***Etiopathogenesis and modern laboratory diagnostics of liver diseases***

Many pathologies that do not cause deep damage to the liver can go asymptomatic for a long time. For this reason, laboratory tests that show liver cell damage, metabolism, synthesis and excretion functions are used to investigate and diagnose liver diseases. These indicators include liver parenchyma enzymes (ALT, AST), cholestasis enzymes (ALP (alkaline phosphatase), GGT (gamma-glutamyl transferase), albumin, PT (INR) and serum bilirubin levels. These tests are the most commonly used primary tests in liver pathologies. Pathological changes in the mentioned tests help to determine more specific tests and find the etiology of the pathology. In addition, these tests are used to determine the type of disease, the extent of damage, and to monitor the body's response to treatment.

* ***Tests showing damage to hepatocytes (parenchymal enzymes)***
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
* These enzymes are normally found in hepatocytes and physiologically play a role in the transport of amino groups from amino acids.
* Apart from the liver, AST is found in the heart muscle, muscles, leukocytes, erythrocytes, brain, kidneys, and pancreas. In some heart and muscle diseases, it can increase in the blood.
* ALT is found insufficiently in extrahepatic tissues and is more specific for liver damage.

The normal amount of ALT and AST in the blood serum is 10-40 IU/L. High levels of these enzymes are a prominent indicator of liver damage. But the fact that it is normal does not negate a liver disease. This indicator may be normal in patients with minimal inflammation or delayed cirrhosis. ALT and AST are mildly to moderately elevated in many liver diseases and are usually less than 300 IU/L. These diseases are as follows:

* Steatohepatitis (the most common)
* Chronic hepatitis
* Metabolic liver diseases
* Drug-induced and toxic hepatitis
* Systemic diseases
* Diseases in which ALT and AST > 500 IU/L are as follows:
* Acute viral hepatitis
* Toxic hepatitis
* Acute liver ischemia
* Acute right ventricular failure
* Acute biliary obstruction
* Diseases in which ALT and AST > 1000 IU/L are as follows:
* Ischemic hepatitis
* The effect of high doses of paracetamol
* Severe form of viral hepatitis
* Acute severe autoimmune hepatitis
* The presence of AST / ALT > 2 is an indication of alcoholic hepatitis.
* Lactate dehydrogenase (LDH)
* There are 5 isozymes of LDH. LDH 5 isozyme is specific for liver damage.
* LDH increases in pathologies with damage to hepatocytes.
* LDH is very elevated in ischemic hepatitis due to heart failure.
* ***Cholestasis tests.***
* Alkaline phosphatase (ALP)
* It is synthesized in many organs and tissues. These include:
* Hepatobiliary system: hepatocyte, bile duct epithelium
* Bones: the main cause of elevated bone-derived alkaline phosphatase is Paget's disease of bone. In addition, alkaline phosphatase increases in blood serum during bone fractures.
* Epithelial cells of the small intestine: increased in ischemic diseases of the intestine.
* Placenta: it can be high in pregnant women.
* Proximal tubule epithelium of the kidney: increases in chronic renal failure because it is not metabolized.

The norm is 30-140 IU/L in blood serum. Since it is synthesized in many tissues, its specificity is low in liver diseases, and if it is elevated alone, it is necessary to think about pathologies outside the liver. Physiologically, it can increase during the growth period, pregnant women, climacteric period.

* Gamma-glutamyl transferase (GGT)
* It is the most specific indicator of cholestasis. It rises earlier than ALP and remains in blood serum longer. A normal serum value is 0-45 IU/L.
* In alcoholic patients, GGT is high, while ALP is normal.
* 5' – Nucleotidase and Leucine Aminopeptidase:
* These enzymes are more specific for the liver and are elevated in hepatobiliary pathologies.
* Like GGT, it is used to distinguish whether an increase in ALP is of hepatic origin. It can increase physiologically in pregnant women.

***Liver synthesis function assessment tests***

* **Albumin:**
* It is synthesized in the liver, the norm is 3.5-5 g/dL.

In chronic liver diseases, the level of albumin in the serum decreases, and globulin increases. In this case, the albumin globulin rate rises at the expense of globulin.

It is used in the prognosis of the disease and the determination of fibrosis in chronic liver diseases.

