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Cerebral Hemodynamics Influence on the Current and Prediction of Hepatic Encephalopathy

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Abstract: Among patients of different ages with hepatocirrhosis of A, B, C virus viral etiology in Child-Pugh, chronic hepatic encephalopathy of all stages may occur along with discirculatory disorders with the development of chronic cerebrovascular insufficiency. The Reitan test duration is more than 200 seconds, blood flow hemispheric asymmetry is more than 40%, the decrease in the velocity parameters of the blood flow and the indices of vascular resistance in the basins of the middle cerebral arteries decrease below the reference values are associated with the adverse hepatic encephalopathy prognosis. The degrees of cognitive and discirculatory disorders are interrelated with the compensation stages for hepatocirrhosis. An increase of cognitive impairment degree from the logical thinking ability and attention to time and space disorientation is registered along with discirculatory disorders and cirrhosis compensation stage decrease.

Keywords: Hepatocirrhosis, Hepatic Encephalopathy, Cerebral Hemodynamics, Dyscirculatory Disorders, Discirculatory Encephalopathy

1. Introduction

Worldwide, there has been a steady increase in hepatocirrhosis cases with rapid disability of patients. Researches have been initiated for the past decades of hepatocirrhosis effect on the hepatic encephalopathy severity, etiology, disease stage, and psychological characteristics of the personality [5, 7, 11, 17]. The modern approaches to hepatocirrhosis therapy, should necessarily consider the etiologic factor, the relief of pathogenetic reactions that support the process activity, the prevention of hepatocirrhosis growth, the treatment of disease symptoms and complications such as portal hypertension, hepatic encephalopathy, ascites, ascitic peritonitis and hepatorenal syndrome. Hepatic encephalopathy can be subclinical, but patients mortality is up to 10% and it is closely related with concomitant pathology, but not with portal hypertension complications [2, 14, 18, 19]. Therefore, the evaluation of the hepatocirrhosis degree and the corresponding individualized approach to each patient in terms of therapy selection can significantly reduce its stage, which also allows improving the quality of patients life [12, 13].

The emergence of hepatic encephalopathy warnings of the brain metabolism violation, formed by blood-brain barrier violation, toxic substances effect, cerebral ischemia, cerebral hypoxia, endotoxins formation, neurotransmitter disorders. There is a combination of several pathophysiological mechanisms, in most cases. Leading in the clinical picture of encephalopathy are cognitive, emotional and motor disorders. At the same time, despite numerous experimental and clinical studies on chronic hepatic encephalopathy, the mechanism of its development remains controversial and contradictory, and the effect of concomitant pathology on its clinical course and outcome is not excluded [3, 4, 10, 21].

The purpose of research is to study the peculiarities of cerebral hemodynamics parameters in extra- and intracranial

divisions in case of hepatocirrhosis of types A, B and C on Child-Pugh viral etiology to determine the dyscirculatory disorders possible effects on the chronic hepatic encephalopathy clinical course and outcome.

2. Methods

107 (87 (81.3%) men and 20 (18.7%) women) of patients with hepatocirrhosis in the outcome of chronic viral hepatitis were examined. In case of PCR diagnosis, HBV infection, HCV infection, HBV + HCV infection were registered in 35.1, 46.1 and 18.8% of cases. The patients' age ranged from 35 to 70 years (average age was 58.5 ± 4.7 years). All the patients were divided by the Child-Pugh classification (1996), into 3 groups: group I (n = 35) comprised patients of Child-Pugh class A, group II (n = 37) - patients Child-Pugh class B, in III group (n = 35) included patients Child - Pugh class C. The control group consisted of 30 healthy volunteers (blood donors).

