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PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT OF ALCOHOLIC LIVER DISEASE: A COMPREHENSIVE REVIEW

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Abstract: Alcoholic liver disease (ALD) remains a leading cause of morbidity and mortality worldwide, with excessive alcohol consumption contributing to 3.3 million deaths annually. ALD encompasses a spectrum of liver disorders, ranging from reversible alcoholic fatty liver (steatosis) to alcoholic hepatitis and cirrhosis. The progression of ALD is influenced by factors such as the quantity and duration of alcohol intake, viral hepatitis infections (HBV, HCV), and metabolic comorbidities. Pathophysiologically, ethanol metabolism primarily occurs via alcohol dehydrogenase, cytochrome P450 2E1, and catalase systems, producing acetaldehyde and reactive oxygen/nitrogen species that induce hepatocellular damage, steatosis, inflammation, and fibrosis.

Clinical manifestations vary with disease stage, from asymptomatic fatty liver to jaundice, portal hypertension, and liver failure in cirrhosis. Diagnostic evaluation includes a combination of clinical history, screening questionnaires (CAGE, AUDIT), liver function tests, fibrosis assessment (FibroTest, elastography), imaging, and, when indicated, liver biopsy. Effective management relies on sustained alcohol abstinence, nutritional support, pharmacotherapy (e.g., ademetionine for hepatoprotection, baclofen for alcohol use disorder), and behavioral interventions. Early detection and comprehensive care are essential to reduce disease progression and improve outcomes in patients with ALD.

Keywords: Alcoholic liver disease, alcohol abuse, steatosis, alcoholic hepatitis, cirrhosis, ethanol metabolism, fibrosis, hepatoprotection, ademetionine, alcohol use disorder, non-invasive diagnostics, liver function tests.

Introduction

Globally, excessive alcohol consumption is a leading cause of adult mortality and the development of severe liver disease. A World Health Organization report indicates that 3.3

million deaths (6% of all deaths globally) are related to alcohol consumption, and alcohol abuse is a risk factor in approximately 50% of cases of liver cirrhosis.

A linear relationship between mortality from liver disease and total alcohol consumption has been confirmed in many countries worldwide.

According to official Russian statistics, alcohol is one of the leading causes of death in the Russian population, accounting for 11.9%. Almost half of deaths (47.7%) are due to fatal changes in internal organs, while 21.7% are due to accidents. Thirty-five percent of alcoholics die at a young, more active age (20-50 years).

The results of screening patients with gastroenterological profile in Moscow medical institutions for alcohol consumption with harmful consequences (testing using the CAGE and AUDIT questionnaires) indicate that every second (49.8%) patient

A majority of working-age adults (43.18±13.04 years) abuse alcohol, of which 30.1% were men and 19.7% were women, respectively. Among patients who abuse alcohol, alcoholic and alcoholic-viral cirrhosis were detected in 32% of patients, alcoholic and alcoholic-viral hepatitis - in 18%, and a combination of ALD and non-alcoholic fatty liver disease (NAFLD) - in 11%.

Alcohol is also a common co-factor in patients with other liver diseases such as hepatitis C virus (HCV), hepatitis B virus (HBV), autoimmune hepatitis, hemochromatosis, accelerating the development of liver fibrosis.

There are three stages of ALD, which can occur sequentially. The first stage involves the development of potentially reversible alcoholic fatty liver disease (alcoholic steatosis), which is usually asymptomatic. Continued alcohol consumption can lead to hypertension, the second stage, which often becomes chronic. Clinical manifestations at this stage include jaundice, fatigue, and fever. In the final stage, the patient develops alcoholic cirrhosis. More than 80-90% of alcohol drinkers develop steatosis, but only 20-40% of patients in this group develop more severe forms of ALD, including fibrosis, alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.

Carcinoma (HCC). These stages are classified based on histological examination of the patient's liver. Often, the pathological processes overlap rather than being distinct diseases. Several risk factors are known that can play a significant role in the development of severe forms of the disease. The main ones include the hepatitis B virus (HBV), the hepatitis C virus (HCV), and the human immunodeficiency virus (HIV).

