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MORPHOLOGICAL CONCEPT OF ULTRASOUND ELASTOGRAPHY OF THE LIVER

Abstract: Invasive and non-invasive methods of research are used to diagnose fibrosis in alcoholic liver disease (ALD). The article highlights the current state of the problem, analyzes the literature to assess the diagnostic accuracy of non-invasive methods, and presents data from an original study of ultrasound elastography of the liver.

Key words: Alcohol, liver, elastography, morphological concept

In 2016, alcohol consumption was the seventh leading risk factor for both death and age-adjusted life-years lost (DALYs) worldwide (13.6%), with age-standardized deaths of 2.2% of women and 6.8% of men attributed to alcohol consumption. According to 2016 data, 32.5% of the world's population (2.4 billion people) were chronic alcohol abusers, with 2.8 million deaths worldwide attributed to alcohol consumption. It is worth noting that liver cirrhosis, mainly of alcoholic and viral etiology, was the cause of death from gastrointestinal diseases in 50–80% of cases [5]. A screening examination for liver disease was conducted in Moscow among 5,000 randomly selected residents, and the prevalence of ALD in the population was 6.9% [6]. According to the National Institute on Alcohol Abuse and Alcoholism in the United States, in 44–48% of cases, cirrhosis leading to death is caused by the toxic effects of alcohol [7].

ALP is a clinical and morphological concept that includes several variants of liver parenchyma damage due to alcohol abuse - from steatosis to alcoholic hepatitis (steatohepatitis), leading to the development of successive stages - fibrosis, cirrhosis and hepatocellular carcinoma. Hepatotoxic doses of alcohol: for men - more than 40-80 g / day in terms of pure ethanol; for women - more than 20 g of ethanol per day [5]. PBP is an invasive diagnostic method, currently it is the "gold standard" for assessing the activity and stage of liver tissue damage, the effectiveness of ALP therapy. However, to date, regulatory documents have not been developed in Russia to regulate this manipulation. Possible complications of liver biopsy include vasovagal reactions with transient hypotension, intrahepatic bleeding, and cases of chylopetoneum, intestinal perforation, and sepsis have also been reported [5]. It is important to remember that the results of morphological assessment of liver biopsy depend on the experience and qualifications of the morphologist, his ability to objectively describe and quantify morphological features. Errors can also be caused by lack of continuity in the work of the attending physician and morphologist, and violation of the rules for collecting biopsy [6]. In view of the above, the issue of assessing the stage of the disease (severity of fibrosis) in ALD using non-invasive methods remains very relevant [8], which include determining the levels of serum markers and other laboratory tests, as well as visualization methods. Serum markers of fibrosis are divided into direct and indirect. Direct markers are fragments of liver matrix components produced by hepatic stellate cells during fibrogenesis and molecules involved in regulating fibrosis progression and regression. 1. Hyaluronic acid is a component of extracellular matrix (ECM) glycosaminoglycan. Studies have shown that it has the highest correlation with histological findings of liver fibrosis [1]. 2. Carboxyterminal propeptide of type I procollagen and aminoterminal propeptide of type III procollagen (PIIINP), type VI procollagen. The content of type I collagen increases several-fold during fibrogenesis. PIIINP is an important component of connective tissue. Its relative concentration in the basement membrane is higher during liver fibrogenesis, which in turn is accompanied by an increase in its level in the blood serum [3]. 3. Metalloproteinases (MMPs) form a family of structurally related proteolytic enzymes that participate

