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PRINCIPLES OF DIAGNOSIS AND TREATMENT OF HEPATIC ENCEPHALOPATHY

MONOGRAPHY

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

CNS- central nervous system

DVV - dilatation of varicose veins

EEG - electroencephalography

ExoKG- echocardiography

GERD - gastroesophageal reflux disease

GIS- gastrointestinal system

GRS-hepato-renal syndrome

HE- hepatic encephalopathy

LC- liver cirrhosis

LT-line test

MHE - minimal hepatic encephalopathy

MRI - magnetic resonance imaging

NALD- non-alcoholic liver dystrophy

NCT- Number connection test

PBC - primary biliary cirrhosis

PET- positron emission tomography

PH- portal hypertension

PHS- portal hypertension syndrome

RAAS- renin-angiotensin-aldosterone system

USE- ultrasound examination

INTRODUCTION

Complications cirrhosis of liver cirrhosis such as liver encephalopathy resulting from it remain a major social problem, reducing the quality of life of patients and their relatives and endangering our society. In the world, many researches aimed at improving the effectiveness of early diagnosis and treatment of hepatic encephalopathy are being conducted. Development of new aspects of the etiopathogenesis of liver encephalopathy, methods of assessing severity levels, improvement of the diagnostic value of laboratory and instrumental examination methods, optimization of pathogenetic treatment, as well as determination of measures to prevent complications are considered urgent issues.

In our country, large-scale works aimed at fundamentally improving the quality of medical services provided to the population and developing the health care system are being carried out . As a result of specific targeted measures, it is important to achieve high results in providing high-quality medical care to the population, in particular, to increase the efficiency of medical and social care for patients with liver cirrhosis, to reduce disability rates, and to improve the quality of life. In 2017-2021, in accordance with the strategy of actions on the five priority areas of development of the Republic of Uzbekistan, in raising the level of medical services to the population to a new level, "...increasing the convenience and quality of specialized medical services, further reforming the system of quick and urgent medical assistance, preventing disability.. .." [1]such tasks are set. Therefore, in addition to raising the level of medical services to the population to a new level, clarifying the specific characteristics of liver cirrhosis and liver encephalopathy syndrome, which may develop as a result, is one of the current scientific directions . development of the principles of detection and treatment allows to improve the quality of life of patients , reduce the rates of early disability and death .

Decree of the President of the Republic of Uzbekistan dated January 28, 2022 No. PF-60 "On the new development strategy of Uzbekistan for 2022-2026", No.

[1]Decree of the President of the Republic of Uzbekistan dated February 7, 2017 No. PF-4947 "On the Strategy of Actions for the Further Development of the Republic of Uzbekistan".

PQ-5124 dated May 25, 2021, "On measures for comprehensive development of the health sector" and This thesis research serves to a certain extent the implementation of the tasks defined in the Decisions of PQ No. 215 of April 25, 2022 "On additional measures to bring primary medical and sanitary care closer to the population and increase the efficiency of medical services" and other regulatory and legal documents related to this activity. .

The growth of chronic liver diseases is called the "second epidemic of the 21st century" after the "epidemic" of cardiovascular pathology. Liver diseases are a global public health problem, and more than 1 million people worldwide die from cirrhosis of the liver every year. According to the chief gastroenterology professor of the Republic of Uzbekistan, M.M. Karimov, cirrhosis of the liver will account for 3% of the diseases of the gastrointestinal tract in Uzbekistan by 2022. An important aspect of the pathology that leads to death is that the majority of patients with cirrhosis, about 75%, are aware of their disease for the first time only when complications of the disease (such as liver failure, bleeding from esophageal varices, or ascites) appear. The conversion of compensated cirrhosis without clinical symptoms to decompensated cirrhosis is approximately 5-7% per year. Cirrhosis of the liver remains the cause of 1 million deaths each year, but most of these deaths are preventable (Rowe IA. Lessons from Epidemiology: The Burden of Liver Disease. Dig Dis. 2017;35(4):304-9.). According to *AAMokdad et al., the average death rate from liver* cirrhosis is 22 per 100,000 population. Many researchers have noted a significant increase in the number of liver diseases in recent decades , the main reasons for which are the increase in alcohol consumption, the spread of viral hepatitis and the epidemic of obesity (I. G. Bakulin , I. A. Oganezova , M. I Skalinskaya , V. " Cirrhosis management " . 2021 . The course and prognosis of liver cirrhosis depend on etiology , stage and adequacy of treatment. However , regardless of the etiology of the disease, the development of one or more complications of the disease leads to the death of the patient, despite the fact that a lot of money is allocated by the health care system for the treatment of patients. Therefore, studying the causes of disease complications is one of the important tasks of therapy and

hepatology (I.G. Bakulin, I.A. Oganezova, M.I. Skalinskaya, E.V. Skazyvaeva. "Cirrhosis pecheni i upravlenie riskami oslojneniy". Journal Therapeutic Archives 2021; 93(8): 963–968. Knowing the mechanisms of development and eliminating the reasons involved in their development leads to the transition of the disease to decompensation and prevention of fatal complications. EASL (European Association for the Study of the liver) According to the 2018 recommendation, decompensated liver cirrhosis is characterized by pronounced clinical signs, including ascites, hemorrhages, liver encephalopathy , jaundice , etc. The appearance of any of the above clinical signs leads to rapid development of the disease. The average life expectancy of patients with decompensated liver cirrhosis is 1.8 years. The Association of European scientists for the study of the liver cited hepatic encephalopathy as one of the causes of decompensation . There are several etiological reasons for the development of liver encephalopathy in liver cirrhosis . For example: excessive consumption of diuretics, diarrhea , dehydration of the body, excessive intake of protein preparations, etc. However, some drugs, such as proton pump inhibitors , are recommended by doctors in the treatment of complications developed by the gastrointestinal system in patients with JTs , in uncorrected doses, or patients take them irregularly for a long time. also plays an important role in the development of liver encephalopathy .

LIVER CIRRHOSIS DEFINITION, EPIDEMIOLOGY, ETIOLOGY, DIAGNOSTIC CRITERIA

Liver cirrhosis - (according to WHO recommendations) is a diffuse damage to the liver, characterized by a change in the normal structure-architectonics of the liver with the growth of connective tissue (fibrosis) and the formation of nodules. Liver cirrhosis (JTs) is the terminal stage of a number of chronic liver diseases and occupies an important place among gastroenterological diseases. JTs are not only a medical problem, but also an important social problem in all countries of the world (Rowe IA. Lessons from Epidemiology: The Burden of Liver Disease. Dig Dis.

2017;35(4):304-9.). Chronic liver disease is one of the most common diseases and is currently the fifth leading cause of death in many developed countries. The life prognosis of patients with JTs largely depends on the development of its complications, the most important among JTs complications are:

- hepatic encephalopathy (JE);
- bleeding from varicose veins of esophagus and stomach;
- ascites (ascites fluid with or without infection);
- Hepatorenal syndrome (GRS);
- Hyponatremia;
- Infectious complications.

Classification of liver cirrhosis

The classification of liver cirrhosis has been reviewed several times, and the last change was introduced at the 5th Pan American Congress of Gastroenterologists in Havana in 1956 (Cirrhosis cake and portal hypertension / A. E. Borisov, V. A. Kashchenko. — SPb., 2009. — 112 p.).

I. According to the etiology:

1. viral - B , C, D ;
2. due to drugs;
3. alcoholic;
4. autoimmune hepatitis;
5. primary biliary cirrhosis;
6. secondary biliary cirrhosis;
7. due to metabolic disorders (α1-antitrypsin deficiency, idiopathic hemochromatosis, etc.);
8. primary sclerosing cholangitis (PSC);
9. non-alcoholic liver dystrophy (NAJD);
10. venous flow disorder (Baddi-Chiari syndrome, Baddi-Chiari disease);
11. right ventricular failure in the decompensation stage (cardiogenic cirrhosis);
12. cryptogenic (cirrhosis of unknown etiology).

II. According to clinical signs:

1) initial

2) clinical symptoms are clearly expressed

3) terminal

III. According to morphological forms:

1. Macronodular (nodules larger than 3 mm, including 2 or more false lobes);

2. Micronodular (the size of nodules is less than 3 mm, includes 1 lump);

3. Mixing.

IV . Complications of liver cirrhosis:

A) Edema-ascitic syndrome;

B) Hemorrhagic syndrome;

C) Hepatic encephalopathy and coma;

G) Hepatocellular carcinoma: cirrhosis-cancer.

Clinical manifestations. The clinical manifestation of JTs symptoms is related to the development of portal hypertension syndrome and its complications, liver cell failure, systemic damage caused by the effect of an etiological factor, immunological and metabolic diseases. The main manifestations of hepatocellular failure include astheno-vegetative syndrome, vasodilatation and hyperdynamic type of blood circulation, jaundice and hepatic encephalopathy. The hyperdynamic type of blood circulation can be manifested as tachycardia, decreased blood flow to the brain, kidneys and liver, low blood pressure, etc. Skin changes can be manifested in the form of telangiectasias on the upper half of the body and "Palmar erythema" on the palm of the hand. Changes in the endocrine system can also be observed: gynecomastia in men, and excessive growth of hair in women - hirsutism, menstrual cycle-period disorder. In patients with cirrhosis of the liver, the blood clotting system is also disturbed and hemorrhagic syndrome develops. Due to the formation of liver fibrosis, the blood flow in the hepatic vein is disturbed and portal hypertension develops. The main clinical signs ***of portal hypertension*** (PG) include splenomegaly, dilated gastric cardia and esophageal varices, dilated vessels of the anterior abdominal wall ("Caput medusae"), and dilated anorectal veins. In addition,

portal hypertension can be detected using ultrasound and radiological examinations. It is determined that the diameter of the portal vein (usually, the diameter of the portal vein does not exceed 1.4 cm) and the splenic vein (usually, the diameter of the splenic vein in the portal area is 5-7 mm) are increased. The porta-caval collaterals are also enlarged. Complications of PG include: ascites - accumulation of fluid in the abdominal cavity, swelling-ascites syndrome, hepatic encephalopathy, bleeding from gastric/esophageal varices and/or anorectal veins, hepatorenal syndrome, hypertensive gastropathy, enteropathy, hypersplenisms. The severity of clinical symptoms depends on the stage of the disease, the etiology of cirrhosis and increases in proportion to the duration of the disease: in the initial stage of compensated liver cirrhosis, unconsciousness, pain and heaviness in the upper abdomen, temporary subicteric sclera, subfebrile temperature, increased fatigue, flatulence, weight loss of the patient, decreased performance , bleeding from the nose, slight itching of the skin may be observed; and in the acute stage of the disease, hepatomegaly and splenomegaly, the appearance of "spider veins" - telangiectasias in the upper half of the body, "liver palms", mainly parenchymal jaundice, fever, esophagitis, expansion of gastric varicose veins, gynecomastia, hepatolienal syndrome, ulcers of the gastrointestinal tract , hepatopancreatitis, hepatorenal syndromes, anemia, reflux esophagitis, heart failure, symptomatic ulcers of the stomach and duodenum (hepatogenic and central nervous system changes) may occur.

According to the Child-Pugh scale of liver cirrhosis

severity levels

Currently, the Child-Toretto-Pugh scale is widely used to assess the severity of liver cirrhosis and determine the patient's prognosis. This system was created by Child and Tercott in 1964 and modified by Pugh in 1973 (Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. 2023 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.PMID: 31194448). According to it, the severity of liver cirrhosis is assessed according to the following indicators:

Class A (Child-Pugh A) - 5-6 points

Class B (Child-Pugh V) - 7–9 points

Class C (Child-Pugh C) - 10-15 points

The severity of liver cirrhosis is determined by the sum of points from 1 to 3 for each of the 5 parameters. The Child-Pugh scale is evaluated according to the following parameters:

Determination of severity of cirrhosis according to Child-Pugh

Table 1.

Parameters	**1 point**	**2 points**	**3 points**
Bilirubin, µmol/l (mg%)	Less than 34 (2.0).	34-51 (2.0-3.0)	More than 51 (3.0).
Albumin , g/l	More than 35	28-35	less than 28
PTT (sec) or PTI (%)	1-4 (more than 60)	4-6 (40-60)	More than 6 (less than 40)
Ascites	No	mild, disappears after treatment	contracted ascites

One or another class of liver damage (A , B , C) is determined based on the sum of points for all parameters. After all tests are completed, total points are calculated. If the sum of points is 5-6 A to class , if the sum of points is 7-9 to class B , if the sum of points is 10-15 C corresponds to the class .

The quality of life and prognosis of patients with liver cirrhosis largely depend on the development of its complications. The most important **complications of PH** are:

• Ascites (accumulation of free fluid in the abdominal cavity);

• Bleeding from varicose veins of the esophagus and stomach due to portal hypertension;

• Hepatic encephalopathy;

• Hepatorenal syndrome (combination of kidney failure).

