T.G. Dmitrieva, V.A. Savvina, S.N. Alekseeva, V.P. Afanasieva, N.T. Sosina, N.A. Afanasieva, V.E. Chervonyuk

Role of hepatotropic viruses in the development of liver pathology in newborns

ABSTRACT

Viral infections that cause liver damage have a greater prevalence in the population, the tendency to recurrent course during pregnancy, similar epidemiological path and the effect on the occurrence of diseases of the fetus and newborn. Early prenatal diagnosis of viral infections is extremely important, as the outcome of treatment depends on the timely treatment. The aim of this work is the study of clinical manifestations antenatal infection with different hepatotropic viruses of newborns.

Keywords: viral infections, newborns, liver.

INTRODUCTION

Viral infections are the most common and dangerous diseases that can lead to an unfavorable clinical course and outcome of pregnancy, fetal and neonatal pathology. Among the infections that cause intrauterine infection, embryo- and fetopathy, obstetric pathology, the most common are cytomegalovirus, herpes virus, hepatitis B and C. [4]

According to the works of authors [2] the DNA of CMV virus is detected in liver biopsy in 80% of patients with biliary atresia, in blood - 25 %, in the urine - 20 % of cases. It is assumed that the neonatal hepatitis, biliary atresia and common bile duct cyst are manifestations of the same inflammatory process that occurs at different stages of fetus development. The cause of cirrhosis of the liver with biliary atresia is an intrauterine lesion of bile ducts and the hepatic parenchyma due to affection of an infectious agent - cytomegalovirus and, in some cases, in association with other viruses.

Despite the widespread use of vaccination against hepatitis B and significant success in modern antiviral therapy against chronic HBV- and HCV- infection, the problems of chronic viral hepatitis among pregnants and perinatal infection among newborns remain one of the most vital in modern medicine.[3] Therefore, verification of fetal viral infection for infants is the barest necessity.

MATERIALS AND METHODS

A retrospective study of patient medical records was carried out at the Department of Perinatal and Pediatric centers of Republican hospital № 1 of the National Medical Center in Yakutsk : 16 infants and their case stories who were treated in the infectious diseases department for newborns, 12 case histories of infants treated in the nursing premature department, 4 case histories of patients in neonatal pathology department and 15 case histories of children who had treatment at the surgical ward . 5 patients were watched at the City Children's Clinical Hospital № 2 of Yakutsk. The amount of patients directed from regions of the republic and the institutions of Yakutsk was almost equal, the differences in the gender composition also was not noted. To identify the causative agent of the intrauterine disease for all children a study of biological fluids was conducted. The direct method of polymerase chain reaction (PCR) and indirect immuno-fermental analysis (IFA) method was used.

RESULTS

Cytomegalovirus infection was diagnosed among 21 newborns. CMV was detected by PCR in

blood at 5 infants (23.8 %) and urine in 8 (38%) in blood and urine at 3 (14,2 %), negative PCR result was observed at five children (23,8 %), but the IFA of these patients had specific anti-CMV-bodies of IgG and IgM type.

The analysis of the frequency risk factors for intrauterine infections shows that complicated obstetric and gynecological history, pathological course of pregnancy and delivery were observed in 100 % of cases. 19 women (91 %) were diagnosed with anemia, 7 women (33.3 %) had the threat interruption of pregnancy in the 1st half, severe toxemia against acute pyelonephritis had 6 women (28.5 %), which required early delivery.

The physical development of infants with CMV was marked by low birth weight 2939.1 ± 704. Half of the newborn Apgar score at the end of the first minute was less than 7 points and has averaged 6.5 ± 1.5, 5 minutes 7.7 ± 0.9. The birth state was estimated as severe among 11 children (52.3 %). Reanimation measures were conducted for 8 infants (38 %).

The most of infants with CMV was noted with multiple organ failure. The most common diagnose was perinatal brain lesions in 80.9% of cases (17 children). Brain damage in the form of a brain malformation, intraventricular hemorrhage, hydrocephalus was detected among 7 infants (33.3%). The second highest frequency of occurrence of clinical manifestations of CMV infection was detected in the form of cardiovascular system (CVS) pathology: 11 patients (52.3 %) had a combination of heart defects such as STLV (supplementary trabecula of left ventricle, VSD (ventricular septum defect), FAD (functional artery duct), OOW (open oval window), AVS (aneurysm of ventricular septum), and one newborn (4.7%) had LCA (less cardiac anomaly). The pathology of the respiratory system made up 38 % (8 infants) dominating by acute pneumonia: at 2 infants (9.5 %) it was intrauterine, 3 newborns had community-acquired pneumonia (14.2%), also recorded 1 patient (4,7%) had DRS (disturbance respiration syndrome) and 3 children (14.2%) had bronchitis. The gastrointestinal tract defect in the form of necrotizing enterocolitis was observed at 3 patients (14.2%). Infant increase of liver with CMV infection was observed among 19 newborns (90.4 %). In this case visual jaundice was reported among 9 children (42.8 %), and 5 children from this amount (28.5 %) had clinic cholestasis: a significant increase of the liver, bile-tinged, earthy coloring of the skin, achole defecation, dark urine, increased total bilirubin through direct fraction, the level of bilirubin reached more than 189 pmol / l. Clinical signs of acute hepatitis observed at 12 children (57.1 %): the increase of bilirubin averaged 48,5 ± 2,4 mmol / l, there was an increase of transaminases in 3-4 times, in 3 cases (14.2%) coagulation pathology was noted.

