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DYNAMICS OF FUNCTIONAL AND MORPHOLOGICAL PARAMETERS OF MICROCIRCULATION IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS DUE TO AN INFECTIOUS MONONUCLEOSIS

ABSTRACT

The aim of our work was to assess the effectiveness using of the combination of a hepatoprotector phosphogliv and immunomodulator cycloferon on the state of functional and morphological parameters of microcirculation in patients with non-alcoholic steatohepatitis (NASH) after infectious mononucleosis (IM).

We examined 78 patients with a diagnosis of fatty liver disease after infection mononucleosis in age from 19 to 46 years, divided into two groups. The main group included 40 patients who received as therapy combination of drugs phosphogliv and cycloferon. The comparison group consisted of patients (n=38) who received conventional NASH treatment. To examine the state of microhemodynamics we used the slit lamp universal ml-2M, morphometry of capillaries of the nail bed capillaroscope carried the M-60 A.

For MCR morphological study we calculated indices of vascular, intravascular, extravascular disorders and General (integrated) conjunctival index using the formula $KI. = KI1+KI2+KI3$. In the result, it was found that patients with fatty liver disease was due to infectious mononucleosis there are significant violations on the part of all departments of the MCR. Standard treatment for patients with this comorbid pathology improves morphological and functional parameters of microcirculation, but not effectively and rapidly than the combination of phosphoglyceride and cycloferon. So, using the combination of hepatoprotector phosphogliv and immunomodulator cycloferon in patients with fatty liver disease after infectious mononucleosis authentically significantly contributes the elimination of the phenomena of stasis and sludge syndrome in the arterioles and capillaries, and accelerate blood circulation.

Keywords: non-alcoholic steatohepatitis, infectious mononucleosis, indicators of microcirculation.

Introduction. Knowing about modern literature information, chronic diseases of liver, in particular non – alcoholic steatohepatitis (NASH), are becoming increasingly common and relevant. For the residents of ecologically unfavorable, large industrial region of Donbass, the situation is complicated by the fact that in conditions of high level of environmental pollution by xenobiotics, the functional state of liver parenchyma is significantly disturbed due to the negative influence of toxic compounds, which contributes to the increase in the incidence of chronic diffuse liver diseases, including NASG [4, 12]. Moreover, in the conditions of ecologically unfavorable regions the probability of secondary immunodeficiency states [9, 10], which becomes the cause of infectious mononucleosis (IM) in Donbas. There are assumptions that immune disorders, which are characteristic of NASH and IM, correlate with shifts in microhemodynamics, reducing the amount of perfusion with arterial blood of the liver, and thus play a significant role in the progression of chronic lesions of its parenchyma [6, 11, 12].

There is no consensus according to the NASH therapy, is it necessary to use some hepatoprotector's. Several sources indicate that hepatoprotective funds are first-line drugs, others do not give them so much importance [5, 8]. Hepatoprotector phosphogliv contains two active substances: phosphatidylcholine (P) and glitizirrinova acid (GLA). This successful combination has allowed as a highly effective hepatoprotector [1]. We

believe that the scope of phosphogliv can be expanded. So, we thought it promising to analyze the influence of hepatoprotector phosphogliv in combination with the inductor of endogenous interferon cycloferon, often used to treat infectious mononucleosis at the state of the microcirculation (MC) in patients with fatty liver disease was due to infectious mononucleosis.

The aim – to study the efficacy using the combination of medicines of phosphogliv and cycloferon on the functional and morphological characteristics of microcirculation in patients with NASG as a result after IM.

Materials and methods of research. Under our supervision there were 78 patients with diagnosis of NASH as a result of IM. The age of the examined patients ranged from 19 to 46 years, including 36 men (46.2%) and 42 women (53.8%). All patients were divided into two groups: basic, consisting of 40 people and a comparison group, consisting of 38 people. Both groups were randomized by age, sex, duration of course and frequency of NASH exacerbations.

