



Correction of Intestinal Disbacteriosis in Children with Chronic Hepatitis B Associated with Lamblasis

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Annotation. Analysis and evaluation of the state of intestinal microbiocenosis in 85 children with chronic hepatitis B associated with lamblasis for the purpose of correction of disbiotic disorders in the intestine of children with individual approaches to the treatment choice.

Keywords: Chronic hepatitis B, disbacteriosis, lamblasis, therapy, probiotics, children.

The disbiotic events in the intestine are one of the pathogenic part in the development of pathological process and simultaneously unfavourable outcome of chronic viral hepatitis (CVH) in children [4,6,16]. Our previous studies of the state of intestinal microbiocenosis in children with chronic viral hepatitis confirmed that irrespective of the presence or absence of lamblasis the disturbances in the contents of the intestinal microflora were revealed in 99.7 % of cases [7,10,12,15]. Under the conditions of chronic viral persistence the disbiosis contributes to development of disturbances of secretory, motor and barrier functions of the intestine and all ways of the lamblia brining appear to be real. In turn, lamblia under conditions of intestinal disbacteriosis at CVH in children, in the aggressive environment excrete a plenty of toxins which promote generalization of the viral infection with the appropriate consequences - polysystem organ insufficiency, that results in inhibition of the macroorgan resistance and then under the conditions of associated viral-parasitary infection provide development of two parallel already mutually aggravating processes [2,3,5,13,17]. Now the question about a choice of an optimum biopreparation remains rather problematic, because of presence of a huge arsenal of medicinal means in the pharmaceutical market used for correction of intestinal disbiosis. The results of our early performed investigations showed that the existing methods of treatment of disbalance in the intestinal microecology are not always effective (62.2 %). Taking into account this fact, and also recently registered characteristic development of microbiota resistance to the biological agents noted over the last time [1,9,14], a question arose for us about development of a method allowing in short terms (1-2 days), in comparison with bacteriological research (5-7 days) to carry out a choice of a biopreparation for treatment of disbacteriosis in the children with chronic viral hepatitis, ensuring the maximal effect from its application. In this connection the searches of means rendering influence on restoration of intestinal microecology are represented by the extremely urgent

problem and, are rather perspective for maintenance of a choice of optimal preparation individually for each patient. The above-stated facts were the basis for more detailed study of a condition of microbiocenosis of the intestine and revealing more effective approach to correction of the damaged intestinal microbiocenosis in children with chronic hepatitis B (CHB) on the background of lamblia invasion.

The purpose of research was the estimation of efficacy of application of a biological agent on the basis of a method of an individual estimation of lymphocyte sensitivity in the test in vitro in children with chronic hepatitis B on the background of lamblia.

Materials and methods of research. Under supervision there were 85 children with CHB and intestinal lamblia at the age of 3 to 14 years hospitalized to the hepatological center of the RSSPMC of Pediatrics of the MH of RUz. The distribution of the patients in dependence of activity of CHB showed that disease on the background of lamblia developed in the progressing form. So, the overwhelming majority (80.0 %) of the patients had moderate (49.4 %) and marked (30.6 %) activity of illness. The duration of CHB was 4.1 ± 0.2 years. The diagnosis of CHB was based on data of medical history of disease, clinical examination, biochemical and instrumental investigations. The verification of a HBV-infection was performed with use of methods IFA and PCR (HBsAg, HBsAb, HBeAg, HBeAb, HBcorAb, HBV-DNA). The intestinal microflora was studied according to the methodical recommendations offered by I.B.Ershova (2002). The study of intestinal microflora was carried out by technique of R.V.Epshtein-Litvak and F.L.Vilshanskaya (1977), the classification offered by B.M. Granitov was also used (2002). Lamblia diagnosis was carried out by methods: immunofluorescence - definition of an antigen G. *Lamblia* in feces; PCR- definition of DNA G. *Lamblia* in blood/feces and, three-multiple microscopic examination of residual components of the feces.

