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NON-ALCOHOLIC FATIAL DISEASES OF THE LIVER: HISTORICAL ASPECT OF THE FORMATION OF NOSOLOGICAL UNIT, ETIOLOGY AND PATHOGENETIC PECULIARITIES OF THIS PATHOLOGY (LITERATURE REVIEW)

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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ: ИСТОРИЧЕСКИЙ АСПЕКТ ФОРМИРОВАНИЯ НОЗОЛОГИЧЕСКОЙ ЕДИНИЦЫ, ЭТИОЛОГИЯ И ПАТОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ ДАННОЙ ПАТОЛОГИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Abstract. This literature review focuses on non-alcoholic fatty liver disease (NAFTLD). Today, the world practice of researching diseases is characterized by a multifactor approach, in particular, it concerns pathologies, which are based on a cascade of metabolic disorders, where insulin resistance is one of the key places. Today, NAFTLD is considered an integral part of the metabolic syndrome. The frequency of occurrence of NAFTLD varies from 14 to 26%, in addition, 10% of patients show signs of steatohepatitis non-alcoholic etiology. The pathogenesis of steatosis and metabolic steatohepatitis is poorly studied and there are very contradictory data in the literature, which served as the basis for the creation of this review. The authors consider in detail the historical aspect of the formation of the NAFTLD as an independent nosological unit. A number of etiological aspects of the formation of NAFTLD, but to a large extent, the review is devoted to the mechanisms and pathogenesis of the formation of NAFTLD. A concept has been put forward that reflects the role of oxidative stress and the death of mitochondrial complexes in initiating the initiation of apoptosis and/or necrosis of hepatocytes (under these conditions there is an

activation of leukocytes and Ito cells in Disse space, which contributes to the fibrosis proliferation and the formation of NAFTLD). Also, in this paper, there is also a place for searching for the cause-and-effect relationships of such comorbid diseases, such as NAFTLD and carbohydrate metabolism disorders.

Аннотация. Данный обзор литературы посвящен неалкогольной жировой болезни печени (НЖБП). Сегодня мировая практика исследований заболеваний характеризуется мультифакторным подходом, в особенности это касается патологий, основу которых, составляет каскад метаболических нарушений, где ключевое место принадлежит инсулинорезистентности. На сегодня НЖБП рассматривают как составную часть «метаболического синдрома». Частота встречаемости НЖБП варьирует от 14 до 26%, помимо этого, у 10% пациентов выявляются признаки стеатогепатита неалкогольной этиологии. Патогенез стеатоза и метаболического стеатогепатита малоизучен и в литературных источниках встречаются весьма противоречивые данные, что и послужило основой для создания данного обзора. Авторами детально рассматривается и исторический аспект формирования НЖБП как самостоятельной нозологической единицы. Рассмотрен ряд этиологических аспектов формирования НЖБП, но в большой степени обзор посвящен механизмам формирования и патогенезу НЖБП. Выдвинута концепция, отражающая роль оксидативного стресса и гибель митохондриальных комплексов в инициации запуска апоптоза и/или некроза гепатоцитов (в этих условиях происходит активизация лейкоцитов и клетки Ито в пространстве Диссе, что способствует фиброзному разрастанию и формированию НЖБП). Также в данной работе отводится и место поиску причинно–следственных связей таких коморбидных заболеваний, как НЖБП и нарушения углеводного обмена.

Keywords: non-alcoholic fatty liver disease, pathogenesis, steatosis, steatohepatitis.

Ключевые слова: неалкогольная жировая болезнь печени, патогенез, стеатоз, стеатогепатит.

Today, the world practice of researching diseases is characterized by a multifactor approach, in particular, it concerns pathologies, which are based on a cascade of metabolic disorders, where insulin resistance (IR) is at the forefront [1, p. 2063].

Many researchers consider non-alcoholic fatty liver disease (NAFTLD) as an integral part of the metabolic syndrome. The frequency of occurrence of NAFTLD varies from 14% to 26% [7, p. 510], in addition, 10% of patients show signs of steatohepatitis non-alcoholic etiology.

Previously it was thought that NAFTLD is quite a benign pathology, until it became clear that NAFTLD leads to the development of cirrhosis in 4–30% of cases [20, p. 25], and actually, steatohepatitis predetermines the development of fibrosis, and subsequently liver necrosis [3, p. 332; 12, p. 475]. Starting from 2003, following the results of the 1st World Congress on Insulin Resistance, held in the USA, it was decided that, along with AH and type 2 diabetes mellitus (DM), should be considered a component of the metabolic syndrome [22, p. 7].

NAFTLD is an independent nosological unit. The history of the study of NAFTLD begins with the 19th century when Frerich described the presence of morphological changes in the liver in patients with the so-called “sugar disease” [2, p. 389].