Alcoholism is a very common cause of chronic liver disease. One of the main signs of alcoholism is significant alcohol consumption: for men, more than 210 grams of pure ethanol per week; for women, more than 140 grams of pure ethanol per week.

Pathogenesis of ABP Ethanol, a polar molecule, is soluble in both water and various lipids. After consumption, it is absorbed into the bloodstream via the gastrointestinal tract. Typically, more than 95% of absorbed ethanol is metabolized in the liver, with a small amount excreted directly through the lungs, urine, and sweat. Three main metabolic systems participate in the oxidative metabolism of ethanol to acetaldehyde. The first is the hepatocyte cytoplasmic alcohol dehydrogenase (ADH) system, which oxidizes ethanol to acetaldehyde using nicotinamide adenine dinucleotide (NAD+). The ADH1 isoenzyme plays a major role in ethanol metabolism in the liver. Acetaldehyde, produced by ADH, is further oxidized to acetate by acetaldehyde dehydrogenase (AADH). The second metabolic system for ethanol involves cytochrome P450 2E1 (CYP2E1) enzymes, which convert chemical molecules into polar metabolites before excretion. CYP2E1 is considered the primary component of this system. Under normal physiological conditions, CYP2E1 catalyzes the oxidation of approximately 10% of ethanol to acetaldehyde. The third metabolic system is the endoplasmic reticulum catalase (CAT) system, which relies on the coenzyme nicotinamide adenine dinucleotide phosphate (NADP). This heme-containing catalase enzyme typically catalyzes the removal of H2O2 but is also capable of catalyzing the oxidation of ethanol to acetaldehyde.

When the concentration of ethanol in the blood and tissue fluids is low, it is mainly metabolized by ADH. However, when the concentration of ethanol is above 10 mol/L, two other enzyme systems also begin to participate in ethanol metabolism.

Alcoholic liver steatosis. Hepatic steatosis, the earliest liver reaction to alcohol abuse, usually resolves completely with abstinence. At this stage, fat vacuoles are visible microscopically in liver tissue sections. Excessive alcohol consumption increases the ratio of reduced to oxidized NAD in hepatocytes. This leads to alcoholic steatosis by impairing mitochondrial fatty acid β-oxidation.

Alcoholic steatosis can develop through direct or indirect regulation of lipid factors associated with metabolism. Alcohol abuse increases the expression of sterol-regulatory binding proteins (SRBP-1c) and decreases the expression of peroxisome proliferator-activated receptors-α (PPA-α), leading to increased fatty acid (FA) synthesis and suppression of FA oxidation. Furthermore, ethanol consumption induces acetyl-CoA carboxylase (ACC) activity

and suppresses carnitine palmitoyltransferase I (CPT-1) activity through the inhibition of AMP-activated protein kinase (AMPK), leading to increased FA synthesis. Furthermore, ethanol modulates hypoxia-inducible factor 1 (HIF-1) and inducible nitric oxide synthase (iNOS), which contribute to the development of alcoholic steatosis.

Increased fatty acid peroxidation leads to direct damage to plasma and intracellular membranes due to decreased phosphatidylcholine levels, resulting in increased membrane permeability, impaired membrane transport, and impaired receptor function. Normally, phosphatidylcholine is formed from phosphatidylethanolamine via methylation involving β-adenosylmethionine (BAME). In ALD, phosphatidylethanolamine methyltransferase activity is reduced. Furthermore, in these patients, BAME levels in the liver are already reduced at the steatosis stage, while BAME synthetase activity remains normal. A decrease in BAME levels correlates with indicators of oxidative stress, such as increased levels of 4-HE (a toxic aldehyde) and decreased glutathione levels, which are associated with mitochondrial damage. In the body, BAM is formed during the conversion of methionine, with the participation of ATP and the enzyme β-adenosylmethionine synthetase, into homocysteine and the antioxidants cysteine and glutathione. As a result of these effects, the elimination of free radicals and other toxic metabolites from hepatocytes is enhanced.