In addition to liver diseases, the serum albumin level may decrease in the following pathologies:

* Nephrotic syndrome and other renal pathologies
* Chronic infections
* Maldigestion and malabsorption syndromes, etc.
* **Prothrombin time (PT/INR)**
* It is the time that passes from the activation of factor VII to the formation of thrombin in the extrinsic pathway of coagulation. The norm is 9.1-12.1 seconds.

PT is prolonged in liver diseases, as all factors, the most important of which is factor VII, are synthesized in the liver.

Of the functional tests of the liver, it is the test with the highest prognostic value, indicating acute liver damage.

A prolongation in PT of more than 5 seconds (despite vitamin K injection) indicates a poor prognosis for either acute or chronic liver disease.

Taking into account the difference in measurements (variability of measuring devices, substances) in the determination of PT in clinical laboratories, PT is expressed in INR (international normalized ratio). The norm is 0.9-1.1.

* In the case of vitamin K deficiency due to cholestasis, the synthesis of factors II, VII, IX and X in the liver decreases and PT is prolonged.

PT normalizes within 12-24 hours if vitamin K is prescribed to those who are deficient in vitamin K due to cholestasis.

As a result of damage to the liver parenchyma, PT is prolonged, and when vitamin K is prescribed, PT does not normalize.

The difference between PT prolongation caused by parenchymal damage and cholestasis is shown in the table.

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| **Liver synthesis function assessment tests** | |
| Albumin | PT/INR |
| * The half-life of albumin in the serum is 20 days * It is normal in acute injury and decreases in chronic pathology * It is a prognostic indicator in chronic injury | * The half-life in the serum is short (hours) * It is prolonged in both acute and chronic injuries * The test has the highest prognostic value in acute injuries * It is also a prognostic indicator in chronic injury |

* **Partial thromboplastin time (aPTT-N-24,3-35 sec)**
* Indicates factor activity in the internal pathway of coagulation.
* The most important factor in this pathway, factor VIII, is synthesized outside the liver, so it is less altered by PT in liver diseases.

**Tests showing the transport and elimination functions of the liver**

* For this, most serum bilirubins are checked.
* ***Free bilirubin:*** Insoluble in water, not excreted in urine. Combined with albumin, it is transported to the liver. The normal amount in serum is between 0.3-0.7 mg/dL.
* Hemolytic anemias (free bilirubin increases, reticulocytosis occurs)
* Reduction of free bilirubin entry and conjugation in the liver (Gilbert and Crigler-Najjar syndrome)
* ***Conjugated bilirubin.*** Its amount in serum is 0.1-0.3 mg/dL. Cholestasis increases in posthepatic jaundice.
* If there is an obstruction in the intra- or extrahepatic bile ducts (cholestasis, tumor, stone, etc.)
* Violation of the excretion of conjugated bilirubin from the liver (Dubin-Johnson, during Rotor syndromes)
* ***An increase in both free and conjugated bilirubin (total bilirubin***)
* Damage to hepatocytes (all hepatitis)
* Persistence of obstruction in the bile ducts for a long time

***Total bilirubin*** (norm 0.2-1.0 mg/dL) in serum is mainly hyperbilirubinemia if it exceeds 1.5 mg/dL.

***Other serological tests***

* Immunoglobulins (IgG, IgM, IgA)
* Autoantibodies
* Antimitochondrial antibody (AMA): primary biliary cholangitis
* Anti-smooth muscle antibody (ASMA): autoimmune hepatitis type I
* Anti–liver-kidney microsomal antibody (Anti LKM): autoimmune hepatitis type II

**ACUTE HEPATITIS**

Acute hepatitis is an acute inflammatory-necrotic disease of the liver of various etiologies, clinically observed with symptoms of general intoxication syndrome, hepato-splenomegaly, jaundice of varying intensity and inflammation. If the disease lasts up to 6 months and mostly results in recovery, it is called acute hepatitis, if it lasts more than 6 months, if permanent inflammatory changes occur in the liver, it is called chronic hepatitis.

As a rule, acute hepatitis ends with recovery, but in 5-10% of cases it can become chronic. In recent years, there has been a significant increase in the number of patients with acute hepatitis of various etiologies, up to 50% of all cases are caused by excessive use of alcohol and drugs.

