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Herpes Virus Hepatitis In Children

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***Abstract* — Investigating the causation and course of the herpesvirus hepatitis in groups of children and the results of treatment of different types. 173 children with herpesvirus hepatitis were examined. The causation of the disease was verified in all patients with the detection of CMV, EBV, HHV-6 DNA in blood, urine, saliva, and hepatocytes, and of CMV LA, EBNA-2 and EBV LMP1 in hepatocytes of the patients after needle biopsy of the liver. Clinical implications and laboratory findings in acute and chronic herpesvirus hepatitis in children showed no differences in virus hepatitis as a whole. 113 children receiving Viferon® for the treatment of the chronic herpes virus hepatitis were monitored. The Interferon dose of all children was 5 mln/m^2 three times a week. In the course of the treatment, the primary biochemical remission was achieved in 15 (13.3%) children, the primary virological: in 8 (7.1%) children, the stable biochemical: in 7 (6.2%) children, the stable virological: in 5 (4.4%), the stable complete: in 3 (2.6%) children, the long-lasting biochemical: in 10 (8,8%) children, the long-lasting virological: in 4 (3.5%) children, the long-lasting complete remission: in 26 (23.1%) children with chronic herpes virus hepatitis. The disease recurrence was found in 7 (6.2%) patients; there were no remission in 28 (24.8%) children. 1/3 of the patients the decrease was recovered with complete recovery of the functional status of the liver within 1-3 months. The result of the symptomatic herpes virus hepatitis the disease of 64.9% of the patients had chronic progression**

Keywords — Human cytomegalovirus; Epstein-Barr virus; human herpesvirus 6; interferon.

1. INTRODUCTION

The diagnostics of the infectious diseases based on the polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) that is widely used in the clinical practice showed that the viruses of the herpes family and primary Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Human Herpesvirus (HHV)-6 [1-4] are significant in the causal structure of infectious liver involvement apart from the Hepatitis A, B, C, D, E, G, TT viruses.

This issue is commonly addressed in the clinical papers. The greatest number of studies is devoted to CMV hepatitis. Cytomegalovirus is assumed to primary damage the bile ducts with the development of cholestatic hepatitis. It shall be noted that available publications mainly consist of clinical examples describing CMV hepatitis in the small number of patients [5-7].
The advanced analysis and generalization of the accumulated material are a matter of the distant future. There is no uniform knowledge of the place and the implication of herpes viruses in the genesis of liver involvement and bile ducts [8,9]. Although some researchers propose to consider CMV, EBV, and HHV-6 as hepatotropic viruses, other authors consider them as infectious agents having no significant role in the development of chronic hepatitis and liver cirrhosis.
There is an experience of acyclovir application as an etiotropic treatment of patients with EBV-hepatitis and as an etiotropic treatment of patients with CMV hepatitis with Ganciclovir. Other researchers combined antiviral treatment with intravenous immunoglobulin including immunocompromised patients. In some cases, the recombinant interferon medications were used for herpes hepatitis treatment. However, the common treatment approaches are not developed until now [10,11].