A complex of clinical, laboratory and instrumental diagnostic methods was conducted to confirm the hepatocirrhosis diagnosis, its etiology, the stage of compensation and complications, the clinical presentation and anamnesis were studied. Clinical and biochemical blood tests were performed by enzymatic, colometric, enzymatic-colometric, immunoturbidimetric and kinetic methods using the diagnostic complex Cobas 6000 (Roche Diagnostics). The hepatocirrhosis stage was estimated by METAVIR and ISHAK using Bonacini cirrhosis discriminant score. Clinical hepatocirrhosis diagnosis, its severity estimation, basic and additional instrumental examinations were carried out according with the recommendations the 11th World Gastroenterologists Congress working group protocol (2015).

The hepatic encephalopathy stages evaluation was carried out with West-Haven criteria and Reitan test (Number Connection Test). For differential diagnosis of hepatocirrhosis and its complications a number of examinations were performed: abdominal and brain using CT and MRI methods, electroencephalography, diagnosis of esophagus and ventricle varicosity with the method of fiberoptic gastroduodenoscopy.

Ultrasound diagnostics of cerebral hemodynamics was performed with ultrasound equipment "PHILIPS EPIQ 7G" (USA) according to W. J. Zwiebel, J. S. Pellerito method (2010). Cerebral blood flow diagnostics included registering blood flow parameters of the internal carotid (ICA) and middle cerebral arteries (MCA) of the first order of both hemispheres: maximal, minimal, average blood flow velocities, contralateral asymmetry of LCS, angle-independent blood flow parameters (RI and PI).

Obtained clinical and laboratory-instrumental data processing was performed with parametric and nonparametric statistics criteria. The resulting statistical material was grouped into variational series, which were further analyzed for the distribution correspondence with descriptive statistics and the Gauss-Laplace law. The value of the Gaussian density distribution was estimated in terms of the interquartile range (QR). The relationship extent between the individual characteristics was determined with Spearman's statistics. The obtained data statistical processing was performed directly with computer statistical software Stat Soft Statistica, version 10.0.

3. Results and Discussion

When studying the blood flow parameters, CMM in the ICA of hepatocirrhosis types A, B and C, it was revealed that significant differences are noted between the CMM values, hemispheric asymmetry of blood flow of hepatocirrhosis types A, B, C values and normal values. At the same time, there were no significant differences between the angle-independent indices for all hepatocirrhosis types and normal values, their reference values were within the normal range (see Table 1).

Table 1. *Structural and hemodynamic parameters in the ICA with hepatocirrhosis types A, B and C and normal values.*

Characteristic	Hepatocirrhosis type A	Hepatocirrhosis type B	Hepatocirrhosis type C	Control Value
CMM, mm	0.69±0.21* (0.00041)	0.74±0.21* (0.00003)	0.79±0.35* (0.00001)	0.61±0.06
BFLV hemispheric asymmetry,%	25.1±2.42 (0.00693)*	29.±7.05 (0.00015)*	39.5±7.94 (0.00003)*	20.6±1.45
RI	0.62±0.09 (0.24584)	0.61±0.08 (0.25574)	0.60±0.12 (0.28678)	0.63±0.09
PI	1.23±0.19 (0.07138)	1.22±0.21 (0.07233)	1.21±0.25 (0.39679)	1.24±0,16

Note: * - p values comparing parameters of hepatocirrhosis types A, B and C and normal values.

Analyzing the blood flow parameters of the first order middle cerebral arteries of both hemispheres with hepatocirrhosis types A, B and C, statistically significant differences are noted: between the values of the blood flow hemispheric asymmetry of all hepatocirrhosis types and the normal values, between A and C types, between the angle-independent blood flow parameters of B, C types the normal values. The highest indices of statistical significance of the parameters differences are typical between hepatocirrhosis type C and the normal values, among all hemodynamic parameters - between values of hemispheric asymmetry of blood flow (see Table 2).

