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Laboratory And Molecular-Genetic Markers Of The Progression Of Non-Alcoholic Fatty Liver Disease (literature review and own data)

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is one of the most common diseases in hepatology. First of all, this is associated with a high risk of progression of NAFLD with the development of non-alcoholic steatohepatitis (NASH), liver failure, and hepatocellular carcinoma. Epidemiological and genetic studies have shown the relationship between the morphological stage of NAFLD and hereditary factors. The article provides a review of the literature on the cytokines, MBOAT7 and GCKR genes. Also, a variant of the MBOAT7 and GCKR gene is associated with a high risk of fibrosis in patients with NAFLD and elevated serum triglyceride levels.

KEYWORDS

Non-alcoholic fatty liver disease, nonalcoholic steatohepatitis, cytokines, MBOAT7 gene, GCKR gene, cirrhosis, lipids, obesity.

INTRODUCTION

The urgency of the problem. Today, non-alcoholic fatty liver disease (NAFLD) attracts the attention of a wide range of specialists both in our country and abroad. Currently, non-

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alcoholic fatty liver disease (NAFLD) is one of the most common diseases in hepatology, leading to a deterioration in the quality of life, disability and death. The overall prevalence of NAFLD in the population ranges from 10 to 40% [3,5,9,19,38].

Non-alcoholic fatty liver disease is not related to alcohol consumption, a chronic disease characterized by the accumulation of fat in liver cell and that plays an important role in diseases of the gastrointestinal tract [3,11].

Thus type of NAFLD may be, as independent disease, combined with obesity, 2nd type of diabetes mellitus and dyslipidemia, and according to a several authors, secondary functional violations of liver, for instance, with dyslipidemia, they can manifest as a NAFLD. In the early stages of the NAFLD are characterized by ineffectiveness of specific treatment and progressive progression of the disease due to the nonspecific clinical signs [3,25,27].

NAFLD - progressive, chronic multifactorial steatosis of liver – (accumulation of fat in the liver, fatty dystrophy of hepatocytes), steatohepatitis – formation of inflammatory infiltrate around the site of necrosis in hepatocytes, non-alcoholic fibrosis-cirrhosis: destruction of liver architectonics and the disease complicated by connective tissue growth, that has been the main focus of local and foreign hepatologists for the last 10 years [3,15,34]. When the disease is periodic in 12-40% patients after 8-13 years may convert to non-alcohol steatohepatitis, from that in 15% patients may be liver cirrhosis and liver failure. After 10 years liver cirrhosis may convert to hepatocellular carcinoma in 7 % patients. NAFLD - the facts in last 10 years confirm growth of disease [26,35,37]. NAFLD is widespread in western Europe and USA. The spreading in common population of NAFLD L is not learnt well, but some authors determined that occurs 3-58% in Italy and USA [9,35].

The growth rate of NAFLD is problem and that will evaluate with propensity to obesity. As the level of obesity increases, the severity of the disease also increases [3,7,15,17,29]. NAFLD 3-100 % occurs with obesity. In that situation when patients are checked at ultrasound examination, fatty dystrophy of liver will found [7,30]. The scientific researches show that, NAFLD occurs 70% with 2nd type diabetes mellitus [2,24,30]. Thus, the progressive progression and prevalence of the disease is one of the current problems of clinical medicine due to the observation of the time when the working capacity of the population is preserved, close clinical signs are observed in the late stages of the disease [38,39].

There are many causes of development of the fatty steatosis of liver. Primary steatosis mostly, appears on the basis of obesity, hyperlipidemia, 2nd type diabetes mellitus [4,10,15]. The cause of developing secondary fatty hepatosis is consumption drugs of some groups (steroid hormones, substitution hormonal therapy, antiarrhythmic and antibacterial drugs, cytostatic, non-steroideal anti-inflammatory drugs), chronic inflammatory diseases of the gastrointestinal tract, sudden weight loss, parenteral nutrition, gestational age hypoxia, Wilson Konovolova disease, lipoproteinemia, familial liver steatosis, glycogen accumulation disease [10,12,13]. Based on the entry of free fatty acids (FFA) into the liver, triglycerides accumulate in the liver the beta oxidation rate of FFA in the liver mitochondria decreases, and the synthesis of fatty acids increases. As a result, the synthesis of very low-density lipoproteins is

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reduced, triglycerides are excreted from the liver [12,13].

In developing of steatosis "First impact" is – gathering of FFA in hepatocytes, decreasing of oxidation and inhibition of triglyceride elimination. Different level of inflammation and fibrinogenase are observed in response to oxidative stress molecules (aldehydes). Oxidative stress products induce the expression of matrix – linked genes. Oxidative stress associated with the immune response, fibrinogenase develops in the trigger. Stress of hepatocytes with lipids and FFA leads to the development of functional insufficiency in the mitochondria and the formation of steatosis occurs. Progressive progression of steatosis makes condition for developing steatohepatitis. Additional oxidative stress, peroxidase oxidized lipids disturb the cellular defense mechanism and inflammation and necrosis occur. NAFLD stimulates formation of free radicals from endogenous ketones, food nitrosamines, aldehydes, cytochrome P450 (CYP) 2E1. 18 CYP 2E1 ketone and fatty acids can be cytochrome mediators [10].