2. METHODOLOGY

First, confirm that you have the correct template for your paper size. This template has been tailored for output on the A4 paper size. If you are using US letter-sized paper, please close this file and download the file "MSW_USltr_format".
This investigation had received official institutional and ethical approval of the Administration and Local Ethical Committee of the Federal State-Financed Institution Russian Children's Clinical Hospital of the Ministry of Healthcare of the Russian Federation.
173 children with herpes virus hepatitis were examined. 92 of them had CMV, 74 had EBV and had 7 HHV-6 hepatitis.
Acute or chronic hepatitis was diagnosed according to the generally accepted criteria. The causation of disease was verified in all patients with the detection of CMV, EBV, HHV-6 DNA in blood, urine, saliva and hepatocytes, and of CMV late antigen (CMV-LA), EBV nuclear antigen (EBNA-2) and EBV latent membrane protein (LMP1) in hepatocytes of the patients after needle biopsy of the liver.
The causation evaluation was performed by the enzyme-linked immunoassay (ELISA), polymerase chain reaction (PCR), immunohistochemistry (IHC) by the standard procedure described in the record books of manufacturing companies.
The blood serum of the examined children was tested for markers of Cytomegalovirus, Herpes simplex virus I/II, Epstein-Barr virus, Hepatitis A, B, C, D viruses, Toxoplasma gondii during hospitalization and in catamnesis. The identification of serologic markers by ELISA included the identification of Cytomegalovirus infection markers (anti-CMV IgM and anti-CMV IgG), Herpes simplex virus (anti-HSV I/II IgM and anti-HSV I/II IgG), Epstein-Barr virus infection (anti-VCA IgM, anti-VCA IgG, anti-EA IgM, anti-EA IgG), markers of Hepatitis A virus (anti-HAV IgM), Hepatitis B virus (HBsAg, HBeAg, anti-HBcore IgM, anti-HBcore IgG, anti-HBe, anti-HBs), hepatitis C virus (anti-HCV), hepatitis D virus (anti-HDV), Toxoplasma gondii (anti-Toxo IgM and anti-Toxo IgG).
Virological examination with the determination of DNA Cytomegalovirus (CMV DNA), Epstein-Barr virus (EBV DNA), Herpes simplex virus I/II (HSV I/II DNA), Human herpesvirus 6 (HHV VI DNA), nucleic acids of Hepatitis B virus (HBV DNA), Hepatitis C virus (HCV RNA), Hepatitis D virus (HDV RNA), Hepatitis G virus (HGV RNA), TTV (TTV DNA), Toxoplasma gondii (Toxoplasma gondii DNA), Enteroviruses (Enterovirus RNA) was

performed by PCR method following the standard procedure described in the record books of manufacturing companies.
Identification of CMV, EBV, HHV-6 DNA in hepatocytes was carried out by the record books of the manufacturers [12].
Immunohistochemistry (IHC) was carried out using a monoclonal antibody (QB1/06 clone), the late Cytomegalovirus antigen (CMV-LA) was identified in the hepatocytes. The study was carried out using reagents of Novocastra Laboratories Ltd (Great Britain) under the standard procedure described in the record books of manufacturing companies [13, 14].
Using monoclonal antibodies (CS1, CS2, CS3, CS4 clones), the latent membrane protein EBV (LMP1) was identified in hepatocytes [15-18]. The study was carried out using reagents of Novocastra Laboratories Ltd (Great Britain) by the standard procedure described in the record books of manufacturing companies [19-22].
Various forms of the chronic herpes virus hepatitis were diagnosed based on the data of the clinical laboratory and diagnostic set of studies. This work has used the classification of the chronic hepatitis of V.J. Desmet et al. [23], the basis of which form morphological characteristics of chronic hepatitis. However, taking into account the severity of the health condition and age of the examined patients, the possibility of needle biopsy of the liver was limited in some cases. Accordingly, various forms of the chronic herpes virus hepatitis were diagnosed based on criteria that were selected considering the clinical practice of the sub-department [23].
68 children received monotherapy with Viferon® in the form of rectal suppositories for the treatment of chronic herpes virus hepatitis. 36 patients received Viferon® in combination with intravenous immunoglobulin. 9 children received Viferon® in combination with Ganciclovir.
The 78-patient treatment duration was 6 months; the 22-patient treatment duration was 9 months, and the 13-patient treatment duration was 12 months.
The interferon (IFN) dose of all children was 5 mln/m2 three times a week. The effectiveness criteria of IFN treatment were determined following the EUROHEP Consensus Report [24].
The control group consisted of 43 children with chronic herpetic hepatitis. They received no etiotropic treatment.

3. RESULTS

A. Acute herpes hepatitis

Acute herpes hepatitis was diagnosed in 37 children, in 20 patients it was of CMV, in 17 patients: of EBV causation.
Clinical implications and laboratory findings in acute herpetic hepatitis were typical. The pre-jaundice period was detected in 25 of 37 patients. The duration of the pre-jaundice period was 3.2± 0.5 days in a mild form, in moderate form – 4.3± 1.7 days, and in severe form – 6.3± 4.4 days. After the appearance of jaundice, the intoxication symptoms remained and even grew (Table 1).