Acute hepatitis is classified as follows:

A. According to the etiology: drug-induced, alcohol, bacterial, toxic, traumatic, radiation, viral (A, B, C, D, E, F, G, cytomegalovirus, herpes virus, infectious mononucleosis, etc.).

B. According to the clinical form: asymptomatic, subclinical, icteric, cholestatic, anicteric.

C. According to the course: acute, chronic.

D. By degree of severity: light, medium, heavy.

E. Due to its complications:

a) early: hepatic encephalopathy; hepatic coma; portal hypertension, ascites, damage to the bile ducts and pancreas (acute catarrhal cholecystitis, acute pancreatitis), myocarditis, myocardial dystrophy, acute nephritis, Guillain-Barré syndrome;

b) delayed: progression to chronicity, hepatocellular carcinoma, damage to the biliary tract and pancreas (chronic cholecystitis, chronic pancreatitis, biliary dyskinesia), portal hypertension, hepatomegaly.

***Acute viral hepatitis***

Currently, 6 types of viral hepatitis are known: A, B, C, D, E, G. They differ from each other according to the incubation period, the severity of the main symptoms of the disease, the course and consequences.

***Hepatitis A***

**Etiology -** for the first time hepatitis A virus (HAV) was discovered in 1973. It is a virus with a diameter of 27-32 nm and containing RNA. The virus is found in blood, feces, hepatocytes and bile.

The way of transmission is fecal-oral in 95% of cases. The incubation period can last from 7 to 45 days.

**Pathogenesis -** the virus passes through the mouth, pharynx and intestines, first enters the regional lymph nodes, and then penetrates the liver via lymphogenous and hematogenous routes from the portal vein. Its entry into the hepatocyte is due to the presence of specific receptors on the cell membrane. The virus entering the hepatocytes intensively grows and multiplies there, enters the bile ducts, and then the intestines and is excreted in the feces.

**Clinic -** it can be observed in symptomless (subicteric), icteric, cholestatic, fulminant forms. Hepatitis A does not become chronic.

**Laboratory diagnostics -**

* **Anti-HAV IgM-positive** indicates an acute form of the disease. The IgM level reaches its maximum level in the blood 4 weeks after infection and remains at a high level for 2 months. The disease can remain at a measurable level for 6 months after its onset.
* **Anti-HAV IgM-negative** indicates the absence of acute hepatitis A infection.
* **If anti-HAV IgG is positive,** it indicates that immunity against hepatitis A has been developed or vaccination.

The level of IgG generated against HAV in the blood serum rises sharply after the virus is cleared and remains at measurable levels in the serum for many years.

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| **HAV serological tests used in the clinic** | |
| **Anti-HAV IgM-positive** | There is an acute infection |
| **Anti – HAV IgM-negative** | No acute infection |
| **Anti-HAV IgG-positive** | Previous exposure to hepatitis A infection |

***Hepatitis B***

**Etiology** - is a DNA-containing virus from the hepadnavirus family. The incubation period is 30-180 (average 80) days. The risk of becoming chronic is high. There is a 90% risk of becoming chronic in those infected perinatally, 20-50% in those infected between 1-5 years of age, and 1-5% in those infected in adulthood.

*Transmission routes -* vertical route: the risk of infection in children born to HVeAg-positive mothers is 90%. Horizontal route: the most common of this route is the sexual and intravenous route. Because HBV can survive for a long time in the environment outside the body, infection can also occur through toothbrushes and razors. The virus can also enter the body through small cracks in the skin and mucous membranes.

**Clinic -** acute hepatitis B can progress to subclinical, icteric and fulminant form and result in liver failure. Loss of appetite, fever, pain in the right rib area, jaundice, etc. symptoms are observed.

**Pathogenesis** - hepatitis B virus (HBV) enters the liver by hematogenous route. This virus moves towards the pre-S1 receptors in the protein layer of the membrane of hepatocytes, that is, it has tropism. In hepatocytes, the virus is freed from the DNA-genetic matrix, and its individual components (HBsAg and HBeAg in the nucleus, HBsAg antigens in the cytoplasm) are replicated, and complete assembly of the virion occurs. Because HBsAg and HBeAg antigens are synthesized a lot, they pass into the blood. Then, in the membrane of the hepatocytes, the “recognition"of these antigens by the immunocytes takes place.As a result of the interaction of the virus and the immune system of the macroorganism, activation is observed in individual parts of this system. For example, in T - and B - lymphocytes, macrophages, cytokines, etc.

