IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir
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Original Article

First-Day Direct Hyperbillirubinemia in an Infant with Congenital Cytomegalovirus Infection

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ABSTRACT

The human cytomegalovirus (CMV) is widely distributed among the human population as one of the most common causes of congenital infection with an incidence of about 0.15-2.0% in developed countries. In this case report we present a female neonate (with a maternal history of flu-like syndrome in 30 weeks of pregnancy) delivered via caesarian section with good reflexes and appropriate APGAR score, without any obvious anomalies. Its cerebrospinal fluid and unigrams were found to be normal. The CMV diagnosis was confirmed by neonate serology (IgM-positive). Additionally, positive results for CMV were obtained from the neonate's urine polymerase chain reaction test. Therefore, the necessity for differential diagnosis (e.g. hemolysis, ABO RH mismatch, biliary duct obstruction) was eliminated. Treatment with ganciclovir and granulocyte-colony stimulating factor (Gancyclovir induced neutropenia) was provided, as a result of which a dramatic immediate and short-term response was observed. It is proposed that multisystem involvement in congenital CMV should be suspected and medical treatment should be administered especially in life threatening conditions.

Keywords: Cytomegalovirus, Early Direct Hyperbilirubinemia, Gancyclovir

Introduction

Congenital infections can occur in 30% of maternal primary infections during pregnancy (occurring in 1-5% of pregnancies). Therefore, more clinical suspicion and evaluations are required to prevent neonatal delivery with poor neurodevelopmental outcome (1).

In this study, the case of a newborn with congenital infection symptoms, namely early cholestatic jaundice and thrombocytopenia, is presented.

Case report

A female neonate with intra-uterine growth retardation (IUGR) delivered via cesarean section with APGAR score of 8-9, birth weight, head circumference and length of 2050 g, 31cm and 45cm, respectively and without any obvious anomalies, was studied.

Within the first six hours of birth, jaundice appeared and she was admitted to the neonatal intensive-care unit (NICU) of Imam Reza Hospital, Mashhad, Iran. In past medical history of the mother a flu-like disease during the 30th week of gestation was reported.

In physical examination the neonate was found to have jaundice and hepatosplenomegaly with normal neonatal reflexes and without any distress.

The results of the first laboratory data were as follows: total bilirubin: 12 mg/dl, direct bilirubin: 0.312 mg/dl, WBC: 9500 microliter, Hb: 20 gr/dl, PLT: 20000 microliter. Both neonate's and mother's blood group was A^+.

Despite intensive phototherapy and transfusion of platelet, hyperbillirubinemia and thrombocytopenia grew worse. Thus, with a suspicion of hemolysis, intra-venous immunoglobin (IVIG) was infused for the neonate, and the primary investigations for infection were conducted and then antibiotics started.

After 24 hours of admission, hepatosplenomegaly and diffused petechiae on her trunk were found in the physical examinations. Also, conjugated bilirubin intensified and clinical cholestatic pattern appeared.

The laboratory data obtained on the first and second days were as follows: SGOT: 341 U/L, SGPT: 150 U/L, ALP: 753 U/L, T. bilirubin: 12.8 mg/dl, D. bilirubin: 9.7 mg/dl, PT: 15.5s, PTT: 33s,

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Na: 135 mEq/L, K: 4.2 mEq/L, Ca: 9.4 mg/dl, direct combs: negative, indirect combs test: Negative, UA: normal, WBC: 7900/microliter, RBC: 4.28*10^6/microliter, Hb: 14.9 g/dl, MCV: 109 fl, PLT: 48000/microliter, BS: 30 mg/dl, urea: 24mg/dl, creatinine: 0.5 mg/dl, CSF: WBC: 0/mm3, RBC: 50/mm3, protein: 118 mg/dl, sugar: 23 mg/dl, CRP: 14 mg/Lf.