Clinical course of abp steatosis (alcohol-related fatty liver disease, fatty liver infiltration, fatty hepatosis) is the initial stage of alcoholic fatty liver disease, a reversible condition in which hepatocytes accumulate triglyceride droplets. Fatty liver infiltration develops in approximately 90% of individuals consuming approximately 60 grams of ethanol per day.

Alcoholic fatty liver disease is usually asymptomatic, but patients may experience nonspecific complaints such as fatigue, nausea, or upper right quadrant abdominal discomfort. Seventy percent of hospitalized patients with steatosis have hepatomegaly, and one-third of them have abnormal biochemical parameters. Alcoholic steatosis is generally considered a reversible, prognostically favorable stage of ALD; however, this is not may serve as a reason for the patient to continue drinking alcohol.

Alcoholic hepatitis (alcoholic steatohepatitis) is a progressive inflammatory and degenerative liver disease that can develop at any stage of alcoholic liver disease, most often due to steatosis, and sometimes due to established cirrhosis, as well as prolonged, systematic alcohol consumption. The incidence of hypertension in hospitalized patients with alcoholic

liver disease ranges from 10% to 35%. Among patients with alcoholic liver disease, hypertension accounts for approximately 20%.

Alcohol-induced cirrhosis is the final stage of alcoholic liver disease. The risk of developing alcoholic cirrhosis increases proportionally with the dose of alcohol consumed and the duration of alcohol consumption. While liver function remains intact, patients may feel well; some complain of general weakness, fatigue, decreased performance, pain, and a feeling of heaviness in the right upper quadrant. With decompensation of portal hypertension and liver function, corresponding clinical signs appear: jaundice, hepatic embolism, hemorrhagic syndrome, and edematous-ascitic syndrome.

ABP diagnostics the basis for diagnosing ALD is establishing the direct etiological role of alcohol in a particular patient, making medical history collection crucial. Unfortunately, patients in this group tend to conceal their alcohol abuse.

Legend: AMPK - 5'adenosine monophosphate-activated protein kinase, CPT-1 - carnitine palmitoyltransferase I, SIRT1 - sirtuin 1, STAT3 - signaling protein and activator of transcription 3, PPARa - peroxisome proliferator-activated receptor a, ACC - acetyl-CoA carboxylase, SREPBlc - sterol regulatory binding protein 1c, HIF-1 - hypoxia-inducible factor 1, iNOS - inducible nitric oxide synthase, ROS - reactive oxygen species, RNS - reactive nitrogen species, IL-1 - interleukin-1, IL-6 - interleukin-6, IL-8 - interleukin-8, IL-17 - interleukin-17, TNFa - tumor necrosis factor a, TGFP - transforming growth factor B, CXCL1 - chemokine, TfR1 - transferrin receptor 1, DAMPs - damage-associated molecular fragments, LPS - lipopolysaccharides.

A-ethanol and its metabolites, by increasing ROS/RNS levels and ACC and SREBP1c expression, cause alcoholic steatosis. Furthermore, the expression of AMPK, CPT-1, SIRT1, STAT3, adiponectin, and zinc is reduced, leading to decreased PPARα expression.

B, C - Excessive alcohol consumption increases colonic mucosal permeability, allowing lipopolysaccharides to enter the liver via the portal vein. Increased intestinal permeability in patients with ALD occurs before bacterial translocation, suggesting that it is a cause rather than a consequence of the disease. Activated Kupffer cells release cytokines IL-1, IL-17, TGF-β, iNOS, and TNF-α, which activate stellate cells. Stellate cells release IL-8 and CXCL1. Activated stellate cells also release extracellular matrix, leading to liver fibrosis. D - Regulation of hepcidin, one of the main pathogenic factors in ALD.

Once alcoholic steatosis develops, if the patient is left untreated, liver fibrosis and cirrhosis may develop, accompanied by possible liver failure.

Interviewing the patient's relatives and using special questionnaires (e.g., CAGE, AUDIT, AUDIT, etc.) [4, 16, 17]. The diagnosis of ALD is usually suspected with documented regular alcohol consumption in terms of pure ethanol of more than 20 g/day in women and more than 30 g/day in men in the presence of clinical and/or histological indicators indicating liver damage.