TABLE I. CLINICAL IMPLICATIONS AND LABORATORY FINDINGS IN ACUTE AND CHRONIC HEPATITIS IN CHILDREN (N = 37)

Clinical symptoms	**Pre-jaundice form (*n*=9)**	**Mild form (*n*=15)**	**Moderate form (*n*=10)**	**Severe form (*n*=3)**
Temperature rise	4	6	3	1
Intoxication symptoms	4	9	10	3
Enlarged liver	9	15	10	3
Enlarged spleen	8	13	10	3
Enlarged peripheral	no	no	no	no

lymphatic glands				
Changes in the oral pharynx	no	no	no	no
Laboratory findings				
Abnormal mononucleocytes	no	no	no	no
Total bilirubin, *µmol/l*	15.2 ± 3.01	35.1 ± 7.9	136.7 ± 21.9	178.6 ± 20.2
Conjugated bilirubin, *µmol/l*	5.2 ± 1.4	17.8 ± 2.4	85.6 ± 20.4	60.2 ± 5.5
ALT, *U/l*	109.1 ± 34.1	135.5 ± 42.6	179.3 ± 61.1	214.1 ± 83.3
AST, *U/l*	96.2 ± 25.3	141.3 ± 42.9	221.7 ± 69.1	250.1 ± 87.4

The duration of the jaundice period was 16.8± 5.1 days in a mild form, in moderate form – 18.9± 6.9 days, and in severe form – 26.1± 2.8 days.
The disease progression in 13 (35.1%) of 37 children was acute and ended with recovery with the complete recovery of the functional status of the liver within 1-3 months. 24 (64.9%) patients had a chronic progression.

B. Chronic herpes virus hepatitis

In 77 examined children with acquired chronic herpes virus hepatitis 28 had CMV causation, 42 – EBV causation, 7 – HHV-6 causation). Whereas, in 33 patients with chronic herpes virus hepatitis developed as a primary chronic process, and in 44 of them: in the result of the primary symptomatic herpes virus hepatitis.
In 37 (48.1%) of 77 children with chronic herpes virus hepatitis the minimum process activity in the liver was diagnosed, in 20 (25.9%) children: low activity, in 17 (22.2%): moderate activity, and in 3 (3.8%): high activity. In 10 (12.9%) of 77 examined children, the hepatic fibrosis was absent, in 41 (53.2%) children it was ill-defined, in 19 (24.7%) children it was moderate, and 7 (9.2%) children had advanced fibrosis. Liver cirrhosis was not detected in any of the children.
Clinical implications and laboratory findings were typical (Table 2).

TABLE II. CLINICAL IMPLICATIONS AND LABORATORY FINDINGS IN ACQUIRED CHRONIC HERPES VIRUS IN CHILDREN (N = 77)

Clinical symptoms	**Minimum activity (n=37)**	**Low activity (n=20)**	**Moderate activity (n=17)**	**High activity (n=3)**
Jaundice	16	17	15	3
Extrahepatic signs	16	7	8	-
Enlarged liver	37	20	17	3
Enlarged spleen	30	19	16	3
Hemorrhagic syndrome	no	no	no	no
Enlarged peripheral lymphatic glands	no	no	no	no
Changes in the oral pharynx				
Laboratory findings				
Abnormal	no	no	no	no

mononucleocytes				
Total bilirubin, μmol/l	92.1 ± 18.2	188.1 ± 23.5	161.2 ± 36.2	249.5 ± 51.6
ALT, U/l	81.9 ± 10.1	167.1 ± 34.1	315.5 ± 34.2	551.8 ± 77.8
AST, U/l	92.1 ± 9.2	154.1+29.6	355.4 ± 42.1	521.4 ± 91.6

n the period of remission, extra-liver signs in most of the children disappeared. Dimensions of the liver and spleen were reduced. The enzyme activity in the blood serum was normal.