In the 1970s concepts began to emerge in which an association was established between the appearance of fatty dystrophy and the further progression of cirrhosis of the liver [10, p. 357].

In 1980, a group of researchers led by J. Ludwig introduced the concept of steatohepatitis to non-alcoholic etiology (later the term acquired the form “non-alcoholic steatohepatitis”) [5, p. 84], describing the features of liver damage in patients with type 2 diabetes [13, p. 665]. J. Ludwig discovered morphofunctional alterations of the liver together with pathognomonic signs that were inherent in alcoholic liver disease [11, p. 15].

Although such alterations were referred to as “non-alcoholic Laenekovskaya liver disease”, “diabetic hepatitis”, etc. [19, p. 30].

The term “non-alcoholic steatohepatitis» is used to refer to the morphofunctional changes in the liver caused by infiltration against the background of fatty liver dystrophy [14, p. 305].

NAFTLD significantly changed the modern understanding of the etiological structure of chronic diffuse lesions of the liver. The risk of developing NAFTLD significantly higher with obesity. Thus, in studies conducted under the guidance of S. Bellentani (2010), steatosis was diagnosed in 20% of people who do not drink alcohol and are not susceptible to obesity. In the presence of obesity, the prevalence of NAFTLD rises to 60,3–75,9% [8, p. 788], and in the case of a combination of obesity and type 2 diabetes, the detection rate according to various authors can reach 78% [9, p. 7240].

The pathogenesis of steatosis and metabolic steatohepatitis is poorly understood and there are very contradictory data in the literature. The generally accepted concept is that steatosis precedes steatohepatitis, therefore, the “2 blows” theory is one of the modern models of the primary NAFTLD [4, p. 2006; 14, p. 305]. Changes in tissue tolerance to insulin, due to receptor desynchronosis, lead to disruptions in glucose uptake by the cells, which initiates an increase in the lipolysis rate in adipose tissue and an increase in free fatty acid (FFA) concentrations in the blood. Hyperinsulinemia affects the decrease in the rate of FFA oxidation in the liver, which results in an increase in the synthesis of very low-density lipoproteins. The whole cascade of factors is excessive transportation of FFA to the liver, inhibition of the processes of mitochondrial oxidation of FFA, and so on — have a positive effect on the consolidation of triglycerides in hepatocytes, which undoubtedly lead to fatty degeneration of the liver (“first strike” or “first push”).

At the next stage of the pathology, the formation of steatohepatitis occurs, the integral companions of which are destructive–inflammatory and necrotic changes in the liver, developing according to classical mechanisms. FFAs have a direct damaging effect on cellular structures. The toxic effect of FFA leads to destabilization of the mitochondrial complexes with the further destruction of the latter; inhibition of K^+/Na^+ ATPase activity and glycolytic enzymes, desynchrony of oxidative phosphorylation; neutralization of excess fatty acids peroxisome by.

The severity of the damaging effect depends on many factors, this is the state of antioxidant systems, the rate of initiation of alternative ways of FFA metabolization, and of course, the functionality of the protective cellular mechanisms of mitochondrial β–oxidation. In addition, FFAs act as a highly aggressive substrate of lipid peroxidation (SLP), the metabolites of which are triggers of chemotaxis of leukocytes, causing the transition of steatosis to steatohepatitis. Oxidative stress and the death of mitochondrial complexes initiate the launch of apoptosis and / or necrosis of hepatocytes, under these conditions there is an activation of leukocytes and Ito cells in the Diss space, which contributes to fibrous growth.

So, back in 1979, D. Pessayre put forward the hypothesis that oxidized fat is the initiating factor of POL. But, in the course of a number of studies, it was found that in a number of patient’s liver steatosis does not develop to the stage of fibrosis and necrosis. Based on this, it was found that the development of steatohepatitis requires the presence of additional factors of the “second shock” or “second strike”.

It is the disorganization of the functions of cell components that causes inflammation, so the research team led by H. Enomoto (2015) proved that under the influence of FFA and β–oxidation metabolites, patients with steatohepatitis undergo changes in the structure and functions of mitochondrial complexes [5, p. 90]. Mitochondrial complexes begin to act as a depot of atomic forms of oxygen, leading to POL. When experimentally modeled nonalcoholic steatohepatitis in animals, excessive expression of cytochromes P450 and cyp2E1 is observed. Cytochrome cyp2E1 is involved in the generation of hydroperoxides from ketones, nitrosamines and aldehydes of endogenous origin. A possible initiating factor for the induction of cytochrome in patients who do not drink alcohol may be FFA, which in turn can increase the activity of cyp2E1, as noted by some researchers. So, a group of researchers led by L. Leclerq, proven cyp2E1 provides NADPH–dependent lipid oxidation. L. Leclerq et al. (2010) proved experimentally the relationship of cyp 1a, cyp 3a, cyp 4a in the occurrence of non-alcoholic steatohepatitis with the mediated interaction of the POL system [5, p. 90]. It has been proven that chronic drinking can lead to peroxide production. Sore et al. (2010) in animal experiments revealed a relationship between the presence of NAFTLD in combination metabolic syndrome and higher production of endogenous ethanol [8, p. 789]. Since 2011, a number of studies under the guidance of S. Nuer have revealed high ethanol content in exhaled air in people with obesity, compared with people who have normal body weight.

