I. NEONATOLOGY

NEONATAL HEPATITIS WITH CYTOMEGALOVIRUS

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Abstract

Hepatic disorder is frequent during congenital infection with cytomegalovirus. The clinical expression ranges from subclinical to serious, even fatal forms of disease. The hepatic manifestations can dominate the clinical symptomatology or, within the multisystemic involvement clinical or only biochemical signs of hepatitis can occur. The evolutive forms of disease, progressing towards the chronic stage, have an important potential towards chir.

Key words: cytomegalvirus infection, neonatal hepatitis

Introduction

Infection with cytomegalovirus (CMV) represents one of the most frequent congenital infection in Europe, with a rate of 4-5 to 1,000 births.

The newborn liver is particularly predisposed to transplacentar or perinatal infection with CMV, whereas in other ages the hepatic disease occurs rarely and only in certain circumstances (e.g. immunity deficiency)

Hepatic disorder is mainly manifested as a hepatocellular disease (hepatitis), but the CMV infection has been associated, in many studies, with three other clinical-pathological distinct entities:

- inflammation and reduplication of the biliary duct in the portal spaces, which in some circumstances results in paucity of the biliary duct;
- lesions of the main intrahepatic biliary ducts with evolution towards sclerosing cholangitis;
- diseases of the extrahepatic biliary ducts, mainly biliary atresia (2)

In all these cases there is a stereotype response, neonatal cholestasis, which creates difficulties in diagnosis, and the primary pathological impact can be common, respectively an inflammatory chollangiopathic process, with various degrees of involving the hepatocytes and the biliary ducts.

Aim of study

The authors target the evaluation of hepatic involvement in the congenital infection with CMV, as well as the study of clinical manifestations, of the biological modifications and of the evolution in the neonatal hepatitis with CMV.

Material and method

A number of 11 newborns were under study, that had been diagnosed with maternal-fetal infection with CMV, in the Maternity of Reşita Hospital, during 1996-2004.

The serological diagnosis of the congenital infection with CMV was carried out by determining the IgM type CMV antibodies, with the ELISA method. In 2 cases the diagnosis was confirmed by the detection of pp65 antigen, specifically CMV in leucocites and the isolation of the CMV infected cells in urine. The presence at birth of the IgM type CMV antibodies indicated the intrauterine infection. Diagnosis of neonatal hepatitis with CMV was based on clinically documented hepatopathy and/or by altering the hepatic tests.

Results

Out of the 11 analysed cases, 8 presented clinical symptoms at birth or during the early neonatal period and 3 cases were asymptomatic, the diagnosis being exclusively serological, based on the presence of CMV IgM type antibodies. The asymptomatic cases have been included in the study for the following up of subclinical forms of disease.

In order to study the occurrence of the hepatic clinical manifestations in the CMV congenital infection, the 8 cases of children with symptomatic congenital infection were analysed .

The clinical signs in the CMV congenital infection were: jaundice, in 5 cases (62,50%), hepatomegaly present in 5 cases (62,50%), splenomegaly in 3 cases (37,50%) hypoxic-ischaemic encephalopathy in 3 cases (37,50%) convulsions in 1 case (12,50%) petechiae in 4 cases (50%) ascites in 1 case (12,50%) the hemorragipary syndrome 1 case (12,50%), microcephaly in 1 case (12,50%), chorioretinitis in 3 cases (37,50%), pneumonia in 3 cases (37,50%). The clinical signs of neonatal hepatitis were present in 5 of the 8 cases of transplacental infection with CMV

For the study of subclinical forms of disease, 1 asymptomatic case was included in the study, case where the hepatic disease was proved by altering the biological hepatic tests. According to the cases' genders, age of pregnancy, Apgar score, birth weight, it comes out that the male gender was affected to a degree of 66.66%. According to the age of pregnancy, as determined by anamnesis and Ballard score, 16,66% were born premature. According to the placement on the intra-uterine growing curves, 5 newborns (83,33%) were appropiate for gestational age, 1

children (16,66%) was small for gestational age. According to the Apgar score, 2 cases (33,33%) presented obstetrical asphyxia.

Clinical manifestations in neonatal hepatitis with CMV

Jaundice was present in 5 cases. The early onset of jaundice was present in 2 cases: 1 case in the first 24 hours, respectively, 1 case in the first 36 hours. In most of the cases, the jaundice was a colestatic type (4/5), of medium intensity and associating hyperchrome urine (2 cases), and hypocolic stools (1 case). In all cases, jaundice was prolonged, with a winding evolution present in 2 cases and progressive evolution, towards worsening, noticed in 2 cases. Hepatomegaly was present in 5 cases, associated with splenomegaly in 3 cases. The associated digestive symptoms were: biliary vomiting, difficulties in sucking, low digestive tolerance, anorexia, abdominal distension with meteorism. Within the systemic disease, the hepatic symptoms were associated in 2 of the cases with pathological neurological symptomatology: hypotonia, apnea , convulsions. Other general symptoms: marble-like skin, fever were also assessed.