Grades of liver fibrosis

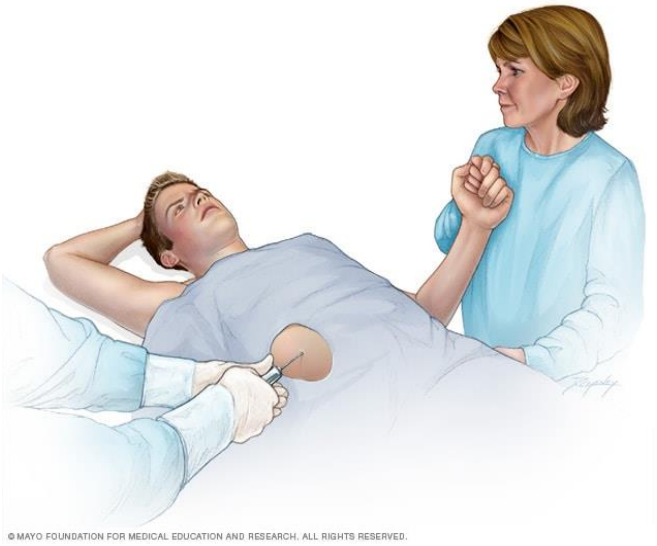
Liver fibrosis develops over many years, sometimes decades. The speed of its development is mainly influenced by the activity of the disease and individual characteristics of the person, as well as additional damaging factors and comorbid course of the disease. A doctor who suspects liver fibrosis may perform a liver biopsy. The degree of fibrosis is difficult to determine. Clinicians and physicians use several diagnostic scales to determine the stage of fibrosis. These include the METAVIR scale and the Batts-Ludwig scale. The results of these scales take into account the effect of fibrosis on the portal vein, which supplies blood from the intestine to the liver. Basically, many scales measure the degree of fibrosis and the location or number of septa, which are fibrous bands of tissue in a biopsy sample. Special scales, mainly the METAVIR scale, can be used to classify the degree of liver fibrosis. Five levels of liver fibrosis are distinguished according to this scale.

Table 2

Grades of liver fibrosis	Signs
F0 level **1.5-5.8 kPa**	a healthy liver, in which the liver has a normal structure .
F1 – level **5.9-7.2 kPa**	Connective tissue is located only around the branches of the hepatic artery and vein , in special places called portal tracts, where partitions (septa) are not formed. In stage F 1, there are no clinical signs, liver enzymes (ALT, AST) may also be normal. Usually, ultrasound examination does not detect changes in the liver tissue, sometimes there may be an increase in the size of the organ - hepatomegaly and the presence of heterogeneity.
F2 – level **7.3-9.5 kPa**	at this level, fibrous tissue septa form, separating the main liver cells from the blood entering the liver. This condition causes a violation of the process of blood purification by the hepato ts dogs and prevents the substances produced by the hepato ts dogs from entering the blood. Blood bypasses the liver cells in the places where barrier septa are formed and is discharged from the afferent vessels to the hepatic veins. Often, these symptoms at this stage are mild. In the biochemical blood test, liver enzymes and signs of inflammation increase, in all patients, the presence of heterogeneity in the structure of the liver and hepatomegaly is revealed in the ultrasound examination of the liver.
F3 – level **9.6-12.4 kPa**	It usually occurs 6-8 or more years after the onset of the disease. There is a significant increase in the barrier and fibrous tissue in the portal tracts. Usually, at this stage, the first clinical symptoms begin to appear - fatigue, weakness, bruises on the skin, drowsiness, etc. Also, the amount of hemoglobin and platelets decreases, liver enzymes and inflammatory markers increase, more dense areas are added on ultrasound, hepatomegaly and diffuse changes in the liver are detected. Up to the third stage, fibrotic changes in the liver can be lost with complete treatment of the etiology factor .
F4 – level **< 12.4 kPa**	at this stage, liver tissue is replaced by fibrous, connective tissue. This stage of fibrosis is irreversible.

Portal hypertension

Portal hypertension syndrome (PGS) is a clinical syndrome (group of symptoms) caused by increased pressure in the portal vein system due to obstruction of blood flow in the portal vein / hepatic veins / inferior vena cava. The most common cause of portal hypertension is cirrhosis of the liver, but thrombosis can also be the cause (TonyI. Oliver; Bashar Sharma; Savio John. NCBIBookshelf. A service of the National Library of Medicine, National Institutes of Health. StatPearls [Internet]. PortalHypertension. 2022). The development of PG occurs due to an increase in vascular resistance and an increase in blood volume in the portal vein. Blood is also deposited in the spleen, which leads to the formation of collateral blood circulation through portocaval anastomoses. One of the most dangerous complications of PG is the formation of anastamoses . These anastomoses are the formation of anastomoses that transfer portal blood through the common vein and the left main gastric vein to the thin-walled submucosal venous tangles of the lower third of the esophagus and the gastric cardia, as well as the portal formed on the anterior abdominal wall, around the rectum, and between the splenic and left hepatic veins. and inferior cava are anastomoses between venous systems. As J Ts develops, it leads to the expansion of these anastamoses and the risk of bleeding (PanZ, WuXJ, LiJS, LiuFN, LiWS, HanJM. Functional hepatic flow in patients with liver cirrhosis . *World J Gastroenterol* 2004; 10 :915–8 .). Esophageal and gastric varices (VVK) usually occur when the pressure gradient exceeds 10 mm Hg, and variceal bleeding occurs when the gradient of varices exceeds 12 mm Hg . According to the World Association of Gastroenterology , risk factors for the development of varicose veins are defined as: MNO> 1.5; portal vein diameter > 13 mm; thrombocytopenia.



Classification of portal hypertension.

In 1974 M. D. Patsiora proposed the following classification of portal hypertension (Cirrhosis pecheni i portalnaya hipertensiya / A. E. Borisov, V. A. Kashchenko. — SPb., 2009. — 112 p.):

1. **According to the form** portal hypertension is divided into portal or segmental types. PG is classified according to the distribution of the high pressure field. In the portal form, the entire network of the portal system is damaged, and in the segmental form, blood flow is disturbed only in the splenic vein.
2. **According to localization:**

- **Prehepatic - suprahepatic.** The pathological process occurs as a result of damage and increased pressure in the portal vein or splenic vein.
- **Intrahepatic - inside the liver.** A common form often preceded by presinusoidal, postsinusoidal or sinusoidal block.
- **Posthepatic - subhepatic** . It is usually caused by thrombosis and damage to the portal vein (Baddi-Chiari syndrome, Baddi-Chiari disease).
- **Mixed form.** It can develop if the cause of the condition is cirrhosis of the liver and thrombosis of the portal vein.

Clinical signs of portal hypertension.

- Flatulence - accumulation of excess gas in the intestines;
- unstable stool;
- decreased appetite;
- feeling of stomach fullness;
- nausea, sometimes vomiting;
- pain in the right subcostal area;
- quick fatigue;
- jaundice;
- weight loss etc.
- **Enlargement of the spleen (splenomegaly)** is also a sign of pathology.

After bleeding from the organs of the gastrointestinal system, the volume of the

organ decreases as a result of the decrease in pressure in the portal vein. Due to the accumulation of ascites fluid in the abdominal cavity, the volume of the abdominal cavity increases, the ankles swell, and the branching of vessels similar to the visible "jellyfish head" is visible on the anterior abdominal wall. Portal hypertension has no specific symptoms, but manifests itself only as a complication. With the accumulation of ascitic fluid, the volume of the abdominal cavity increases, which is accompanied by pain. An enlarged spleen can give the patient a feeling of discomfort or heaviness in the left side of the abdomen (PodymovaS.D. Bolezni pecheni: rukovodstvo dlya vrachey. Izd. 5-e, pererab.idop. M.: Med. Informatsionnoe agenstvo, 2018) . As a result of damage to enlarged varicose veins, bleeding occurs from the esophagus, stomach and hemorrhoidal veins. Depending on which part of the gastrointestinal system is bleeding, vomiting with blood and dark-colored clots may appear. When bleeding from enlarged varicose veins in the rectum, the presence of blood in the stool is observed. Heavy profuse bleeding from dilated varicose veins in liver cirrhosis increases the risk of death.

- **Ascites** is a pathological accumulation of fluid in the abdominal cavity. Ascites is one of the most common complications of liver cirrhosis, and its development is a sign of severe portal hypertension. Ascites with a volume of more than 1.5 liters can usually be detected during a physical examination. The development of ascites in cirrhosis of the liver is caused by: a decrease in blood volume (despite a compensatory increase in cardiac output), narrowing of renal vessels, followed by sodium retention and extracellular fluid retention (2,3,18).

As ts it development. The main reason for the accumulation of ascites fluid in the abdominal cavity is sodium retention in the body due to the expansion of the vessels of the abdominal organs as a result of a significant decrease in arterial blood flow. Activation of arterial and cardiopulmonary volume receptors then occurs , leading to compensatory activation of vasoconstrictor and sodium-retaining systems, namely, the sympathetic nervous system and the renin-angiotenzin-aldosterone system (RAAS). As a result of sodium retention by the kidneys, it leads to an

increase in the volume of extracellular fluid and the appearance of ascites and edema (5,8,23).

IAC (International Ascites Club, 2003) classification of the level of development of As ts it

Table 3.

As ts it degrees	Explanation
Level I	ts it , which is not expressed clinically , can be determined only by ultrasound
Level II	Moderately expressed as ts it is determined by a symmetrical enlargement of the abdomen on physical examination.
Level III	A pronounced as ts it is determined by abdominal tension.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a brain dysfunction resulting from acute and chronic liver disease that causes a range of neuropsychiatric symptoms in the absence of other nervous system disorders. (12,26,44). American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) according to the guidelines, Hepatic encephalopathy is defined as "a brain dysfunction caused by liver failure and / or portosystemic shunting , with a broad spectrum of neurological/psychiatric abnormalities that can range from subclinical changes to coma ." (AASLD-EASL guideline, Hepatology 2014 In Press). Many complications of liver cirrhosis, including the development of liver encephalopathy, can lead to a decrease in the patient's life expectancy and quality of life. The presentation and prevalence of hepatic encephalopathy (HE) are related to

the degree of liver failure and portasystemic shunting. 10-14% of the total number of patients with HE with pronounced symptoms at the time of diagnosis of liver cirrhosis. Overall, severe HE occurs in 30-40% of patients with cirrhosis, while minimal or latent HE has been shown to occur in 20% to 80%.

According to the 2014 guidelines of the American and European Association for the Study of the Liver, JE is defined as "cerebral dysfunction caused by liver failure and/or portosystemic shunt, characterized by neurologic or psychiatric changes that may progress from subclinical symptoms to coma." The term "encephalopathy" means diffuse changes in the brain, which can develop in many diseases and, accordingly, its various types are distinguished (hyperglycemic, dyscirculatory, perinatal, hypertensive, hepatic encephalopathy , etc.). Of these, the sum of changes in the brain as a result of liver diseases means hepatic encephalopathy.

Pathophysiology of hepatic encephalopathy

Under normal conditions, the intestinal excretion of ammonia leads to an increase in portal venous ammonia levels. The microbiota is also responsible for the formation of ammonia and endotoxins. In cirrhosis, the liver cannot extract ammonia from the portal vein. An increase in arterial blood ammonia levels then leads to an increase in ammonia in other tissues. Neither the brain nor the muscles have a complete cycle of urea and rely on the production of glutamine. Thus, the brain and muscles become organs that absorb ammonia and release glutamine. In the brain, astrocytes metabolize ammonia using glutamine synthetase, which converts glutamate and ammonia to glutamine, which is osmotically active and promotes the movement of water into the astrocytes , causing intracellular swelling and edema. Ammonia is the main agent in protein metabolism (58,61). U a person in the diet consumption to be done amino acids and of purines bacterial metabolism as a result work is issued . Physiological in the circumstances to 90% of ammonium near basically in the liver (Krebs in the cycle) urea synthesis through is released , then while kidneys and less level muscles through is issued .

Hyperammonemia in liver cirrhosis is caused by two factors: the first is a decrease in the number of healthy hepato ts dogs, which leads to a deficiency of NH3 detoxification; second, the presence of porto-systemic shunting, which leads to systemic circulation without hepatic detoxification of ammonia-rich portal blood, followed by extrahepatic ammonia exchange by brain and skeletal muscle cells. Skeletal muscles play an important role in ammonia metabolism because they contain glutamine synthetase , but muscle atrophy that occurs with progressive cirrhosis of the liver can exacerbate hyperammonemia. The kidneys produce glutaminase and play a role in ammonia production to some extent. Similarly, the kidneys play a key role in the production of glutamine synthetase and in the metabolism and excretion of ammonia . Ammonia crosses the hemato e n ts ephalic barrier and is metabolized by glutamine synthetase in astro ts dogs, which converts NH3 and glutamate to glutamine. In astrocytes , increased glutamine creates an osmotic gradient, favoring the passage of water into astrocytes , leading to edema and the formation of reactive oxygen species, thereby leading to the development of brain dysfunction seen in HE. (4,17,22) .