Considering suspected congenital infectious disease, TORCH study was carried out, the results of which are reported below:

Total IgM: 45, anti TOXO Ab IgM 0.1 u/ml, IgG: 3.4 u/ml (Neg), anti-Rubella Ab IgM: 0.1 u/ml, IgG: 0.4 u/ml (Neg), anti-CMV Ab IgM: 1.6 u/ml (POS), IgG: 1.7 u/ml (Neg).

In abdominal sonography, hepatosplenomegaly and normal biliary tract were reported. In brain sonography, some hyperechoic lesions were reported around brain ventricles. In addition, brain computed tomography (CT) scan showed periventricular calcification.

The polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) was negative for Herpes Simplex Virus (HSV) infection; however, urine PCR for CMV was positive. In ophthalmic funduscopic examination, pigmentation changes with salt-and-pepper appearance were detected. Audiometric examination was also done; the results showed that her otoacoustic emissions and auditory brainstem response were in normal range.

Consequently, with diagnosis of symptomatic congenital CMV, treatment with gancyclovir (initially intravenous and then orally) began. Granulocyte-colony stimulating factor (GCSF) was prescribed for three days due to drug induced neutropenia.

Following three weeks of treatment, thrombocytopenia and hepatosplenomegaly gradually improved (the treatment continued for two months).

At six months of age, the infant's general condition, growth and physical examination was good and Denver Development Scoring System (DDST) was normal for her age.

Discussion

The incidence of CMV among human population is about 0.15-2% in developed countries. In developing countries, however, 80-90% of reproductive-age women are CMV immunoglobulin G (IgG) positive (2, 3). Virus transmission during pregnancy is dependent on primary infection or reactivation of latent infection (30-50% versus 0.5-3%).

Approximately 90% of the infected infants are asymptomatic; however, 5-15% of these infants show sensorineural hearing loss, chorioretinitis or neurologic problems later in life. Roughly 10% of the infected infants are symptomatic at birth with mortality rate of 10-30% and 90% of survivors experience late severe morbidities (e.g. neurodevelopment sequels) (2, 4). In our case, during follow-up until six months of age, the infant's physical examination was norma.

First-line diagnostic test is used for detection of CMV DNA in various body fluids (saliva, urine or CSF) by PCR. However, serologic studies should be interpreted cautiously due to maternal IgG crossing the placenta.

Immunoglobulin M (IgM) in cord or systemic blood indicates fetal infection. IgM is produced in fetus three to four weeks following CMV exposure and it remains positive for three to four months (3, 5).

The gold standard for diagnosis of congenital CMV infection is isolation of virus from human fibroblasts in the first two weeks of life. Urine and saliva are clinical samples of choice; in this study, urine was used for diagnosis and the test results showed high level of IgM.

Brain imaging in these neonates (MRI, CT scan or ultra-sonography) can detect periventricular calcifications, white matter lucencies ,ventriculomegaly, brain atrophy and neuronal migration disorders and other brain lesions in 78% of patients (6). In our study, sonography showed hyperechoic lesions which were found to be calcifications in brain CT scan.

Ganciclovir should be used for infants with life threatening CMV infections. It has been reported that up to six months of antiviral therapy may be required to control chorioretinitis in the symptomatic congenitally infected infants.

Although ganciclovir improves neurodevelopmental outcomes for the symptomatic infants, still its efficiency in preventing sensorineural hearing loss in symptomatic patients is not clear.

The potential role of valganciclovir in long-term (suppressive) CMV therapy in congenital infections is currently under investigation. Prolonged therapy of symptomatic congenital CMV infection with intravenous ganciclovir followed by oral valganciclovir was safe, and seemingly it leads to a better auditory outcome as compared to short-term therapy (4, 7).

In our case, the patient showed good clinical response to medication. In addition, during follow-up until six months of age, her physical

examinations and growth were highly satisfactory and DDST was normal for age.

Acknowledgment

The authors would like to thank the Vice-Chancellory for Research of Mashhad University of Medical Sciences.

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