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THE CONCEPT OF FATTY LIVER DISEASE ASSOCIATED WITH METABOLIC SYNDROME

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Abstract
Fatty hepatosis is the most common chronic liver disease. According to statistics, non–alcoholic fatty liver disease is found in 6.3-33% of adults worldwide. In obese patients, this figure is even higher: it reaches 62-93%. The peak incidence in both men and women occurs at the age of 40-50 years. The mechanism of development of fatty hepatosis is quite complex and includes environmental factors (nutrition and physical activity of a person), hormonal background, genetic prerequisites. Normally, lipids should be transformed in the liver into other substances necessary for the proper functioning of the digestive system. But instead, they penetrate into the hepatocytes and accumulate there. The liver tissue in the areas of fatty infiltration becomes dense and can no longer perform its tasks. Steatosis develops - the initial stage of non-alcoholic fatty liver disease.

Keywords: fatty hepatosis, metabolic syndrome.

Introduction

Fatty hepatosis is an independent metabolic disease or syndrome caused by fatty degeneration of liver cells. In the 1950s, the incidence of fatty hepatosis was 6-8% of cases, and by the end of the 20th century it had increased to 15-20%. Normally, liver cells should contain about 1.5% of fatty inclusions. With fatty hepatosis, the volume of lipid inclusions is more than 5%. Clinical manifestations of fatty degeneration of the liver are nonspecific, while their severity does not depend on the degree of morphological changes in the liver. Quite often, the disease is first diagnosed during a biochemical blood test, which reveals an increase in the level of liver enzymes, as well as on the basis of ultrasound scanning. Treatment begins with lifestyle modification - weight loss, sufficient physical activity and a balanced diet. Drug therapy is the second line and is connected with an increased risk of pathology progression. In most cases, the disease proceeds with minimal clinical manifestations, which determines the insidiousness of fatty hepatosis. Only a small proportion of patients complain of minor pain in the right hypochondrium. The pain syndrome is associated with the stretching of the capsule due to the accumulation of lipid particles in the liver. Other symptoms of fatty hepatosis are nonspecific.

At present, the problem of fatty hepatosis (FH) is very relevant not only for hepatologists, but also for many specialists. Over the past decade, the incidence of liver steatosis has increased significantly. In the middle of the 20th century, it was observed in an average of 68% of cases in the urban population of developed countries, and at the end of the century - already in 15-20%.

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According to foreign authors (J. D. Browning, L. S. Sczepaniak), almost one third of the urban population suffers from FH. For every sixth liver biopsy with an unclear diagnosis, there is one case of FH. According to A. S. Loginov (1969), S. P. Lebedev (1980), about 30% of patients with liver damage have FH [18,21,28,29,30,32,42].

In the literature, FH is called by different names: fatty degeneration, fatty infiltration, fatty liver, liver dystrophy, liver steatosis [3,6,7,17,18,21,28,32,35,50]. However, the most common term is "fatty hepatitis", and when talking about morphology, the term "fatty degeneration" is used. In a normal liver, the fat content does not exceed 1.5% of its mass, and it is not detected during a routine histological examination. Small drops of fat in hepatocytes begin to be detected by light microscopy if its amount increases to 2-5%, which is regarded as a pathological condition - fatty degeneration of the liver. If more than half of the hepatocytes contain fat drops that are larger than the cell nucleus, then the fat content in the liver is above 25% [1,21,32].

FH can develop as a result of exposure to a wide variety of factors. Among the etiologic factors leading to the development of FH, alcohol is of primary importance, followed by obesity and diabetes mellitus. The most probable causes of FH are the gastrointestinal and biliary tracts, intestinal bypass anastomosis, long-term parenteral nutrition, maldigestion and malabsorption syndrome, gluten enteropathy, Wilson-Konovalov disease, bacterial infections, viruses, and systemic diseases. In chronic infections, fatty liver dystrophy is detected in almost half of the cases [11,21,45,46,58,59,67,72].

FH also develops as a syndrome in diseases of the lungs, heart (congestive heart failure), cancer, severe purulent processes (E.M. Tareyev, 1948) and metabolic diseases (Cushing's syndrome, myxedema, thyrotoxicosis, acromegaly, gout, hyperlipidemia, hypothyroidism, hypo-β-lipoproteinemia) [21, 36,49]. Chemicals with hepatotoxic action (compounds of mercury, boron, barium, carbon, phosphorus, chromium, thallium, etc.) and many drugs (corticosteroids, estrogens, isoniazid, methotrexate, tetracyclines, salicylates, non-steroidal anti-inflammatory drugs) can cause FH. It can be caused by unbalanced nutrition, especially protein deficiency in the population of underdeveloped countries. Genetic predisposition is also not excluded in the development of FH [8,14,18, 25,26,30].