The diagnosis of NASH was confirmed on the basis of anamnesis morbi et vitae, clinical, laboratory and instrumental methods of research. The generally accepted routine laboratory methods of the study included the clinical analysis of blood and urine, the study of the content of glucose in the blood. To assess the functional state of the liver, biochemical parameters in the blood were studied: the level of total bilirubin and its fractions (direct and indirect), the

activity of serum aminotransferase – AlAT and ASAT; the content of cholesterol and albumin, the activity of excretory enzymes – alkaline phosphatase (AF) and gamaglutamyltranspeptidase (GGTP), the thymol sample indicator. Ultrasound examination of the liver was performed using a digital diagnostic system SonoScape SSI 8000 (sensors-C362 2-6 MHz; L743 5-15 MHz; 6V3 3-11 MHz; 2P1 1-4.4 MHz), at the same time we noted diffuse hyperechogenicity of liver parenchyma, heterogeneity of its structure and fuzzy vascular pattern [4]. To exclude viral infection of the liver, a study was conducted of serum for markers of viral hepatitis (VH) – HBV, HCV and HDV using ELISA method. Persons who, according to the medical history, abused alcoholic beverages and were registered with a narcologist, or had experience in the introduction of narcotic substances, were also excluded from the work.

The diagnosis of IM was made taking into account epidemiological data and clinical picture. Laboratory confirmation of the disease was lymphomonocytosis and the content of atypical mononuclears over 10%, the detection of specific antibodies of IgM class to the capsid antigen VCA, to the early antigen (EA) and to the nuclear antigen (NA-1) in the acute period of the disease in the serum of ELISA method, as well as the identification by polymerase chain reaction (PCR) DNA virus [7]. At the time of the study, patients were predominantly in the convalescence stage, which was confirmed by an

increased content of IgG antibodies to virus antigens. Mandatory conditions were the exclusion of HIV infection, other forms of replicating herpesvirus infections: HSVS, BB3, CMV, HSV 6.

All the examined patients received conventional treatment. The therapy included diet food-table № 5, enriched with lipotropic ingredients with limited animal fats and cholesterol, and common treatment, which included detoxification therapy, herbal hepatoprotectors, enterosorbents, antioxidants and vitamins. In General, the treatment of the examined patients was carried out in accordance with the methodological recommendations «Diagnosis and treatment of non-alcoholic fatty liver disease» [5]. Patients of the main group received additional hepatoprotector phosphogliv 2 capsules 3 times a day for the first 2 weeks, and then 1 capsule 3 times a day for 30-40 days, and cycloferon 12.5% 2 ml/m 1 time a day for 5 days, then 2 ml/m a day (total for the course of treatment 10-12 injections), if necessary, patients were transferred to the tablet forms. Patients of comparison group received only conventional treatment as hepatoprotectors of plant used (karsil or silibor).

As the main method of studying the state of microcirculation in the examined patients, we used a universal lamp designed for visual biomicroscopy of bulbar conjunctiva (BBC), and we performed morphometry of capillaries of the nail bed using a capillaroscope M-60 a [2]. We analyzed the course and caliber of microvessels, the presence of vascular aneurysms and glomeruli, the speed and nature of blood flow in the microcirculatory bed, the number of functioning capillaries and the state of the extravascular zones. For the quantitative analysis of the expression of morphological change, we calculated the vascular index (KI1), intravascular (KI2), extravascular (perivascular) (KI3) violations [2, 12], and the total (integral) conjunctival index (KI.) according to the formula: $KI. = KI1 + KI2 + KI3$. The obtained results were statistically processed with the calculation of mean values ($M \pm m$) using the Student's reliability criterion (statistically reliable results were considered at the value $P \leq 0.05$, and highly reliable at $P \leq 0.01$). The results of the study were processed using the Microsoft Excel and PAST software.