When diagnosing ALD, screening tests should include not only liver function tests such as gamma-glutamyl transpeptidase (GGT), serum alanine aminotransferase (ALT), and aspartic aminotransferase (AST), but also tests for liver fibrosis (e.g., FibroTest), as progressive liver fibrosis can be present with normal liver function tests. If any abnormalities are detected, an abdominal ultrasound is performed. To exclude other causes of liver injury, additional laboratory tests are performed, including determination of hepatitis A, B and C viruses (Anti-HAV IgM, HBsAg, Anti-HCV IgM), autoimmune markers (ANA, AMA-M2, M2-3E, SP100, PML, GP210, LKM-1, LC-1, SLA/LP, SSA/RO-52), transferrin saturation, transferrin level, alpha1-antitrypsin, and in some cases also serum ceruloplasmin. If progressive liver fibrosis or cirrhosis is suspected, serum albumin, prothrombin time or international normalized

The INR (International Normalized Ratio), serum bilirubin levels, and platelet and white blood cell counts are used to assess liver function and signs of portal hypertension. If signs of cirrhosis are present, upper gastrointestinal endoscopy should be performed to detect esophageal varices, unless there is a low risk of developing varices (Baveno criterion):

■ platelets >150*109/l,

■ liver density by elastography <20 kPa.

Non-invasive diagnostics of ALD. Biochemical

These tests can be very useful in diagnosing ALD, but using these parameters alone is impossible to accurately determine the severity of the process and its etiology. AST and ALT levels rarely exceed 300 U/ml. In patients with ALD, the AST/ALT ratio often exceeds 2. Aminotransferase levels exceeding 300 U/ml in a patient who abuses alcohol may be a consequence of liver tissue damage from another etiology.

In patients with ALD, alkaline phosphatase (ALP) levels are often normal or slightly elevated. Y-glutamyl transpeptidase (GGT) levels are typically elevated in heavy alcohol drinkers, regardless of the presence of liver disease. The specificity of GGT testing is limited,

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as most medications cause an increase in this enzyme. Furthermore, GGT is elevated in most liver diseases. The table presents typical laboratory findings in ALD.

Signs Interpretation serum enzymes AST > ALT (with AST t and ALT t). An AST/ALT ratio > 1 indicates hepatocellular damage. In non-alcoholic fatty liver disease, the ratio is inverse, i.e. less than 1. AST t when ALT is normal or only slightly elevated. GGT t (GGT is a good indicator of excessive alcohol consumption that has occurred over several weeks. However, it may be normal in 70% of patients with alcohol abuse. GGT is also not particularly helpful in distinguishing between alcohol abuse and established acute hepatitis). ALP t is an indicator of cholestasis.

Macrocytic anemia, thrombocytosis (thrombocytosis indicates an acute inflammatory reaction. Thrombocytopenia may be present due to myelosuppression), absolute neutrophilic leukocytosis may be present. Serum ferritin T is a protein complex responsible for iron storage. During the acute phase of hepatitis, it increases in response to systemic inflammation. Serum ferritin is the parameter of choice for determining iron deficiency (decreased ferritin) and iron overload (increased ferritin).

CDT T is carbohydrate-deficient transferrin. It is the most specific biomarker for high-dose alcohol consumption, regardless of the presence of liver disease. Levels are elevated for up to 6 weeks after alcohol abuse.

Metabolic disorders: Hyperglycemia, Hypertriglyceridemia, Hyperuricemia, Electrolyte disturbances (low potassium, magnesium, and phosphorus)

Liver function tests: Serum albumin - in cases of liver dysfunction. Bilirubin t - an indicator of cholestasis. Bilirubin is usually a mixture of conjugated and unconjugated bilirubin. Prothrombin time t - usually changes only in cases of severe liver damage. Vitamin K administration does not correct this coagulopathy.

Hematological parameters: Macrocytic anemia, thrombocytosis - chronic alcohol abuse often leads to malnutrition, resulting in vitamin B12 and/or folate deficiency. Platelet counts range from normal to low.

