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Chapter

Formation of Systemic Changes Features with Fatal Complications of Metabolic Syndrome and Chronic Diffuse Liver Diseases

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Abstract

Chronic liver disease at initial stages often occurs with no symptoms or with very non-specific symptoms, so timely diagnosis of chronic liver disease is of great importance, and there are significant difficulties involved therein. Not being able to diagnose the hepatic disease early, difficulties with the management of the disease and treatment arise. Different aspects of the clinical and laboratory evaluation may be of assistance in providing an early diagnosis, ranging from laboratory tests, to ultrasound, to EGD, and to rheohepatography (not used that frequently) among others. Stages of hepatitis affect the hepatic and general symptoms, and morphological changes in liver tissue are presented and discussed, followed by a section devoted to hepatic encephalopathy (HE) and how it is influenced by cerebral hemodynamics and state of liver cirrhosis (LC).

Keywords: liver, chronic hepatitis, liver cirrhosis, chronic diffuse liver disease, hepatic encephalopathy

1. Introduction

Chronic hepatitis (CH) and liver cirrhosis (LC), especially the latter, are the most common cause of portal hypertension (PH), leading to changes in the functional ability of the affected organ, which is manifested by corresponding changes in blood biochemical parameters. At the same time, among the many clinical manifestations of the disease, there is no symptomatology pathogenic for these conditions, which allows for a timely diagnosis. That leads to the difficulties of early detection of the transition of the inflammatory process of the liver to the cirrhosis, and the possibility of initiating timely treatment.

In patients of different age groups with liver cirrhosis of viral etiology of classes A, B, and C according to Child-Pugh, chronic hepatic encephalopathy of all stages can occur against the background of dyscirculatory disorders with the development of chronic cirrhosis (LC) with the rapid disability of patients. In recent decades, studies have been conducted on the effect of LC on the severity of hepatic

encephalopathy (HE), etiology, stages of the disease, and psychological characteristics of the personality [1–4]. In modern approaches to the treatment of LC, it is necessary to take into account the etiological factor, the reduction of pathogenetic reactions that support the activity of the process, prevention of progression of cirrhosis, treatment of symptoms, and complications of the disease such as portal hypertension, HE, ascites, ascites-peritonitis, and hepatorenal syndrome. HE can be subclinical in nature, and mortality among patients is up to 10% and is mostly associated with comorbidities, and not with complications of portal hypertension [5–8]. Therefore, the assessment of the degree of HE and the corresponding individualized approach to each patient in terms of the selection of therapy can significantly reduce its stage, which also improves the quality of life of patients [9, 10]

1.1 Materials and research methods

The most common methods of laboratory diagnosis of chronic diffuse liver disease (CDLD) are biochemical analysis of blood, the study of coagulation with the assessment of coagulation, anticoagulation systems, and special tests to determine some of the complications of the underlying disease. The case of active and complicated course of the disease can be obtained from a general blood test. Indicators of coagulation and blood rheology are important, excluding in the postoperative period a number of serious complications due to impaired microcirculation can develop and including acute hepatocellular insufficiency, gastrointestinal bleeding, and even with inactive liver cirrhosis.

1.2 Materials and research methods used for assessing hepatic encephalopathy

One hundred seven patients (87 (81.3%) men and 20 (18.7%) women) with viral etiology LC were examined: HBV infection (n = 35.1%), HCV infection (n = 46.1%), and infection HBV + HCV (n = 18.8%) aged from 30 to 69 years (average age was 57.3 ± 4.6 years). According to the compensation stages by Child-Pugh LC, the patients were divided into three groups: the first group (n = 35) consisted of Class A LC patients, the second group (n = 37) consisted of Class B patients, and the third group (n = 35) included patients with Class C LC. To confirm the diagnosis of LC and its etiology and stage of compensation and complications, the clinical picture and history of the disease were studied; a complex of clinical, laboratory and instrumental diagnostic methods was conducted. To match the fibrosis index and the LC for METAVIR and ISHAK, a classification counting scale (Bonacini) was used. Patients with cardiac arrhythmias and hormonal status were excluded from the study, without heart defects and an increase in blood pressure above stage III.