C. Neonatal herpes virus hepatitis

83 children with neonatal herpes virus hepatitis were examined (57: of Cytomegalovirus causation, 26: of Epstein-Barr virus causation). The process had a primary chronic course in all patients. Chronic CMV hepatitis in all 57 patients was combined with the involvement of other organs and systems. In 7 patients it combined with organic CNS lesions, and in 50 children: with the involvement of the bile ducts (45 - bile duct atresia, 5 children had bile duct cysts). Among 26 children with neonatal EBV-hepatitis, the biliary tract involvement (4 patients had bile duct atresia, 3 patients had bile duct cysts) was diagnosed in 7 of them.

In 30 of 83 (36.1%) patients the minimum process activity in the liver was diagnosed, in 25 (30.1%) children – low activity, in 7 (8.5%) – moderate activity.

In 2 (2.4%) of 83 children the hepatic fibrosis was absent, in 19 (26.9%) children it was ill-defined, in 18 (21.7%) children it was moderate, and 22 (26.5%) children had advanced fibrosis. Liver cirrhosis was detected in 22 (26.5%) children with neonatal herpes virus hepatitis.

Clinical implications and laboratory findings in neonatal herpes virus were typical (Table 3).

TABLE III. CLINICAL IMPLICATIONS AND LABORATORY FINDINGS IN NEONATAL HERPES VIRUS IN CHILDREN (N = 83)

Clinical symptoms	**Minimum activity (n=30)**	**Low activity (n=25)**	**Moderate activity (n=21)**	**High activity (n=7)**
Jaundice	27	25	21	7
Extrahepatic signs	4	8	6	2
Enlarged liver	27	25	21	7
Enlarged spleen	27	25	21	7
Hemorrhagic syndrome	-	-	7	5
Enlarged peripheral lymphatic glands	no	no	no	no
Changes in the oral pharynx				
Laboratory findings				
Abnormal mononucleocytes	no	no	no	no
Total bilirubin, μmol/l	92.5 ± 18.1	191.2 ± 21.1	178.3 ± 20.3	246.1 ± 41.2
ALT, U/l	85.8 ± 9.8	171.1 ± 15.3	310.2 ± 27.5	537.1 ± 46.2
AST, U/l	92.2 ± 8.1	170.4 ± 32.2	381.2 ± 32.3	631.2 ± 41.1

In the period of remission dimensions of the liver and spleen were reduced. The enzyme activity in the serum blood was normal.

D. Viferon® treatment of the chronic herpes virus hepatitis in children

A number of 113 children receiving Viferon® for the treatment of the chronic herpes virus hepatitis (85 patients with CMV, 21 - with EBV, 7 - with HHV6 hepatitis) were monitored.

Among 113 examined patients in 63 children, the process was neonatal (including 54: with CMV- and 9: with EBV-hepatitis). 50 patients had acquired herpes virus hepatitis (31: of CMV, 12: of EBV, 7: of HHV-6 causation).

68 children received monotherapy with Viferon® in the form of rectal suppositories, (45: with CMV, 16: with EBV, 7: with HHV-6 hepatitis). 36 patients received Viferon® in combination with intravenous immunoglobulin (31: with CMV, 5: with EBV-hepatitis). 9 children with chronic CMV hepatitis received Viferon® in combination with Ganciclovir. The treatment duration was 6 months in 78; 9 - in 22 and 12 - in 13 patients.

The IFN dose of all children was 5 mln/m2 three times a week.

The control group consisted of 43 children with chronic hepatitis of CMV-, 23: of EBV-, and 5: of HHV-6 causation. These children received no etiotropic treatment.

By the effectiveness criteria of IFN treatment of EUROHEP Consensus Report, the primary biochemical remission was achieved in 15 (13.3%) children, the primary virological: in 8 (7.1%) children, the stable biochemical: in 7 (6.2%) children, the stable virological: in 5 (4.4%), the stable complete: in 3 (2.6%) children, the long-lasting biochemical: in 10 (8.8%) children, the long-lasting virological: in 4 (3.5%) children, the long-lasting complete remission: in 26 (23,1%) children with chronic herpes virus hepatitis. The disease recurrence was found in 7 (6.2%) patients; there were no remission in 28 (24.8%) children.