White blood cell counts are usually elevated. Leukemoid reactions are possible with alcoholic hepatitis. Thrombocytosis indicates an acute inflammatory reaction. Thrombocytopenia may be present due to myelosuppression. Absolute neutrophilic leukocytosis may also be present.

Leukocytosis and thrombocytopenia are characteristic of hypertension. Chronic alcohol abuse is also often accompanied by hypertriglyceridemia, hyperuricemia, hypokalemia, hypomagnesemia, and an increase in red blood cell corpuscular volume. Carbohydrate transferrin can be a specific indicator of ALD, but this test lacks sensitivity, limiting its use in diagnosing chronic alcoholism.

To confirm systematic alcohol abuse in clinical practice, two indicators are used: carbohydrate-deficient (desialized) transferrin and GGT. For alcohol consumption exceeding 50 grams per day, the sensitivity of UDT is 69% and the specificity is 92%; for GGT, these indicators are 73% and 75%, respectively.

Currently, the following tests are available in clinical practice to determine the stage of the disease (severity of fibrosis) in ALD:

■ by biochemical parameters of blood serum: APRI index (ratio of AST value to platelet level), FibroTest, Fibrometer, Hepascore, AshTest;

■ by measuring the density of liver tissue: transient elastography (Fibroscan).

Non-invasive imaging methods are not essential for establishing the disease's genesis; however, they play a significant role in staging, differential diagnosis, and identifying complications of ALD. Abdominal ultrasound can verify hepatomegaly, indirectly assess the severity of fatty liver disease, and rule out liver damage due to other diseases. Indirect elastography helps non-invasively determine the severity of fibrotic changes in the liver. Computed tomography and magnetic resonance imaging are used to identify liver cirrhosis, the extent of collateral hepatic blood flow, and detect subclinical ascites and associated pathologies.

Invasive diagnostics of ALD. Liver biopsy is the most sensitive and accurate test for assessing the degree of liver tissue damage and fibrosis. Liver biopsy in patients with signs of steatohepatitis reveals liver fibrosis in 20-40% of cases and liver cirrhosis in 8-20%. According to biopsy results, the risk of developing cirrhosis increases in patients with steatohepatitis compared to patients with steatosis. In patients with suspected hypertension, transjugular liver biopsy is recommended in cases where the clinical picture is combined with another etiology of liver disease or there is an uncertain history of alcohol consumption.

In asymptomatic patients, biopsy remains the only method that allows for an accurate determination of the presence of steatohepatitis. However, in clinical practice, not all patients with ALD require a liver biopsy with subsequent morphological examination. Usually, a contraindication to this procedure is a high risk of bleeding due to common coagulation

disorders. When performing liver biopsy on patients with low platelet counts or increased prothrombin time, a transjugular approach should be used rather than the more common percutaneous approach.

Although hypertension is a relatively rare form of ALD, it is associated with high mortality (up to 50%). Therefore, identifying individuals at high risk of death is crucial in determining treatment strategies for this clinical form of ALD. Several prognostic models of hypertension progression are used in clinical practice to assess prognosis and select treatment strategies. The most well-known and relevant are the Maddrey index, the Glasgow GAHS score, and the MELD index.

Differential diagnosis of ALD. The differential diagnosis should include the following conditions: non-alcoholic steatohepatitis, drug-induced liver injury, acute and chronic viral hepatitis, Wilson's disease, hemochromatosis, autoimmune liver diseases, alpha1-antitrypsin deficiency, and drug-induced hepatitis. To exclude these conditions, a thorough medical history, the judicious use of laboratory tests, instrumental methods, and, in some cases, a liver biopsy are necessary.

Patients with ALD suffer from two distinct disorders: alcohol use disorder and alcohol-induced liver disease . Therefore, treatment for patients with ALD should be aimed at managing these disorders. Typically, ALD therapy should be performed by multidisciplinary teams of physicians, including alcoholism specialists.

Alcohol abstinence is one of the main therapeutic measures for any form and stage of ALD. Continued alcohol consumption significantly worsens the patient's prognosis: there is a risk of liver disease progression, the development of severe fibrosis and cirrhosis, and complications such as portal hypertension, hepatocellular carcinoma, and others.