Results and discussion. Most of the examined patients (73 people, 93,6%) with non-alcoholic steatohepatitis as a result of infectious mononucleosis before treatment had complaints of periodic general weakness, fatigue, which often did not disappear after rest. Characteristic (pattern 79,5%) for them was also a decrease

in appetite, periodically arising a sense of «gravity» in the right hypochondrium (69,2%), bitterness or metallic taste in the mouth (78,2%). 18 patients (23,1%) had low-grade fever often occurs, mostly in the evening. At objective examination we observed a slight subicteric sclera in 43 patients (55,1%), while 69 people (88,4%) - presence of blue sclera (a sign of Vysokovich), in 36 patients (46.2 per cent) increase in size of the liver, which has performed at 2-3 cm from under the rib cage, the seal, the sensitivity of the liver edge palpation. In general, this clinical picture corresponded to the exacerbation of steatohepatitis due to infectious mononucleosis.

Biochemical examination found that in some patients (34 people, 58.6 %) there was an increase in the content of total bilirubin in serum, which averaged 29.5-36.5 mmol / l; at the same time, the activity of Alat in all patients was increased within 0.9-1.6 mmol/ g·l, ASAT was also increased and amounted to 0.7 – 1.55 mmol/ g·l. The activity of GGTP and SCF corresponded to the values of the norm, which indicated the absence of a cholesterol component in the examined patients. However, we have seen an increase in thymol samples in the range of 5.6 to 7.9 units. In general, according to clinical and biochemical studies, we noted a moderate exacerbation or unstable remission of NASH in all patients. Ultrasound of the liver in the majority of patients (92,3%) revealed diffuse enlargement of the «brightness» of the hepatic parenchyma with the presence of small amounts of fine-grained inclusions, the uniformity of its contours, blurring of vascular pattern, the distal attenuation of the echo signal, which is a characteristic sonographic picture of NASH. Noninvasive diagnosis was performed on the FibroScan device, where in most cases a moderate stage of fibrosis was detected from F1 (54 people, 69.2%) to F2 (24 people, 30.8%).

Analysis of the obtained data on the morphological and functional parameters of MCR showed that before the start of therapeutic measures in patients we found the same type of microcirculation disorders. All departments of MCR – vascular, intravascular and paravasal-were involved in the pathological process. We have established a generalized spasm of arterioles, dilation of venules with unevenness of their caliber, a significant reduction in the total number of functioning capillaries with the formation of sufficiently large avascular zones. There were also clearly expressed intravascular disorders, namely, slowing blood flow in the veins, sometimes up to the development of the stasis, against the background of

sludge syndrome of II-III degree. In a number of patients, we were able to detect more pronounced disorders of microhemodynamics - sludge syndrome of III-IV degree not only in venules, but also in capillaries and arterioles. Extravascular disorders manifested perivascular edema, and the presence of microhemorrhage and pigmentation (dark-brown to yellow-brown), indicating long-existing disorders. When the morphometry of capillaries of the nail bed in patients, we noted the pallor and the haze of the background, the lack of visibility of the capillary loops due to edema pericapillary. A number of capillaries had a different shape due to deformation: twisty, comma, dots or eights. Therefore, the use of both methods – BBC and morphometry of capillaries of the nail bed confirmed the presence of expressed violations of microhemodynamics.

In the study of conjunctival indices, we found that the studied KI were significantly higher than normal (table.1). It can be seen from the table that before the start of therapeutic measures the index KI1 in the examined patients of the basic group significantly exceeded the norm, on average - 3.4 times ($P < 0.05$). At the same time, KI2 was significantly increased by an average of 2.6 times ($P < 0.05$), which indicates intravascular disorders. Coefficient KI3 before treatment was significantly increased-8.5 times ($P < 0.05$) relative to the norm. After all, the integral index is KI, was above the norm before the start of therapeutic measures 3.4 times ($P < 0.05$). In comparison group group: index KI1 exceeded normal values 3.3-fold ($P < 0.05$); KI2 – similar to almost 2.6 times ($P < 0.05$); the coefficient KI3 – 9.5 times ($P < 0.05$). Integral index – KI. in patients of comparison group were also above normal by 3.4 times ($P < 0.05$). The obtained data indicate the presence of pronounced disorders in the MCR system of both morphological and functional character.