High energy consumption for this process leads to oxidative stress, which is accompanied by cell dysfunction and disruption of neurotransmission mainly of glutamate and γ-aminobutyric acid. In the brain, NH3 leads to inactivation of neuronal chloride extrusion pumps; these processes lead to paralysis of both axonal conduction and excitatory postsynaptic potentials , subsequently suppressing the formation of postsynaptic potentials and depolarizing neurons. Thus, ammonia plays a central role in the pathogenesis of HE . Under physiological conditions, ammonia is mainly removed by the synthesis of urea in the liver (2,16,48). If liver function is impaired or there is a portosystemic shunt, this function is impaired and extrahepatic ammonia exchange in the brain and muscles becomes more important. Ammonia accumulation in the brain of patients with minimal hepatic encephalopathy (MHE) is determined directly by positron emission ion tomography (PET). Astrocites are the only brain cells in dogs that can fix ammonia through the formation of glutamine. In astrocites, intracellular glutamine concen tration

increases with blood ammonia levels and causes cell swelling due to osmosis . In general, this leads to the development of a mild brain tumor, which is associated with the deterioration of psychometric parameters. Ammonia is mainly produced in the large intestine by the breakdown of amino acids and urea by bacteria. Ammonia is taken up by the liver in dogs and converted to urea, which enters the blood stream in the urea cycle. Urea is mainly excreted by the kidneys (75%) and intestines (about 25%). But studies have shown that the severity of MHE may not be related to the severity of liver disease or the level of ammonia, which suggests the presence of other pathogenic stimuli, not just ammonia, in the development of HE.

Factors that cause the development of liver encephalopathy :

1. Bleeding in the gastrointestinal system;
2. infections;
3. Dehydration as a complication of diuretic therapy ;
4. vomiting;
5. diarrhea ;
6. constripation;
7. hyponatremia;
8. hypo- and hyperkalemia;
9. Benzodiazepine, drug use;
10. Shunt injection (TIPS);
11. Stomach softeners (Lactuloza), etc.

In some cases, patients with cirrhosis of the liver develop liver encephalopathy, even if the amount of ammonia in the blood is normal. This situation indicates that in the development of HE, not only the increase in blood ammonia concentration, but also the presence of factors that can cause additional HE. Examples include low sodium levels in the blood, increased levels of inflammatory cytokines in the blood due to inflammation or injury , diuretics, or sedative medications. For these reasons, astrocytes in patients with liver cirrhosis become swollen, leading to dehydration of osmolytes (33, 55). In addition, the increase in the amount of aromatic amino acids (tryptophan, tyrosine) and their

absorption into the brain also develops encephalopathy due to the deficiency of branched chain amino acids and the partial increase in the permeability of the hemato-encephalic barrier. An increase in inhibitory substances (serotonin, dopamine) leads to a violation of neuron transmission. When nerve transmission dysfunction occurs, patients experience fine motor disorders, i.e. impairment of fine motor skills.

The diagnosis of HE is based on the results of clinical observations, laboratory and instrumental research methods. The diagnosis of overt HE is made based on clinical signs and, of course, by excluding other disorders that may cause mental disorders in the patient. For example, the most common other causes of encephalopathy include: conditions related to the side effects of various drugs, severe electrolyte disturbances (hyponatremia and hypercalcemia), uremia, systemic infection, central nervous system infection, psychiatric disorders, alcoholism, hypoglycemia, hypercapnia, nonconvulsive epilepsy and intracranial hemorrhage or stroke.[2,4]

In the process of diagnosing HE, the physician must classify the type and severity of encephalopathy. In most cases, the West Haven criteria are the gold standard for assessing the severity of HE. The *West-Haven* criteria mainly evaluates the severity of hepatic encephalopathy based on the clinical signs of expressed HE from 0 (no clinical signs of HE) to 4 (coma). [9,10] However, the Glasgow Coma Scale is widely used in the diagnosis of severe encephalopathy and critically ill patients with marked mental impairment.

The diagnosis of minimal hepatic encephalopathy, which is not clinically expressed, requires specific psychometric tests, because the detection of latent (minimal) HE cannot be determined based on clinical symptoms alone [11,12,13]

Classification of hepatic encephalopathy.

As medicine progresses, the sensitivity of diagnosing diseases also increases, and many changes are made to the classification of HE from year to year. In the 1970s,

after the introduction of the "Number connection test" into medical practice, the latent or latent form of HE, which is not clinically expressed, was added. In 2002, *Ferenci et al.* distinguished 3 types of HE: latent, episodic, and persistent. At the suggestion of some scientists, in 1998, a proposed classification of HE was published at a congress of specialists in hepatology. According to him, hepatic encephalopathy was divided into the following types (Table 4):

Table 4.

Depending on the damage to the liver, JE is divided into three types:	
A type (Acute)	- observed in acute liver failure;
B type	- occurs in portosystemic shunting of blood, but there is no liver disease;
S type (Cirrhosis)	- occurs in patients with liver cirrhosis, portal hypertension, and portosystemic bypass surgery

Hepatic encephalopathy clinic

Hepatic encephalopathy is the result of toxic effects of nitrogen compounds on the central nervous system. In normal healthy people, the final product of this metabolism - ammonia - is inactivated by the liver (Tianzuo Zhan, Wolfgang Stremmel. The Diagnosis and Treatment of Minimal Hepatic Encephalopathy. Deutsches Ärzteblatt International | Dtsch Arztebl Int 2012; 109(10): 180–187). A clear proof of this is that, as a result of experimental investigations, therapeutic procedures aimed at neutralizing protein metabolites or removing them from the body have been confirmed with positive effectiveness in the initial stages of hepatic encephalopathy and in the treatment of coma. Hepatic encephalopathy can

complicate liver failure in almost all known acute and chronic liver diseases. HE is caused by exposure to the central nervous system of neurotoxic substances, which are formed in the gastrointestinal tract (GI) and are usually metabolized in the liver.

Hepatic encephalopathy, which develops as a result of LC, leads to the development of the following clinical manifestations: disturbance of consciousness, sleep disturbance: first of all, drowsiness appears, then sleep and wake rhythm disturbances; up to delirium, personality changes, sometimes euphoria, mood swings, irritability even for trivial reasons; It is manifested by intellectual disorders, which are manifested by decreased attention, inability to concentrate, disorientation in relation to time and place, decreased ability to calculate arithmetic, impaired handwriting and writing, and an increase in the time required to perform the Reitan test for connecting numbers.Speech can slow down to the level of dysphasia (38,59).

The West-Haven-Criteria (WHC) for differentiating the severity of HE was used by *Conn et al.* Based on the criteria, there are five levels of hepatic encephalopathy (table. 1):

0 stage: Minimal HE- patients have mild impairment of attention and concentration, memory, visual-spatial perception and fine skills. Since these symptoms cannot be determined by clinical examination, additional methods such as psychometric tests should be used.

Level 1: patients experience changes in sleep patterns, mood swings, and patients make mistakes in simple arithmetic problems. But orientation is completely preserved in patients.

Level 2: patients have a clear thinking disorder, disorientation in relation to time. Asterixis, hyperreflexia and dyspraxia are observed.

Level 3: patients suffer from a high level of consciousness disorder with insomnia and disorientation. The reaction to painful stimuli is preserved.

Level 4: patients are in a comatose state, loss of consciousness, loss of pain response is observed.

Neuropsychiatric disorders observed in hepatic encephalopathy

Hepatic encephalopathy is manifested by a wide range of nonspecific neurological and psychiatric symptoms. As the disease progresses, clinical symptoms become more obvious. Such signs may include personality disorders, changes in sleep cycles, apathy, disorientation in relation to time and place, inappropriate behavior of patients, confusion of consciousness. Such changes are noticed first of all by the close relatives of patients at home. Patients may also have motor abnormalities, such as hyperreflexia, positive Babinski reflex, and hypertonus. In the case of coma, deep tendon reflexes may decrease or disappear altogether (12,19,33). From the early stages of HE, tremor-asterixis, a variant of negative myoclonus, rather than tremor, can be observed. Negative myoclonus is characterized by sudden, involuntary, irregular, short and rapid movements of muscle activity. Asterixis in HE is usually bilateral in nature, but the strength of irregular movements in the hands is asymmetrical, more pronounced on one side than the other. During asterixis in HE, the oscillation frequency of this hyperkinesis is 1-2 per second (7,40,52). Asterixis is characterized by intensification when the patient extends his arms. Another method of detecting this phenomenon is proposed: the patient squeezes two fingers of the researcher with his palm, and if the patient has asterix, the researcher feels how the compression force changes from time to time. Asterixis is a characteristic clinical sign of HE, but it is not a pathognomonic sign observed only in HE, because asterixis can also be observed in pathological conditions such as cerebral hypoxia, hypercapnia, uremia, heart failure. It should be noted that at the time of examination, the patient may not have the characteristic asterixis sign of HE. (7,45,61). In the pronounced stages of HE, significant disturbances in attention and memory, changes in speech and writing, constructive apraxia, acalculia, psychomotor disorders, dysarthria and dysphasia, disorientation, confusion, behavioral disorders, and apathy are characterized. With the development of the pathological process (including the development of coma), there is a loss of deep reflexes, a decrease in muscle tone.

Results of physical examination of patients.

We used psychometric testing (number connection test and linear test) and psychoemotional tests (Beck scale, MMSE - short cognitive state assessment scale) to assess the level of depression and panic in patients. Clinical signs in HE are very diverse in terms of presentation and can range from minimal changes in the patient's behavior to coma. In the early stages, patients may have mild behavioral disturbances and cognitive impairments, which are more noticeable by the patient's relatives and friends than by the doctors examining the patient. In HE, regardless of whether psychomotor disorders are clinically manifested or not, patients have impaired attention, slowing down of the speed of psychomotor processes. In such cases, when HE is hidden, it can only be determined using psychometric tests.

Characteristics of clinical signs characteristic of hepatic encephalopathy and their frequency of occurrence in different severity levels of HE

Table 5.

HE degrees / Main clinical symptoms	HE observed sick patients n = 27	0- I degree n = 45	II degree n = 43	III degree n = 17
Cognitive dysfunction	1 (3.70%)	10 (22.22%)	26 (60.46%)	13 (76.47%)
Coordination disorder	0 (0%)	7 (15.55%)	18 (41.86%)	14 (82.35%)
Sleep disturbance	0 (0%)	5 (11.11%)	27 (62.79%)	17 (100%)
Loss of consciousness	0 (0%)	0 (0%)	14 (32.56%)	8 (47.05%)
Intellectual disability	0 (0%)	14 (31.11%)	25 (58.13%)	7 (41.17%)
Personality change	0 (0%)	0 (0%)	1 (2.32%)	8 (47.05%)
Speech disorder	0 (0%)	8 (17.77%)	20 (46.51%)	16 (94.11%)
Change of character	2 (11.76%)	17 (31.11%)	28 (65.11%)	17 (100%)
Asterixis	0 (0%)	5 (11.11%)	15 (34.88%)	12 (70.58%)

As can be seen from the table, clinical symptoms of HE are manifested in different proportions in different degrees of liver cirrhosis. For example, there were 27 patients without liver encephalopathy, of which 1 (3.70%) had cognitive dysfunction and 2 (11.76%) had mood changes. The 0-I level of HE was determined in 45 patients, and 10 (22.22%) of them had cognitive impairment, 7 (15.55%) had coordination disorders, 5 (11.11%) had sleep disorders, 14 (31.11%) had 1 person had intellectual disorders, 8 (17.77%) had speech disorders, 17 (31.11%) had personality changes, and 5 (11.11%) had asterixis. Grade II HE was observed in 43 patients, of which 26 (60.46%) had cognitive disorders, 18 (41.86%) had coordination disorders, 27 (62.79%) had sleep disorders, 14 (32.56%) had consciousness disorder, 25 (58.13%) intellectual disorders, 1 (2.32%) personality disorder, 20 (46.51%) speech disorders, 28 (65.11%) mood changes and 15 (34.88%) had asterixis. Level III HE was detected in 17 patients, 13 (76.47%) of them had cognitive impairment, 14 (82.35%) had coordination disorders, 17 (100%) had sleep disorders, 8 (47.05%) had consciousness disorders, 7 (41.17%) intellectual disorders, 8 (47.05%) personality disorders, 16 (94.11%) speech disorders, 17 (100%) mood changes and 12 (70.58 Asterixis was detected in %). So, as the severity of the disease increases, the number of clinical symptoms increases, they become more obvious, and they are accompanied by dangerous symptoms such as personality disorders and changes in consciousness.

Diagnosis of hepatic encephalopathy.