Treatment of alcohol use disorders. Several pharmacological agents have been used, including disulfiram, acamprosate, gabapentin, naltrexone, topiramate, sertraline, and baclofen. Of these, only baclofen, a Y-aminobutyric acid-B receptor agonist, has been found to be safe for patients with ALD and cirrhosis. Its effectiveness has been demonstrated with increased duration of abstinence.

Non-pharmacological treatments. Another main approach to promoting or maintaining alcohol abstinence in patients with ALD are behavioral interventions, such as motivational enhancement therapy, cognitive behavioral therapy, motivational interviewing, supportive therapy, and psychoeducation.

Alcohol withdrawal syndrome (abstinence syndrome) is a common disorder affecting alcohol-dependent patients who abruptly stop or markedly reduce alcohol consumption. Mild to moderate withdrawal symptoms typically develop within 6-24 hours after the last alcohol consumption, and symptoms may include nausea/vomiting, hypertension, tachycardia, tremor, hyperreflexia, irritability, anxiety, and headache. These symptoms may progress to more severe forms of alcohol withdrawal, characterized by delirium tremens, generalized seizures, coma, and even cardiac arrest and death. Elderly patients are at higher risk of delirium tremens. The "gold standard" in the treatment of alcohol withdrawal syndrome are benzodiazepines, of which diazepam and chlordiazepoxide are first-line drugs. Alternatives to benzodiazepines in the treatment of alcohol withdrawal syndrome include anticonvulsants with mood-stabilizing properties, including carbamazepine and valproate; topiramate and lamotrigine are used less frequently; There are also reports of the effectiveness of pregabalin and gabapentin in reducing the severity of withdrawal symptoms.

Treatment of alcohol-related liver damage. Alcohol use disorders are the adverse medical consequences of alcohol use, including alcohol-related organ damage (including alcoholic liver disease) and alcohol-related nervous system damage (including alcoholic polyneuropathy), as well as mental disorders (e.g., alcohol-related psychosis).

Nutrition. The vast majority of individuals who abuse alcohol exhibit nutritional deficiencies. The most common are severe protein deficiency, thiamine deficiency, folate deficiency, pyridoxine deficiency, zinc deficiency, and vitamins A and E deficiency.

In patients with ALD, it is advisable to prescribe a diet rich in protein (at least 1.0-1.5 g/kg body weight), with a high energy value (at least 2000 kcal/day, 35-40 kcal/kg/day), with a sufficient vitamin content (especially group B, folic and lipoic acids), replenishing the deficiency of fat-soluble vitamins (A, E) and microelements - magnesium, selenium, zinc. To restore nutritional status, the enteral route of administration of drugs and nutritional mixtures is preferable, since it is more economical, helps stabilize the integrity of the gastrointestinal mucosa, and reduces the risk of bacterial translocation and infectious complications.

The concepts of pharmacotherapy for ALD are based on the relief of the pathogenetic components of this pathology depending on the severity of the disease.

To obtain a rapid “hepatotropic” effect, parenteral administration of Heptor in a saturating dose (at least 800 mg/day for 10-14 days) is initially recommended, followed by long-term administration of the drug in tablet form (1200-1600 mg/day).

Parenteral and oral administration of ademetionine increases glutathione concentrations in liver tissue. The drug restores impaired glutathione transport from the cytosol across the mitochondrial membrane. Experimental models of liver tissue damage in patients with alcoholic cirrhosis have shown that ademetionine reduces the production of proinflammatory cytokines and tumor necrosis factor (TNF-α), leading to restoration of liver function and normalization of clinical and laboratory signs of alcohol-related damage.

Below is a clinical example of the formulation of diagnosis and treatment of a patient with ALD.

CONCLUSION

Thus, the use of ademetionine in patients with ALD reduces liver damage by preventing the decline in endogenous SAMe and glutathione levels. Ademetionine is appropriate for patients with compensated and subcompensated cirrhosis and milder forms of ALD. Treatment should be monitored for liver function tests over several weeks to several months. With long-term use, ademetionine improves the prognosis of patients with ALD.

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