As a rule, the syndrome of jaundice and hyperenzymia appeared at 2 weeks age. The clinic had a gradual, long duration .

Clinical Example № 1: the third child, the third pregnancy which took with the threat of interruption in its 1st half. The third normal delivery was with the cephalic presentation. Jaundice appeared on the 5th day after birth. At the age of 1 month jaundice began to increase, bilirubin index reached 81.28 mmol / L by direct fraction (58.63 pmol / L), antibodies to CMV - IgG 1:1600. The method of polymerase chain reaction (PCR) defined active replication of CMV. The survey revealed a congenital biliary atresia of bile ducts (proximal parts). The mother also had antibodies to CMV in high numbers. The child was discharged home on the insistence of his mother. After 3 weeks the child returned in serious state with symptoms of ascites, after puncture of the abdominal cavity 2,340 ml of liquid was received. The biopsy of the liver was performed, which found a violation of the structure of the liver due to broad layers of connective tissue with lymphoid infiltration, clumps of pigment in proliferating bile ducts, dystrophy of hepatocytes with accumulation of bile pigment in false lobules. Clinical and ultrasound way of a patient revealed the signs of portal hypertension. Thus by the age of 8 months the child's disease took form of a liver cirrhosis of a cholestatic genesis.

The pregnant women carriage of HbsAg in the Republic of Sakha (Yakutia) is in 2-3 times higher than the national average, and the rate of perinatal infection of newborns from mothers with HCV-infection is 7,2-10,2 % [1.5]. However, during the observation period was diagnosed for sure

in 2 cases of intrauterine fetal virus hepatitis B. The virus hepatitis C was diagnosed at 4 children. Unlike CMV, intrauterine infection with hepatitis B and C does not cause malformations at newborns. All six women had complicated obstetric and gynecological history, in 2 cases - the threat of interruption of pregnancy, 4 - anemia, 2 - severe preeclampsia against exacerbation of chronic pyelonephritis. Taking this into account 4 newborns' condition was regarded as satisfactory, 2 - as average weight, Apgar score was on average 7.2 ± 0.6.

All children indicated moderate hepatomegality in the neonatal period. Three infants within 5-8 days had conjugation jaundice - increasing total bilirubin due to indirect fraction, but the signs of hemorrhagic syndrome and hiperenzymia were not revealed.

Diagnosis was established on the basis of finding at 2 children HbsAg (1 of them had HBV DNA), and 3 infants had RNA HCV at their first month of life, and in one case the newborn was at the age of 36 days.

The clinical picture of hepatitis developed from the second month of life. State of two patients was regarded as acute hepatitis of moderate degree (1 - AVHV and 1 - AVHC), 4 cases were regarded as mild.

Clinical Example number two: the infant P. was born from 6th pregnancy, the 4th birth at 38 weeks, delivery operation. The mother had CVHV + D. Pregnancy passed with the threat of interruption, at the period of 32 weeks the mother was diagnosed by the polymerase chain reaction (PCR) DNA HBV (+).

The baby's condition at birth was regarded as satisfactory. The patient was discharged from the hospital in 10 days. Birth weight was 3544.5 g., length 56 cm, physiological jaundice was not observed. It should be noted that in spite of mother's diagnosis, the immunoglobulin was not put to the newborn.

At the age of 1 month baby suffered ARI, acute bronchitis. The pediatrician noted the yellowness of a skin. In the biochemical analysis of blood serum total bilirubin was determined to 22.24 mmol / L by direct fraction 18.04 pmol / L, ALT hyperenzymemia by 9.5 standards and ACT to 10.2 standards. The maximum values of total bilirubin (68 mmol / L) and cellular enzymes (12 standards) reached at the 36th day of illness, and then the positive dynamics was marked. Diagnosis was confirmed by method of polymerase chain reaction (PCR) DNA HBV (+). Now baby is 4 months being under medical supervision.

It should be noted that five women who were examined at neonatal pathology unit were first discovered hepatitis C, which reveals inadequate check-up of pregnant women in the consultation.