For definition of the lymphocyte sensitivity to biopreparations there was used method of an individual estimation of a choice of biopreparation based on definition of the functional activity of T-lymphocytes of the peripheral blood (Patent UZ IAP 04570 is used, 2012) [8]. In this method the performance of the "loading" test is proposed for the estimation of functional activity of the T-lymphocytes in the reaction of E-rosette formation in vitro in incubation with probiotics, that allowed taking into account of the body individual sensitivity in each concrete case to choose an effective biopreparation. As the control the contents of E-rosette-forming cells (E-RFC) was measured in the blood serum in the same patients without stimulation of preparations. The criteria for estimation were the results of E-RFC > 5 % to the control - hyperergic, E-RFC < 5 % - hypoergic and E-RFC without changes (Inoyatova F.I., 2012; IAP 04570). There were used bacterial preparations with various contents of biocultures: Bifilax-immuno - 10×10^9 COE, *L.paracasei* CRL-431, *B.animalis* BB-12 in capsule (Pharmaxx International, Denmark), Lacto-G - 5×10^9 , *L.acidophilus*, *B.longum*, *B.bifidum*, *B.infantis* and fruitooligosaccharides in capsule (GMP, Georgia) and Narimax-plus- 2×10^8 COE *L.acidophilus*, *L.rhamnosus*, *B.bifidum*, *St.thermophilus*, *L.bulgaricus*, *L.salivarius* in capsule (JSC-Vitamax-E, Yerevan).

At the comparative analysis of the test in vitro with addition of biopreparations used for restoration of the intestinal microflora we revealed positive result to the preparation Bifilax-immuno in 68.7 % of cases, Lacto-G – 38.7 % and Narimax-plus – 30.0 %. In this connection the basic group was made of 55 children who have received on a background of basic therapy chosen in test in vitro a high-sensitive biopreparation in age dependent doses. Other 30 children (control group) on the background of basic therapy have received dry bacterial preparations: bifidum- and lactobacteria in the standard doses within one month. The eradication of lamblia was carried out with use of preparation Macmiror

(nifurantel) in dose 15 mg/kg 2 times per day for 7 days, taking into account its small hepatotoxicity. The estimation of efficiency of used therapy was performed on the clinical, biochemical and bacteriological data.

The statistical processing was performed with use of a method of variational statistics with application of t-criterion Student test under the special program Excel-2000. The differences were considered to be reliable at values of $p < 0.05$.

Results and discussion. The study of the intestinal microbiocenosis has allowed us to establish prevalence (more than 3.5 times) of disbacteriosis (D) of more marked degrees in children, being ill with CHB on the basis of lamblasis,

D-IV (48.2 %) and D-III (35.3 %), respectively. It testifies about pathogenic influence of lamblia antigens and their toxins on the intestinal mucosa, aggravating not only already available inflammatory processes, but also immunological tolerance of the gastrointestinal tract, as a whole. The features of the type landscape of microorganisms in the intestine depended on the degree of disbacteriosis which were characterized by a phase of aggression of aerobic flora that is expressed by reduction of the number of anaerobes in relation to aerobes, presence of deficit of bifidobacteria and lactobacteria, or their full absence on the background of significant growth of the facultative flora and their toxic metabolites.

The use of individually chosen biopreparations showed significant effect on the dynamics of the main clinical symptoms in children with CHB on the basis of lamblasis. The comparative analysis of application of biopreparations has shown that use of individually chosen preparations had more effective influence on the development of CHB in comparison with multicomponent preparations. In particular, clinical response of 78.4 % of children (against 38.3 % in group of the control, $p < 0.05$) was positive, that was reflected in improvement of the state of health of children, reliably more rare the symptoms of asthenovegetative syndrome were registered as complaints on rapid weakness and fatigue as well as headaches, dizziness and sleep disturbances, ($p < 0.001-0.05$). The skin integuments were pale and dry in the third part of patients of group I (34.5 ± 4.7 % and 30.9 ± 6.3 %, respectively), that was 2,1 times less often in relation to the patients of group II, $p < 0.001$. Positive dynamics was noted in the symptoms of dyspeptic syndrome (DS). Such symptoms as poor appetite and furred tongue were registered in 2.0 and 2.3 times less often, respectively, in children of the main group ($p < 0.05$ and $p < 0.001$ concerning the control). Dyspeptic syndrome was noted predominantly among the children from control group - 61.6 % of cases. Such symptom, as the nausea was observed in 4 patients of the main group (10.9 ± 4.2 %), which was met in 2,7 times less often concerning group of the control (30.0 ± 8.4 %), $p < 0.05$. The vomiting symptoms disappeared in the patients receiving polycomponent biopreparations, whereas this parameter at the patients of control group was registered in 13.3 ± 6.2 % of the patients, $p < 0.05$. The symptoms of the dyspeptic syndrome as a pain in the abdomen, meteorism reduced in 2.3 and 2.6 times, respectively, collywobbles in the abdomen was more frequent than 2.7 times and stool disorders were registered in 13.3 ± 6.2 % of the patients, $p < 0.05$. Cholestatic syndrome (CS) was more characteristic for children from group of the control, thus subicteric skin integuments after treatment was found in 20.0 ± 7.3 % of cases, while in the basic group this parameter decreased to 10.9 ± 4.2 % ($p > 0.05$). There were not revealed reliable differences in subicteric sclera in the both groups. The complaints on skin pruritus were reliably rare in the patients from the main group in 10.9 ± 4.2 % of children, whereas, in control group this parameter was registered in 33.3 ± 8.6 % of cases ($p < 0.05$). Hemorrhagic syndrome (HS) in form of nasal bleeding was noted after treatment reliably more rare – in 2.5 times in children of main group, ($p < 0.05$). The intensity of extrahepatic signs in CHB, as a capillary network and vascular asterisks in children of the