Clinical diagnosis of HE, assessment of its severity, and basic and additional instrumental studies were conducted in accordance with the recommendations of the working group of the 11th World Congress of Gastroenterologists. Evaluation of the stages of HE was carried out according to a descriptive scale of West-Haven symptoms and Reitan test (number connection test). Ultrasound diagnosis of cerebral hemodynamics was performed using the PHILIPS EPIQ 7G ultrasound machine (USA) using the W. J. Zwiebel, J. S. Pellerito method (2010). Diagnostics of brain blood flow included the study of blood flow parameters in the internal carotid (ICA) and middle cerebral arteries (MCA) of the first order of both hemispheres, maximal, minimal, and average BFV; contralateral asymmetry of the mean BFV; carbon-dependent blood flow indicators (RI and PI); cerebral perfusion pressure; reactivity of blood flow; cerebrovascular blood reserve; cerebrovascular reactivity index; and vasomotor reactivity, were determined by the functional reserve of

the connecting arteries of the circle of Willis Matas sample. To study the function of the heart in LC, echocardiography was performed in the M-modal and two-dimensional modes according to the standard method of the American Association of Echocardiography. In 15.9% of cases, autopsy material served as the object of research of the abdominal cavity and brain. For the differential diagnosis of LC and its complications, CT, MRI, FGDS, Reitan's combination test, and electroencephalography were performed.

The study of the parameters of cerebral hemodynamics with LC of classes A, B, and C consisted of several stages. At the first stage, the parameters of central hemodynamics were studied. The central element in this question was the study of the systolic function of the left ventricle. At the second stage, the parameters of cerebral hemodynamics were studied. The results of the average values of blood flow parameters and intima-media complex (IMC) thickness in the internal carotid arteries with LC of classes A, B, and C were analyzed. In addition, the presence of hemisphere asymmetry was associated with the development of dyscirculatory disorders, confirmed by neuroimaging and autopsy of the brain. Thus, in the prospective observation, the autopsy material of the brain served as confirmation of the comorbidity of HE and dyscirculatory disorders from minimal to irreversible with the LC.

All patients with clinical and instrumental signs of chronic HE and cerebrovascular insufficiency were given a psychometric test of Reitan for the connection of numbers.

Processing of the obtained clinical and laboratory and instrumental data was carried out using the criteria of parametric and nonparametric statistics. The magnitude of the distribution of the Gauss density was estimated from the values of the interquartile range. The correlation matrix method was used to determine the degree of interrelation between individual signs. Statistical processing of the material obtained was carried out using the program Stat Soft Statistica, version 10.0.

2. Chronic hepatitis of minimal activity

The clinical picture of patients with minimal activity CH was characterized by a paucity of symptoms. The majority of patients (21) had an asymptomatic course of the disease. The admission of patients to the hospital was associated with symptoms of chronic cholecystitis or the presence of changes in the biochemical blood tests detected during the preventive examination. In some cases, treatment was associated with the appearance of some symptoms of asthenic and dyspeptic syndrome in individuals who considered themselves practically healthy. However, some patients complained of weakness (31.4%) and nausea (23.4%).

Careful collection of anamnesis showed that 66.2% (131) of the patients previously had AVH, 15.6% (31) had contact with patients with AVH, 12.1% (24) shortly before the disease underwent surgery and blood transfusion or long-term (more than 1 month) received intramuscular injections, and only 12 patients pointed to alcohol abuse.

In patients with chronic hepatitis (**Tables 1** and **2**), with minimal degree of activity, no statistically significant expansion of the diameter and cross-sectional area of the portal and splenic veins was compared with the control group.

There were also no statistically significant changes in the maximum and volumetric blood flow velocities through the portal and splenic veins with pulsed-wave Doppler sonography.

An increase in portal pressure primarily affects the volume velocity of the blood flow in the portal and then in the splenic veins, depending on its size. So, at the level of portal pressure up to 128.3–134.3 mm H_2O, a further increase in pressure in the

Indicators	CH of minimal activity (n = 207)		M ± SD in patients of control group (n = 40)	p
	Limits of variation	M ± SD		
Inner diameter, mm	9.0–13.0	10.71 ± 1.25	10.22 ± 0.71	>0.05
Cross-sectional area, sq. cm.	0.64–1.33	0.91 ± 0.05	0.83 ± 0.03	>0.05
Max BFV, cm/s	18.2–25.0	21.63 ± 1.56	21.63 ± 2.71	>0.05
BVF, ml/min.	686.3–1910.3	1161.91 ± 341.19	1075.8 ± 83.61	>0.05
Portal vein pressure, mm H_2O	98.3–164.3	123.3 ± 10.49	113.0 ± 4.41	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 1.
Results of hemodynamic studies in the portal vein in patients with chronic hepatitis of minimal activity (M ± SD).

Indicators	CH of minimal activity (n = 207)		M ± SD in patients of control group (n = 40)	p
	Limits of variation	M ± SD		
Inner diameter, mm	6.0–8.0	6.63 ± 0.69	6.41 ± 0.61	>0.05
Cross-sectional area, sq. cm.	0.28–0.51	0.37 ± 0.02	0.33 ± 0.02	>0.05
Max BFV, cm/s	17.0–22.2	18.94 ± 0.97	19.22 ± 2.23	>0.05
BVF, ml/min.	274.3–539.6	379.51 ± 74.33	345.41 ± 34.62	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 2.
Results of hemodynamic studies in the splenic vein with chronic hepatitis of minimal activity (M ± SD).

portal vein to 140.3–146.3 mm H_2O leads to initial changes in hemodynamics in the splenic vein.

