

Cytomegalovirus Infection in Twin Pregnancy and Coincidence of Type I Tyrosinemia in One of Twins

Gholamhosein Fallahi *1, MD, Pediatric Gastroenterologist; Fatemeh Farahmand¹, MD, Pediatric Gastroenterologist; Mohammad Sobhani Shahmirzadi², MD, Fellowship in Pediatric Gastroenterology

1. Department of Pediatrics, Tehran University of Medical Sciences, IR Iran

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Abstract

Background: Cytomegalovirus (CMV) is the most common cause of congenital infection. Although most of the involved neonates are asymptomatic but virus can cause a range of problems from mild to severe illness with involvement of different organs like central nervous system, gastrointestinal and liver. Proneness to CMV is very high (up to 1% of neonates). In the other hand tyrosinemia type I is a rare metabolic disorder with involvement of liver, neurologic, bone and other organs.

Case Presentation: A 3-month-old infant, product of twin pregnancy was hospitalized because of jaundice, FTT, hepatomegaly and sepsis. The other twin showed normal growth with no problems. Work up for cholestasis and FTT was suggestive of two different entities. Polymerase chain reaction for CMV in liver tissue and serum was positive. Meanwhile laboratory findings for metabolic disorder led to the diagnosis of type 1 tyrosinemia. The other twin was infected with CMV too.

Conclusion: Although coexistence of two causes for cholestasis is very rare, it is sometimes necessary to study more to rule out other entities like metabolic disease including tyrosinemia (if any symptoms exist).

Key Words: Twin; Cytomegalovirus; Type 1 tyrosinemia; Neonatal Cholestasis

Introduction

Cytomegalovirus (CMV) is one of the seven members of herpes viridae^[1] and has the highest morbidity and mortality rate among them^[2]. CMV is the most common cause of

congenital infections and in 5% of cases leads to cytomegalic inclusion disease which is the most severe congenital manifestation of CMV infection, and presents with hepatosplenomegaly, jaundice, petechiae, purpura, and microcephaly^[3]. Most involved

* Correspondence author;

Address: Children's Medical Center, Dr Gharib St, IR Iran

E-mail: ghfalahi@tums.ac.ir

cases are asymptomatic, but the virus can cause a range of mild to severe and mortal symptoms^[3]. In developing countries, most children are infected at the beginning of their life; and about puberty, serologic prevalence rate is almost 100%^[2].

Acquirement of CMV is common in neonatal period and up to 1% of all neonates are infected. Transmission can occur before, during or after birth^[2]. Infection in mother may be primary or a relapse; infant's severe disease is often due to maternal primary infection. Probability of infection transmission to fetus in maternal primary infections is much higher than a relapse during pregnancy (30% compared with less than 1%)^[3]. About 96% of infected mothers have CMV in their breast milk. Infected infants discharge the virus from their urine and saliva for years^[3].

The signs and symptoms of the disease are variable with an incubation period from 3 to 12 months^[4]. Primary infection may cause pneumonitis, hepatomegaly, hepatitis and petechiae. In older patients, the disease may present as infectious mononucleosis-like syndrome which lasts 2 to 3 weeks. Relapse in patients with appropriate immunity is asymptomatic^[3]. Manifestations of con-genital infection are intrauterine growth retardation, prematurity, hepatospleno-megaly, jaundice, thrombocytopenia, micro-cephaly and periventricular calcification^[3]. Alimentary problems and presentations are: esophagitis, gastritis, gastroenteritis, pyloric obstruction, hepatitis, pancreatitis, colitis, cholecystitis^[2].

Maximal increase in serum transminases is 200 units^[4]. Rarely, acute infection may cause diffuse hepatocellular necrosis in a normal individual which presents with fever, jaundice, very high increase in trans-aminases and coagulopathy^[5,6].

Case Presentation

The patients that are going to be introduced, are twins born by cesarean section in Ahvaz (Southern Iran). They were term neonates.

The first twin had no problems at birth but the second one was admitted because of respiratory distress after birth; jaundice was present from the first day and was treated by phototherapy. This infant was readmitted at 3 months of age because of continuation of jaundice that had been of direct type and had an increase from the age of 2 months.

