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THE ROLE OF SEVERAL GENES IN NON-ALCOHOLIC FATTY LIVER DISEASE

Anotation: Nonalcoholic fatty liver disease (NAFLD) is It is the most frequently diagnosed pathology of the liver. As part of liver diseases in adolescents, there is an increase in the percentage of patients with CKD, which is directly related to the increase in the prevalence of obesity. The spectrum of liver tissue changes in NAJYK varies from benign hepatocyte steatosis to nonalcoholic steatohepatitis (NASG), fibrosis, cirrhosis, and hepatocellular carcinoma. With the increasing prevalence of NCDs in adolescents, we can expect an increase in adverse outcomes among people of working age. A major challenge in NAJYK remains the prediction of disease outcomes. Epidemiological and genetic studies have shown the relationship between the morphological stage of NAJYK and genetic factors. Currently, there are two NAJYK-related genes (TM6SF2 and GCKR) that determine the fatty liver disease phenotype, along with genes responsible for insulin resistance, lipid synthesis, inflammation, and fibrogenesis in hepatocytes. There is information about the modern understanding of genetics, the development of hepatic steatosis and the development of NASG. It is expected that this knowledge will change our strategies for risk stratification in patients with NAJYK and help identify new therapeutic targets.

Key words: nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, gene, TM6SF2, GCKR, PNPLA3, PCKS9, Apolipoprotein C3.

Аннотация: Неалкогольная жировая болезнь печени (НАЖБП) – наиболее часто диагностируемая патология печени. В составе заболеваний

печени у подростков отмечается увеличение процента больных ХБП, что напрямую связано с ростом распространенности ожирения. Спектр изменений ткани печени при NAJYK варьирует от доброкачественного стеатоза гепатоцитов до неалкогольного стеатогепатита (НАСГ), фиброза, цирроза печени и гепатоцеллюлярной карциномы. С ростом распространенности НИЗ среди подростков можно ожидать увеличения неблагоприятных исходов среди людей трудоспособного возраста. Основной проблемой в НАДЖИКе остается прогнозирование исходов заболеваний. Эпидемиологические и генетические исследования показали связь между морфологической стадией НАЙЫК и генетическими факторами. В настоящее время существуют два гена, связанных с NAJYK (TM6SF2 и GCKR), которые определяют фенотип жировой болезни печени, а также гены, ответственные за резистентность к инсулину, синтез липидов, воспаление и фиброгенез в гепатоцитах. Имеются сведения о современных представлениях о генетике, развитии стеатоза печени и развитии НАСГ. Ожидается, что эти знания изменят наши стратегии стратификации риска у пациентов с NAJYK и помогут определить новые терапевтические цели.

Ключевые слова: неалкогольная жировая болезнь печени, неалкогольный стеатогепатит, ген, TM6SF2, GCKR, PNPLA3, PCKS9, аполипопротеин С3.

Enter

Non-alcoholic liver oily disease (NAJYK) obesity with dependent was liver parenchyma in the cells of lipids to plan no different natural pathological o'changes is a group. Many in cases, u steatosis as manifestation will be

(histological to the inspection rather, fat vacuoles in hepatocytes inflammation process without signs liver from 5% of the lobule many programs occupies) and good good quality to the process enters That's it with together with the disease active form - non-alcoholic steatohepatitis - hepatocytes damage to the liver tissue inflammation with It is described liver of fibrosis to the formation of the liver of cirrhosis development, hepatocellular deficiency and hepatocellular to carcinomas take coming can Har year NAJYK of the problem relevance obesity and metabolic syndromic people number increase because of new importance occupation is enough From 1989 to 2015 it was done to research See, the world in 25 percent of the population NAJYK determined. However, the spread information being studied population to the number (country, ethnic come exit) depending difference by doing and diagnosis methods come change from 6.3 % to 33 % can According to the results of DIREG 1, DIREG-L-01903 and DIREG 2 population studies conducted in the Russian Federation, in 2007, the incidence of NAJYK among outpatients was 27%, and in 2014 - 37%. At the same time, NAJYK was the most common pathology among liver diseases: according to 2014 data, it was diagnosed in 72% of cases. 77% of patients suffering from NAFLD were diagnosed with liver steatosis, 23% with non-alcoholic steatohepatitis and 3% with liver cirrhosis. In the United States, between 2004 and 2013, there was a 1.7-fold increase in the waiting list for liver transplantation due to NASG and liver cirrhosis due to NASH as the incidence of NASH increased. In addition, it is part of the instructions for liver transplantation of this etiology second in place stands