Echographic signs of chronic cholecystitis with calculi of various sizes were found in 51.5% of patients.

CT scan, performed in 15.2% of patients, also showed no changes in the liver, with the exception of 60% of patients with chronic cholecystitis, where gallbladder calculi were visualized.

Radiocontrast study in eight (24.2%) patients revealed a diffusely uneven distribution of radiopharmaceuticals in the liver at normal sizes and even and clear contours of the organ.

Esophagogastroduodenoscopy in 24.4% of patients found superficial, in 21.2% atrophic, and in 3% subatrophic gastritis, in 21.2% duodenitis, in 12% duodenogastric, and in 15% gastroesophageal reflux, in some cases with erosive esophagitis.

Thus, the clinical diagnosis of minimal activity CH is based on a thorough collection of anamnesis, clarification of complaints, clinical symptoms, and laboratory data, which allows to establish a clinical diagnosis and determine the tactics of further research and treatment by the first day after admission. The information content of noninvasive additional research methods in patients of this group is

extremely low. In this regard, morphological study is the most objective and informative diagnostic method.

A histological study conducted in 16 patients showed that 12 of them have a morphological picture of chronic persistent hepatitis, including 7 patients with chronic calculous cholecystitis.

Biopsy in this category of patients is very problematic, due to the frequent rejection of patients from the study, due to the invasiveness of the technique. At the same time, we consider it unnecessary to conduct histological studies on a universal basis, limiting the indications for its implementation only to those who need histological monitoring of the effectiveness of the treatment or surgical intervention, due to the long-term, uncorrected conservative therapy, and activation of the pathological process in the liver. In other cases, the activity of the pathological process should be determined by the level of transaminases (an increase in the ALT level to three norms).

3. Chronic hepatitis of moderate activity

The clinical manifestation in 39 patients with moderately active chronic hepatitis was different from the previous group by more intense symptoms than in the previous group. Most patients (30) were admitted to the clinic due to the existing symptoms of abdominal pain and dyspeptic, asthenic, and hemorrhagic syndromes. Twenty-three patients complained of pain (9) and severity (14) in the right hypochondrium, especially after an error in diet or exercise. In nine of them, the pain was paroxysmal. Six patients indicated nausea and vomiting (3) after ingestion of fatty foods, 7 patients indicated disorders of the stool, 6 patients indicated irritability, 14 patients indicated weakness, 7 patients indicated decreased performance, and 3 patients indicated bleeding from the nose and gums.

According to case records it turned out that 15 patients had previous AVH, 3 of them received hormonal therapy due to severe disease, 5 pointed to jaundice of unknown etiology, 6 contact with AVH patients, and 4 undergone surgery, blood transfusion, or prolonged (up to 1 month) intramuscular injections.

The general condition was assessed in 25 patients as satisfactory and in 14, moderate. Reduced nutrition occurred in 15 patients, single telangiectasia on the upper half of the chest in 4 patients. Yellow skin extinguishing and icteric sclera were observed in eight, palmar erythema in five patients. Visually abdominal distension was determined in four patients. On palpation, in 26 patients, an enlarged liver was protruded, projecting 2–3 cm from under the edge of the right costal arch. In 23 of them its compaction and tenderness was determined. The spleen in six patients was slightly enlarged; its lower pole was felt at the edge of the left costal arch without any subjective sensations.

Hypochromic anemia of grade 1 occurred in grade 7, grade 2, and grade 6, moderate transient thrombocytopenia in seven, and accelerated ESR in 22 patients. However, when recalculating the peripheral blood indices for the total number of patients with moderately active chronic gastritis, a moderate decrease in the number of red blood cells was obtained with relatively normal values of other peripheral blood indices. Evaluation of the functional state of the liver using a complex of biochemical research methods showed the depression of its function, which was expressed by a significant increase in bilirubin (58.1 ± 1.4 mmol/l) fractions of aminotransferases more than three standards (ALT, 2.27 ± 0.06; AST, 1.17 ± 0.06 mmol/h l). Dysproteinemia was observed (albumin 49.1 ± 0.89% and globulins 23.3 ± 0.35%), with a decrease in albumin/globulin coefficient (A/G ratio) to 0.96, with relatively normal indicator total protein levels.