The course and outcome of the disease depend on many factors, namely the nature of the immune response, the degree of manifestation of symptoms, genetic determination and the properties of the virus itself.

Hepatitis B virus is not cytopathic. The process of cytolysis of infected hepatocytes is related to the immune system, and this process is carried out by cytotoxic T-lymphocytes after recognition of viral antigens. HBcAg is taken as the main target. The immunogenicity of this antigen is 100 times higher than others. The presence of HBsAg alone in hepatocytes does not cause cell lysis, but the HBeAg antigen secreted into the blood reduces antibody formation and interferon secretion.

During the humoral response, specific antibodies (anti-HBc, anti-HBe, anti-HBs) are collected, which, as a result of their combination with the corresponding antigens, stop the free circulation of antigens in the blood. At this time, immune complexes formed from antibodies, antigens, C3 complement fragment are formed. These are captured by macrophages, phagocytosed and removed from the body. The fact that the rate of formation of immunocomplexes is higher than the rate of their elimination leads to the development of an autoimmune process. Particular importance is given to autoimmune mechanisms in the immunopathogenesis of the hepatitis B virus. Cell membranes, the structure of which has changed from the effects of viruses, are recognized by T-lymphocytes as “foreign” cells, therefore, both cellular and humoral reactions are directed not only against “foreign”cells, but also against “own” cells of the body. The increasingly progressive autoimmune process deepens the cytolysis of hepatocytes and causes the spread of liver necrosis. Autoimmune processes usually develop during a hyperimmune response. If the immune response is weak, the disease has a chronic course, clinical symptoms are not clear, long-term persistence of the virus is observed. Only an adequate immune response can prevent the infectious process and rid the body of the pathogen.

The immune response is genetically determined and is related to histocompatibility antigens (HLA). B8, A1-B8 antigens are detected in the blood of patients with a hyperimmune response, and B7, B18, B35 antigens are detected in those with a weak response.

Recently, it has been proven that external replication of the virus from the liver can also occur in blood cells, bone marrow, spleen, lymph nodes. This also causes viruses to “evade” immune control, because lymphocytes and monocytes are not controlled by immunocytes. Cases of avoidance of control cause the virus to mutate.

**Laboratory diagnostics**

1. Determination of HBV markers in blood serum:

* **Hepatitis B surface antigen (HBsAg) and antibody (anti - HBs):** 1-10 weeks after infection, HBsAg is initially determined before elevation in ALT. HBsAg is the protein that forms the outer membrane of the virus. Finding it in the blood indicates infection with the disease.
* In recovered patients, it decreases in the blood within 4-6 months.
* If HbsAg remains high for more than 6 months, it indicates that the disease has become chronic.
* **Anti-HBs:** it is not determined until the end of the acute period of the disease, and usually HBsAg is not detected for several weeks or months after the antigen disappears.Anti-HBs antibody is found in the blood for life and ensures the protection of the body. Finding this antibody indicates that the body has developed immunity to hepatitis B.

**Hepatitis B core antigen (HBcAg):** It is an antigen found only inside infected hepatocytes. It is not found in blood serum. But the anti-HBc antibody produced against this antigen is used to diagnose acute hepatitis.

* **Anti-HBcIgM:** is the main indicator of acute hepatitis. During the course of acute hepatitis B, the period between the disappearance of HBsAg and the formation of anti-HBs is called the "window period" ("gap period"). During this period, while HBsAg and anti-HBs are negative, anti-HBcIgM becomes positive.
* **Anti-HBcIgG:** is an indicator of postponed hepatitis B disease. It is positive throughout life both in chronic infection and in those who have acquired immunity.
* **HBeAg:** It is a viral protein synthesized by the hepatitis B virus that passes from the liver cells into the blood. It is an indicator of HBV replication. It is found in the blood in the early stages of the disease and indicates a high risk of developing chronic hepatitis.
* **Anti-HBe:** It is an antibody that is synthesized against HbeAg and reduces contagiousness.
* **HBV DNA:** It is the gene of hepatitis B virus. The higher the HBV, the more HBV DNA is found in the blood. If HBs antigen is negative in blood serum and HBV DNA is found in small amounts, it is considered as latent hepatitis B. HBV DNA is the most reliable indicator of viral replication.