Table1. Clinical findings in CMV neonatal hepatitis

Symptoms	**Nr. of cases**	Occurrence
Jaundice		
-average intensity	4	80%
-intens	1	20%
Hepatomegaly		
< 2 cm	2	40%
2-4 cm	2	40%
> 4 cm	1	20%
Splenomegaly	3	60%
Hypocolic stools	1	20%
Hyperchrome urine	2	40%
Hemorragipary syndrome	1	20%
Ascites	1	20%
Biliary vomiting	1	20%

Hepatic biological investigations in the neonatal hepatitis with CMV

- Hepatocytolythic syndrome

Hepatocytolysis was pointed out by high levels of serum transaminase (ALAT/SGPT and ASAT/SGOT) in all the studied cases. In 4 cases mild elevation of transaminase were noticed, important cytolysis (TGP over 200 UI/l, upon repeated analysis) occurred in 1 case and was associated with intense jaundice, important hepatosplenomegaly and colestasis. Slightly increased levels of transaminase (1.5xN) were recorded in 1 asymptomatic case. Minor increased levels of transaminasis, upon repeated analysis, associated with slightly modified levels of direct bilirubin, led, by means of additional investigation, to diagnosis of clinically asymptomatic transplacental CMV infection. (table 2)

Table 2. Hepatocytolythic syndrome

SGPT			**SGOT**		
<50 UI/l	50-100UI/l	>100UI/l	<70UI/l	70-100UI/l	>100UI/l
-	4 66,66%	2 33,33%	-	5 83,33%	1 16,66%

- Hepatoprive syndrome

Prolongation of prothrombin time (PT) ocured in a single case, with a value of IP 83%. The hepatic synthesis deficit was proved by carrying out the Koller test (the intravenous administration of K vitamin and repeating the PT after 2 days). The hepatocellular dystrophy, affecting the capacity of synthesis, revealed the decrease in the total proteins under 60 g/l in 1 cases (proving the lowering of hepatic synthesis). The albuminemia was normal in all 6 cases. The alfa-1 globulin levels were normal in 4 cases. Even though this parameter is not considered accurate in assessing the hepatoprive syndrome, due to its unspecificity, the slighlty increased values occurred in 2 cases were included in this inflammatory context.(table 3)

Table 3. Hepatoprive syndrome

P.T.	**P.I**	**Proteines**	**Albumines**
≥20s	≤50%	<60g/l	≤50%

1 16,66%	1 16,66%	1 16,66%	- -

- Cholestatic syndrome

The cholestatic syndrome was revealed by higher values of conjugated bilirubinemia in all cases, and mixed hyperbilirubinemia was present in 1 case. Higher values of colestasis enzymes (alkaline phosphatase and gamma-glutamil-transpeptidase) were noticed in 2 cases. (table 4)

Table 4. Colestatic syndrome

Bilirubin		**A. Ph.**	**gama-GT**
D> 0,3mg%	T>12mg%	>400U/L	>130U/L
6 100%	1 16,66%	2 33,33%	2 33,33%

- Immunologic investigations

The quantitative finding of immunoglobulins: IgA, IgM and IgC, according to the nephelometric procedure indicated:

- normal values for IgA in all new-born babies
- higher values for IgG in 1 new-born baby (16,66%)
- higher values for IgM in 3 new-born babies (50%).

The changes noticed at the immunoglobulins levels were interpreted as a reaction to the persistent viral stimulus, with an important IgM reaction. The determination of lymphocyte subpopulations with the Beckton-Dickinson flowcytometry in 4 cases did not indicate cellular immune deficit.

Evolution

Out of 6 infants, 4 (66.66%) presented a favourable evolution, towards healing, with the improvement of the clinical symptomatology and normalisation of the biological values until the age of 6 months. In one patient, hepatomegaly and the colestatic jaundice lasted until the age of 7 months.

The evolution towards chronicity occured in 2 infants (33,33%), with the persistency of clinical and inflammatory laboratory signs, hepatic disfunction and cholestasis. Decease was recorded in one case (16,66%), at the age of 8 months, due to a progressive evolution towards biliary cirrhosis.

Treatment of neonatal hepatitis with CMV

1. Etiological treatment. The treatment with Ganciclovir, dosage of 6 mg/body kg, intravenous, in one hour perfusions each 12 hours, for 6 weeks, was carried out together with the monitoring of possible side effects (especially, the myelosupressive effect, firstly severe thrombocytopenia and neutropenia). Two cases of new-born babies with severe forms of disease, with systemic symptomatology, were administered the treatment.

2. Treatment of cholestasis. Phenobarbital was used in a dosage of 3-5 mg/day, as an inductor of mitocondrial enzymes and stimulator of the billiary flow, acting independently from the biliary acids.

3. Prevention and fighting the main complications of the prolonged cholestasis:

For lipidic malabsorption the diet was modified by lowering the long chain triglycerides and by supplementing medium chain triglycerides. Substitution of liposoluble vitamins: A vitamin (10,000 units/month, intramuscular), D3 vitamin (25-OH) 800 units/day orally), K vitamin (5-10 mg x 2/week, intramuscular), E vitamin (5-300 units/day) was performed. Administration of 0.5 g of Calcium per day was done.

Conclusions:

1. The occurrence of hepatic manifestations of the congenital CMV infection was in this study of 54,54%.The clinical forms ranged from subclinic forms, present in 16,66% of newborns, mild forms in 33,33% of the cases, medium forms in 33,33% of the cases and severe forms in 16,66% of the cases.

2. In the neonatal CMV hepatitis the hepatic clinical manifestations were associated, in 33,33% of the cases, within the systemic disease, with pathological neurologic symptoms.

3. In 66.66% of the cases the evolution of CVM hepatitis was favourable, towards healing. Improving the clinical symptomatology and normalisation of the biological values were achieved, in most cases, until the age of 6 months. The chronic evolution was noticed in 33,33% of the cases, with the persistency of clinical and inflammatory laboratory signs, hepatic disfunction and cholestasis. Decease was recorded in 16,66% of the cases at the age of 8 months, due to a progressive evolution towards biliary cirrhosis.

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