake of valproic acid, diltiazem, amiodarone, high doses of vitamin A, aspirin, ibuprofen, 5-aminosalicylic acid preparations, zidovudine and tetracycline [26].

Mitochondria play a dominant role in fatty acid oxidation, and one of the factors underlying drug-associated steatosis is mitochondrial dysfunction and, as a result, lipid metabolism. The following mechanisms are known that are associated with impaired oxidation of fatty acids in mitochondria and leading to the formation of microsteatosis: direct suppression of mitochondrial enzymes (amiodarone), impaired generation of cofactors (valproic acid), inhibition of the mitochondrial respiratory chain (amiodarone, perhexiline, tamoxifen), inhibition

of the mitochondrial DNA (didanosine, azidothymidine, stavudine).

The following mechanisms are involved in the development of macrosteatosis: impaired oxidation of fatty acids in mitochondria, inhibition of microsomal triglyceride-carrying protein, increased absorption of fatty acids by cells, and stimulation of lipid synthesis in the liver. Thus, non-esterified fatty ones undergo increased esterification into triglycerides with their subsequent accumulation in liver cells, as well as the development of lipid over-oxidation [27].

It has been established that the development of steatohepatitis can be caused both by a direct effect on hepatocytes (amiodarone, perhexiline, biseptol, indomethacin, paracetamol, ketoconazole, methyldopa, naproxen, nifedipine, valproic acid), and by indirect induction of metabolic risk factors such as insulinresistance (steroids, antiepileptic drugs). Disruption of the transmembrane transport of metabolites (rifampicin, ceftriaxone, tetracycline, estrogens) can also lead to the formation of steatosis and liver fibrosis. The presence of obesity and diabetes exacerbates the risk of developing steatohepatitis when taking tamoxifen, methotrexate, estrogens, nifedipine, isoniazid [26, 27].

According to the Swedish hepatology clinic, 6.6 % of patients had liver damage due to the influence of drugs used [28]. It has been found that 2 % of cases of NASH are drug-induced [27]. At the same time, data on the prevalence of drug-associated liver damage in the pediatric population are limited, and research on this problem mainly concerns individual drugs and pathologies.

Researchers from all over the world are actively studying the mechanisms of fibrosis in juvenile idiopathic arthritis (JIA), including the mechanisms of liver damage in JIA [29].

In the modern literature, the issues of drug-induced liver damage are actively considered, including, according to a meta-analysis of 88 studies, long-term use of MTX in various diseases, a long-term persistent increase in liver enzymes was found, as well as signs of liver fibrosis [30]. The issues of studying liver fibrosis and steatosis in pediatrics, including in JIA, where both systemic inflammation and treatment with methotrexate are combined, remain topical.

Methotrexate is an antimetabolic, folic acid antagonist and a key drug in the treatment of juvenile idiopathic arthritis. It is believed that methotrexate promotes the accumulation of polyglutaminated metabolites, homocysteine, promotes mitochondrial dysfunction, activation of stellate liver cells, which leads to the formation of steatosis and organ fibrosis [28].

A recent meta-analysis found that abnormalities in the biochemical blood test, characterizing the functional state of the liver, were found in 10.2 % of children with IBD who received methotrexate, while a dose reduction and drug withdrawal were required in 6.4 % and 4.5 % of patients, respectively [31]. That is, on the one hand, the development of steatosis and fibrosis was noted for the use of a number of drugs that are widely used in the clinical practice of a pediatrician, and on the other hand, NAFLD and other components of the metabolic syndrome can be predisposing factors for the development of further liver damage when taking such drugs.

4. Conclusions

Thus, the data accumulated in recent years indicate that NAFLD is associated with the main components of the metabolic syndrome, such as obesity, hypertension, dyslipidemia, disorders of carbohydrate metabolism already in childhood and, having common mechanisms of formation with diseases of various organs and systems, can act as a comorbid pathology. At the same time, it becomes clear that there is a bi-directional relationship: extrahepatic pathology can be both a cause of aggravation of liver steatosis and a consequence of the progression of fatty degeneration of the liver. It is established that a number of drugs widely used in pediatric practice have a steatogenic and fibrogenic effect on the parenchyma and stroma of the liver. Monitoring the structural and functional state of the liver in childhood and adolescence is advisable and necessary for adequate treatment of the underlying disease and prevention of the formation of comorbid pathology, including steatosis and liver fibrosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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Larysa Strashok, MD, Professor, Department of Adolescent Medicine, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176
E-mail: laspediatr1984@gmail.com

Svetlana Turchyna, MD, Senior Researcher, Head of Department, Department of Endocrinology, State Institution "Institute of Child and Adolescent Health of National Academy of Medical Sciences of Ukraine", Yuvileinyi ave., 52-A, Kharkiv, Ukraine, 61153
E-mail: svetlanaturchina00@gmail.com

Natalia Shevchenko, MD, Head of the Department, Department of Pediatrics No. 2, V. N. Karazin Kharkiv National University, Svobody sq., 4, Kharkiv, Ukraine, 61022
E-mail: natalia.shevchenko@karazin.ua

Zalina Yeloyeva, MD, Professor, Head of Department, Department of Pediatrics, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176
E-mail: pdnev@med.edu.ua

Olga Belousova, MD, Professor, Head of Department, Department of Pediatric Gastroenterology and Nutritiology, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176
E-mail: olga.yu.belousova@gmail.com

Olha Tsodikova, MD, Professor, Head of Department, Department of Outpatient Pediatrics, Kharkiv Medical Academy of Postgraduate Education, Amosova str., 58, Kharkiv, Ukraine, 61176
E-mail: tsodikova.olga@gmail.com