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| **HBV serological tests used in the clinic** | |
| **HBsAg** is an indicator of infection (acute, chronic active or carrier) | **Anti-HBs:** immunity |
| **Anti- HBc IgM:** acute infection | **Anti-HBc IgG:** infection with the virus before |
| **HBeAg, HBV DNA:** replication | **Anti HBe:** reduced replication |

***Hepatitis C***

**Etiology -** The causative agents of hepatitis C are RNA-containing viruses belonging to the flavivirus family. HCV is the most common cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma worldwide.

The main route of entry into the body is the parenteral route. The incubation period is 15-160 days.

**Clinic -** the disease is often asymptomatic. Sometimes fatigue, loss of appetite, jaundice, unexplained weight loss, diarrhea, dark colored urine, and other signs can be observed. According to its course, it becomes acute and chronic.

**Pathogenesis -** both immunological reactions and cytopathic effects of viruses play a role in the pathogenesis of hepatitis C. Poor immunogenicity of HCV also slows down their excretion from hepatocytes. One of the main factors in keeping viruses out of immune control is that their antigen structure is constantly changing and renewing. As a result, the immune system cannot adapt to the new variants that have been formed. This causes the newly formed strains to be stored and replicated in the body. In this case, the rate of mutation exceeds the activity of replication and results in long-term persistence of hepatitis C viruses in the body.

The weak rate of replication of viruses in HCV, having an active antigen change, leads to a low level of viremia, as a result of which the immune response is insufficient. Human genetic factors can also affect the recognition of antigens of hepatitis C viruses, leading to a weak immune response. This results in a weakening of the activity of T-lymphocytes, a decrease in the formation of antibodies and their late appearance. The resulting antibodies, on the other hand, differ in their specificity, they do not affect the newly formed variants of the virus. It has also been found that viruses have the ability to induce peptides, which are functional antagonists of the receptors of T-lymphocytes. At this time, anergy of T-cells occurs. Their helper and cytotoxic activity is to some extent blocked. It is assumed that apoptosis of antiviral-specific T-lymphocytes can also lead to a weakening of cellular immunity.

Remaining in the liver for a long time, for years, leads to the destruction of hepatocytes and the development of chronic HCV, and even malignant tumors of the liver.

**Laboratory diagnostics:**

* **HCV-RNA:** This marker can be positive in the blood before ALT rises. It is detected in acute hepatitis C and in chronic hepatitis C during the persistence of viruses.
* **Anti-HCV:** It appears after the elevation of ALT in the blood serum. HCV becomes positive after RNA.

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| **Serological examination of hepatitis C virus** | | | |
| **Anti HCV** | **HCV RNA** | **ALT** | **Pathology** |
| - | **+** | Raised to a remarkable level | Acute hepatitis C (early stage) |
| + | **+** | Raised to a remarkable level | Acute hepatitis C |
| + | **+** | Weak-moderately elevated | Chronic hepatitis C |
| + | **-** | Normal | Postponed hepatitis, inactive chronic hepatitis |

***Hepatitis D***

**Etiology -** It is an RNA virus. The incubation period is 15-80 days. One of the important features of hepatitis D virus is its absolute dependence on helper virus. A helper virus conditions its reproduction. Hepatitis B viruses play this role. Helper virus D is necessary for entry of viruses into hepatocytes. Thus, HBsAg surface antigen of B virus covers hepatitis D viruses, plays the role of its outer membrane and ensures its entry into hepatocytes. There are two clinical forms.

1. Hepatitis D coinfection: Hepatitis B virus and D virus cause disease together. Both hepatitis B virus and hepatitis D cause acute inflammation.
2. Hepatitis D superinfection: it is the infection of a patient who is a carrier of chronic hepatitis B with an acute D virus infection. In these patients, 20% of the disease is observed in a fulminant form. The risk of becoming chronic is 95%.

The routes of transmission are almost the same as those of HBV.