There are no detected significant differences in the effectiveness of Viferon® treatment for children with CMV, EBV, and HHV-6 hepatitis. P-values ranged from $p>0.05$ to $p>0.2$.

Therefore, the specific weight of children with chronic herpes virus hepatitis, whose long-lasting complete remission generated on the background of Viferon® treatment, was not high – a little below ¼ of the patients. There was remission in almost 1/3 of the patients. However, the combined group of children who had any remission was 69% of the total number of treated patients. Whereas, in similar terms, the spontaneous remission did not generate in any child of the control group.

The comparative analysis of the Viferon® treatment in children with neonatal and acquired herpes virus hepatitis did not detect any significant differences in remission development. P-values ranged from $p>0.05$ to $p>0.2$.

E. As an example, there is the following examination

Patient #34, male, 9 years old, born from normal pregnancy, childbirth: spontaneous vaginal delivery in time. Early development: with no abnormalities. He was vaccinated according to age. At the age of 1.5 years old he underwent pneumonia, on which the comprehensive treatment was carried out including transfusion of fresh frozen plasma. During prophylactic medical examination at the age of 3 it was found the increased liver and in the blood serum – increased activity of ALT and AST by 3 times more than normal. Abdominal ultrasound detected a low increase of the liver; its parenchyma was homogeneous, slightly indurated in the periportal zone due to fine-focal structures. During esophagogastroduodenoscopy, there were no signs of the esophagus varicose vein. Duplex ultrasonography screening of the abdominal vessels showed no signs of portal hypertension. Anti-HHV-6 IgG was detected in the blood serum of the boy using the ELISA method. PCR method detected DNA HHV-6 in the blood serum, urine, and saliva. The results of an examination of the mother and child for markers of HAV, HBV, HCV, HGV, G, TTV, HSV I/II, CMV, EBV, Enterovirus RNA,

Toxoplasma gondii DNA were negative. Markers of HHV-6-infection were not found in the mother.

These symptoms and signs lasted for 6 months. The clinical diagnosis was established: Chronic HHV-6 hepatitis of moderate activity, ill-defined hepatic fibrosis, HHV-6 replication phase.

To suppress the replication and cytolytic activity of the process in the liver the 6-months course of Viferon® treatment was set in the amount of 5 mln IU/m2 for the first 10 days once a day, then – 3 times a week.

The normalization of ALT and AST activity appeared by the end of the 4th month of treatment. HHV-6 DNA continued to be identified in blood and saliva after 6 months from the beginning of the Viferon® treatment.

The course of treatment was extended to 12 months. The level of hepatocellular enzymes remained normal, and HHV-6 DNA ceased to be identified in blood serum, urine and saliva during examination in 9 and 12 months from the start of the treatment.

In the course of a case, follow-up after the termination of the treatment within 3 years the ALT and AST activity remained normal, and there was no HHV-6 DNA in the blood, urine, saliva. So, the child was diagnosed with the long-lasting complete remission of the chronic acquired HHV-6 hepatitis, established in the course of Viferon® treatment within 12 months.

To reply to the question of the dependency of the remission achievement frequency in the course of the treatment on the treatment schedule with the EBV- and CMV hepatitis, 3 groups were defined. The first group included the patients receiving the sole Viferon® treatment. The second group included the children who received Viferon® in combination with intravenous immunoglobulin. Among children with chronic CMV hepatitis, there was the third group of patients who received combination treatment with Viferon® and Ganciclovir.

In the course of a 3-year case follow-up, there was no significant difference in intensity of the cytolytic activity in patients from different groups. There was the only tendency to the lower intensity of the cytolytic activity in children in the course of Viferon® and intravenous immunoglobulin combination treatment. P-values ranged from $p>0.05$ to $p>0.1$.

A similar regularity was observed in estimating the replicative CMV and EBV activity in chronic herpes virus hepatitis in children receiving different treatment regimens. The detection frequency of DNA herpes viruses in the course of case follow-up did not practically differentiate in children of all groups. There were only insignificant lower replicative CMV and EBV activity in patients in the course of Viferon® treatment in combination with intravenous immunoglobulin. P-values ranged from $p>0.05$ to $p>0.2$.