main group decreased in 1.5 times ($p < 0.01$ concerning group of the control). It is necessary to note, that after the therapy carried out in children of the main group there were also revealed changes in the sizes of a liver and spleen. The increase in the sizes of a liver - hepatomegalia (GM) more than 3 cm was reliably revealed 2,0 times more rare in children of the main group, than in children of control group ($p < 0.05$). In the basic group splenomegalia (SM) was registered 1,8 times less often concerning group of the control ($p < 0.01$). Thus, after application of sensitive biopreparations on the background of basic therapy we reveal significant improvements of clinical syndromes of CHB in comparison with control group.

At the comparative analysis in the studied children on the background of the used therapy the changes of a number of biochemical parameters (Tab.1) were observed. Considering parameters of biochemical homeostasis it is necessary to note, that all studied parameters before treatment in children with CHB accompanying with lamblia and disturbance of intestinal microbiocenosis considerably exceeded parameters of healthy children (corresponds to reliability from $p < 0.02$ to $p < 0.001$). The inclusion into therapy of the chosen polycomponent probiotics rendered positive influence on dynamics of parameters of the syndrome of cytolysis. So, the average parameter of AlAT decreased 2,5 times ($p < 0.001$ in relation to a parameter before treatment), reached normalization in 56.6 % of children. The same changes occurred with AsAT, which average level before treatment was 1.42 ± 0.11 mmol/l, after treatment – 0.40 ± 0.08 mmol/l ($p < 0.001$). After a course of basic therapy the level of AlAT decreased to 2.06 ± 0.14 mmol/l ($p < 0.05$), exceeding, however, parameters of norm in 5.2 times.

Table 1. Dynamics of the biochemical parameters changes in children with CHB associated with lamblia (%)

Parameter	Health	Before treatment n=85	After treatment		P
			Main group n=55	Control group n=30	
AlAT, mmol/l	0.49 ± 0.03	$2.30 \pm 0.20^*$	$0.89 \pm 0.14^*$	$2.06 \pm 0.14^*$	< 0.01
AsAT, mmol/l	0.34 ± 0.02	$1.42 \pm 0.11^*$	0.40 ± 0.08	$1.0 \pm 0.12^*$	< 0.01
Bilirubin, total					
Bilirubin, mcmol/l	14.85 ± 0.57	$26.9 \pm 2.9^*$	15.4 ± 2.25	22.8 ± 5.7	< 0.05
Protein total, g/l	71.32 ± 0.86	$55.3 \pm 2.78^*$	69.0 ± 0.80	$64.2 \pm 0.6^*$	> 0.05
Albumins, %	54.5 ± 0.72	$46.0 \pm 3.48^*$	$49.3 \pm 0.64^*$	$39.8 \pm 0.98^*$	< 0.01
Gamm-globulin, %	15.7 ± 0.47	$24.2 \pm 2.32^*$	$18.2 \pm 0.66^*$	$28.3 \pm 1.44^*$	< 0.001
Thymol test, Un/l	4.5 ± 0.28	$8.8 \pm 0.41^*$	5.96 ± 0.42	$11.9 \pm 1.03^*$	< 0.001
PTI %	75.0 ± 0.66	$66.0 \pm 1.28^*$	74.2 ± 0.78	$66.8 \pm 1.73^*$	< 0.05
Fibrinogen, g/l	3.01 ± 0.09	$2.42 \pm 0.07^*$	$2.73 \pm 0.07^*$	$2.25 \pm 0.09^*$	< 0.05
SMP, mmol/l	0.136 ± 0.04	$0.280 \pm 0.01^*$	$0.230 \pm 0.01^*$	$0.270 \pm 0.01^*$	< 0.01

Note: * - reliability of differences in relation to parameters of healthy children;

P- reliability of parameters between groups on the background of therapy.