Table 2. *Average middle cerebral artery blood flow values with hepatocirrhosis types A, B, C and normal values.*

Blood flow parameters	Hepatocirrhosis type A	Hepatocirrhosis type B	Hepatocirrhosis type C	Control Value
BFLV (max), см/с	110.7±9.21 (0.31703)	115.1±9.03 (0.12595)	119.2±10.03 (0.00315)*	108.15±5.03
BFLV (min), см/с	48.5±9.76 (0.07599)	50.9±9.66 (0.00068)*	52.1±10.95 (0.00000)*	46.55±1.76
BFLV (average), м/с	69.6±8.45 (0.127354)	72.1±9.67 (0.158141)	74.1±11.57 (0.000238)*	67.05±2.67
BFLV hemispheric asymmetry,%	24.9±7.53 (0.00693)*	27.5±9.06 (0.00015)*	35.9±9.54 (0.00001)* (0.00218)**	22.55±1.51
RI	0.62±0.07 (0.24584)	0.57±0.11 (0.02030)*	0.49±0.22 (0.00277)*	0.571±0.01
PI,	1.98±0.13 (0.07138)	1.07±0.14 (0.05000)*	1.02±0.21 (0.01233)*	0.922±0.04

Note: * - * - p values comparing parameters of hepatocirrhosis types A, B and C and normal values; ** - p values comparing hepatocirrhosis types A and C.

The main signs of discirculatory disorders (DD) in ultrasound examination were the BFLV hemispheric asymmetry due to carotid and middle cerebral arteries blood flow qualitative and quantitative changes. The presence of blood flow hemispheric asymmetry was associated with the development of discirculatory disorders and was confirmed by neurovisualization and the brain autopsy. Thus, depending on the stage of discirculatory encephalopathy during the brain CT were revealed such parameters as: the enhanced vascular pattern, the dilatation of the diploid veins channels, the cerebral and cerebellum sulcus expansion, leukoarzosis of different types, territorial infarctions and lacunae of various numbers and widths, the lateral ventricles widening, hemisphere lobes and cortex atrophy. In a prospective monitoring, the brain autopsy material served as confirmation of hepatic encephalopathy and discirculatory disorders comorbidity from minimal to irreversible along with hepatocirrhosis. Morphological studies of the arterial bed showed destructive nature changes due to thickening of the internal membrane, endothelial cells swelling, plasmorrhagia, endothelial layer loosening and edema, thinning of the middle muscle membrane until its complete disappearance, muscle cells destruction, the presence of perivascular edema and macrophage infiltration. The change of the venous bed was revealed by plethora, stenosis and sclerosis. In dialated veins and venules the signs of plethora and stasis, minor deep lacunar infarcts, as well as cascading and fascicular arteriolo-venular anastomoses were noted. Apparent edema and features of hypoxia (lysis of cells with "shadow" formations, fibers loosening and nerve cells prolapse) marked the nervous tissue around and near the vessels. In this case, insignificant number of astrocytes persisted or died.

Realization of Reitan test with patients with clinico-instrumental signs of hepatic encephalopathy and discirculatory disorders comorbidity relation, it was revealed that increasing stages of hepatic encephalopathy along with discirculatory disorders development of all types of hepatocirrhosis, the duration of the Reitan test increased (see Table 3). So the minimum time (75.6 ± 7.1 seconds) for the number combination in the test was recorded with 1st stage of hepatic encephalopathy without discirculatory encephalopathy comorbidity, the maximum time (239.9 ± 26.2 seconds) - was recorded with 3rd stage of hepatic encephalopathy in combination with discirculatory encephalopathy. Determining the significance among the stages of hepatic encephalopathy along with discirculatory encephalopathy comorbidity, it was found that, firstly, as the hepatic encephalopathy stages increase, there was a statistically significant increase of the Reitan test duration. Secondly, the effect of the discirculatory encephalopathy stages on the course of hepatic encephalopathy stages is not single-valued, the minimum is with the 1st stage of the hepatic encephalopathy, the maximum - with the 3rd stage hepatic encephalopathy.