The diagnosis of hepatic encephalopathy is made in patients with liver failure and clinical signs of HE, while other alternative causes of encephalopathy must be excluded in order to confirm this diagnosis in patients. In the development of liver encephalopathy, changes similar to the pathology of the hepatobiliary area are also observed. For example, "liver odor" and hyperventilation are often observed in patients with HE. [11]. The presence of JE risk factors (gastrointestinal bleeding, constipation, infection, etc.) also confirms this diagnosis. The European and American Association for the Study of the Liver (AASLD-EASL) experts recommended that the presence of disorientation and asterixis in patients is an

important diagnostic criterion for the diagnosis of pronounced HE. But in recent times, the West-Haven scale is considered the "Golden Standard" in the diagnosis of HE and is widely used in clinical practice. In order to determine the depth of coma in comatose patients, the Glasgow scale is recommended. In the Glasgow scale, scores are calculated depending on the response of patients to external influences.

West Haven criteria . Until recently, there was no consensus on diagnostic criteria, and thus there was much confusion regarding the nomenclature and classification of HE. Most of these were resolved after the first consensus conference at the 11th World Congress of Gastroenterology in Vienna in 1998, which published its consensus comprehensive definition and classification of HE in 2002. Nevertheless, the subject of HE classification and nomenclature continued to be a subject of debate and modification. In 2011, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) published a consensus statement describing the recommended classification and nomenclature of HE. The primary objective of the consensus was to review the current classification and develop consensus guidelines for the design and conduct of future clinical trials. This has led to a more practical, descriptive classification system that incorporates clinical aspects of patients with HE and has implications for research trials. A joint AASLD-EASL task force has summarized its guidelines for the management of HE associated with chronic liver disease (11,28,31).

The clinical diagnosis of clinically expressed HE is based on a combination of mental, neuro-psychic disorders, asterixis, hyperreflexia and neuromotor function disorders such as hypertonus and can be determined only after excluding other causes of mental state changes. HE mental status disorders are classically classified according to the West-Haven criteria (**West-Haven criteria**), which are classified from HE grade I to IV based on various clinical indicators such as changes in the level of consciousness, intellectual function and behavior, as well as the presence or absence of asterixis (18,27,60). The presence of disorientation and asterixis is considered a clear cutoff between minimal and expressed HE. Studies have shown that the reliable presence of advanced HE can be determined by using "disorientation

over time" as a criterion for grade II HE. The term "minimal HE" is a latent HE condition that is not clinically evident and can only be detected by specific psychometric or neurophysiological tests, replacing the older term "subclinical HE". Despite the absence of clinically apparent signs or symptoms, minimal HE has been found to have a significant impact on the quality of life of a patient with chronic liver disease. Most importantly, minimal HE predicts future onset of overt HE. Therefore, early detection of HE in the latent period and timely initiation of treatment in patients with cirrhosis of the liver leads to the improvement of the ability to perform complex tasks, the prognosis of the disease and the quality of life of the patient (*Conn HO Hepatic encephalopathy. In: Schiff L., Schiff ER, editors. Diseases of the Liver, 7th ed., Philadelphia: 1036–1060.)*

Table 6

According to the West-Haven classification, hepatic encephalopathy is divided into 4 stages:

Stage	Clinical signs
0 (minimal encephalopathy)	Basically, it is characterized by the absence of clinically obvious neurological symptoms and disorders. They are identified and diagnosed only with the help of special neuropsychological tests (number association test, number-letter test, alphabet test, etc.).
Stage I	It is mainly characterized by sleep disorders: sleep inversion, hypersomnia, insomnia. It is characterized by emotional lability: depression, euphoria, irritability, anxious movements. This stage is characterized by a decrease in the ability to perform mental tasks, a decrease in the ability to memorize. Also, the writing function is impaired, tremors, constructive apraxias are observed.
Stage II	This basically intellectual of disorders the first stage appear to be of symptoms increase , lethargy and / or apathy , speech incomprehensibility , intellectual tasks perform of ability progressive deterioration with is described . A sterixis appear will be - trembling , Shivering , that's it the brain dysfunction with depends problem
Stage III	This stage mainly , time and to the place relatively significant disorientation , drowsiness , confusion , amnesia , speech disorder , mental tasks do it not getting , getting angry and e extrapyramidal disorders with increases .

Stage IV	pain response in hepatic coma . In coma, lethargy and sleepiness occur as a result of damage to the astrocytes . Clonus of the muscles of the neck and limbs and decerebral rigidity appear. Clonus of leg muscles, pathological reflexes (Zhukovsky, Gordon, Babinsky) are detected. Some patients with prolonged coma experience stereotypic (grasping, chewing, sucking, etc.) movements.

All patients were examined by a neuropathologist in order to identify signs of underexpressed movement disorders that can develop in liver encephalopathy: dysarthria, decreased movement speed, increased deep tendon reflexes, hypomimia, ataxia, tremor, asterixis, increased tone, and changes in sensation. Also, with the help of a neuropathologist's examination, other causes of encephalopathy in these patients (such as cerebral circulation disorders, subdural hematoma) were excluded.

Glasgow Coma Severity Scale

The Glasgow Coma Scale (Glasgow Coma Scale) was first used in 1974 by *Graham Teasdale, professor of neurosurgery at the University of Glasgow.* and Published by *Bryan Jennett (Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974 Jul* y 13;2(7872):81-4). Glasgow Coma Scale used in all types of emergency medical situations and traumas, to objectively assess the level of unconsciousness in patients in a short period of time. Patients score on three aspects of perception: eye opening, movement , and verbal responses. Each of them is scored separately . Findings from each component of the scale can be summed into a total Glasgow Coma Score . The sum of the points is taken and the level of consciousness disorder is diagnosed.

Signs	Ball
1. Eye - opening reaction to impressions	
E rkin	**4**
When addressed	**3**
Only to pain	**2**
The answer is no reaction	
2. Verbal response reaction	
Orientation is fully preserved	**5**
Speech is slurred	**4**
words are incomprehensible	**3**
Only sound, words are not separated from each other	**2**

The answer is no reaction	
3. Action reaction	
Being able to follow orders	**6**
Localization of effect	**5**
Pick up	**4**
Pathological choking reaction (decortication)	**3**
Pathological writer 's reaction	**2**

Summary analysis based on the results of the accumulated points: it is the sum of the maximum points - from 3 to 15.

- maximum score-15;

- mild disturbance of consciousness (stupor) -13-14 points;

- deep disturbance of mental state (sopor) -11-13 points;

- deep coma-less than 11 points.

In this case, the patients' ability to open their eyes to different sounds, or to react to simple external influences is checked. It is also taken into account that before the coma patients had disorders of the state of consciousness, such as sopor, stupor . Experts of the European and American Association for the Study of the Liver (AASLD -EASL) recommend conducting various neurophysiological and psychometric tests in patients to determine latent (minimal) HE . These are simple pen-and - paper tests (number association test, line test, alphabet test , etc.), as well as computerized tests (Stroop test, response time delay test, SCAN test) and neurophysiological (electroencephalography) tests. recommended for diagnosis [1]. The clinical presentation of HE is characterized by impairment of consciousness, intelligence, motor skills, personality, and speech. This classification allows for the assessment of 5 components of HE: intellectual-behavioral status, asterixis ("clapping" tremor"), speed of performing the test of association of numbers, changes in the electroencephalogram, and the level of ammonia in the blood. These indicators are described in detail in the West-Haven classification.

There are several diagnostic methods in the diagnosis of HE, but recently, more attention has been paid to determining the levels of HE according to the West-Haven criteria and it is widely used in practice.

Until recently, there was no consensus on diagnostic criteria, and thus there was much confusion regarding the nomenclature and classification of HE. Most of these

were resolved after the first consensus conference at the 11th World Congress of Gastroenterologists in Vienna in 1998, which published its comprehensive definition and classification of JE in 2002. Despite this, the debate on the subject of classification and nomenclature of JE continues (7,18,37) . In 2014, a joint task force of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) summarized all guidelines on HE associated with chronic liver disease. The clinical diagnosis of pronounced HE is based on a combination of neuropsychological disorders and neuromotor function disorders such as asterix, hyperreflexia, and hypertonus, and can be determined only after excluding other causes of mental state changes. In HE, one or another level of mental disturbance is classically classified according to the West Haven criteria, which is classified from HE grade I to grade IV based on various clinical indicators, such as changes in the level of consciousness, intellectual ability and behavior, as well as the presence or absence of asterix (table) . Before the West Haven criterion was used, the Glasgow scale was used in clinical practice. But the Glasgow scale is currently used only in neurosurgery and acute brain trauma to quickly and briefly determine the severity of coma.

In our study, the Glasgow scale and the West-Haven criteria were simultaneously used to assess the state of consciousness of patients, and the sensitivity and specificity in determining the level of the pathological process between the two methods were determined in the diagnosis of levels of hepatic encephalopathy. Analysis of sensitivity and specificity (specificity) of test methods allows to evaluate the efficiency of one or another test method/test. It was calculated using the additional statistical program XLSTAT in Excel . Several parameters are taken into account when determining the sensitivity and specificity of a certain diagnostic method:

A ***true positive result (TP - "True positive"):*** the number of cases in which the test method was found to be positive and which were actually positive.

False positive result (F P - "False positive"): the number of cases in which a test or test method is declared positive, but is actually negative.

True negative result (TN -"True negative"): the number of cases in which the test or test method is negative and is actually negative.

False negative result (FN - "False negative"): the number of cases in which the test or examination method is negative, but in fact there is a positive pathological condition.

Sensitivity (Sensitivity) - this is to determine the percentage of patients who have a real disease through a certain examination method or test (Moore CL , Amen J , Gidding HF , Law MG (2014) A New Method for Assessing How Sensitivity oath Specificity of Linkage Studies Affects Estimation . PLoS ONE 9(7): e 103690. https :// doi . org /10.1371/ journal . pone .0103690). Sensitivity is equivalent to true positive results and is determined by the following formula:

Sensitivity = True Positives / (True Positives + False Negatives).

This formula through sensitivity to determine for real positive of results total results to the number relatively division through is considered

Table 7.

Of the disease existence or non- existence / Check method is positive or negativity	**Disease present (+)**	**Disease not present (-)**
Positive (+)	True Positive (TP)	False Positive (FP)
negative (-)	False negative (FN)	Real negative (TN)

Specificity (specificity) is the correct identification of healthy individuals by a certain screening method or test, determined against false positive results (Moore CL, Amin J, Gidding HF, Law MG (2014) A New Method for Assessing

How Sensitivity and Specificity of Linkage Studies Affects Estimation. PLoS ONE 9(7): https://doi.org/10.1371/journal.pone.0103690 . Specificity is the percentage of healthy people without the disease and is determined by the following mathematical formula:

Specificity = True Negatives / (True Negatives + False Positives).

In this real negative to the results relatively , real negative and fake positive results amount is taken .

In our scientific study, we determined the degree of hepatic encephalopathy in patients with liver cirrhosis based on the Glasgow coma scale and West Haven criteria, and determined the specificity and sensitivity of both diagnostic methods in determining HE. The total number of patients with cirrhosis of the liver is 136, of which 30 have no symptoms of HE, clear consciousness, no cognitive disorders. 106 have symptoms of HE of various degrees. In our Glasgow Coma Scale assessment, 70 patients were rated as lucid and 66 were found to have varying degrees of JE symptoms. In 4 patients diagnosed with HE, psychometric tests, Beck's scale, EEG, analysis of ammonia levels in blood revealed that the patients did not have JE. When we assessed HE using the West Haven criteria, 102 patients (of 106) were found to have HE, and 4 had a false-negative result. A true negative result was obtained in 28 patients and a false positive result was obtained in 2 patients.

Table 8.

Test methods in the diagnosis of HE	**West-Haven Criterion**	**Glasgow scale**
Sensitivity	96%	62%
Specificity	93%	86%

As can be seen from the table, the sensitivity and specificity of the West-Haven criteria in the diagnosis of HE was 96%, and the specificity was 93%, which means that the diagnosis based on the West-Haven criteria is less prone to errors. According to the Glasgow coma scale, the sensitivity was 62%, and the specificity was 86%. Therefore, our scientific study found that the diagnosis based on the West-Haven criteria provides more and more accurate information in the accurate and correct assessment of HE.

The mental state, cognitive activity and neuropsychological changes during the course of the disease using the following ***scales*** .

Beck scale - is used to assess depression in patients, and is carried out for the purpose of quantitative assessment as a result of clinical observations before and after treatment. This method was created by the American psychiatrist Aaron Beck in 1961 (Beck AT et al. Beck depression inventory (BDI) //Arch gen psychiatry. - 1961. - T. 4. - No. 6. - S. 561-571.) . The sum of points: 0-12 is a normal indicator, 14-19 is mild depressive disorders, 20-28 is moderate depressive states, 29-63 is marked depressive states, 63< is considered severe depressive states.