With “oxidative stress”, the production of TNF–a, as well as other forms of TNF–induced cytokines (IL-6, IL-8), which, together with oxygenated forms, dicarboxylic acids and oxidation derivatives, increases, increases which ultimately leads to necrosis and apoptosis of hepatocytes.

So, in their research T. Henbert et al. (2010), showed that TNF–a can be conditionally considered as an early marker of liver damage, as well as facilitating the proliferation process by fibrinolysis along with other cytokines [14, p. 305].

The increased production of TNF–a may be due to the activation of Kupffer cells by bacterial antigens entering the portal vein into the liver. The results of the hydrogen respiratory test, in 50–70% of cases of non-alcoholic steatohepatitis revealed excessive bacterial proliferation in the small intestine. The maximum severity of bacterial growth is observed in patients with non-alcoholic steatohepatitis with an outcome in cirrhosis of the liver.

A. Greenberg and M. McDaniel (2012) showed an increased TNF–a activity in patients with NAFTLD with obesity and IR. Increased hepatic expression of TNF–a occurs when IR, experimentally induced diet with an increase in FA. Metabolic syndrome there is an increased expression of TNF–a in conjunction with other pro-inflammatory cytokines, which are additionally secreted by adipocytes of adipose tissue.

Signs of iron overload are detected in the majority of patients with NAFTLD. According to B. Bacon et al. (2004) and S. Chitturi (2012) indicators of iron are detected pathological in 50–65% of cases [17, p. 28; 8, p. 788]. D. Driton (2016) noted that an excessive increase in iron is due to POL. According to E. Buganrssi (2010), an increased level of ferritin is a marker of severe damage, which is histologically verified in more than 97% of cases, rather than iron overload [17, p. 21].

Some researchers found His63Asp HFE mutations in a number of patients with NAFTLD, which are characteristic of hemochromatosis.

In a study by H. Borovsky et al. (2011), in patients with such mutations, liver fibrosis was more pronounced. E. Buganrssi (2014) believes that iron overload and HFE mutations do not contribute to the development of liver fibrosis [16, p. 5; 21, p. 74].

Other authors also note that there is no evidence of iron overload in patients with NAFTLD. R. Vorand et al. (2015) associated hepatic iron overload with IR, regardless of liver damage. Hepatic lipid synthesis is stimulated as a result of increased intake of long-chain fatty acyl–CoA acids in the liver, and the production of intermediate lipids increases, in addition to diacylglycerols

[15, p. 322; 18, p. 42]. Many of these intermediate lipids lead to the development of hepatic inflammation and increase the risk of progression of NAFTLD to NASH. Non-esterified hepatic lipids also induce endoplasmic reticulum stress, leading to the activation of N–terminal kinases and the nuclear factor κB (NF–κB) β–cells [20, p. 26], which are the two main regulators of inflammatory pathways (interleukin-6 and other pro-inflammatory cytokines transcription), which also inhibit phosphorylation insulin receptor substrate 1 (IRS-1) [6, p. 18], which, in turn, aggravates the degree of hepatic IR and increases intrahepatic cytokine production [7, p. 510].

Despite the many works on this topic, which reflect the dietary aspects of the formation of metabolic syndrome and NAFTLD, the role of the alimentary factor has not been practically studied.

It is still not clear whether the accumulation of fats in the liver causes inflammation, or if inflammation is caused by other causes, causing impaired hepatocyte function leading to steatosis. Many researchers doubt that excessive accumulation of lipids as such is the cause of secondary inflammation. Argument is the fact that pronounced hepatic steatosis is not always accompanied by the phenomena of hepatitis and fatty degeneration, because the latter is observed more often than steatohepatitis. In contrast, experimental data suggest that fatty acid infiltration promotes the formation of fibrous tissue in the liver and there is a direct correlation between the degree of steatosis and fibrosis.

Thus, in spite of the recent achievements of the medicine NAFTLD, it still remains a little studied pathology, which requires further research in this area.

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