After completion of the course of treatment, a repeated study of the state of MCR allowed to establish that in patients of the basic group there was almost complete normalization of vascular, intravascular and extravascular indices, and as a consequence – normalization of the conjunctival index, while in patients of the comparison group receiving conventional treatment, there was only a tendency to improve the studied parameters, with their data significantly different from those of the norm and the basic group. So (table.2), KI1 in the examined patients of the basic group were 1.08 times higher than normal ($P < 0.05$), KI2 only 1.2 times higher than normal ($P < 0.05$), figure KI3 on average 2 times higher than normal ($P < 0.05$). Finally,

the integral index KI after the course of treatment exceeded an average of 1.2 times the corresponding rate ($P < 0.05$). So, the indicators of MCR after treatment in patients of the comparison group, they are significantly higher than the norm and similar indicators of the basic group, were as follows: KI1 was 1.6 times higher than the norm, KI2 - 1.8 times KI3 – almost 5 times, and finally, the integral index KI. in patients of this group exceeded the average of 1.85 times the corresponding index norm ($P < 0.05$).

In addition, when conducting a BBC it was found that the treatment of basic group patients receiving the combination of drugs phosphogliv and cycloferon, had disappeared avascular zones and stasis of blood, accelerate blood circulation, elimination of sludge syndrome in the arterioles and capillaries. A similar trend was found in capillary morphometry: in patients of the basic group pallor and background turbidity disappeared, the number of functioning capillary loops increased, the shape of capillaries and their caliber normalized, blood flow accelerated. Morphometry of capillaries in patients of the comparison group showed that the murky and pale capillaroscopic background was noticeably preserved, the number of non-functioning capillaries remained, their poor visibility due to the presence of pericapillary edema.

Thus, the obtained data testify to positive influence of combinations of drugs in the form of a hepatoprotector phosphogliv and inducer of endogenous interferon-cycloferon on the state of the MCR and microhemodynamics in patients with this comorbid pathology. It is proved that the use of this combination of drugs contributes to the restoration of morphological and functional parameters of MCR and improve microcirculation. On this basis, it is possible to recommend the use of a combination of drugs in the form of phosphogliv and cycloferon in the treatment of patients with non-alcoholic steatohepatitis due to infectious mononucleosis.

Summary:

1. In patients with non – alcoholic steatohepatitis as a result of infectious mononucleosis revealed distinct functional and morphological disorders of the MCR, which cover all its departments-vascular, intravascular and extravascular.

2. Prior to treatment, all patients in both groups had similar changes of conjunctival indices in the form of a significant excess of their normal values.

3. The inclusion of a combination of drugs with phosphogliv and cycloferon in the treatment of patients with non-alcoholic steatohepatitis on the background of

Conjunctival indices in patients with non-alcoholic steatohepatitis on the background of infectious mononucleosis before and after treatment ($M \pm m$)

Conjunctival indice	Norm	Before treatment		After treatment	
		basic group (n=40)	comparison group (n=38)	basic group (n=40)	comparison group (n=38)
KI1	2,4±0,12	8,1±0,04***	7,9±0,02***	2,6±0,02***	3,8±0,04***
KI2	1,4±0,05	3,7±0,1**	3,6±0,12**	1,7±0,03**	2,6±0,02**
KI3	0,2±0,01	1,7±0,02***	1,9±0,04***	0,4±0,5***	0,98±0,3***
KI	4,0±0,2	13,5±0,2***	13,4±0,2***	4,7±0,5***	7,4±0,4***

KI. 4,0±0,2 13,5±0,2*** 13,4±0,2***

Note. Reliability of the difference relative to the norm ** $p < 0.01$, * * $p < 0.001$; $p > 0,005$ reliability of the difference between the indicators of the main group and the comparison group.

infectious mononucleosis contributes to the almost complete normalization of the studied conjunctival indices, namely the reduction of KI1, KI2, KI3, and as a consequence - KI. In carrying out only the conventional treatment, there is also a tendency to decrease vascular, extracurricular and intravascular indices, but significantly less pronounced, so at the time of completion of the main course of treatment, most of the analyzed indicators remain elevated relative to the norm. Thus, the use of conventional therapy does not provide full normalization of microcirculation.