Table 3. *The Reitan test data of hepatic encephalopathy and discirculatory encephalopathy comorbidity.*

Diagnosis	Parameters					
	Me	25%-75%	Min.	Max.	M±SD	Reitan test
hepatic encephalopathy 1st stage	77	70÷80	65	87	75.6±7.1	60-90
hepatic encephalopathy 1st stage with discirculatory encephalopathy	90	90÷91	89	93	90.3±1.1 0.000001*	
hepatic encephalopathy 2nd stage	103	100÷114	100	119	105.9±7.5	90-120
hepatic encephalopathy 2nd stage with discirculatory encephalopathy	124	120÷131	120	131	125.5±4.9 0.000000**	
hepatic encephalopathy 3rd stage	151	144÷155	136	156	148.9±7.1	>120
hepatic encephalopathy 3rd stage with discirculatory encephalopathy	251	209÷255	203	285	239.9±26.2 0.000000***	

Note: * ** *** - the values of p are given respectively to hepatic encephalopathy indicators of 1st, 2nd and 3rd stages.

In addition, as the stage of hepatic encephalopathy increases, there is an increase of middle cerebral artery blood flow hemispheric asymmetry and the Trail Making Test duration. In addition, when studying the type of relation between the hemispheric asymmetry of lineal blood flow velocity of middle cerebral artery and the hepatic encephalopathy stages, it was revealed that a distinct relation exists between the hemispheric asymmetry of middle cerebral artery blood flow and the hepatic encephalopathy stages, although with no presence of a direct relation. Thus, as the hepatic encephalopathy stage increases, the hemispheric asymmetry of middle cerebral artery blood flow increases: the minor hemispheric asymmetry of middle cerebral artery blood flow is observed within hepatocirrhosis with clinical presentations of the hepatic encephalopathy stages I-II, the major - with hepatic encephalopathy stages III-IV (see Table 4).

Table 4. *Middle cerebral artery blood flow hemispheric asymmetry and the Reitan test with hepatic encephalopathy of different stages parameters.*

Parameters	hepatic encephalopathy 1st stage	hepatic encephalopathy 2nd stage	hepatic encephalopathy 3rd stage	Control Value
Middle cerebral artery blood flow hemispheric asymmetry,%	24.9±7.53 (0.00693)*	27.5±9.06 (0.00015)*	38.9±7.54 (0.00001)* (0.00218)**	22.55±1.51
Trail Making Test, sec	81.2±7.1 (0.00036)×	115.9±7.5 (0.00011)× (0.00025)××	198.9±7.1 (0.00000)× (0.00091)×××	38.81±3,88

Note: * ×-p between the hepatic encephalopathy stages and the control value; ** ××-p between the 1st and 2nd stages; ×××-p between the 2nd and 3rd stages.

The obtained research shows that changes of cerebral hemodynamics with hepatocirrhosis are already noted at the level of the extracranial section of carotid arteries due to thickening of the intima-media complex and hemispheric asymmetry development and associated with the hepatic encephalopathy stages. Functional changes of cerebral hemodynamics at the level of the intracranial section were revealed by the blood flow velocity parameter changes, by the lability of vascular resistance indexes, by blood flow hemispheric asymmetry, and by a decrease of the functional reserve of the Willius circle connecting arteries. Against the backdrop of atherosclerotic changes of the vascular wall and the lability of vascular resistance, there were large variations of the interquantile range of the blood flow velocity parameters and middle cerebral artery blood flow hemispheric asymmetry with a general tendency of its' medians to increase, which did not contradict the researches of other authors [8]. With the hepatic encephalopathy stages increase, the middle cerebral artery blood flow hemispheric asymmetry increased, which was caused by the atherosclerosis process on the one hand, and on the other - by the lability of the vascular resistance due to vasoconstrictive substances (nitric oxide, endothelin-1), whose concentrations in the blood often increase with hepatocirrhosis and atherosclerosis, which was confirmed in other studies [1, 9At the same time, the non-dependent indices of vascular resistance decreased and were associated with the severity of hepatic encephalopathy and the stage of hepatocirrhosis compensation. Thus, the lowest RI and PI values were typical for hepatocirrhosis type C. The imbalance of vascular tone can be explained by the development of varicose veins of various sizes with decompression development and endothelial dysfunction, nitric oxide level imbalance, often encountered with hypercytokinemia. It is also proven now, that the essential direction of endothelial function is participation in an adequate blood flow formation. But, at the same time, along with the damaging agents effect, its positive role changes dramatically and its dysfunction develops: vasodilation, vasoconstriction and the changes of biologically active substances production, nitric oxide particularly. Also, due to hepatocirrhosis, endothelial cells of hepatic sinusoids damage occurs, and it leads to a significant increase of the endothelin level. Along with liver damage and portal hypertension development, production of intrahepatic nitric oxide decreases, which leads to its imbalance. It should be noted that among the known endothelial dysfunction mechanisms of involvement, one can mark the depression of excretion or inactivation of endothelial NO synthase and decrease of NO synthesis, caused by an increase of cytokines and TNF-α suppressing the nitric oxide synthesis level. During the portal hypertension developing, there is a process of organ and total blood flow dissociation due to development of an imbalance between vasodilating and vasoconstrictive substances. The inflow of vasoactive substances (histamine, serotonin), circulating vasodilators into the blood from damaged hepatocytes leads to generalized vasodilation and decrease in vascular resistance, which is confirmed in studies [22 ± 25]. The results indicate the violations of endothelium vasomotor function with hepatocirrhosis of different compensation types, and to a certain extent they are confirmed by studies [6, 15, 16, 20, 26]. Therefore, the brain hemodynamics of a constant level was possible due to the normal functioning of the autoregulation mechanism, which provided an invariable level of volumetric cerebral blood flow in the form of vasodilation or vasoconstriction.