Fatty liver disease is often associated with gallbladder dyskinesia, especially gallstone disease. Chronic viral hepatitis, especially hepatitis C (genotype 3) is often accompanied by fatty liver disease. Canadian scientists noted that fatty liver disease was registered in 20% of cases after transplantation of the pancreatic islet apparatus [40,51]. Acute fatty liver of pregnancy is very rare [32]. Sometimes fatty liver disease develops in people without any reason [1,7,21].

By etiology, FH is classified as alcoholic and non-alcoholic, by time of occurrence as acute and chronic. Acute FH develops against the background of alcohol and drug poisoning and during pregnancy [39,52,57].

Depending on the diagnostic methods, alcoholic steatosis is detected with different frequencies. According to A. V. Kalinin, isolated alcoholic steatosis is detected in 50% of patients with alcoholism, according to L. G. Vinogradova (1991) - in 60-75%. According to S. Bellentano (2000), during an examination of 6917 people in Northern Italy, alcoholic steatosis was detected in the control group in only 16%, among "heavy drinkers" - in 46%, among the "obese" - in 76%, among "heavy drinkers and obese" - in 94% [8,18,29,30,39,43]. Viter V.I., Permyakov A.V. noted

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that when examining 100 corpses of people who died from acute ethanol poisoning, the analysis of histological data made it possible to establish the presence of liver disease in 73%, including FH in 65% [5].

Based on morphological features, fatty liver disease can be classified depending on the prevalence of fat droplets of a particular size: small-droplet, large-droplet, and mixed forms (Z.A. Bondar et al., 1970; 1971; S.D. Podymova, 1975) [29,32]. Large-droplet obesity is mainly observed in zone 3 (centrilobular) and is characterized by the presence of large single lipid droplets in the cytoplasm of hepatocytes with the nucleus shifted to the periphery of the cell. In small-droplet obesity, numerous small lipid droplets are detected in hepatocytes, with the nucleus located in the center of the cell. Mixed-type obesity should be classified as small-droplet [8,24].

H.Thaler (1982) distinguishes 4 forms of fatty degeneration: 1) focal disseminated, not manifested clinically; 2) pronounced disseminated; 3) zonal (in different parts of the lobule); 4) diffuse. S.D. Podymova (1993) offers her own version of classification: zero degree - small droplets of fat capture individual groups of liver cells; I degree - moderately expressed focal medium-, and large-droplet obesity of liver cells; II degree - moderately expressed diffuse small-, medium-, large-droplet, mainly intracellular obesity; III degree - pronounced diffuse large-droplet obesity with extracellular obesity and the formation of fatty cysts. Obesity is considered as an independent risk factor and is associated with the development of fatty liver [21,22,38,48,50,58,59,66,68]. According to Brazilian researchers, among patients with a body mass index (BMI) of 35-40 kg/m^2, based on ultrasound examination (US), FH was detected in 75% of cases [61]. Abrams G.A., Kunde S.S. prove that when analyzing liver biopsy of patients with obesity, FH was detected separately in 30.3% of cases; with portal fibrosis - in 33.3%; NASH - in 36.4% [35]. According to other authors, FH was established in 87.1% of cases [60].

Theoretically, there are 4 mechanisms of fat accumulation in the liver due to: I. Increased intake of fat or fatty acids (FA) with food. Fat ingested with food is transported with blood, mainly in the form of chylomicrons. During lipolysis, FAs are released in adipose tissue. In adipocytes, they are included in triglycerides (TG), but some FAs can be released into the bloodstream and captured by the liver. The remains of chylomicrons also enter the liver; 2. Increased synthesis or inhibition of FA oxidation in mitochondria. Both of these processes increase TG production; 3. Impaired TG excretion from hepatocytes. TG excretion from hepatocytes includes binding to apoprotein, phospholipid, and cholesterol to form very low density lipoproteins (VLDL). Conjugation of TG with apoproteins occurs on the surface membranes of the endoplasmic reticulum with the participation of a number of enzymes and coenzymes called lipotropic factors. VLDL, which were secreted from the hepatocyte under the influence of lipoprotein lipase in the blood, are broken down into low-density lipoproteins and fatty acids; 4. Excessive amounts of carbohydrates entering the liver, which can be converted into fatty acids [1,7,10,12,30,41,62].