4. The inclusion of a combination of drugs consisting of hepatoprotector phosphoglyphiv and endogenous interferon inducer cycloferon, contributes to the elimination of morphological and functional disorders of the MCR, as well as to improve microcirculation in patients with this comorbid pathology.

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PRE-NOSOLOGICAL DIAGNOSIS OF PEDIATRIC PATHOLOGY WITH THE USE OF AUTOMATED DISPENSARY EXAMINATION COMPLEXES

ABSTRACT

The article discusses the results of the use of ACDE (Automated complex of dispensary examinations) in the regions of the Republic of Sakha (Yakutia). In the course of the work, the main organizational approaches were identified in the study of the health status of children, and the most advantageous use of automated complexes of dispensary examinations in the Republic of Sakha (Yakutia) was identified to improve the quality of preventive examinations.

Key words: children, ACDE, preventive examinations.

Introduction. We have analyzed the statistical data of the general morbidity of the child population of the RS (Y) over the past 10 years. It was revealed that over the past 10 years there has been an increase in the incidence of children in almost all classes of diseases.

In practical pediatrics, the early intervention strategy is much more effective. It is based on the earliest possible recognition of deviations from normal development or the onset of disease and timely correction of the environment and the conditions that caused them. Screening tests and systems targeting different types of pathology help detect children at risk of developing a disease. The best results are demonstrated by universal systems designed for multidisciplinary screening. Such systems, in particular, include the complex «ACDE», which has become widespread in the pediatric service of Russia [1]. ACDE is an automated complex of dispensary examination of children and adolescents. It was developed in 1991. Scientific Research and Design and Technological Institute of Biotechnical Systems of the Ministry of Education and Science of the Russian Federation in conjunction with specialists from the St. Petersburg State Pediatric Medical Academy. The ACDE system issues a decision about

the presence of a pathology or the degree of its probability and focuses on the tactics of further monitoring and counseling of the child. Calculation of the pathology spectrum is provided in the following areas: rheumatology, cardiology, cardiology in the aspect of neurocirculatory dystonia, immunology in the aspect of immunodeficiency states, neuropathology, endocrinology, pulmonology, otolaryngology, gastroenterology, allergology, nephrology, hematology, ophthalmology, orthopedics, speech therapy, surgery, phthisiology, oncology, nutrition, psychoneurology, dermatology, dentistry, genetics, activity of the process HIV infection.

The results of the child's examination, presented in the conclusion of the ACDE, clearly demonstrate the child's health status in the form of an «expanded map» and «highlight» its most vulnerable places. For preventive work, it is extremely important that the medical worker receives a list of profiles where hardly any pathological deviations have been observed. Thus, the child enters the zone of minimal risk or border state [2].

Objective isto study the features of the ACDE system complex in the districts of the Republic of Sakha (Yakutia) and to identify the most appropriate options for ACDE work in the districts of the RS (Y) to improve the quality of preventive

Table 1

Dynamics of number and age structure of children in the Oleneksky district

Index	Year		
	2010	2011	2012
Populationintotal	4028	4113	4155
Children from 0 to 17 years old	1349	1372	1376
includingfrom 0 to 14 years	1104	1127	1142
adolescents	245	246	234
childrenunder 1 yearold	95	80	99

Table 2

The number and frequency of pathology by pathology profiles in the Oleneksky district of the RS (Y)

Name	Allchildren		
	Total	boys	girls
Totalsurveyed	166	82	84
Total healthy children	2	0	2
Total children with pathology	164	82	82
Cardiology	92,8	92,7	92,9
Endocrinology	51,2	56,1	46,4
Ophthalmology	40,4	36,6	44,0
Stomatology	36,7	36,6	36,9
Pulmonology	21,1	24,4	17,9
Neuropathology	20,5	26,8	14
Allergology	13,3	14,6	11,9
Orthopedics	12,0	18,3	6,0
Otolaryngology	11,4	13,4	9,5
Gastroenterology	7,2	7,3	7,1