In patients with chronic hepatitis of moderate degree of activity, the contours of the liver were even in only 154 (74.4%) patients, and the pointed edge of the liver was found in 169 (81.6%) patients. The echogenicity of the parenchyma is irregularly increased in 197 (80.7%) patients. In 143 (69.1%) patients, the phenomenon of "distal attenuation" of ultrasound was observed, while the oblique size of the right lobe of the liver was more than 160 mm. In addition, 28 (13.5%) patients with chronic hepatitis had abdominal lymphadenopathy at the gate of the liver.

In patients with chronic hepatitis of moderate activity of the inflammatory process (**Tables 3** and **4**), expansion of the portal vein diameter and, accordingly, an increase in its cross-sectional area against a background of pressure increase in it were noted. At the same time, there was no statistically significant increase in the internal diameter and cross-sectional area of the splenic vein; although in some patients, there was a change in both signs indicating increased portal pressure.

Doppler study of the blood flow in the portal vein did not show a statistically significant decrease in the maximum and increase in the volumetric flow rate. From the data presented in **Table 4**, it is also clear that signs of hemodynamic disturbances are observed in the splenic vein, which coincide in their direction with those in the portal vein, but quantitatively these changes are not so significant ($p > 0.05$).

Indicators	**CH of moderate activity (n = 23)**		**M ± SD in patients of control group (n = 40)**	**p**
	Limits of variation	**M ± SD**		
Inner diameter, mm	11.0–14.0	12.81 ± 1.11	10.2 ± 0.71	<0.05
Cross-sectional area, sq. cm.	0.95–1.54	1.29 ± 0.04	0.83 ± 0.03	<0.05
Max BFV, cm/s	16.1–23.2	18.92 ± 1.72	21.6 ± 2.71	<0.05
BVF, ml/min.	686.7–1898.1	1257.51 ± 355.23	1075.8 ± 83.61	<0.05
Portal vein pressure, mm H_2O	145.6–190.9	164.4 ± 9.34	113.0 ± 4.41	<0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 3.
Results of hemodynamic studies in the portal vein in patients with chronic hepatitis of moderate activity (M ± SD).

Indicators	**CH of moderate activity (n = 23)**		**M ± SD in patients of control group (n = 40)**	**p**
	Limits of variation	**M ± SD**		
Inner diameter, mm	6.0–9.0	7.11 ± 0.83	6.4 ± 0.61	>0.05
Cross-sectional area, sq. cm.	0.28–0.64	0.41 ± 0.03	0.33 ± 0.02	>0.05
Max BFV, cm/s	15.2–20.1	17.81 ± 0.94	19.2 ± 2.23	>0.05
BVF, ml/min.	280.2–608.3	402.01 ± 84.41	345.4 ± 34.62	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 4.
Results of hemodynamic studies in the splenic vein in patients with chronic hepatitis of moderate activity (M ± SD).

It is noted that the increase in portal pressure to the level of 170.3–174.4 mm H_2O led to changes in hemodynamic parameters: diameter and linear and volumetric blood flow velocity in the portal vein. A further increase in portal pressure to 178.4–182.6 mm H_2O influenced the change in the above parameters of hemodynamics in the splenic vein. First of all, these changes concerned the diameter of the portal vein and the volumetric blood flow in the hepatoportal bed.

CT, as well as in the previous group of patients, was performed in a limited number of 42 patients (20.3%). In the study in addition to moderate hepatomegaly, changes in the parenchyma of the liver were not found. In 32 cases, along with an increase in the size of the liver, concrements of the gallbladder were detected.

Radiocontrast study performed in 39% of patients revealed a moderate increase in the size of the liver and, in 82% of cases, a diffuse decrease in the accumulative function of the organ. In 5% of cases there was a redistribution of the radiopharmaceutical in the spleen.

EGD was performed in 149 (72%) patients; in 69 of them inflammatory, changes of the upper digestive tract were found in the form of superficial (32), erosive gastritis, duodenitis (32), duodenogastric (1), and gastroesophageal (4) reflux.

Thus, patients with chronic hepatitis of moderate activity are characterized by the presence of more constant clinical and laboratory changes that characterize the patient's true state. In a similar situation, conducting additional noninvasive research methods (ultrasound and radiocontrast study) allows a certain part of patients to reveal data (a uniform increase in the size of the liver, changes in the parenchyma of the organ) characterizing the morpho-functional state of the affected organ.

Histological studies of liver tissue carried out in 28 patients, in order to detect the morphological state of the liver; 61% of the examined patients found a picture of chronic persistent (CPH), and 39% had chronic active hepatitis (CAH).