The reaction to alcohol is individual for each person. This is due to the genetically determined activity of enzymes, gender, age, ethnicity, etc. Thus, in women, the hormonal background contributes to an increase in the damaging effect of alcohol on the liver, and in half of the representatives of the Mongoloid race, toxic products of ethyl alcohol breakdown are neutralized significantly more slowly than in Europeans due to the presumably different degree of provision of the body with the enzyme alcohol dehydrogenase (AlcDH) [3,8,11,31,55]. Modern research

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does not allow us to make an unambiguous conclusion about the connection between the genes of the main histocompatibility complex and alcoholic liver disease. AlcDH is determined by five different genes located on chromosome 4. People with different AlcDH isoenzymes differ in the degree of alcohol elimination. Polymorphism of the most active forms of this enzyme, AlcDH2 and AlcDH3, may have a protective effect, since rapid accumulation of acetaldehyde leads to lower tolerance to alcohol. However, if such a person drinks alcohol, then more acetaldehyde is formed, which leads to an increased risk of liver disease [15,21,44,54,69].

In addition, alcohol is metabolized by microsomal cytochrome P450-II-E1. The gene encoding it has been cloned and sequenced, but the role of different variants of this gene in the development of alcoholic liver disease has not been studied. In case of enzymopathy in the cytochrome P-450 system, it is transformed into cytochrome P-420, which most activates the formation of free radicals and does not neutralize O_2- into hydroperoxide [8,27]. FH as a disease is most often diagnosed in middle and old age [4,8,16,19,21,23], more often in men than in women, by 2.7 times (S.D. Podymova). A number of authors noted cases of FH in children [11,43, 48,65,72].

In most cases, FH is asymptomatic, and only some patients experience moderate pain in the right hypochondrium. Pain in the liver area is usually associated with increased accumulation of fat in the liver and stretching of the liver capsule. The nature of other complaints is nonspecific. Depending on the etiology, patients may have certain subjective and objective symptoms associated with the underlying disease. According to physical examination data, some patients have an enlarged liver with smooth edges. Palpation pain in the liver area is rare [7,9,16,17,21,32,47]. Biochemical blood tests reveal an increase in gamma-glutamyl transpeptidase (GGT) and only a slight increase in transaminase (ALT and AST) and alkaline phosphatase activity [7,18,21]. Bilirubin, albumin, and prothrombin levels are usually normal. Although a number of authors note a slight increase in bilirubin and a decrease in albumin. Significant help in the diagnosis of FH is provided by a violation of the glycemic profile, triglyceridemi, and an increase in cholesterol levels. Additionally, informative indicators may include urobilinogenuria and delayed retention of bromsulfalein. In one third of patients, a change in the thymol test and an increase in the level of a2-, b-, and gamma-globulins are noted [7,20,21,32,36,49].

Modern instrumental methods are used in the diagnosis of GI: ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), radionuclide hepatography and liver biopsy [4,6,7,13,17]. Ultrasound examination allows not only to assess the condition of the liver, but also to identify abnormalities in the gallbladder, liver vessels and pancreas. With ultrasound, the echogenicity of liver tissue can be normal or increased [2,3,4,7,32]. CT reveals a decrease in the absorption coefficient. When examining without contrast, the branches of the portal and hepatic veins are clearly visible. The absorption coefficient is less than that of the spleen and kidneys [30]. Fatty infiltration can also be detected with MRI [32]. Radionuclide examination of the absorptive and excretory function of the liver reveals a distinct decrease in absorption and a slowdown in excretion of dye [21].

Additional examination, including determination of immunological parameters, CT and liver biopsy, is prescribed if there are special indications [3]. Despite numerous studies of FH, the issues

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of pathogenesis and clinical features have not been sufficiently studied [42,45,71]. The patient examination program should be aimed at excluding other liver diseases, namely:

- viral infection (examine HBs-Ag, HCV-Ag);
- Wilson-Konovalov disease (examine the level of ceruloplasmin in the blood);
- congenital deficiency of b1-antitrypsin;
- idiopathic (genetic) hemochromatosis (examine iron metabolism, assess the condition of other organs);
- autoimmune hepatitis (assess the titers of antinuclear antibodies, antibodies to smooth muscles, it is advisable to study antimitochondrial antibodies and antibodies to liver and kidney microsomes) [8].