**Clinic -** Fever, joint pain, enlarged spleen, jaundice, and other symptoms are observed.

**Pathogenesis -** The pathogenesis of hepatitis D has not been sufficiently studied. It is believed that HDVs play the main role compared to HBVs. So, unlike B viruses, they have a direct cytopathic effect. Therefore, cytolytic changes in hepatocytes in hepatitis D exceed inflammatory processes.

**Laboratory diagnostics:**

* **HDV Ag:** In acute infection, it may be positive for a short time.
* **Anti-HDV IgM:** Clinical signs are observed shortly after the onset, they are not found in the blood after 2-3 months. It is an indication of acute infection.
* **Anti-HDV IgG:** if it is positive, it means that the patient is infected with the hepatitis D virus.
* **HDV-RNA:** Indicates replication. It is a marker of the replication phase of acute hepatitis or chronic hepatitis.

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| **Serological examination of hepatitis D virus** | | | | |
| **HbsAg** | **Anti-HBs** | **Anti-HBc-IgM** | **Anti-HDV IgM** |  |
| + | - | + | + | B+D coinfection |
| + | - | - | + | B+D superinfection |

***Hepatitis E***

**Etiology -** The causative agent of hepatitis E is an RNA virus. The incubation period of the disease is 15-60 days. It is transmitted through the oral-fecal route.

**Pathogenesis -** Although the pathogenesis of hepatitis E is not sufficiently studied, it is believed that its course is very similar to the pathogenesis of hepatitis A. Thus, hepatitis E viruses also have a direct cytopathic effect, and immune mechanisms do not play a significant role in liver damage.

**Clinic -** Intoxication, dyspeptic symptoms, jaundice, pain in the right subcostal area, and other symptoms are observed. In pregnant women, hepatitis E is severe in 60% of cases. In this case, the lethality can reach 80%. In pregnant women, the disease occurs in a fulminant form due to hormonal imbalance.

**Laboratory diagnostics:**

* **Anti-HEV IgM:** It is positive in acute infection.
* **Anti-HEV IgG:** Indicates a previous exposure to infection.

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| **Serological examination of hepatitis E virus** | | |
| Anti-HEV-IgM | + | It is positive in acute infection |
| Anti-HEV-IgM | + | Indicates a previous exposure to infection |

**Chronic hepatitis**

Chronic hepatitis is damage to the liver parenchyma with degeneration, necrosis and fibrosis as a result of inflammation in the liver lasting longer than 6 months.

**Etiology**

* Viruses: hepatitis C (mostly), B, D
* Steatosis
* Alcohol
* Medicines: Aspirin, dantrolene, isoniazid, methyldopa, nitrofurantoin, etc.
* Other: Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis.

**Clinic -** It is asymptomatic at first. The most common symptom is weakness and fatigue. When the disease progresses, jaundice, loss of appetite, nausea, vomiting, and other signs appear. When the process results in cirrhosis, symptoms of portal hypertension are observed.

**Laboratory diagnostics -** in chronic viral hepatitis, liver tests and serological examination are mainly performed.

* Liver enzymes are weak-moderately increased, in inactive hepatitis they are completely normal and close to normal.
* HBsAg and Anti-HCV are determined. If these are negative, autoimmune hepatitis, metabolic diseases, and other the causes are investigated.
* An accurate diagnosis is obtained with a liver biopsy.

***Alcoholic hepatitis***

It is a pathology ranging from steatosis to cirrhosis due to excessive alcohol consumption. Taking more than 30 grams of ethyl alcohol every day can damage the liver. The effects of alcohol on the liver can vary considerably between people depending on genetic and environmental factors.

**Pathogenesis -** Serious liver damage does not occur in every person who uses alcohol. The occurrence of damage is closely related to the metabolism of alcohol. Alcohol is converted to acetaldehyde in the liver by **MEOS** (microsomal ethanol oxidizing system) and **ADH** (alcohol dehydrogenase). Acetaldehyde is broken down to acetylCoA, CO2 and H2O. When acetaldehyde accumulates in the liver, it causes hepatocellular damage. In the process of conversion of ethanol to acetaldehyde, the synthesis of NADH from NAD+ increases, NAD+ is necessary for the oxidation of fatty acids in the liver. Its deficiency causes the accumulation of fats in the liver. This initially leads to fatty infiltration of the liver and, if the process continues, to fatty dystrophy. Both processes are reversible when alcohol intake is stopped. If alcohol abuse continues for a long time, irreversible changes in hepatocytes occur and result in the development of liver cirrhosis. ADH is also active in the stomach and small intestines, and alcohol undergoes some metabolism here as well. Gastric ADH activity is lower in women, for this reason liver damage occurs more quickly.