The Beck scale is a questionnaire containing 21 different categories of the most common symptoms and complaints in patients suffering from depression. The questionnaire is filled out by the patient himself. Each category item on the Beck scale is rated from 0 to 3 points, with a total score from 0 to 62. Test results on this scale are evaluated according to:

0 to 9 - no symptoms of depression;

10 to 15 - mild depression;

16 to 19 - moderate depression;

From 20 to 63 - severe depression.

All patients in the main group were administered a Beck depression questionnaire test on the day of hospitalization, that is, before treatment. The Beck scale results were as follows:

Beck scale test results .

Table 9.

Depression level	Number of patients (n=%)
No signs of depression	18 (13.2%)
Mild depression	47 (34.6%)
Moderate depression	41 (30.1%)
Severe depression	30 (22.1%)

MMSE test (Minimental State Examination, MMSE) - a short cognitive state assessment scale - consists of 30 parts used to determine cognitive disorders, in particular dementia. This scale includes tests of orientation, concentration, attention, verbal memory, naming, and visual acuity. (Folstein 1975). Also MMSE It is also used to evaluate the effect of the treatment. This scale was developed in 1975 and later modified for practical use. (Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12(3):189-98. [PMID:] [PubMed] [Google Scholar]

A short examination of cognitive functions - MMSE test (Mini-Mental State Examination).

Cognitive sphere	Max. score
Ask the patient to name the full year, season, date, day of the week, month. The maximum score (5) is given if the patient names the day, month and year independently and correctly. Each wrong answer or no answer reduces the score by 1 point.	5
Ask the patient: "Where are we?" The patient must clearly state the name of the country, region, city, institution, floor where the survey is being conducted. Each wrong answer or no answer reduces the score by 1 point.	5

Instruct the patient: "Repeat and try to remember three words: apple, table, coin." You must pronounce the words as accurately as possible at a rate of one word per second. The correct repetition of the word by the patient is scored one point for each of the words.	3
7 from 100 in a row , five subtractions are enough (up to 65 results). Each wrong answer reduces 1 point . If the patient is unable to perform this task, ask him to say the word " sky " backwards. Each wrong answer reduces the score by 1 point.	5
recall the words memorized in step 3 . Each correctly named word is worth 1 point.	3
Show the patient 2 simple objects, such as a pen and a watch, and ask them to name them.	2
Ask the patient to repeat the following sentence: “Any, if, and, or but"	1
Give the patient a piece of paper and ask him to follow your commands in sequence: "Take the paper in your right hand, fold it in half and put it on the table"	3
Ask the patient to do the task written on the paper: "close your eyes"	1
Ask the patient to independently write the desired phrase (the phrase must consist of a possessive and a participle)	1
Give the patient a piece of paper and ask him to repeat the picture below. If the patient can draw all 10 angles represented on the paper, the task is considered completed .	1

The test usually takes 10 minutes, during which a person's arithmetic abilities, memory and attention span are briefly assessed.

The resulting scores are interpreted as follows:

29-30 points - no mental and neurological disorders;

28 - 25 points - there is a cognitive impairment;

20-24 points - mild dementia;

10-19 points - moderate dementia;

score below 10 is severe dementia

One of the advantages of this method is that it takes 10 minutes to complete the test, and it also evaluates the arithmetic skills, memory and orientation of a person.

A question-and-answer session between the doctor and the patient is not enough to make a diagnosis of minimal hepatic encephalopathy. At this stage of HE, patients have mild cognitive impairment, and laboratory analysis, computer tomography or magnetic resonance imaging of the brain also give us little information. Psychometric and neuropsychological tests are the most informative and highly sensitive diagnostic method in MHE.

Psychometric tests

Psychometric tests are mainly used to detect minimal or latent HE and to detect detailed mental disorders in the early stages of hepatic encephalopathy. Many simple psychometric tests have been developed for early screening of HE, and these tests can be used in various combinations. For example, number linking test, copying test, letter test, etc. Two groups of tests are distinguished: tests for cognitive reaction speed and tests for the accuracy of fine motor skills. For example, the digit association test, which is widely used in clinical practice, is often used. With the help of this test, the examined patient connects numbers from 1 to 25, randomly written on paper, in the correct sequence in a certain time interval with a pen or pencil. Evaluation of the test - the time spent by the patient to complete it, including the time needed to correct errors, is taken into account. The sensitivity of psychometric tests in detecting minimal hepatic encephalopathy (MHE) is 70-80%. (*Tianzuo Zhan, Wolfgang Stremmel . The Diagnosis and Treatment of Minimal Hepatic Encephalopathy . Deutsches Ärzteblatt International | Dtsch Arztebl Int 2012; 109(10): 180–187).*

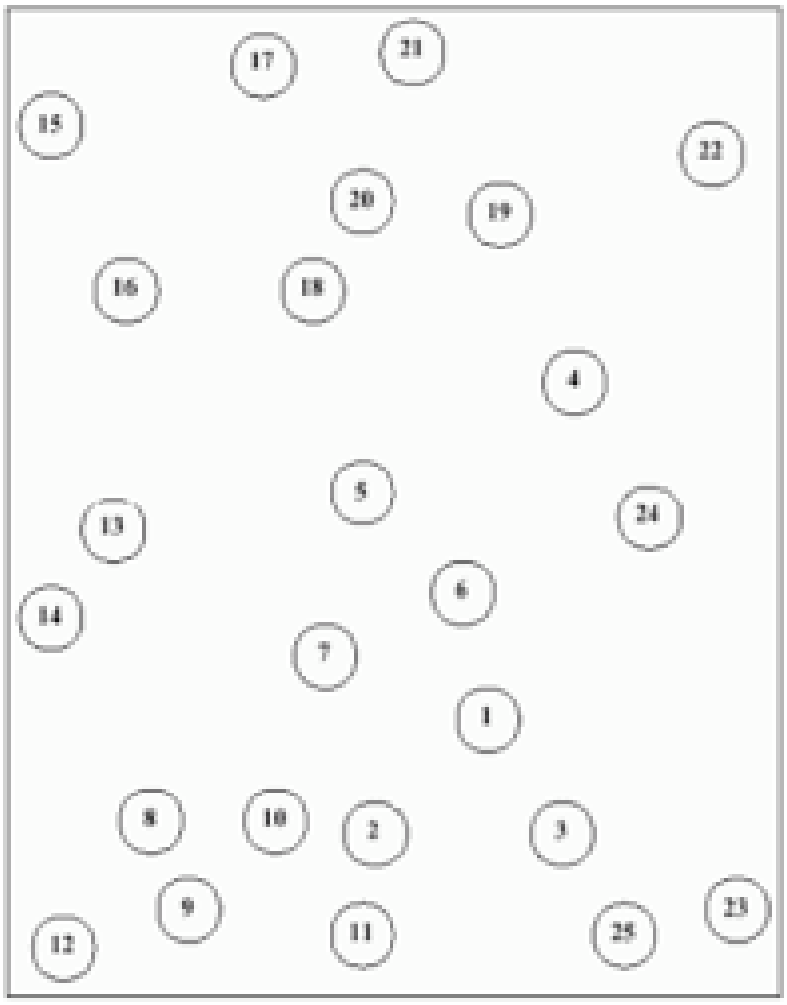
Recently, psychometric tests have been widely used in correct and early diagnosis of liver encephalopathy. Historically, the first research in the field of psychometrics was carried out in 1879 by the Wund Institute in Leipzig, Germany. Meanwhile, Francis Galton's first scientific article in this field ("Psychometric Experiments") was published in the journal "Brain". Galton was able to very accurately measure the test takers' reaction time to various text questions . In 1884, visitors to the International Exhibition in London took part in psychometric tests. Experiments were continued in a number of European universities and institutes. Based on the

results of the experiments, the researchers tried to determine the level of intellectual development of the examinees. At the beginning of the last century (1905-1908), the French researcher Galton Binet developed a series of tests to detect mental abnormalities in children. These tests determined the subject's intellectual age based on his biological age and were also based on psychometric test methods. As you can see, psychometric tests are still being used in various fields even though they are more than a hundred years old.

For psychometrics, the following can be used: to determine the speed of cognitive activity, we used a number association test, and to determine fine motor accuracy, we used a linear test (labyrinth). The Number Connection Test (NCT) and Linear Test (LT) are most commonly used. Their diagnostic sensitivity is 70-80%. To diagnose and differentiate hepatic encephalopathy, Reitan's test (Number association test) and Linear test were applied to all patients. The advantage of these psychometric tests is that they are easy and simple, do not require extra money from the patients, and can be taken by the patients on the spot without going to other places. Psychometric tests are diverse and numerous, and among them we have selected the "Test of connection of numbers", i.e. the Reitan test and the Linear test.

Examples of psychometric tests:

Number Connection Test (REYTAN TEST)



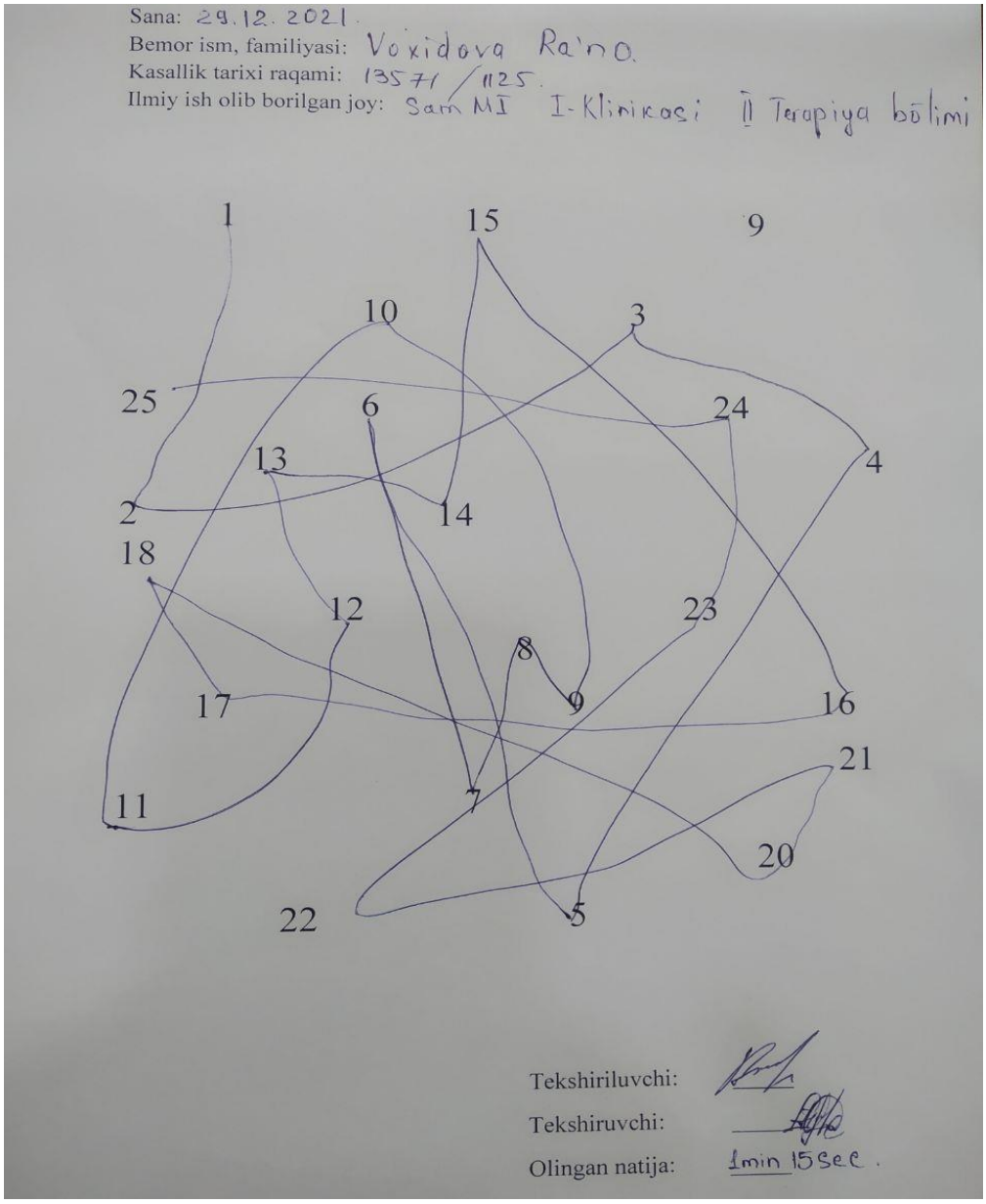
In this, the patient is given a sheet of random numbers from 1 to 25, and the patient is required to connect them in the correct sequence within a certain time. But for the first time, patients are given time to prepare and take the test, and for the second time, they are given a test paper with different numbers, and the time spent on the test is considered valid.