The inflammatory process may develop endotoxinemia in intestinal dysbacteriosis. Lipopolysaccharide, a gram-negative bacterium that enters the portal vein, activates Toll-like receptors in response to type 4 immunity and develops inflammation and fibrosis (30,33). In NAFLD, endotoxemia pro-inflammative cytokines (TNF), Interleukin-6,8 and this increase the expression of cytokine receptors [27,34]. Serum concentrations are elevated in obese individuals TNF-α. TNF-α activates a protein that stimulates protective inflammatory reactions - inhibitor of kappa kinase beta (IKKβ) in adipocytes and hepatocytes, which leads to impaired binding insulin receptor. Smooth muscle and endothelial cells of the vessel wall under the influence of TNF-α enhance the production of monocytic chemotactic protein-1 (MCP-1), which plays a leading role in the pathogenesis of atherosclerosis. It is noteworthy that cytokines are one of the main stimulants of liver regeneration. It is known that TNF-α is able to initiate liver necrosis, but necrosis does not occur in normal hepatocytes, because TNF-α-celeft genes are usually expressed at minimal level [8,14]. Serum TNF-α levels are not the same in patients patients with hepatic steatosis and NASH and, as a rule, higher in patients with NASH, although the difference is not always statistically significant [2,8,14]. Interleukin-6 (IL-6) has a special role as a "hepatocyte-activating factor". IL-6 can induce the synthesis of many acute phase proteins, such as fibrinogen and C-reactive protein (CRP), an increase in which is common a known risk factor for CVD. It has been proven that cytokines are important mediators of steatohepatitis [14]. In this process the primary role is played by the tumor necrosis factor holi alpha (TNF-a) and interleukin 6 (IL-6). TNF-a stimulates the synthesis of fatty acids in the liver, increases the level of serum triglycerides [8,13,14] and stimulates the production of VLDL by the liver [12]. TNF-a can cause both the death of hepatocytes and their proliferation, and is critically involved in the pathogenesis of liver fibrosis in NASH [2,8,14].

Last studies have shown that adipose tissue, namely, visceral fats, alters endocrine content, produces adipokin-hormones, which affect lipid metabolism, as well as the function of other organs and systems [5,18,36]. Changes in the amount of adipokines increase tissue infiltration monocytes and macrophages, pro-inflammation induct cytokines. Prolonged steatosis and local inflammation can lead to

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fibrosis and then may convert cancer. NAFLD over time increases the risk of cirrhosis, hepatocellular cancer, which results in liver resection and transplantation [6].

In obesity, the release of high concentrations of leptins in the blood stimulates the secretion of other neuropeptides: melanocytostimulating hormone, propiomelanocortsin, neuropeptide, corticotropin, corticotroping releasing factor. All of the above peptides cause dysfunction of the sympathetic nervous system, activate lipolysis in fat storage, accelerate the entry of FFA into the liver. FFA stimulates glycogenesis in the liver, inhibits insulin secretion, develops insulin resistance [3,11,16,39].

The development of fatty liver dystrophy occurs through exogenous and endogenous mechanisms. As a result of intestinal absorption of exogenous fatty acids, glycerin, glucose, galactose, fructose, the endogenous mechanism - increased peripheral lipolysis, decreased consumption of fatty acids from liver cells, increased fat synthesis, protein deficiency in liver cells, decreased liver enzyme activity, very low lipoprotein density increase in excretion by hepatocytes [3]. Dyslipoproteinemia (DLP) is characterized by a change in homeostatic constant, a violation of the functioning of systems. DLP can damage the liver as a target organ and cause atherosclerosis in the arteries parallel to it. A group of researchers have noted that dyslipidemia is a disorder of the process of bile formation and secretion as a result of damage to the hepatocyte membrane. Other authors have suggested that DLP in hepatic steatosis is a "safe condition" and that the etiologic factor must be ruled out [15,23]. These ideas are complicated because in hepatic steatosis mitochondria, liver cell lysosomes are damaged, FFA is not consumed, cholestasis and hyperlipidemia may develop.

In NAFLD liver cell function is impaired, large amounts of cholesterol and small amounts of phospholipids and bile acids accumulate in the bile ducts, bile has lithogenic properties, and gallstone disease develops [15,23], resulting in impaired secondary metabolism [3]. NAFLD is 5 times more common in patients than in gallstone disease in the population. Gallstones were observed in 18.2% and 31.1% of patients with nonalcoholic steatosis and steatohepatitis. At the same time, cirrhosis of the liver and cholelithiasis were observed in 41.7% of patients [19].