**Risk factors**

1. Amount of alcohol: Ethyl alcohol > 20 g/day in women, > 30 g/day in men
2. Time frame: 5-20 years
3. Other causes: female gender, genetic predisposition, patients with hepatitis C, hepatitis B, obesity, continuous daily intake, smoking, improper diet, etc.

**Laboratory diagnostics**

* Blood test: MCV , AST , GGT

Of the aminotransferases, AST is typically increased more than ALT. (AST/ALT>2) A ratio greater than 3 is highly specific for alcoholic hepatitis. ALT and AST use vitamin B6 as a cofactor. ALT binds more to vitamin B6. Because alcohol depletes vitamin B6, ALT levels are lower in these patients despite hepatocyte damage. Plasma gamma-glutamyl transferase (GGT) is usually elevated.

The most common pathology in patients who use alcohol regularly is steatohepatitis. Only 8% to 20% of chronic alcohol abusers develop cirrhosis.

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| **Diagnosis of alcoholic hepatitis** | |
| **MCV** | **High** |
| **AST/ALT >2** | **More than 3 is specific for alcoholic hepatitis** |
| **ALT** | **Normal** |
| **GGT** | **High** |

***Autoimmune hepatitis***

**Etiology -** It has not been sufficiently studied. It is believed that the basis of the pathology is contact with certain antigens of the main complex of histocompatibility (human HLA; DR3 and DR4 alleles detected in 80-85% of patients). Factors that lead to autoimmune processes in genetically predisposed individuals can be Epstein-Barr virus, hepatitis (A, B, C), measles, herpes, as well as some drugs (diclofenac, nitrofunantoin, atorvastatin, etc.).

**Pathogenesis -** autoimmune hepatitis is based on a deficit of immune regulation. Thus, the reduction of T-supersor lymphocytes leads to uncontrolled IgG synthesis of B-cells, which leads to damage of liver cell membranes. As a result, characteristic serum antibodies (ANA, SMA, anti-LKM-I) appear.

Depending on the antibodies formed, I (Anti-ANA, Anti-SMA +), II (Anti-LKM-I +), and type III (Anti-SLA +) autoimmune hepatitis are distinguished.

Type I accounts for 80-85% of autoimmune hepatitis. It is characterized by the finding of antinuclear antibodies (ANA) and smooth muscle antibodies (SMA-smooth muscle anticor) in the serum. 70% of patients are women. 40% of them have a low probability of finding organ-specific antibodies accompanying another autoimmune disease (autoimmune thyroiditis, ulcerative colitis, etc.).

Type II autoimmune hepatitis is characterized by the finding of anti LKM-1 (liver kidney microsomal-1) and ALC-1 (liver cytosol-1) autoantibodies. Most patients with this type of autoimmune hepatitis are children (2-14 years old). Type II autoimmune hepatitis is the most severe form of autoimmune hepatitis. Other autoimmune diseases (vitiligo, insulin-dependent diabetes, autoimmune thyroiditis) and organ-specific autoantibodies are highly likely to be positive.

Type III autoimmune hepatitis is characterized by finding anti-SLA (soluble liver antigen) and anti-LP (antibody formed against liver pancreas antigens) in the serum. Mostly (90%) it is seen in young and female patients.

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| **Types and markers of autoimmune hepatitis** | | | |
| **Marker** | **Type I** | **Type II** | **Type III** |
| **ANA** | **+** | **-** | **-** |
| **Anti SMA(smooth muscle antibody)** | **+** | **-** | **-** |
| **Anti-liver Kidney Ab⁎ (anti LKM)** | **-** | **+** | **-** |
| **Anti-HCV** | **-** | **+** | **-** |
| **Gammaglobulin (IgG)** | **Increased** | **Normal** | **Normal** |
| **Anti SLA (soluble liver antigen)** | **-** | **-** | **+** |

**Figure 1. The damaging effect of alcohol on the liver**