The results of the Reitan test are interpreted as follows:

Time (sec)	**Ball**	**Liver e n ts cephalopathy stage**
≥ 40	0	No
41-60	1	0-I
61-90	2	I-II
90-120	3	II
≤120	4	II-III

Note: For example, if the patient connects the numbers 1 to 25 randomly written on the paper with a line within 1 minute and 25 seconds, the patient is considered to have scored 2 points, and this means that the liver encephalopathy is between stage I and II .

In the Number Connection Test (NCT), patients are presented with a random sequence of numbers from 1 to 25 and are asked to match them in the correct sequence as quickly as possible based on a program loaded on a paper or tablet. Initially, patients are given the opportunity to prepare and for the first time work on a paper with numbers or a home-style test on a tablet. The second time it is given and the result obtained from it is considered valid. Mentally and neurologically normal patients solve this test within 30-40 seconds. The interpretation of NCT is given in Chapter II. A correction coefficient of 0.7 is used to evaluate test results in patients over 50 years of age.



In order to pass ***the line test (LT),*** the patients are given a paper with a picture of two rows of corridors in the form of a maze, and the patient is asked to draw a continuous maze from the interval of parallel lines with a pen to the end of the maze. In order to evaluate the test, the time taken by the patient to draw this line to the end and the errors in leaving the border of parallel lines are taken into account. In mentally and neurologically normal patients, the time taken for LT is usually up to 30 seconds, and the number of errors can be up to 1 at most.

Picture. Linear test

Psychometric test results in different stages of hepatic encephalopathy in liver cirrhosis

n = 102

Table 10 .

HE stages (Total = 102)	Number Connection Test (sec)	Control group (total = 25)
Patients without hepatic encephalopathy	3 8 , 4 ± 0 , 2 sec	36.08 ± 0.71 sec
0-I stage	55 , 6 ± 0 , 78 sec	
II stage	101 , 7 ± 2 , 4 sec	
III stage	1 29 , 0 ± 0 , 6 sec	

Note : We did not tabulate grade IV hepatic encephalopathy because grade IV HE is only hospitalized in acute care centers.

NUMBER ASSOCIATION TEST AND CHANGE OF LINEAR TESTS FOR STAGES OF HEPATIC ENCEPHALOPATHY

Table 11

HE stages (Total = 66)	Number Connection Test (sec)	Linear Test (Sec) duration and the number of errors in it
Patients without hepatic encephalopathy	3 8 , 8 ± 0 , 2 Sec	31 , 1 + 0 , 2 sec; 0.6 +0.0 8
0-I stage	55 , 6 ± 0 , 75 sec	3 7 ,8± 0 , 5*** sec; 2 , 4 ±0, 13 * **
II stage	101 , 7 ± 2 , 2 sec	5 2 , 8 ±1, 01*** sec; 4 , 9 ±0, 15 * **
III stage	1 27 , 0 ± 0,8 sec	8 1 , 1 ± 3 , 2*** sec; 7.6 ± 0.2 * **
Control group	3 5 .08 ± 0.7 2 sec	2 8 .80 ± 0.5 8 sec

(total = 25)		0.36 ± 0.11

Explanation. ****-r < 0.001 was the difference.*

As can be seen from this table, in patients with no signs of hepatic encephalopathy, the result of hip-bracing test before treatment was an average of 38.8±0.2 seconds. According to the results of the linear test in these patients, the time taken to complete the test before treatment was on average 31.1+0.2 seconds, and the number of errors was on average 0.6+0.08 (r<0.001).

In patients with hepatic encephalopathy grade 0-I, the mean time to complete the pre-treatment hip-link test was 55.6±0.75 sec, the line test was 37.8±0.5 sec, and the number of errors during LT was 2.4± was 0.13 (r < 0.001).

In patients with grade II hepatic encephalopathy, the average value of NCT before treatment was 101.7±2.2 seconds, the average time of the linear test was 52.8±1.01 seconds, and the number of errors during its execution was 4.9±0.15 (r <0.001). After treatment, in the same patients, the average value of passing the NCT was 96.2 ± 3.03 s, for the line test 54.3 ± 0.8 s, and the number of errors was 5.5 ± 0.2 (r < 0.001) .

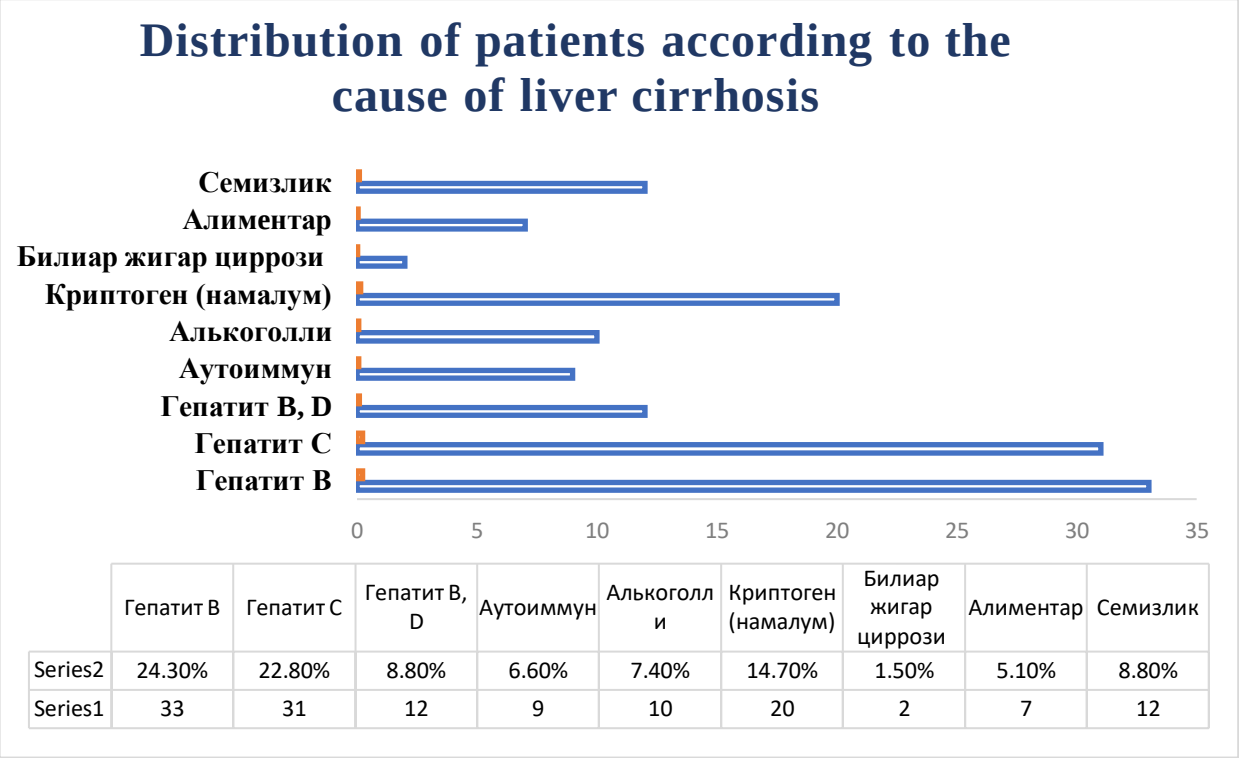
In the group of patients with obvious clinical symptoms of grade III, before treatment, the average value of passing the NCT of patients was 127.0±0.8 sec, the linear test was 81.1±3.2 sec, and the number of errors in its execution was on average 7.6±0.2 (r <0.001) was In the control group, the average value of passing through NCT was 35.08 ± 0.72 seconds, and the linear test was 28.80 ± 0.58 sec and the number of errors in its execution was 0.36 ± 0.11 on average .

CLINICAL COURSE CHARACTERISTICS OF LIVER CIRRHOSIS.

The diagnosis of liver cirrhosis was made on the basis of clinical, instrumental and laboratory tests. Interviews with close relatives of the patients were also conducted in order to determine the mental disorders, personality changes, memory loss, and writing style changes. All patients underwent instrumental examinations such as abdominal USE, liver elastography, EGDFS, EEG, ECG and, if necessary, abdominal CT or brain MRI. Among the laboratory tests: general blood and urine analysis, biochemical blood analysis, ammonia and sodium content in the blood were determined. In order to rule out other causes of encephalopathy in patients, all patients were examined by a neuropathologist. The clinical and neurological examination consists of a standard therapeutic and neurological examination aimed at the diagnosis of HE syndrome in liver cirrhosis. To rule out other causes of encephalopathy, a neurologist and, if necessary, a psychiatrist were examined. Neurological signs - tremor of fingers, paresthesias in hands and feet, increase in tendon reflexes, changes in gait, mood changes, etc. were evaluated. Interviews were also held with relatives of patients about the dynamics of changes in character and behavioral reactions. All the obtained data were recorded in an individual patient card developed based on the research requirements. Interviews with close relatives of the patients were also conducted in order to determine the mental disorders, personality changes, memory loss, and writing style changes.

Patients were studied in several groups according to the etiology factors of liver cirrhosis.

Table 12



	Гепатит B	Гепатит C	Гепатит B, D	Аутоиммун	Алькоголли	Криптоген (намалум)	Билиар жигар циррози	Алиментар	Семизлик
Series2	24.30%	22.80%	8.80%	6.60%	7.40%	14.70%	1.50%	5.10%	8.80%
Series1	33	31	12	9	10	20	2	7	12

The above changes in the gastrointestinal system force patients with liver cirrhosis to recommend proton pump inhibitors for the purpose of gastroprotection in addition to etiotropic and pathogenetic treatments. Patients with cirrhosis of the liver (classes A, B, C according to the Child-Pew scale) and liver encephalopathy from latent to severe level were included in the study. The degree of hepatic encephalopathy was determined according to the criteria of the International Association for the Study of Liver Diseases according to the West-Haven classification.

When analyzing the diseases, the cause of liver cirrhosis in 33.1% of patients was hepatitis B virus (HsbAg), of which 24.3% was isolated hepatitis B virus bmlan and 8.8% was the combination of hepatitis B and D viruses. Hepatitis C virus (HCV) in 22.8% cases, autoimmune hepatitis in 6.6% cases, alcoholic liver cirrhosis due to heavy consumption of ethyl alcohol in 7.4% cases, biliary liver cirrhosis due to common bile duct stone occlusion in 1.5% cases, Alimentary liver cirrhosis caused by lack of external nutrients and vitamins in 5.1% cases, fatty hepatosis caused by obesity and metabolic disorders in 8.8% cases, and in 14.7% cases the cause of liver cirrhosis was not determined, i.e. cryptogenic cirrhosis. In case of liver cirrhosis of alcoholic etiology, the examination of patients was performed at least 2-3 days

before the examination (because the period of elimination of ethyl alcohol from the body is from 1 to 3 days, taking into account the different amount of alcohol dehydrogenase in the liver) and then the examination was carried out.

In all patients, the severity of liver cirrhosis was evaluated according to 5 parameters (bilirubin, albumin, PTT and PTI, ascites and hepatic encephalopathy) and divided into Child-Pugh classes based on the sum of scores (5 to 15 points).

According to Child-Pugh classes of the main group of patients distribution

Table 13

Child-Pugh classes	**Total number of patients n=136**		**p**
	Abs	**%**	
Class A	31	22.8	r > 0.05
Class B	69	50.7	r > 0.05
Class C	36	26.5	r > 0.05

Note : ** - 1st and **2nd** groups did not differ from each other (*- P >0.05).*

In our study, according to the Child-Pugh scale of liver cirrhosis, class A was detected in 31 (22.8%) patients, class B in 69 (50.7%) patients, and class C in 36 (26.5%) patients. In group 1, class A was detected in 12 (18.2%) patients, class B in 37 (56.1%) patients, and class C in 17 (25.7%) patients (r >0.05). In group 2, class A was detected in 19 (27.1%) patients, class B in 32 (45.7%) patients, and class C in 19 (27.2%) patients (r >0.05). There was no statistically significant difference in

the distribution of patients between groups 1 and 2, that is, in both groups, matched patients were selected according to disease severity levels.

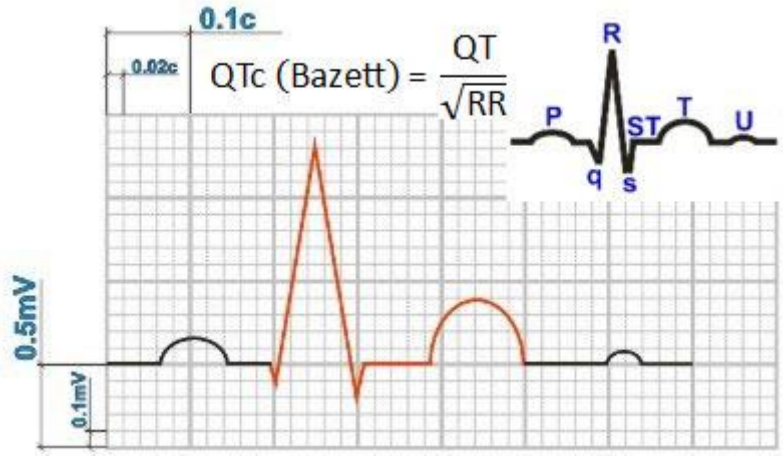
Instrumental inspection methods

Electrocardiography (ECG).