4. DISCUSSION

Based on presented objective findings, the herpes viruses are referred to the hepatotropic pathogens, which is confirmed by detection of the late antigen (CMV-LA) by IHC method using monoclonal antibodies (clone QB1/06) and CMV DNA in hepatocytes of the patients with CMV hepatitis; by EBV DNA detection using PCR method and latent membrane protein (LMP1 EBV), by IHC method using monoclonal antibodies (clones CS1, CS2, CS3, and CS4) in hepatocytes of the patients with EBV-hepatitis; by DNA detection HHV-6 in hepatocytes of the patients with HHV-6 hepatitis.

Acute herpes hepatitis is presented in temperature rise, intoxication symptoms, jaundice, hepatosplenomegaly, a level increase of the conjugated bilirubin and transaminase activity in blood serum.

Chronic herpes hepatitis is presented in jaundice, hepatosplenomegaly, extra-hepatic signs, hemorrhagic syndrome, a level increase of transaminases and conjugated bilirubin, a decrease

of total protein, albumin, prothrombin index, typical changes in ultrasound picture and morphological changes.

Herpes hepatitis can be neonatal and acquired.

Among children with acquired herpetic hepatitis in half of the cases the primary chronic and the remained patients - the initial symptomatic Cytomegalovirus hepatitis was detected, in 2/3 of the cases it was of acquiring chronic progression.

In all neonatal herpetic hepatitis children, the liver involvement was combined with changes in other organs and systems, among which the most often detected was the involvement of the bile ducts with neonatal abnormality (of atresia and cysts - up to 80-90%).

F. Pathogenesis of herpetic hepatitis

Pathogenesis causing the involvement of hepatocytes with herpetic hepatitis is not completely understood. The mechanism of antibody-dependent of cytolysis hepatocytes was affected by herpes viruses under the influence of T-suppressors and natural killers. In the jaundiced form of the acute herpetic hepatitis, the DNA of viruses is mainly identified in CD3, CD4 and CD8 lymphocytes, whereas in the mononucleosis forms without jaundice B-lymphocytes are mainly infected, that seemingly could point at possible participation of T- lymphocytes in the pathogenesis of herpetic hepatitis. However, there is an indication that in liver involvement the T-cells of infiltrate are infected, and not the hepatocytes [11, 12].

It is even more difficult to reply to the question of why the viruses of herpes family in some cases cause indicative clinical aspect of infectious mononucleosis, up to the lymphoproliferative process, while in others - the typical aspect of virus hepatitis without the involvement of pharyngeal ring lymphatic glands.

Analyzing the results of this study allows concluding that these differences could be explained by different ways of infection introduction. When introduction of infection was through pharyngeal ring the lymphoproliferative process started: there was reaction from lymphadenoide, lymphatic glands, spleen; abnormal mononuclear cells appeared in blood, liver size, as a rule, increased due to the proliferation of lymphoid tissue, but this was not hepatitis yet: this was post-primary involvement of liver into the pathological process. In this way of infection introduction, the herpes viruses were not likely to have the ability to overcome the hepatocellular barrier. These diseases were not characterized by typical cytolysis syndrome - the central syndrome of all virus hepatitis.

There is a consideration that the clinic picture of herpetic hepatitis occurs when the infection is introduced by the parenteral way: during transfusion of blood products, medical procedures, while getting through the maternal passage, perinatal infection introduction. In these cases, the tropic organ is not a pharyngeal ring with lymphoproliferative prolongation, but it is liver parenchyma with cytolysis syndrome with the generation of chronic hepatitis.

G. Treatment

The findings are quite promising. In ¼ of children with chronic herpes virus hepatitis in the course of Viferon® treatment, the long-lasting complete remission generated. United group of the patients who had any remission was 69% of the whole number of treated patients. Moreover, there was no spontaneous remission in none of the children from the control group within similar terms.