Morphological studies of patients with chronic CH activity are not only diagnostic and diagnostic but also tactical. More than 1/3 of the patients in this group have a histological picture of CAH, in which the treatment tactics is somewhat different than with CPH. Therefore, for the development of a pathogenetic-based surgical tactics for chronic hepatitis C, we consider it expedient to perform not only intraoperative but also preoperative liver biopsy.

4. Chronic hepatitis of severe activity

This group consisted of 171 patients with the most prominent clinical symptoms of severe disease. Complaints and manifestations of the disease included almost the entire clinical syndromology of CDLD. The majority of patients (84.2%) complained of pain or heaviness in the right hypochondrium and epigastrium (abdominal pain syndrome); 63.2% of patients complained of weakness and fatigue; 47.4% - reduction of working ability (asthenic syndrome); 58% - loss of appetite; 21% - weight loss; 21% - nausea; 15.8% - disorders of the stool and flatulence (dyspeptic syndrome); 15.8% - jaundice; 15.8% - pruritus; 15.8% - dark urine; 10.5% - bleeding from the nose and gums; 5.3% - subcutaneous hemorrhages; 5.3% - menorrhagia; 10.5% - dysmenorrhea (endocrine syndrome); 15.8% - increase in the size of the abdomen and decreased diuresis; 10.5% - leg swelling (edema-ascitic syndrome); 10.5% - by memory loss, drowsiness, and periods of disorientation in time and space; and 5.3% - improper behavior (encephalopathy syndrome). In 26.3% of patients, the appearance of the above complaints was accompanied by an increase in body temperature to 38–39°C.

Anamnestic data showed that 90 patients in the period from 4 months to 11 years ago had AVH, 18 of them received hormonal (prednisolone) therapy due to severe disease, 18 indicated episodes of jaundice of unknown etiology, 36 on contact

with AVH patients, 18 for previous surgical interventions with transfusion of donor blood or long-term infusion and injection therapy, and 9 for taking antituberculosis drugs (rifampicin, isoniazid, streptomycin, and analogues of these drugs) for 1 year or more, according to suspected pulmonary tuberculosis.

Condition of 18 patients at admission to the clinic is regarded as satisfactory, 126 moderate, and 27 severe. Severity of the condition was due to the course of the underlying disease, as well as secondary changes from other organs. Severe jaundice occurred in 27 patients; in 9 of them with subcutaneous hemorrhages; in 18 patients with telangiectasias on the skin of the chest, shoulders, and face; and in 9 patients with urticaria on the face and neck. Yellowness of the skin and sclera was detected in 45 patients. And at 18 it was accompanied by skin itch, as evidenced by the traces of scratches that were present in these patients. Palmar erythema was found in 30 patients. Nutrition in 42 patients was reduced, and in 27 patient, there was pronounced weight loss. However, only nine patients indicated weight loss during the last 6 months.

According to 45 patients auscultation data, systolic murmur at the apex of the heart and at the Erb's point was heard. A moderate increase in the abdomen occurred in 36 patients. On palpation, 108 patients had hepatomegaly, and in 26 of them, the lower edge of the liver protruded more than 5 cm from under the edge of the right costal arch (along the midclavicular line to the right). The edge of the liver, as a rule, is rounded, the surface is smooth, and tissue is somewhat thickened and painful. In 18 cases, an enlarged, painful, slightly tense gallbladder was palpable. In 36 patients enlarged spleen was determined, tissue being compacted and painful on palpation. In 18 of them, the lower pole of the organ emerged from under the edge of the left costal arch by 3–5 cm and in 9 by more than 6 cm. Free fluid in the abdominal cavity was detected in 11 patients with a severe course of the pathological process.

Patients in this group had hypochromic anemia, moderate thrombocytopenia (platelets less than 200,000), and accelerated ESR. Liver function was characterized by severe hyperbilirubinemia (total of 74.2 ± 8.2 mmol/l), mainly due to the direct fraction (49.7, 1.9), increased transaminase levels (AlAT, 2.67±0, 12; AsAT, 1.6 ± 0.15 mmol/h l), and in 7 (21%) dysproteinemia in the form of hypoalbuminemia (45.8 ± 0.53%) and hypergammaglobulinemia (25.9 ± 0.4%). Thymol test result tended to increase (9.0 ± 0.5 units), reaching 31 units in severe patients.

Ultrasound examination in all patients of this group revealed an increase in the size of the liver compared with the data of the previous group (**Table 5**). In patients with chronic hepatitis of high activity in 64 (37.4%) patients, the contours of the liver were lightly wavy; in 54 (31.6%) the edge of the liver was rounded. In 153 (89.5%) patients, the echogenicity of the liver parenchyma was unevenly elevated. The phenomenon of "distal attenuation" of ultrasound was detected in 134 (78.4%) patients, while the oblique size of the right lobe of the liver was more than 180 mm. In addition, 49 (28.78%) patients had lymphadenopathy in the gates of the liver, and 11 (6.4%) patients had a small amount of free fluid in the abdominal cavity, indicating the development of portal hypertension in these patients, which is not rare. It happens with the so-called "active" hepatitis at the height of the clinical and morphological manifestations of the disease.