Hyperinsulinemia is the main link in the development of IR-HI-obesity-IR. Today, an increase in fat tissue reserves based on a high-calorie diet increases the stress on insulin. Lack of physical activity leads to insulin resistance in adipose tissue, hyperinsulinemia is formed as a result of decreased tissue sensitivity to insulin.

The most common risk factors are a diet with an excess of calories, saturated fat, easily digestible carbohydrates and fructose, and low physical activity. In some cases, (especially among children and adolescents), a hereditary predisposition to NAFLD can be confirmed, arising from defects in the genetic material (PNPLA3 and TM6SF2 gene, MBOAT7 gene, GCKR gene) [2,8,13,14,17,32,34]. Nonalcoholic fatty liver disease (NAFLD) is a leading cause of liver damage and is characterized by steatosis. Genetic factors increase risk for progressive NAFLD. The PNPLA3 p.I148M, TM6SF2 p.E167K, and MBOAT7 rs641738 variants represent genetic risk factors for nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease (NAFLD) represents an emerging cause of hepatocellular carcinoma (HCC), especially

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in non-cirrhotic individuals. The rs641738 C > T MBOAT7/TMC4 variant predisposes to progressive NAFLD, but the impact on hepatic carcinogenesis is unknown [1,8,13,14,22].

The GCKR gene encodes a protein involved in the regulation distribution of glucokinase between the cytosol and the nucleus in hepatocytes and, thus, in the process of utilization lysis of glucose by liver cells [1,32]. Option p.P446L (rs1260326) of the GCKR gene, first identified in 2011, inhibits glucokinase indirectly through an increase in the level of fructose-6-phosphate [1,20]. This leads to increased absorption of glucose by cells, liver and, in turn, helps to increase activity of de novo lipogenesis processes and a simultaneous decrease in serum glucose and insulin levels [1,13,14]. The combination of minor alleles I148M and P446L of the PNPLA3 and GCKR genes is associated with steatosis up to 30% in the liver acinus (the severity of steatosis according to histological examination) in obese children [1,13]. Also, the p. P446L variant of the GCKR gene is associated with a high risk of developing fibrosis in patients with NAFLD and elevated serum triglyceride levels [1,20]. The variant rs641738 was recently identified gene MBOAT7 encoding lipophosphatidylinositol acyltransferase. This genetic variant is not only increases the risk of developing cirrhosis of the liver in individuals with consuming alcohol, but also, as was shown later, increases the risk of developing non-alcoholic steatohepatitis and liver fibrosis in patients with NAFLD [1,24,29]. The MBOAT7 gene encodes lipophosphatidylinositol acyltransferase, which catalyzes the remodeling of the acyl chain of phosphatidylinositols, binds arachidonic acid to lysophosphatidylinositol and reduces the level of free arachidonic acid in neutrophils [1,21]. Arachidonic acid, in turn red, induces apoptosis of hepatocytes, causing reproduction palpation and fibrosis of liver tissue [1]. Probably for this reason, the rs641738 variant of the MBOAT7 gene, which leads to a decrease in MBOAT7 expression, is associated with a lower risk of steatosis than PNPLA3 p. I148M or TM6SF2 p. E1267K, but with an increase in the activity of inflammation in the liver and the development of fibrosis in NAFLD [28].

NAFLD is asymptomatic in most patients (48-100%). The remaining patients have abdominal discomfort and blunt pain under the right rib. Patients with cardiovascular pathology, digestive, endocrine and tumor diseases, as well as other diseases of the liver are often diagnosed suddenly at the time of complaint [3,7,29,31,33].

There will be no changes in blood biochemical analysis. Sometimes urobilinogenuria, hypertriglyceremia can be detected. ALT activity can significantly exceed the norm by 1.5-2 times. Obesity, 2nd type DM, hyperlipidemia, thymol test, increased levels of alpha 2 and gamma globulin are seen [2,14].

An anamnesis of alcohol is denied at NAFLD. Transferin, often sialic acid and mitochondrial isoenzyme AST is sensitive and specific, but is rarely used [2,16,19]. Because a perfectly collected anamnesis is an important diagnostic method in general practitioners.

CONCLUSION

Like fatty hepatosis, non-alcoholic steatohepatitis is an independent disease that should be kept in mind when conducting differential diagnostics in patients with a stable increase in serum ALT and AST, especially in the

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presence of obesity, diabetes, and hyperlipidemia. Epidemiological and genetic studies have shown the relationship between the morphological stage of NAFLD and hereditary factors. The data obtained confirm the importance of the discussed cytokines in the evolution of hepatic steatosis into steatohepatitis, and also indicate the possibility of using their indicators as non-invasive markers of steatosis and the activity of inflammation in the liver in patients with NAFLD. Genetic factors increase risk for progressive NAFLD.

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