Hereditary and Non-alcoholic liver oily disease

It is known that NAJYK is a multifactorial disease. The role of genetic factors in the development of NAJYK has been proven in people with insulin resistance and overweight. The results of the research conducted in the last decade show that genetic factors have made a significant contribution to the development of NAJYK. A new understanding of pathogenesis may change our understanding of risk stratification in patients with NAJYK and contribute to the search for new

therapeutic approaches to treat the disease. The genetic nature of NAJYK indicates differences in the prevalence of the disease in different ethnic groups. Thus, according to the results of two large studies conducted in the United States, the prevalence and risk of development of NAJYK have been shown to be significantly higher in Hispanics than in European people living in the United States. Among African Americans, the frequency of necrotic inflammation and fibrosis of the liver tissue was significantly lower than in representatives of the above ethnic groups, even compared to the groups with type 2 diabetes and obesity. A study of familial aggregation of cases of NAJYK showed that, according to morphological examination, family members with overweight children with NAJYK were more likely to have hepatic steatosis compared to family members with overweight children but not NAJYK. more inclined. A study of mono- and di-zygotic twins showed that up to 60% increase in serum hyalanine aminotransferase levels in fatty liver disease in the absence of viral hepatitis or consumption of hepatotoxic doses of alcohol is genetic. determined.

Also, the visibility of hepatocyte steatosis and fibrosis of liver tissue (using magnetic resonance elastography method to measure fat content by proton density) was shown to be more related in monozygotic twins than in dizygotic pairs. When adjusted for age, sex, and ethnicity, the heritability (ratio of genotypic to phenotypic variation) of hepatic steatosis and fibrosis was 52 and 50%, respectively.

TM6SF2 gene

Recent studies have shown that the rs 58542926 C>T variant in the TM6SF2 gene, which encodes superfamily-2 transmembrane protein 6, and the rs 780094 variant in the glucokinase GCKR gene are associated with the risk of developing liver steatosis and fibrosis in NSCLC. The TM6SF2 gene encodes a 351 amino acid protein containing 7 transmembrane domains expressed by human liver and

intestinal cells. The pE 167k variant of the TM6SF2 gene is present in 7.2 % of Europeans, 3.4% of African Americans, and 4.7% of Hispanics.

Later, TM6SF2 gene p. The E167 k gene variant was found to impair lipidation (protein modification affecting the intracellular localization and function of the resulting lipoproteins) and the formation of very low-density lipoproteins in hepatocytes and chylomicrons in enterocolitis. This leads to the accumulation of triglycerides in cells and a decrease in the amount of circulating triglycerides rich in lipoproteins. PNPLA 3 gene p. Similar to variant I 148 M, the TM6SF 2 gene p. The E 1267k variant increases the risk of developing liver diseases with not only steatosis, but also fibrosis formation. This sequence was found in chronic hepatitis C-TM 6 SF 2 gene p. Carriers of the E 167k variant have also been confirmed in patients.

GCKR gene

and the nucleus in hepatocytes and, thus, in the process of glucose utilization by liver cells. GCKR gene p. The P 446 L (rs 1260326) variant, first identified in 2011, indirectly inhibits glucokinase by increasing fructose-6-phosphate levels. This leads to an increase in the amount of glucose by the cells of the liver and, in turn, helps to increase the activity of de novo lipogenesis processes and a simultaneous decrease in the level of glucose and insulin in the blood. The combination of minor alleles I148M and P446L of PNPLA 3 and GCKR genes is associated with steatosis up to 30% (severity of steatosis by histological examination) in liver acinus in overweight children . Also, the p.P446L variant of the GCKR gene is associated with a higher risk of developing fibrosis in patients with NAJYK and elevated serum triglyceride levels.

Lipid metabolism in the liver

In addition to the TM6SF2 gene, which is the most common determinant of hepatic steatosis, other rare or less well-defined genetic alterations have been identified that affect lipid metabolism and may contribute to the development of

hepatic steatosis. Changes in the genes that regulate the processing and synthesis of very low density lipoproteins are associated with NAJYK. For example, hypobetalipoproteinemia, characterized by low levels of the apolipoprotein B (APOB) gene or proprotein convertase subtilisin-type 9 (PCSK9), which in some cases represents the absence of serum Apo B and high-density lipoproteins. APO B protein is responsible for the accumulation and secretion of very low-density lipoproteins in the liver and chylomicrons in the intestine. Loss-of-function or missense mutations in the APO B gene lead to decreased plasma cholesterol levels and accumulation of triglycerides in hepatocytes. In addition, the presence of this genetic defect is associated with the development of steatohepatitis, liver cirrhosis and hepatocellular carcinoma.