In most cases, the course of FH is favorable, especially when the etiologic factors are eliminated. Unfavorable prognostic indicators for this pathology include: severe and multiple disturbances in liver function tests, the presence of hepatocyte necrosis and disorders of regeneration processes; significant immunological disturbances; signs of cholestasis, portal hypertension syndrome [1,55,64].

The course of large droplet fatty liver is usually relatively benign. In small droplet obesity, the rate of progression of liver damage is higher, the prognosis is more serious.

Complications of liver steatosis include: development of steatohepatitis with progression to fibrosis and cirrhosis of the liver, formation of intrahepatic cholestasis with or without jaundice (obstructive intrahepatic intralobular cholestasis), development of transient portal hypertension, often with the presence of transient ascites and portocaval anastomoses, narrowing of intrahepatic venules and veins with the formation of Budd-Chiari syndrome (edema, ascites, signs of hepatocellular insufficiency) [1,3,17,35,56,60]. Steatohepatitis with the development of liver cirrhosis can even lead to the development of hepatocellular carcinoma [48,53,63,72].

It is quite difficult to substantiate and systematize the treatment of FH given such a variety of causes. Modern approaches to treatment are aimed mainly at eliminating or weakening the factors leading to the development of FH, at relieving syndromes of impaired digestion and absorption, and at restoring the function of the liver and biliary system [7,9,10]. Drug therapy can significantly affect the consequences of steatosis, namely, reduce the level of lipid peroxidation, bind and inactivate toxic substrates in the hepatocyte as a result of increased synthesis of detoxifying substances: block the activity of mesenchymal-inflammatory reactions, slow down the progression of fibrosis [1,37]. During treatment, the use of certain drugs and alcohol abuse are excluded. Gradual, moderate weight loss is most effective in cases of FH development against the background of obesity and diabetes mellitus and is accompanied by positive dynamics of clinical and laboratory parameters, a decrease in the histological activity index. Rapid weight loss can lead to a worsening of the disease [8]. After eliminating the etiological factor, a course and symptomatic treatment is determined, and patients should be advised to remain under medical supervision for another year, and possibly longer. Every 2 months, the well-being and physical status should be assessed, once every 3 months, serum transaminase studies should be repeated, and an ultrasound should be performed once every 6 months. Treatment should be prolonged for 1 year or more [7]. Patients with FH are prescribed a diet rich in proteins (1 g of protein per 1 kg of body weight) and water-soluble vitamins, but poor in fats and, first of all, fatty acids formed during the thermal

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hydrolysis of fat, as well as carbohydrates to normalize the blood levels of glucose, lipids, and uric acid in the presence of corresponding disorders [1].

In some cases, with alcoholic etiology of the process, additional parenteral administration of water-soluble vitamins (B1, B2, B6, B12, PP, C) in generally accepted therapeutic doses for 10-14 days is required in addition to basic therapy [1,34,62]. The main indications for drug therapy of non-alcoholic metabolic liver damage are: development of steatohepatitis and steatosis of unknown etiology or the impossibility of stopping the action of etiological and additional risk factors for its development [1,62].

The choice of the drug is determined by: - the etiology of the process; - the leading pathogenetic mechanism of hepatocyte damage; - the level of mesenchymal-inflammatory reactions. In most cases, fatty liver is completely reversible provided that the causes leading to its formation are eliminated. It is this indisputable fact that should primarily attract the attention of both doctors and patients, since timely recognition of FH allows preventing the development of inflammation, which is much more difficult to treat [2,3,9].

The most important problem is to reduce alcohol consumption by the population. As is known, alcohol consumption has increased significantly over the past half century. An increase in alcohol consumption is observed throughout the world, especially in European countries, including Russia and the USA. According to WHO (2002), alcohol consumption and its consequences have also increased in recent years, especially in developing countries. In Mongolia, when comparing 2003 and 2002, a significant increase in alcoholic beverages was noted - alcohol by 23.7%, and wine and vodka - by 9.4%. According to statistics (1985-1997), alcohol abuse was found in 51.2% of cases among adults in Mongolia, with women accounting for 8%. At the same time, in recent years, a clear trend towards an increase in the number of patients with FH has been noted among the population of Mongolia, but its actual prevalence remains unclear. The features of the etiology, pathogenesis and course of FH in Mongols, depending on the factors that form this pathology, have not been finally established. In this regard, there is a need to study the problem of FH using modern diagnostic methods.

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