Fifteen infants with biliary atresia were observed in the surgical ward. In the case history of almost all infants are after full-term pregnancy, half of which proceeded with the threat of interruption in the 1st half and preeclampsia of varying degrees in the 2nd half of pregnancy. The most of children of this group were evaluated at Apgar score at 8/ 9 - 7/8 points. Yellowness of the skin was marked by 3-4 days of life, carried a wavy character with a tendency to progression. The defecation in the early neonatal period of most children had myconial character, acholia progressing with age, up to 2-4 weeks of age, the majority of patients had unstable acholia of defecation, stools more " lemon " in color, after 4 weeks there was no doubt in the symptom of "acholia" stool. Most of mothers did not establish the fact of color change of urine, but all babies had rich dark urine during hospital entrance. At the hospital in the period of 1-1.5 months severe increase of liver was noted, and 2 months later increase of liver and spleen was clearly manifested with signs of portal hypertension, of hepatic etiology - with hemorrhagic syndrome, vein varicous at lower third of the esophagus.

Prenatal pathology is suspected in three cases: the lack of visualization of the gallbladder during the 3rd ultrasonography III (2 cases) and cystic atresia of the common bile duct (1 case). As to timing and direction of hospitalization in a surgical department it is as follows: the majority of cases were admitted at the age of 1 month – (53 %); at age of 2 months – (33 %); and one case each of 7% - at the age of 2 days (abdominal cystic formation of large size in infants with atresia of

common bile duct); and at the age of 3 months (because of late diagnosis).

The algorithm of diagnostic measures includes ultrasound examination of the liver and bile ducts, if necessary the CT scan of the liver, endoscopy of the esophagus, stomach, and the duodenum, laboratory diagnostics to eliminate neonatal hepatitis. All patients had laboratory signs of cholestasis and in most cases CMV hepatitis (75 %). In order to avoid Alagille syndrome the patients undergo a series of diagnostic tests in the last 2 years: spinal radiography, echocardiography, consult an ophthalmologist, neurologist, and geneticist.

In the laboratory diagnosis of biliary atresia, the earliest sign is the increase in biochemical markers of cholestasis: hyperbilirubinemia due to the predominance of direct fractions in serum (average of 160-420 pmol / L total bilirubin, 91 - 280 pmol / L through direct fraction, increased levels of gamma- glutamintransferasa (up to 885), alkaline phosphatase (650), cholesterol (up to 6.0). The level of cytolytic enzymes (ALT, ACT) within 1 month of life of these patients increased moderately grows to 2 months of life in the progression of cytolysis of hepatocytes. The level of protein - synthetic function of the liver has not diagnostically relevant changes. It is possible to reveal the changes of coagulation during late diagnosis.

In order to identify the causes of neonatal cholestasis the markers of hepatitis B, C were taken among all patients and also a study of intrauterine infection was conducted - 75% of the blood test for DNA PCR CMV turned to be positive.

Clinical Example number 3: Boy T. He was transformed from the Infectious Diseases Hospital to the surgical department of the Pediatric Center at the age of 3 months with a diagnosis of biliary atresia against CMV infection. According to the history there is a congenital jaundice, lemon-colored stools. The deterioration of the state at the age of 1 month in the community in the form of appearance of neurological symptoms - convultions, soporific state, fever. He was transported in critical condition to the pediatric intensive care unit of Yakutsk by sanitary aviation. After comprehensive survey of the child the CMV infection was identified, brain and liver lesion, diagnosed a massive heart attack at temple-parietal and occipital regions from the right, and subarachnoid hemorrhage in the occipital region at both sides. In addition, the child had clinical symptoms of liver and spleen increase, a periodical acholia defecation. According to the ultrasound and CT the infant gallbladder was not revealed. During the period of treatment in the intensive care unit suffered an ulcer bulb of duodenum with profuse bleeding. The compensation of patient's condition was a success with great effort. After stabilization the child was transferred to CMV hepatitis infectious disease clinic for etiopathogenetic treatment, where a neotsitotekt course was provided, and preventive treatment by ursofalk for 2 weeks. There was not clinical improvement in the treatment of jaundice; the patient was stabilized by neurological disorders. At the age of 3 months porto-enterostomy according to Kasai was performed. During the operation is a rudimentary bile duct of 1.5 x 0.5 cm, containing no bile in the lumen, the bulb duct as a thin thread fell into a duodenum. At the gate of the liver the ducts were replaced by fibrous tissue. Later at the age of 9 months baby related liver transplant was performed at the Research Institute of Transplantation of Moscow.

CONCLUSION

The selection of modern laboratory and instrumental methods, the definition of the algorithm patient testing has particular importance in the diagnosis and verification of viral infections, predicting complicated pregnancy and outcome.

Infants with CMV infection have a low birth weight, low Apgar score; they more often need intensive care at birth. Clinical manifestations of CMV infection in the neonatal period are of polyorgan character with a primary lesion of the liver and nervous system. The diagnostics of intrauterine lesions by virus hepatitis B and C is often inadequate today.

It is necessary to introduce the clear algorithms of women screening in planning pregnancy, and examination of them for presence of hepatotrophic viruses.