PCKS9, in turn, provides serine protease and is considered a factor that increases the degradation of low-density lipoprotein receptors. PCKS9 loss-of-function nucleotide sequence variant k analogically reduces blood cholesterol levels but does not affect hepatic triglyceride accumulation. Phase III clinical studies investigating monoclonal antibodies against PCSK9, aimed at lowering low-density lipoprotein in the blood, did not report adverse events related to liver damage. This PCSK9 defect may exacerbate liver disease in patients with the TM6SF2 gene variant.

Microsomal triglyceride-transfer protein (MTTP) localizes in the endoplasmic reticulum and transfers triglycerides to very low-density lipoproteins in the liver and intestinal chylomicrons, and can serve as a chaperone involved in the accumulation of Apo B in hepatocytes. Mutations in the MTTP gene lead to the development of α betalipoproteinemia, which is characterized by undetectable levels of low-density lipoprotein and Apo B, as well as the accumulation of triglycerides in hepatocytes and the development of liver cirrhosis. Clinical studies have shown that long-term use of the MTTP inhibitor lomitapide in the treatment of familial hypertriglyceridemia and acute pancreatitis increases the risk of developing liver cirrhosis as a result of NASG.

Apolipoprotein C3 (ApoC3) is the main component of very low density lipoproteins and is involved in the secretion of triglycerides. Initially, in 2010, several variants of the APOC3 gene promoter were reported to be associated with increased risk of hypertriglyceridemia and CVD. Inhibition of ApoC3 protein expression is currently being considered as a treatment for hypertriglyceridemia, and the potential risk of developing NAJYK and NASG as a result of such therapy should be kept in mind.

Another rare genetic cause of NASG-induced liver cirrhosis is zosomal acid lipase deficiency. Lysosomal acid lipase is responsible for the hydrolysis of cholesteryl esters, triglycerides, and low-density lipoproteins into free cholesterol and fatty acids. Lysosomal acid wedge deficiency is a rare autosomal recessive disease associated with changes in the LIPA gene, which leads to a sharp decrease in enzyme activity. However, the age of onset of the disease and the rate of its development are variable.

There are two forms of lysosomal acid deficiency - infantile (Volman's disease) and late \ (cholesterol ester storage disease). The infantile form of deficiency is a severe, rapidly progressive disease that manifests itself from the first weeks of life to 3-6 months. Death occurs against the backdrop of progressive multi- organ failure. The average age of death in patients with infantile form without treatment is about 4 months. The late form of lysosomal acid lipase deficiency manifests itself in children and adults, develops more slowly and is manifested by hepatomegaly, cytolysis syndrome (transaminase activity increases by 3-4 normal), hypercholesterolemia and dyslipidemia. Against the background of accumulation of cholesterol esters in hepatocyte lysosomes, the patient develops steatosis, then fibrosis and liver cirrhosis.

Fatty acid transport proteins FATP are integral membrane proteins that mediate the uptake of free fatty acids by hepatocytes. Reduction of FATP5 protein prevents the development of steatosis in mice with diet-induced NAFLD. Conversely, the

rs56225452 variant of the FATP5 gene, which regulates its expression, is associated with a higher risk of hepatic steatosis, higher alanine aminotransferase levels, and increased insulin resistance in the general population.

The LPIN1 gene encodes a phosphorylated phosphatase present in adipose tissue and liver, where it acts as an inducible transcriptional coactivator to regulate fatty acid metabolism. The rs12412852 variant of the LPIN1 gene is associated with a modest incidence of NASG and liver fibrosis in children with NASH . LPIN1 gene rs12412852 causes a decrease in lipolysis, which reduces the accumulation of free fatty acids in the liver.

CONCLUSION

Research conducted over the last decades shows that NAJYK depends on acquired and genetic factors. The main genetic determinants of hepatic steatosis, TM6SF2 p.E167K and GCKR p.P446L, as well as less common genetic variants associated with NAJYK, emphasize the importance of lipoprotein synthesis, lipid metabolism and glucose in the pathogenesis of NAJYK. The genetic nature of inflammation and fibrosis in NAJYK is less well defined, mainly due to the lack of kata phenotype cohort studies. It should be taken into account that genetic factors cannot be the only reason for the development of the disease, and the presence of genetic variation indicates that NAJYK is not a homogeneous disease. Understanding the genetic basis of NAJYK offers promising opportunities to improve our approaches to treating the disease. Further studies include a new vector for changing the prevention and treatment of NAJYK in the direction of personalizing patient monitoring, taking into account the risk of disease development and taking into account the transfer of therapy aimed at the main mechanisms of the disease.

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