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in the degradation of the ECM and basement membrane; their levels increase in various liver diseases. Tissue inhibitors of MMP-1 (TIMP-1) are secreted proteins that interact with MMPs and modulate their activation and functioning. TIMP-1 controls the activity of most MMPs, while TIMP-2 specifically inhibits MMP-2.TIMP-dependent inhibition of ECM degradation may contribute to the development of liver fibrosis. Increased TIMP levels are observed in chronic liver diseases [5]. Indirect markers (platelets, AST, INR, γ-glutamyl transferase (GGT), bilirubin, albumin, cholesterol) are indicators that reflect the functional state of the liver, but do not directly correlate with the level of extracellular matrix deposition and indirectly allow us to judge the stage of fibrosis. In patients with chronic liver diseases and cirrhosis, regardless of its etiology, there is an imbalance in the procoagulant system. Thrombocytopenia, typical for patients with cirrhosis, is caused by increased sequestration of platelets in the spleen as a result of splenomegaly, a decrease in the levels of three main anticoagulants: protein C, protein S and antithrombin III. Such patients often have a mild (50–100 × 109 per ml) or moderate (20–50 × 109 per ml) decrease in the platelet count. However, a wide range of spontaneous (or unprovoked) venous thrombotic complications may occur against the background of "natural hypocoagulation" [5]. GGT reflects the enzymatic activity of the liver, but its level may increase in case of biliary system pathology, cardiac pathology, and intake of certain medications. Alcohol stimulates the expression of the GGT gene. Serum GGT activity is increased in approximately 75% of individuals who abuse alcohol (sensitivity 60–90%, specificity 50–72%) [2]. AST and ALT are protein substances involved in metabolic processes, in particular amino acid processes. These enzymes are produced intracellularly, so an increase in their content in the blood indicates the destruction of cellular structures. In many forms of acute and chronic liver disease, in steatosis, AST/ALT is less than or equal to 1, and in alcoholic hepatitis this ratio often exceeds 2 [1]. Hyperbilirubinemia can be an indicator of liver failure. With increasing severity of APB, bilirubin levels > 50 μmol/l are often observed [4].However, against the background of "natural hypocoagulation", a wide range of spontaneous (or unprovoked) venous thrombotic complications may occur [3]. GGT reflects the enzymatic activity of the liver, but an increase in its level is possible with pathology of the biliary system, cardiac pathology, and the use of certain medications. Alcohol stimulates the expression of the GGT gene. Serum GGT activity is increased in approximately 75% of individuals who abuse alcohol (sensitivity - 60-90%, specificity - 50-72%) [2]. AST and ALT are protein substances involved in metabolic processes, in particular amino acid processes. These enzymes are produced intracellularly, so an increase in their content in the blood indicates the destruction of cellular structures. With many forms of acute and chronic liver damage, with steatosis, AST / ALT is less than or equal to 1, and with alcoholic hepatitis this ratio often exceeds 2 [6]. Hyperbilirubinemia may be an indicator of liver failure. As the severity of APB increases, bilirubin levels > 50 μmol/L are often observed [5].However, against the background of "natural hypocoagulation", a wide range of spontaneous (or unprovoked) venous thrombotic complications may occur [5]. GGT reflects the enzymatic activity of the liver, but an increase in its level is possible with pathology of the biliary system, cardiac pathology, and the use of certain medications. Alcohol stimulates the expression of the GGT gene. Serum GGT activity is increased in approximately 75% of individuals who abuse alcohol (sensitivity - 60-90%, specificity - 50-72%) [2]. AST and ALT are protein substances involved in metabolic processes, in particular amino acid processes. These enzymes are produced intracellularly, so an increase in their content in the blood indicates the destruction of cellular structures. With many forms of acute and chronic liver damage, with steatosis, AST / ALT is less than or equal to 1, and with alcoholic hepatitis this ratio often exceeds 2 [6]. Hyperbilirubinemia may be an indicator of liver failure. As the severity of APB increases, bilirubin levels > 50 μmol/L are often observed [7].

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In clinical practice, MRI, CT, ultrasound, and indirect ultrasound elastography of the liver are used. The advantages of these methods include their high availability, non-invasiveness, and the possibility of using them for screening at early stages of liver damage. These methods allow for quantitative determination of steatosis, exclusion of other causes of liver damage (for example, primary sclerosing cholangitis), and identification of signs of severe fibrosis/cirrhosis and their complications. Ultrasound diagnostics as a routine method for assessing the stage of fibrosis has low sensitivity and specificity, especially at the initial stages of fibrosis, as well as with a steatosis degree of less than 20–30% of the liver tissue volume [7]. MRI and MR spectroscopy are reliable tools for assessing the amount of steatosis and can detect 5–10% steatosis, but it is important to remember that methods for standardizing these studies have not yet been developed, and their high cost and low availability limit their use [1]. Indirect ultrasound elastography of the liver (fibroelastometry) is a pulse-echo ultrasound technique for assessing the nature and propagation speed of oscillations to determine the elasticity of liver tissue. A blinded comparative assessment of the diagnostic accuracy of fibroelastometry in diagnosing the degree of liver fibrosis in patients with ALD was performed. The data obtained by indirect ultrasound elastography (index test) and the results of histological examination of liver biopsy specimens (reference standard) were compared. Fibrosis stage F0 was observed in 2 patients, F2 — in 3, F3 — in 4, F4 — in 81 patients, F1 was not detected. For stage F2, the obtained sensitivity was 33%, specificity — 97.7%, for stage F3 the sensitivity was 33%; specificity — 96.5%, for stage F4 the sensitivity was 92.7%, specificity — 42%. A match between the stage of fibrosis determined by the results of indirect ultrasound elastography and that determined by the results of a morphological examination of a liver was observed in 80 of 90 subjects.

Discussion. Comparison of the results of indirect ultrasound elastography with the data of morphological examination — the "gold standard" for assessing the severity of liver fibrosis — showed that it has high diagnostic accuracy at fibrosis stages F3–F4. Based on the results of our study and taking into account the opinion of foreign experts, we propose an algorithm for using indirect ultrasound elastography to assess the stage of fibrosis in patients with alcoholic liver disease and to select further treatment tactics and patient management. In patients with liver density up to 6 kPa, we can talk about fibrosis stage F0–F1, which requires further clinical observation without biopsy. The obtained intermediate values (from 6.1 to 11.9 kPa) indicate fibrosis progression and dictate the need for a puncture liver biopsy in combination with the use of non-invasive methods to determine treatment tactics. Tissue density of more than 12 kPa indicates severe fibrosis or cirrhosis of the liver (stage F4); in this case, a biopsy is not advisable, but additional examination is required to rule out complications.

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