A statistically significant enlargement of the liver in comparison with the control group was observed due to the total liver lobes: right to 186.13 ± 7.45 mm and 90.61 ± 6.81 mm and the caudate to 24.36±1.43 mm. The area of the spleen in this group of patients was up to 40.93±1.99 sq. cm.

Results presented in **Tables 6** and 7 rather convincingly indicate that patients with chronic hepatitis of a high degree of inflammatory activity show significant disorders of hepatic hemodynamics, manifested by a relatively high level of portal

Indicators Size, mm	CH of severe activity (n = 23)		M ± SD in patients of control group (n = 40)	p
	Limits of variation	M ± SD		
Liver				
Oblique size of the right lobe	120.0–205.0	186.13 ± 7.45	137.81 ± 1.79	>0.05
Anteroposterior size of the left lobe	66.0–114.0	90.61 ± 6.81	55.72 ± 1.87	>0.05
Anteroposterior size of the caudate lobe	21.0–30.0	17.63 ± 1.8	17.63 ± 1.83	>0.05
Spleen				
Area, sq. cm	31.9–45.1	40.93 ± 1.99	31.84 ± 1.49	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 5.
Liver and spleen dimensions in patients with chronic hepatitis of severe activity (M ± SD).

Indicators	CH of severe activity (n = 23)		M ± SD in patients of control group (n = 40)	p
	Limits of variation	M ± SD		
Inner diameter, mm	12.0–15.0	13.79 ± 1.01	10.22 ± 0.71	>0.05
Cross-sectional area, sq. cm.	1.13–1.77	1.51 ± 0.06	0.83 ± 0.04	>0.05
Max BFV, cm/s	15.1–20.0	17.33 ± 1.33	21.63 ± 2.71	>0.05
BVF, ml/min.	772.3–1863.9	1327.73 ± 315.81	1075.81 ± 83.61	>0.05
Portal vein pressure, mm H_2O	169.9–212.4	193.4 ± 9.47	113.0 ± 4.41	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 6.
Results of hemodynamic studies in the portal vein in patients with chronic hepatitis of severe activity (M ± SD).

pressure and dilatation of the portal and splenic veins without changing the velocity parameters of blood flow in them.

It is noted that the increase in portal pressure to the level of 185.5–197.2 mm H_2O leads to a change in hemodynamic parameters: diameter and linear and volumetric blood flow velocity in the portal (mainly) and splenic veins. At first, volumetric blood flow velocity increases due to pressure in the above veins.

Thus, in patients with chronic hepatitis, there were changes in the echographic parameters of the liver and spleen, as well as the parameters of portal hemodynamics, depending on the degree of development of the cytolytic syndrome.

Radiocontrast study performed in 108 patients found an increase in the size of the liver, and in 9 of them there was a diffuse uneven accumulation of radiopharmaceuticals in the liver and its redistribution into the spleen (in 36). In 45 cases, these changes are estimated as CH transition to liver cirrhosis.

Indicators	CH of severe activity (n = 23)		M ± SD in patients of control group (n = 40)	p
	CI (25–75%)	SD		
Inner diameter, mm	7.0–10.0	8.06 ± 0.91	6.41 ± 0.61	>0.05
Cross-sectional area, sq. cm.	0.44–0.81	0.59 ± 0.06	0.33 ± 0.02	>0.05
Max BFV, cm/s	15.1–19.02	16.78 ± 0.90	19.22 ± 2.23	>0.05
BVF, ml/min.	307.26–69,631.9	453.96 ± 99.08	345.41 ± 34.62	>0.05

p—Statistical significance of the difference between control group and patients with chronic hepatitis.

Table 7.
Results of hemodynamic studies in the splenic vein in patients with chronic hepatitis of severe activity (M ± SD).

EGD in 153 patients found inflammatory changes in the esophagus, stomach, and duodenum. At the same time, 18 of them revealed superficial, 72 erosive gastritis, 27 duodenitis, 36 duodenogastric, 27 duodenogastric, and 77 gastroesophageal refluxes; 27 patients with this group showed varicose veins of the lower third of the esophagus grades I–II.

A pronounced clinical manifestation of the disease allows a more correct assessment of the patient's condition and a correct preliminary diagnosis and determination of the correct diagnostic and therapeutic tactics. Ultrasound, radiocontrast study, and EGD in patients with chronic hepatitis of severe activity show an important diagnostic value and make it possible to identify some signs of a complicated course of the disease, which are not determined in a routine clinical study. Radiocontrast study in five patients, long before the liver biopsy, established signs of transition of CH to cirrhosis.