ECG for all patients inspection was conducted at the time of admission and at the end of the inspection. All patients underwent cardiogram examination at the Department of Cardiology, Multidisciplinary Clinic, SamDTU. Electrocardiogram recordings were made on a 12 standard transmitter ECG - EK1T-1/3-07 "AXION" (Russia 2021) device at a tape speed of 25 mm/s. With the help of ECG, changes such as hypertrophy of ventricular and compartment myocardium, changes in myocardium, hypoxia, various disturbances of heart rhythm were detected. The QT interval was calculated according to the Bazett formula in patients with cirrhosis of the liver with various changes by ECG QTc = (QT / (√(RR)).

Bazett: QTc=QT/RR0.5 (QT i RR sec)

Normally, this indicator should not exceed 440 ms.



Prolongation of the QT interval is defined only when the QT interval exceeds 450 ms for men and 470 ms for women, calculated according to Bazett's formula. Prolongation of the QT interval leads to an increase in the mortality rate not only in patients with cardiovascular diseases, but also in patients with chronic liver diseases.

Ultrasound examination.

Currently, one of the most common and non-invasive methods for diagnosing liver diseases is ultrasound examination (UTT). With the help of UTT, the size of the liver is measured, the unevenness of the border of the liver, structural changes of the liver, echogenicity are determined. In addition, USE allows to determine the size of the spleen, the diameter of the portal vein and the splenic vein, and to visualize signs of portal hypertension, such as free fluid-ascites in the abdominal cavity. All patients underwent USE at the X-ray and Radiology Department of the SamMU multidisciplinary clinic. USE was implemented on Mindray Consona N9 (China 2020) hardware. USE Abdominal USE is extremely important to screen any patient with suspected liver cirrhosis. USE is a relatively simple, non-invasive, generally safe examination method for the patient, and it allows to repeat it several times in patients. According to the recommendation of local and foreign scientists, it is advisable to conduct an ultrasound examination of patients every 6 months in order to determine changes in the course of the disease and complications.

Video esophagogastroduodenoscopy

Esophagogastroduodenofibroscopy (EGDFS) is an endoscopic method that allows visualization of the esophagus, stomach and proximal part of the duodenum. This instrumental examination method is *the "Gold Standard" in the diagnosis of esophageal varices.* is considered EGDFS is the most common method for detecting esophageal varices in liver disease. In our scientific work, EGDFS examination of our patients was carried out in the Department of Surgery of the multidisciplinary clinic of SamMU. VideoEGDFS examination was performed on the Videoendoscopy stand (FUJIFILM company, Japan 2020), Processor VP-3500HD, Videogastroscope-EG-530W. In our study, 121 patients underwent EGDFS, and 15 patients refused to undergo the procedure or were not performed due to the instability of the patient's general condition. In cirrhosis of the liver, endoscopy is recommended to check varicose veins due to portal hypertension and, if necessary,

carry out preventive therapy. Gastroesophageal varices, portal hypertensive gastropathy, and gastric antral ectasia can be detected by EGDFS in LC. These changes in liver cirrhosis increase the likelihood of bleeding from the organs of the gastrointestinal system. Treatment tactics are selected depending on the size and degree of expansion of esophageal varicose veins. Esophageal varicose veins were classified according to Shertsinger (A.G. Shertsinger, 1986) and were studied in 3 levels: I level - veins with a diameter of up to 3 mm, II level with veins from 3 mm to 5 mm in diameter, III level - veins with a diameter greater than 5 mm. Endoscopy remains the method of choice for the diagnosis and treatment of hemorrhagic complications of the gastrointestinal tract in chronic liver disease.

Electroencephalography

In order to determine the changes in the activity of the brain in our scientific work, we used electroencephalography (EEG) instrumental examination. EEG is a modern functional diagnostic method that allows you to determine the state of brain activity. EEG is based on the registration of bioelectric potentials generated in the cortex of the brain. In this case, the wave amplitude, the number of phases, and the parameters of the α-rhythm frequency are evaluated, and the presence of th-wave excitation is determined. Diffuse activation of slow waves is usually observed in the EEG in encephalopathies of various etiologies. But the cause of encephalopathy cannot be determined by EEG. In encephalopathy, EEG changes occur without clinical symptoms. Therefore, this method is used for early detection of hidden hepatic encephalopathy. It is possible to diagnose the stage of hepatic encephalopathy depending on the slowing down of the α-rhythm in the EEG. For example, at stage 0 of JE, the frequency of α-rhythm is 8, 5-12 oscillations per 1 second. In stage I, the frequency of a-rhythm is 7-8 oscillations in 1 second, in stage II, the frequency of a-rhythm is 5-7 oscillations in 1 second, and the activity of d- and th-waves increases. In stage III, the frequency of α-rhythm is 3-5 oscillations in 1 second, and

the activity of d- and th-waves can be increased. In the state of coma, that is, in the IV stage of JE, the frequency of α-rhythm is < 3 oscillations in 1 second, and slow small-wave oscillations are formed. EEG shows the general bioelectrical activity of the brain, but cannot accurately assess cognitive impairment. According to most scientists, the sensitivity of EEG in diagnosis is 30-40%. One of the earliest and most obvious signs of HE is the loss of alpha wave frequency in the EEG, which in turn leads to the appearance of very slow waves in the EEG [12] (Parsons-Smith BG, Summerskill WH, Dawson AM, Sherlock S. The Electroencephalograph in Liver Disease (Lancet. 1957; 273: 867-71) . *Marchetti et al.* in their research, they proved that the average fluctuation of waves in the EEG examination of patients with pronounced JE is much lower than the minimum JE [16] Marchetti P, D'Avanzo C, Orsato R, Montagnese S, Schiff S, Kaplan PW, et al. Electroencephalography in patients with cirrhosis. Gastroenterology. 2011;141:1680–9 .]. The EEG examination in our research work was carried out in the consultation polyclinic of the Multidisciplinary Clinic of SamDTU. Twenty-channel EEG was performed on a Nihon Koden EEG9100K (manufactured by Tomioka , Japan) apparatus, with bipolar and monopolar electrodes placed in anteroposterior, transverse, and oblique directions. EEG examination in cirrhosis of the liver allows to obtain more complete information in the diagnosis of latent HE, stages of HE, and to determine the dynamics of HE after the course of treatment.

Elastography examination (fibroscanning)

Liver elastography (fibroelastography) is a modern non-invasive method that examines the level of fibrosis in the liver with high accuracy. Until recently, liver fibrosis was diagnosed only by surgical procedure - biopsy. In this case, a histological biopsy from a certain fragment of the liver was surgically removed using a special puncture needle under local anesthesia, and the liver fibrosis index was determined by the pathologist. However, changes in a certain fragment of the liver were detected and could not provide complete information about the general

condition of the liver. In our study, elastography examination was carried out at SamMU Multidisciplinary Clinic X-ray and Radiology Department, unlike liver biopsy, elastography is a non-surgical procedure, and it is possible to examine not only a part of the liver, but the entire part . Also, the advantage of elastography over other examination methods is that it is painless and highly informative. In elastography, the degree of fibrosis in the liver is evaluated on a score system from 0 to 4 points. Special scales can be used to classify the degree of liver fibrosis, in particular, the METAVIR scale. According to this scale, five levels of liver fibrosis (Table 2) are distinguished.

Transcranial Doppler examination.

Since hepatic encephalopathy is a major social problem, its timely and early detection is important. This situation motivates the promotion of simple and non-invasive methods in the diagnosis of HE. One of such instrumental examination methods is Transcranial dopplerography (TCDG). **Transcranial dopplerography (TCDG)** is an ultrasound examination method based on the assessment of blood circulation in the brain. For the first time in 1982, *Rune Aaslid* examined the blood flow in the blood vessels of the brain through the temporal acoustic hole using transcranial dopplerography, and since then, the blood vessels of the brain have been examined using the method of noninvasive examination of hemodynamic changes in various conditions (*Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording in basal cerebral arteries. 1982 Dec;57(6):769-74)*. Transcranial dopplerography is a completely safe, non-invasive method that uses dopplerography to examine blood vessels of the brain, based on the doppler effect, that is, it describes ultrasound signals caused by the movement of shaped elements in the blood. Transcranial dopplerography (TCDG) is used to check the blood flow in the arteries that form the arterial community in the brain (the intracranial parts of the internal carotid artery, the middle, anterior and posterior cerebral arteries; the main artery and the intracranial part of the vertebral artery). A 4 MHz sensor operating in the

pulsed radiation mode is used. The examination was carried out using the "EDAN TCD system" in the Department of Neurology of the SamMU multidisciplinary clinic. The blood flow in the vessel is determined based on the spectral analysis of the Doppler signal, which depends on the characteristics of the movement of erythrocytes. Dopplerogamm a structure depends on vascular elasticity, effective pressure and peripheral resistance . The ability of modern equipment to register the shift of Doppler frequencies on a high or low basis allows to determine whether the blood flow is in the direction of the sensor or against it. If the direction of blood flow is from the sensor, it is assumed to be above the isoline, and if it is towards the sensor, it is considered to be below. The speed of blood movement in the vein depends on the pressure, so it has the form of a dopplerogram and a pulsogram recorded for the heart cycle. The pulsations that make up it describe certain changes in the blood flow rate in different phases of the heart cycle. In healthy people, the characteristic features of the dopplerogram of blood flow in muscular type arteries (carotid artery, vertebral artery and their branches to the brain) are that it does not reach zero in any phase of the cardiac cycle. Quantitative assessment of blood flow in arteries is calculated on the basis of indicators measured directly in the dopplerogram (amplitude, frequency, frequency distribution, pulse variation) and various indices.

The resistance index (RI) and pulsation index (PI) were automatically calculated using the following formula:

1. Sirculator resistance index - RI is equal to the ratio of the maximum systole k and end- diastolic k frequency difference a to the maximum systole k frequency a : ***RI=(A-Dk) /A***

This index does not depend on total values, angle of artery location and age. An increase in the index indicates an increase in resistance in the distal part of the peripheral flow (stenosis, thrombosis), and a decrease in it indicates a decrease in resistance (arteriovenous malformation).

2. Pulsation index - PI (Gosling index), equal to the ratio of the difference between the maximum systolic and diastolic frequencies to the average frequency of the heart cycle: ***PI=(A-Dm)/Fc***

3. LBR (linear blood flow rate). Doppler waveform is a frequency characteristic that describes the characteristics of changes in blood flow in different phases of the cardiac cycle, which can be expressed in units of linear velocity (cm/s).

Arterial tension decreases with age, describing elasticity .

Magnetic resonance imaging (MRI).

MRI of the brain is a non-invasive, highly informative examination method. MRT is based on the effect of magnetic field and radio frequency pulses on hydrogen atoms in the examined organ. Magnetic resonance imaging studies the composition of the white and gray matter of the brain and allows analysis of deep structural changes by imaging. In our investigation, MRI was performed using the MRI-SIGNA Explorer (USA 2020) scanner at the X-ray and Radiology Department of the SamDTU Multidisciplinary Clinic. Tomography was performed in 3 projections: axial, sagittal and coronal in T and T2 modes. The incisions were made in a standard way. Diagnostic CT and T2 images were obtained in standard projections taking into account anatomical structures. Magnetic Resonance imaging was performed in T1, T2, FLAIR standard modes. It was analyzed in axial, coronal and sagittal planes. For standard MRI, T1- (TR-7.9 ms, TE -3.7 ms, slice thickness -1.5 mm, matrix -240×240) and T2- (TR -6700 ms, TE -110 ms, slice thickness -4 mm, the matrix was taken as -512×512).

Laboratory tests (general blood analysis, biochemical analysis, analysis of ammonia and sodium content), specialist examination

In all study participants, general blood and urine analysis, biochemical analysis including indicators such as Bilirubin, ALT, AST, total protein, γ-glutamyltranspeptidase, alkaline phosphatase, creatinine and urea, cholesterol level

and coagulogram, blood sodium and ammonia analysis were performed. at the same time, they underwent additional examination methods according to the instructions of the therapist and the neuropathologist. Analysis of general blood and blood biochemistry in the Diagnostic-clinical-laboratory department of SamSMU multidisciplinary clinic Mindray BC -200 (China 2014) hematological analyzer was conducted. Hepatitis B, C, D markers were detected in immunoenzyme analyzers. *For detection of HBsAg by immunoenzymatic method* No. RZN 2015/2887 Vektogep V-HBs-antigen (set 2) D-0557 reagent kit was used (Vector Best/Russia). Best-anti-VGS (set 3) D-0773 reagent kit (Vector Best/Russia) was used *for detection of immunoglobulins G and M against hepatitis C by immunoenzymatic method* . As liver cirrhosis develops, various pathogenetic syndromes and laboratory changes characteristic of them are also observed. Below are the changes in the blood that can be observed in various syndromes in patients with cirrhosis of the liver:

In cytolysis syndrome, an increase in the amount of transaminases - ALT and AST, GGT, LDG, glutamate dehydrogenase, an increase in the amount of bilirubin (mainly due to conjugation), an increase in the amount of iron in the blood serum can be observed.