Under action of the complex treatment the parameters of cholestatic syndrome changed. Thus, the reliable decrease was noted in the parameters of the total bilirubin, the level of which after treatment was 15.4 ± 2.25 mcmol/l ($p < 0.05$). The average level of total and direct bilirubin in the patients of control group remained to be higher and accounted for 23.0 ± 5.7 mcmol/l and 8.73 ± 2.3 mcmol/l, respectively, ($p > 0.05$). In the patients of the studied group the reliable (from $p < 0.01$ to $p < 0.001$) increase of average values of albumin ($49.3 \pm 0.64\%$), prothrombin (to $74.2 \pm 0.78\%$) and fibrinogen (to

2.73±0.07 g/l) indicated about increase in the synthetic function of the liver (hepatopril syndrome). The level of total protein in dynamics acquired the tendency to increase ($p > 0.05$). The effect of basic therapy with monocomponent biopreparation on the synthetic liver function we did not found. So, the contents of total protein, albumin, prothrombin and fibrinogen were within the limits of starting meanings. There were also no significant changes in the parameters of mesenchymal-inflammatory syndrome and endogenous system of detoxication ($p > 0.05$). In the patients of the studied group in the parameters describing mesenchymal-inflammatory syndrome there was also noted marked normalizing effect of the biopreparations used that was expressed in the reduction of the level of gamma-globulin (to 18.2±0.66 %) and thymol probe (to 5.9±0.42), $p < 0.001$. The activation of systems of endogenous detoxication was confirmed by significant lowering of the level of middle molecules to 0.230±0.01mmol/l in the at the patients of the main group ($p < 0.01$ in relation to parameters before treatment and group of control). Thus, in children with CHB on the background of lambliaosis with disturbance of intestinal microbiocenosis the use of chosen in the test in vitro of highly-sensitive biopreparations additionally to basic therapy showed positive effect on a number of biochemical parameters of CHB.

At the comparative analysis of quantitative and qualitative changes in the contents of intestinal microflora (Tabl.2) in children with CHB associated with lambliaosis after complex treatment the amount of normal contents of bifido- and lactobacteria in the limits 10⁹-10¹⁰KOE/g was noted in 34.5±4.7 % and 30.9±6.3 %, respectively, that was 2.5 times more frequently in relation to the patients of control group – 13.3±6.2 % ($p < 0.01$; $p < 0.001$, respectively).

Table 2. Dynamics of the changes of the intestinal microflora representatives in children with CHB on the background of lambliaosis (%).

The agents of the intestinal microflora	Main group n=55		Control group n=30		P
	Before treatment	After treatment	Before treatment	After treatment	
Bifidobacteria:					
norm. contents (10 ⁹ -10 ¹⁰ CFU/g)	3.7±2.5	34.5±4.7	3.3±3.3	13.3±6.2	<0.001
moderate reduction (10 ⁶ -10 ⁵ CFU/g)	21.8±5.6	49.1±6.8	20.0±7.3	23.3±7.7	<0.05
significant reduction (<10 ⁵ CFU/g)	74.5±5.9	18.2±5.2	76.6±7.7	63.4±8.8	<0.001
Lactobacteria:					
norm. contents (10 ⁹ -10 ¹⁰ CFU/g)	3.6±2.5	30.9±6.3	6.7±4.5	13.3±6.2	<0.01
moderate reduction (10 ⁶ -10 ⁵ CFU/g)	29.1±6.2	50.9±6.8	30.0±8.4	33.3±8.6	>0.05
significant reduction (<10 ⁵ CFU/g)	69.1±6.3	18.2±5.2	63.3±8.8	53.4±9.1	<0.001
E.coli typical:					
norm. contents (10 ⁷ -10 ⁸ CFU/g)	5.5±3.1	34.5±4.7	6.7±4.5	16.7±6.8	<0.01
amount decrease (<10 ⁷ CFU/g)	74.5±5.9	49.1±6.8	73.3±8.1	70.0±8.4	<0.02
amount increase (>10 ⁸ CFU/g)	20.0±5.4	18.2±5.2	20.0±7.3	13.3±6.2	>0.05
E.coli lactozonegative	30.9±6.3	18.2±5.2	33.3±8.6	26.7±8.0	>0.05
E.coli hemolytic	20.0±5.4	5.5±3.1	20.0±7.3	16.7±6.8	>0.05
Enterococci:					
norm. contents (10 ⁷ -10 ⁸ CFU/g)	7.3±3.5	50.9±6.8	10.0±5.5	16.7±6.8	<0.001
amount decrease (<10 ⁷ CFU/g)	74.5±5.9	49.1±6.8	73.3±8.1	70.0±8.4	<0.02
amount increase (>10 ⁸ CFU/g)	18.2±5.2	-	16.7±6.8	13.3±6.2	<0.05
Staphylococcus aureus	29.1±6.2	9.1±3.9	26.7±8.0	20.0±7.3	<0.05