Pre- and intraoperative morphological studies of the liver in 16 patients of this group, in 7% of cases, established a histological picture of CPH, in 82% CAH, and in 11% CAH with transition to LC.

Thus, in the diagnosis of chronic hepatitis of severe activity, great importance, in addition to clinical, laboratory, and morphological data, is acquired by using modern noninvasive research methods, which provide sufficient information for correct diagnosis. In our opinion, in the diagnosis of CH of severe activity, it is necessary to give preference to noninvasive ultrasound and radiocontrast methods and resort to the use of invasive (biopsy, laparoscopy, etc.) ones only in exceptional cases, because any active interventions in this category of patients can lead to decompensation of the disease.

5. Cerebral hemodynamic influence on the current and prediction of hepatic encephalopathy

In recent decades, studies have been conducted on the effects of cirrhosis of the liver (LC) on the severity of chronic hepatic encephalopathy (HE), etiology, stage, and psychological characteristics of the personality [11–14]. HE can be subclinical, and the mortality rate among patients is up to 10% and is mostly associated with comorbidities, and not with complications of PG [15–18]. That is why the assessment of the degree of HE and the corresponding individualized approach to each patient in terms of the selection of therapy can significantly reduce the degree of encephalopathy, which also improves the quality of life of patients [19, 20]. In many pathological conditions, the occurrence of encephalopathy signals a disorder of brain metabolism, based on the formation of which is a violation of the blood-brain

barrier, the action of toxic substances, cerebral ischemia, cerebral hypoxia, the formation of endotoxins, and neurotransmitter disorders. In most cases, there is a combination of several pathophysiological mechanisms. And those, in turn, may lead to clinical picture of encephalopathy with cognitive, emotional, and motor impairment. However, despite numerous experimental and clinical studies of HE, the mechanism of its development remains controversial and controversial [21–24]. The purpose of this study is to assess the characteristics of cerebral hemodynamics in the extra- and intracranial sections with LC of viral etiology of classes A, B, and C according to Child-Pugh to improve the optimization of early diagnosis of complications of encephalopathy at various stages of its development.

It has been established that with an increase in the stage of hepatic encephalopathy, an increase in hemispheric asymmetry of blood flow in the middle cerebral arteries and in the time of the Reitan test is observed. The minimum time for connecting numbers during the test was noted at stage 1 of HE without comorbidity with circulatory encephalopathy (DE), the maximum with HE stage 3 in combination with DE stage 3.

Matrix analysis showed that, first, with an increase in the stages of hepatic encephalopathy, a statistically significant increase in the time to perform the Reitan test was observed. Secondly, the influence of the DE stages on the course of the HE stages is ambiguous, the minimum during stage I of the HE and the maximum with the HE of stage III. Thus, a statistically significant increase in the time of the Reitan test is recorded at stage I HE only in combination with stage III DE, at stage II HE, stage III DE, and stage III HE with any stage DE. When studying the characteristics of the relationship between the hemispheric asymmetry of the BFV in the MCA and the stages of HE, it was found that there is a fairly clear correlation between the hemisphere asymmetry of the blood flow in the MCA and the stages of the HE. Thus, with increasing stage of HE, hemispheric asymmetry of blood flow in MCA increases: the smallest hemisphere asymmetry of blood flow in MCA is observed with LC with clinical manifestations of HE of stages I–II and the greatest with HE of stages III–IV.

From the obtained results, it follows that the change in cerebral hemodynamics in patients with LC is noted already at the level of the extracranial section of the carotid arteries. The presence of age-related changes in the arteries, such as intimal thickening before the formation of atherosclerotic plaques of different height and length with the formation of stenosis, tortuosity of the vessels led to hemisphere asymmetry of blood flow in them from 25.1 ± 2.42 to 39.5 ± 7.94% with the dynamics of the statistical significance of this parameter in comparison with the norm from $p = 0.006936$ to $p = 0.000003$ for LC of classes A and C, respectively.