Liver-cell failure syndrome - a decrease in the amount of albumin, a decrease in the amount of total protein, a prolongation of prothrombin time, a decrease in blood clotting factors, an increase in the amount of unconjugated bilirubin, a decrease in the amount of urea and cholesterol, hypoglycemia is observed.

In cholestatic syndrome, there is an increase in the amount of alkaline phosphatase, an increase in the amount of gammaglutamyltranspeptidase, and hyperbilirubinemia.

In mesenchymal-inflammatory syndrome - dysproteinemia (increased fraction of immunoglobulins A, M, G and gamma-globulins), increased inflammatory markers (S-reactive protein, haptoglobin, orosomucoid, beta-microglobulin), increased amount of autoantibodies (antinuclear, antimitochondrial, etc.) observed.

Examination of serum ammonia and sodium in liver cirrhosis

As a result of liver damage, there is an increase in the blood composition of about 20 different substances that can cause brain dysfunction. Among them, ammonia is the most important. The importance of hyperammonemia as a leading pathogenetic factor in the development of JE is confirmed by a number of clinical and experimental data.

Ammonia content in the morning serum of patients with cirrhosis of the liver who participated in our study was measured by the enzymatic method from venous blood serum Mindray BC -230 (China) was tested in the laboratory of Amirbek Shifo Pharma LLC under a contract with the help of a biochemical automatic analyzer using Infinity™ (Germany) reagent. The normal value of ammonia in blood is 18–72 μmol/L (31–123 μg/dL).

Normally, the amount of ammonia in the blood is controlled by the liver. Ammonia concentration in portal venous system is 5-10 times higher than in peripheral blood. In liver failure, the clearance of ammonia decreases and it enters the brain with arterial blood. The severity of the clinical manifestations of JE in most cases depends on the level of ammonia in the blood serum and brain tissue. At the same time, hematoencephalic barrier permeability to ammonia is significantly increased in patients with advanced HE.

Ammonia is continuously produced by the body and is always detected in normal blood levels. An increase in the amount of ammonia is observed in pathological conditions (cirrhosis of the liver, Reye's syndrome, kidney diseases, disorders of urea metabolism, etc.). The normal value of this biochemical analysis was 1.1-5.1 mg/dL (11-51 μmol) for women , and 1.6-6.0 mg/dL (16-60 μmol/l) for men. Most patients diagnosed with HE have elevated ammonia levels (more than 90%) [9]. At the same time, its normal indicator cannot rule out the diagnosis of HE [9].

According to the guidelines of the European and American Association for the Study of Liver Diseases, [32] only elevated blood ammonia levels can not be of diagnostic or prognostic value in patients with chronic liver disease. However, if the amount of ammonia in the blood is within normal limits, we evaluate the diagnosis

of HE as doubtful. Therefore, it is reasonable to use repeated measurements of ammonia to assess the effectiveness of treatment in patients receiving drugs that lower ammonia levels.

Sodium. Sodium content, like ammonia, was also determined in patients with cirrhosis of the liver. The amount of sodium in the blood was measured on the Human Count 30 analyzer (using the Human reagent) at the Diagnostic-Clinical-Laboratory Department of SamDTU Multidisciplinary Clinic .

Excessive use of diuretics in liver cirrhosis also leads to hypovolemia and electrolyte imbalance - hyponatremia. Hyponatremia is also considered one of the main factors in the development of HE. Normal serum sodium is 125 to 130 mmol/l.

Principles of treatment hepatic encephalopathy

The first step in the treatment of hepatic encephalopathy is the identification and treatment of the etiology that led to the hepatic encephalopathy and caused its arousal. For example, identifying and eliminating triggers such as infectious diseases, gastrointestinal bleeding, certain medications, or kidney dysfunction. The main line of treatment for HE is diet and drug therapy. Limiting dietary protein intake and reducing ammonia production in the colon, but at the same time the daily protein intake is aimed at ensuring the consumption of 1500 kcal of calories . Daily protein (protein) for severe HE consumption is reduced to 20-30 g , and after the general clinical condition of the patient improves, the amount of protein in the daily diet is increased to 10 g every 3 days .

Medical treatment includes:

1. Drugs that reduce hyperammonemia:

- -Reducing the formation of ammonia in the intestine (lactulose, antibiotics).

- - increase neutralization of ammonia in the liver (ornithine aspartate, ornithine alpha-ketoglutarate).
- - increased concentration of ammonia in the blood (sodium benzoate, sodium phenylacetate).

2. Drugs that reduce inhibition processes in the central nervous system (flumazenil) .

3. Medicines with different mechanisms of action (chain amino acids, zinc, vitamins). But patients with HE are not recommended to take zinc drugs regularly (*EASL Clinical Practice Guidelines on the management of hepatic encephalopathy Montagnese , Sarah eat al . Journal of Hepatology , Volume 77, Issue 3, 807 - 824).*

However, since none of the drugs recommended for the treatment of HE are effective enough and do not cover all aspects of the pathogenesis of HE, a lot of scientific research is being conducted all over the world to search for and create new drugs and their combinations. Once the cause of HE has been addressed, treatment focuses on reducing the levels of ammonia and other toxins in the blood. Since these toxins first appear in the gastrointestinal system, therapy focuses on eliminating or reducing the production of toxins . Three types of drugs are used for this: lactulose, ornithine and antibiotics. The three most common medications used to treat HE are lactulose (a synthetic or artificial sugar), ornithine, and certain antibiotics. Lactulose and antibiotics are sometimes used together.

Effects of lactulose on the body :

- ❖ It draws fluid from the body into the colon, which softens the stool and causes frequent bowel movements. It helps reduce the absorption of toxins in the intestines by flushing them out of the body.
- ❖ Reduces the amount of ammonia in the blood by drawing ammonia into the large intestine.
- ❖ Reduces the likelihood of HE recurrence.

Lactulose syrup is used in an individual dose (15-30 ml is drunk every 12 hours) and is taken 2-3 times a day until defecation with soft or unformed stools. Then the dose of the drug is selected individually, that is, 2 or 3 defecations are maintained during the day. Then the dose of the drug should be gradually reduced. Very high doses of lactulose can cause the following complications: aspiration, dehydration, hypernatremia, perianal fissure, etc.

Effects of antibiotics:

- - Stops the growth of bacteria that produce toxins during digestion . By reducing the number of these bacteria, antibiotics reduce the amount of toxins in the patient's body ;
- -Helps to prevent recurrence of HE and reduce the likelihood of hospitalization of patients due to HE;
- - Various antibiotics are used to treat HE . The doctor will choose the most suitable option.

Rifaximin is an antibiotic with broad-spectrum antibacterial activity, affecting most gram-positive and gram-negative, aerobic and anaerobic bacteria. The drug is almost not absorbed by the gastrointestinal system. Rifaximin has been proven in scientific studies to reduce the amount of ammonia in the blood, to change the clinical dynamics of HE in a positive direction, and it is now widely used in the prevention of HE after portosystemic shunting.

Regardless of the compensation or decompensation stage of cirrhosis of the liver, it is recommended to use a daily dose of 1200 mg of Rifaximin in different stages of HE. Because Rifaximin reduces the amount of ammonia in the blood, improves the patient's mental and cognitive condition, reduces asterixis, and alleviates the level of HE.

Effects of ornithine on the body:

Regardless of the compensation or decompensation stage of liver cirrhosis, the use of Ornithine is recommended for patients at various stages of HE. Ornithine reduces ammonia in the blood and improves the mental state of the patient. Ornithine and aspartate play a major role in the conversion of ammonia to urea. Ornithine enhances ammonia metabolism, which helps improve the patient's clinical condition.

Ornithine is injected intravenously up to 40 g (usually 20 - 30 g can be enough) for 7-14 days. Later, it is switched to 9 - 18 g per day orally. In order to achieve more results, it is advisable to use intravenous and per os tablets and powders in combination. Combination therapy with ornithine allows simultaneous elimination of intestinal ammonia and blood ammonia.It is recommended to limit ornithine in patients with kidney pathology.

In our study, all patients were assigned complex treatment procedures according to the standard in the department, depending on the severity level, class and development of complications of liver cirrhosis. Patients were mainly treated with etiotropic and pathogenetic, and in some cases, symptomatic treatment. Patients diagnosed with hepatitis B, C, D viruses were prescribed anti-hepatitis drugs (*Sofosbuvir, Daclatasvir, Velpatasvir, Ledipasvir, Tenofovir, Entecavir*) with the help of an infectious disease consultation. In autoimmune liver cirrhosis: immunosuppressants such as *Azathioprine, Methylprednisolone, Prednisolone* were prescribed. In liver cirrhosis caused by fatty hepatosis: Fenofibrate 145 mg, 160 mg; Metformin 500 mg, 850 mg, 1000 mg; such as α-lipoic acid was prescribed. Alimentary liver cirrhosis - protein preparations, vitamins, electrolyte solutions, etc. were recommended. Bile acid preparation (*Ursodeoxycholic acid 250,500 mg*) and hepatoprotectors were prescribed to improve liver function. Nonselective β-blockers (*propranalol-anaprillin 10.40 mg*), α- and β-blockers (*carvedilol 6.25 mg, 12.5 mg, 25 mg*) were recommended to reduce portal hypertension . Drugs against portal hypertension and ascites (*Spironolactone 25 mg, 50 mg, 100 mg, Furosemide 20 mg, 40 mg, Torasemide 5.10 mg*) were used. When bleeding (*somatostatin 250 μg bolus + 250-500 μg/s* IV infusion for 3-5 days) or octreotide (50 μg bolus + 50 μg/s IV

infusion for 3-5 days), *Proton pump inhibitors* intravenous into: pantoprazole 80 mg/s and esomeprazole 40 mg/s, then switched to oral administration). Also, hemostatic drugs for bleeding from gastrointestinal and rectal varicose veins in cirrhosis of the liver: *Aminocaproic acid 100 ml* intravenous infusion (no more than 3 days), *Fresh frozen plasma* 10-15 ml/kg intravenously, *Tranexamic acid 5-10 ml* in 200 ml it can be added to a 0.9% solution of sodium chloride and applied drop by drop 2-3 times a day for 5 days. *Platelet mass, Albumin and/or Ermassa* are also placed. Patients diagnosed with liver encephalopathy were mainly prescribed non-absorbable disaccharides (*Lactulose 667 mg/ml*: 200 ml, 500 ml, 1000 ml) and antibiotics (*Rifaximin 200 mg*). Because lactulose also has laxative and ammonia-reducing properties, it is one of the most important drugs in the treatment of HE. In order to reduce the amount of ammonia in the body, hypoammonemic drug L-ornithine L-aspartate was used. L-Ornithine L- Aspartate intravenous infusion and oral form were used. Oral forms of probiotics and oral forms of side-chain amino acids have also been used in the treatment of HE. Proton pump inhibitors were also prescribed to patients with various degrees of changes in the gastrointestinal tract along with complex medical procedures.

CONCLUSIONS

1. Diagnosis of liver encephalopathy is primarily aimed at preventing the development of the disease and identifying the early stages of the disease to ensure timely treatment. Psychometric tests play an important role in determining not only the clinically expressed form of encephalopathy, but also the latent form. Psychometric tests are the easiest and most sensitive method for early detection of hepatic encephalopathy in the latent period.

2. Clinically unexpressed, hidden, that is, minimal hepatic encephalopathy can be diagnosed in time not only with the help of blood ammonia, sodium, psychometric tests and EEG indicators, but also by TKDG. This situation indicates that specific changes can develop in the blood vessels of the brain in cirrhosis of the liver.

3. The Glasgow scale and the West-Haven criteria were simultaneously used to assess the state of consciousness of patients, and the sensitivity and specificity of the two methods in determining the level of the pathological process were determined in the diagnosis of levels of hepatic encephalopathy. According to this, the specificity and sensitivity of the West-Haven criteria in the diagnosis of HE were found to be high.

4. In the treatment of liver encephalopathy, 3 types of drugs were mainly used: lactulose, ornithine and antibiotic (Rifaximin), eliminating the risk factors

present in patients . The effect of all these drugs is aimed at reducing the amount of ammonia in the intestine and blood.

LITERATURE LIST:

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