Staphylococcus epidermidis	29.1±6.2	5.5±3.1	23.3±7.7	20.0±7.3	<0.05
Proteus	14.5±4.8	-	16.7±6.8	10.0±5.5	<0.02
Klebsiella	14.5±4.8	9.1±3.9	13.3±6.2	10.0±5.5	>0.05
Candida fungi	56.4±6.7	18.2±5.2	53.4±9.1	36.7±8.8	<0.02
Two-component associations of the opportunistic microorganisms	20.0±5.4	9.1±3.9	20.0±7.3	16.7±6.8	>0.05
Three-component associations of the opportunistic microorganisms	10.9±4.2	-	13.3±6.2	10.0±5.5	<0.02
Four-component associations of opportunistic microorganisms	5.5±3.1	-	6.7±4.5	3.3±3.3	>0.05

The note: P - statistically reliable distinctions of parameters on the background of therapy.

The amount of significant reductions of bifido- and lactobacteria ($< 10^5$ CFU(colony-forming units/g) in the patients of the main group were revealed 3.7 and 3.1 times less often accordingly to the parameter of control group ($p < 0,001$). The detection of colon bacillus with normal fermentative activity was registered reliably more in the patients of the main group ($p < 0.01$ in comparison with the control). Reduction of quantity of the typical colon bacillus 10^7 CFU/g in the patients of control group after treatment came to light almost 1,4 times more than in the patients of the main group, $p < 0.02$. There were also hemolytic E.coli 2,9 times less often in children of the main group ($p > 0.05$ in comparison with the control). The quantity of the normal contents of enterococci in limits 10^7 - 10^8 CFU/g in the patients of the main group was registered almost in a half of patients (50.9 ± 6.8 % against 16.7 ± 6.8 %, $p < 0,001$). Reduction of quantity of enterococci to 10^7 CFU/g was noted after therapy by chosen in the test in vitro of highly-sensitive biopreparations and was registered in $49.1 \pm 6.8\%$ of cases, whereas in the patients of control group these results were revealed almost 1,4 times more often ($p < 0.02$). The increase of quantity of enterococci higher 10^8 CFU/g in the patients of the main group after treatment was not found out, whereas in group of the control these figures were reached 13.3 ± 6.2 % of cases ($p < 0.05$). From the representatives of opportunistic microflora (OM) - golden and epidermal staphylococci were revealed 2.3 and 3.5 times less often, respectively, in children of the main group after treatment (9.1 ± 3.9 % and 5.5 ± 3.1 % against 20.0 ± 7.3 % of cases, respectively, $p < 0.05$). The determination of non-fermentative bacteria of a sort Proteus after the therapy performed in the patients of the main group was failed, however, in the children of the group of control these characteristics were not changed practically ($p < 0.05$). The yeast-like fungi of a sort Candida also decreased 2.1 times and the revealing of associations of opportunistic microorganisms decreased, and also there were absent three- and fourcomponent associations in children of main group ($p < 0,05$ - $0,001$). The pair combinations of opportunistic microorganisms were met almost 2 times less often in children receiving polycomponent biopreparations, in which there were found combinations Candida+Staphylococcus aureus, $p > 0.05$.

Thus, the correction of the disbiotic disturbances in the intestinal microbiosis in children with CHB on the background of lamblasis resulted in improvement of the microecological status of the patients, at which representatives of the obligatory microflora increased while opportunistic microorganisms as well as their associations reduced. Totally, data received during this investigation indicated about real positive properties of therapy, which application led to improvement of the well being of the studied children, significant improvement of the state of the intestinal microbiocenosis and as well as achievement of the normal levels of the majority of studied biochemical characteristics that provided for development of remission: by clinical signs – 76.5 % (against 23.8 % in group of the control),

biochemical – 64.4 % (against 28.2 % in the control group) and microbiological parameters in 62.0 % of the patients (against 25.2 % concerning the control), $p < 0.05$.

The conclusion. For the effective approach to the correction of the damaged intestinal microbiocenosis in children with CHB on the background of lamblia invasion and for providing of the choice of optimal biopreparation for each of patients it is recommended performance of the “loading” test in vitro before prescription of the probiotic agent. The choice of the individual treatment and evaluation of the efficacy of intestinal biocorrection from the first day of admission to the hospital will promote prolongation of the period of remission and favourable prognosis of the main disease.

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