The comparative analysis of the Viferon® treatment in children with neonatal and acquired herpes virus hepatitis did not detect any significant differences in the remission generation in the course of Viferon® treatment. P-values ranged from $p>0.05$ to $p>0.1$.

In the course of a 3-year case follow-up, there was no significant difference in intensity of the cytolytic activity in patients who received monotherapy with Viferon®, who received Viferon treatment in combination with intravenous immunoglobulin and who received combination treatment with Viferon® and Ganciclovir. There was the only tendency to the lower intensity

of the cytolytic activity in children in the course of Viferon® and intravenous immunoglobulin combination treatment. P-values ranged from $p>0.05$ to $p>0.1$.
A similar regularity was observed in estimating the replicative CMV and EBV activity in chronic herpes virus hepatitis in children receiving different treatment regimens. The detection frequency of DNA herpes viruses in the course of case follow-up did not practically differentiate in children of all groups. There were only insignificant lower replicative CMV and EBV activity in patients in the course of Viferon® treatment in combination with intravenous immunoglobulin. P-values ranged from $p>0.05$ to $p>0.2$.

5. CONCLUSION

So, the findings of the study allow making the following preliminary conclusions:
Cytomegalovirus, Epstein-Barr virus, Human herpesvirus 6 have a hepatotropic effect, which is confirmed by detection of the antigens (CMV-LA, EBV LMP1, and EBNA-2) and CMV, EBV, HHV-6 DNA in hepatocyte of all examined patients.
Clinical acute herpes virus hepatitis is presented in temperature rise, intoxication symptoms, jaundice and hepatosplenomegaly level increase of bilirubin and transaminases activity.
Only in the third part of the patients, the decrease was recovered with complete recovery of the functional status of the liver within 1-3 months. As a result of the symptomatic herpes virus hepatitis, the disease of 64.9% of the patients had chronic progression.
Chronic herpes hepatitis is presented in jaundice, hepatosplenomegaly, extrahepatic signs, hemorrhagic syndrome, a level increase of transaminases and conjugated bilirubin, a decrease of total protein, albumin, prothrombin index, typical changes in ultrasound picture and morphological changes.
In all neonatal herpetic hepatitis children, the liver involvement was combined with changes in other organs and systems, among which the most common detected was the involvement of the bile ducts with neonatal abnormality (atresia and cysts) (88%).
In the patients with herpetic hepatitis (CMV, EBV, HHV-6) there are no lymphomonocytes in the peripheral blood and abnormal mononucleocytes are not detected, there is no lymphadenopathy syndrome in the clinical picture.
In the course of the treatment, the primary biochemical remission was achieved in 15 (13.3%) children, the primary virological: in 8 (7.1%) children, the stable biochemical: in 7 (6.2%) children, the stable virological: in 5 (4.4%), the stable complete: in 3 (2.6%) children, the long-lasting biochemical: in 10 (8.8%) children, the long-lasting virological: in 4 (3.5%) children, the long-lasting complete remission: in 26 (23.1%) children with chronic herpes virus hepatitis. The disease recurrence was found in 7 (6.2%) patients; there were no remission in 28 (24.8%) children.
There are no detected significant differences in the effectiveness of Viferon® treatment for children with CMV, EBV- and HHV-6 hepatitis.
There are no detected significant differences in the generation percent of remission in the course of the Viferon® treatment in children with neonatal and acquired herpes virus hepatitis.
There are no differences between biochemical and replicative process activity in patients with chronic herpes virus hepatitis who received different Viferon treatment regimens. There was the only tendency to the lower intensity of the cytolytic activity and CMV DNA and EBV defection frequency in children in the course of Viferon® treatment and intravenous immunoglobulin treatment.
Children with chronic herpes virus hepatitis are recommended to have 6-9 months or more courses of Viferon® treatment in the form of rectal suppositories at a dose of 5 mln/m^2 a day three times a week.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study. The procedures followed were following the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All the patients gave their agreement to participate in the experiment and do not deny the results of the experiment to be provided in the research paper. Minors' parents and guardians do not deny the results of the experiment to be provided in the research paper.

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