Functional disorders of cerebral hemodynamics at the level of the intracranial section manifested changes in blood flow velocity characteristics, lability of vascular resistance indices, hemispheric asymmetry of the blood flow, and decrease in the functional reserve of the connective arteries of the Willis circle. Against the background of atherosclerotic changes in the vascular wall and the lability of vascular resistance, there were large variations in the interquartile ranges of the velocity parameters of the blood flow and hemisphere asymmetry in the MCA with a general tendency of their medians to increase, which did not contradict the studies of other authors [25]. So, depending on the stage of compensation of the LC, there was a general tendency for the ACK (max) to increase from 110.7 ± 9.21 to 119.2 + 10.03 cm/s, ACK (min) from 48.5 = 9.76 up to 52.1 ± 10.95 cm/s, ASK (mean) from 69.6 ± 8.45 to 74.1—11 × 57 cm/s, and hemisphere asymmetry ASA (mean) from 24.9 ± 9.51 up to 33.9 ± 10.51 with LC of classes A and C, respectively. At the same time, it should be noted that there is a rather clear correlation between

the stages of HE and hemisphere asymmetry of blood flow (r = 0.495). So, with increasing stage of HE, hemispheric asymmetry of blood flow along the MCA increases, caused, in our opinion, on the one hand by atherosclerosis, on the other by the lability of vascular resistance due to vasoconstrictive substances (nitric oxide, endothelin-1), whose concentration in the blood often increases with LC and atherosclerosis, which has been confirmed elsewhere [26, 27]. At the same time, the co-dependent indicators of vascular resistance had a clear downward trend depending on the degree of compensation of the LC. The dynamics of the statistical significance of this parameter in comparison with the norm for RI became reliable from p = 0.245844 to p = 0.002776 and PI from 0.071383 to 0.012336 with LC of classes A and C, respectively.

When conducting a comparative analysis of the blood flow velocity in MCA, two types of blood flow were identified—hypokinetic and hyperkinetic. Thus, with class C LC, in 21.4% of cases, the hyperkinetic type of blood flow was observed and which probably had a compensatory mechanism. In LC, damage occurs to the endothelial cells of the hepatic sinusoids, and the latter leads to a significant increase in the level of endothelin. With liver damage and the development of portal hypertension, the production of intrahepatic nitric oxide decreases, which leads to its imbalance. It should be noted that the known mechanisms of participation of endothelial dysfunction can be distinguished by the suppression of the excretion or inactivation of endothelial NO synthase and a decrease in the synthesis of NO, due to an increase in the level of cytokines and TNF-a, which suppress the synthesis of nitric oxide. During the formation of portal hypertension, the process of separation of the organ and the general blood flow is observed due to the development of an imbalance between vasodilating and vasoconstrictive substances. The release of vasoactive substances (histamine, serotonin), circulating vasodilators into the blood from damaged hepatocytes, leads to generalized vasodilation and a decrease in vascular resistance, which was confirmed in [28–31].

The data obtained by us indicate disorders in endothelium-dependent vasodilation and the vasomotor function of the endothelium in LC at various stages of compensation and are to a certain extent confirmed in [32–36]. Hemodynamics in the brain at a constant level was possible due to the normal functioning of the autoregulation mechanism, which ensured an unchanged level of the cerebral blood flow in the form of vasodilatation or vasoconstriction. At the same time, in the beyond vasodilation, the phenomenon of "sausage string" with segmental dilatation of arterioles may occur, against the background of which there is a danger of blood breakthrough into the brain tissue and the development of acute disorders of cerebral circulation. In the prospective observation, the autopsy material of the brain served as confirmation of this phenomenon and the development of dyscirculatory disorders from minimal to irreversible in LC.

6. Conclusion

Chronic hepatic encephalopathy due to LC with a frequency of up to 75% of cases can occur in comorbidity with dyscirculatory disorders from minimal to irreversible, which aggravates the clinical course of hepatic encephalopathy.

The effect of dyscirculatory disorders on the clinical course of the stages of hepatic encephalopathy is ambiguous. The minimal effect is observed at stage I of hepatic encephalopathy, the maximum at hepatic encephalopathy of stage III in comorbidity with the stages of dyscirculatory encephalopathy. The degree of cognitive and dyscirculatory disorders is interrelated with the stages of compensation for cirrhosis of the liver. With dyscirculatory disorders and a decrease in the stage of

compensation for cirrhosis of the liver, there is an increase in the degree of cognitive impairment from the ability to logical thinking and attention to disorientation in time and space.

The Reitan test duration is more than 200 s, the presence of hemispheric asymmetry of the blood flow is more than 40%, and the decrease in the velocity parameters of the blood flow and vascular resistance indices in the basins of the middle cerebral arteries below the reference values are associated with an unfavorable prognosis of hepatic encephalopathy due to the possibility of the sausage-string phenomenon with the risk of development acute disorders of cerebral circulation of hemorrhagic type, development of venous stasis, and swelling in the brain.

Conflict of interest

All authors have not disclosed potential conflicts of interest regarding the content of this paper. The research was made in the frame of the work plan of Post Diploma Education and Polyclinic Therapy of NovSU and budget financing of city treatment and prevention institutions.

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