So, the patients with hepatocirrhosis of all types on the background of hepatic encephalopathy and discirculatory disorders comorbidity in the brain, get arterial and venous beds hemodynamics violations with nervous tissue edema and, as a consequence, chronic hepatic encephalopathy of all stages can occur against the background of discirculatory disorders with chronic cerebrovascular insufficiency (HCVN) development. The Reitan test duration more than 200 seconds, the presence of the blood

flow hemispheric asymmetry is more than 40%, the decrease of the blood flow velocity parameters (maximum and minimum below 80 cm / s and 40 cm / s, respectively), as well as resistance values below 0.44, is associated with an negative prognosis of clinical course of different stages hepatic encephalopathy for all hepatocirrhosis types. Vascular resistance reduction, blood flow parameters changes, the presence of hemispheric asymmetry lead to chronic cerebrovascular insufficiency, which worsened the course of the hepatic encephalopathy itself. At the same time, the degrees of cognitive and discirculatory disorders are interrelated with the stages of hepatocirrhosis compensation. So, with discirculatory disorders and hepatocirrhosis compensation stage reduction, an increase of cognitive impairment degree from the ability to logical thinking, attention to disorientation in time and space is noted. The obtained data indicate that, depending on the intensity, severity of cirrhosis liver damage, and cerebral hemodynamics parameters disorders, each stage of the pathological process progress and compensation stages has its own peculiarities with their interrelationship, functional liver condition, and a number of laboratory indices. Also, with hepatocirrhosis compensation stage reduction and with an increase in hepatic encephalopathy stage, the degree of the blood flow asymmetry increases. Taking into account all the factors involved in the cerebral hemodynamics regulation, the presence of individual peculiarities of the disease course, such a conclusion, seems to be completely justified.

4. Conclusion

Cirrhosis of the viral etiology of A, B, C types with chronic hepatic encephalopathy of all stages can proceed along with discirculatory disorders developing chronic cerebrovascular insufficiency. The duration of Reitan test is more than 200 seconds, the presence of blood flow hemispheric asymmetry is more than 40%, blood flow rate parameters and the indices of vascular resistance in the basins of the middle cerebral arteries decrease below the reference values are associated with the adverse prognosis of hepatic encephalopathy. The degrees of cognitive and discirculatory disorders are interrelated with the stages of liver cirrhosis compensation. Along with discirculatory disorders and cirrhosis compensation stage decrease, an increase of cognitive impairment degree is noted - from the ability to logical thinking, attention to disorientation in time and space.

Disclosures

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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