In physical examination, the infant appeared to have a generalized jaundice, poor weight gain (birth weight 1600 gr and weight at 3 months of age 2350 gr), microcephaly (head circumference at birth and 3 months of age= 30 cm), liver was palpable 1 to 2 cm and spleen 4 cm below costal margin. There was a 3/6 murmur in heart auscultation.

Anemia and thrombocytopenia were frequently present in blood tests, but leukocyte count and ESR were normal. Total bilirubin was 14, (direct bilirubin 4.6) that reached to total 20 (direct 8.5) in the hospital. Blood gas and electrolytes were normal too. Prothrombin time (PT) and partial thrombin time (PTT) were disturbed severely (in two tests PT activity was reported 40% and 48%). Transaminases were increased [aspartate aminotransferase (AST) 1108, alanine aminotranferase (ALT) 457, Alkaline phosphatase 1083 and Gamma glutamyl trans peptidase 166]. Alpha-fetoprotein was reported over 1000. Urine amino-acid chromatography showed a tryptophan band, urine sugar chromatography had a narrow galactose band.

The infant had two other episodes of hypoglycemia during hospital stay. α 1-antitrypsin level was normal. Chest x-ray demonstrated multiple fractures in ribs bilaterally. In addition to liver and spleen enlargement, sonography detected a round nodule suspicious of accessory spleen, kidney enlargement and two little stones in kidneys. Echocardiography showed a severe aorta coarctation and mild cardiomyopathy. Treatment by balloon or angioplasty was postponed due to general condition of the patient.

Hepatobiliary Iminodiacetic Acid (HIDA) scan ruled out bile duct atresia and severe hepatic injury. The patient had urinary

infections and was treated with co-trimoxazole for 10 days. In bone marrow aspiration, hyperplasia of erythroids was reported.

After detecting of positive CMV serology (IgG and IgM antibodies) in serum of mother and infant, CMV DNA PCR was done and it was positive in both twins, in urine and serum. In addition, PCR detected CMV in liver biopsy sample. Hepatic problems and other laboratory disorders were not related to CMV infection, and according to disturbed PT and PTT, high α -fetoprotein and severe jaundice, further studies for tyrosinemia were performed. Liver biopsy showed changes like metabolic disease, so serum tyrosine level and urine succinyl acetone were estimated. The result was: serum tyrosine 68.525 mg/dl (normal range 1.6-3.7 in newborn), urine succinyl acetone 1.4 μ mol/gcr (normal range: undetectable).

The first twin had an appropriate weight gain (birth weight 2600 gr and weight at the age of 3 months 6300 gr), appropriate head circumference, no jaundice, and positive CMV PCR. This infant had a mild hydrocephaly (proved by CT scanning). Gancyclovir was administered for both infants.

Discussion

This is the first report on simultaneous infection of a pair of twins by cytomegalovirus which was accompanied by type I tyrosinemia and cardiac involvement as coarctation of aorta in one of the infants.

In a study by Yonin et al in 2006, 20 twin pregnancies in which the mothers were infected with CMV, were followed up. Seventeen mothers had primary infection and 3 had a relapse. For studying these neonates, congenital infection was described as having positive culture after birth, and the result was that the incidence of cytomegalovirus infection in twin pregnancies is the same as in single fetus pregnancies (both about 30% of total primary infection and relapses). From these neonates, no one had congenital

infection^[7]. In another study by Kawana et al in 2004, severity of CMV manifestations was completely different in the twins. The authors concluded that the severity of manifestations in neonates is directly related to the number of CMV positive cells in placenta^[8]. Twin fetuses show different reactions to maternal primary infections so that if one of the fetuses is involved, the other one should be examined too^[9].

Accompaniment of CMV infection and tyrosinemia was reported by Wabitsch et al in 1993. A 2-month old infant was admitted because of meningitis and septicemia by *Streptococcus pneumoniae* and had typical signs of type I tyrosinemia. Diagnosis of tyrosinemia was made by proving the low activity of fumaryl aceto acetate enzyme in the patient and parents^[10].

Type I tyrosinemia in young infants presents with hepatic and renal tubular failure, failure to thrive and rickets^[11]. Typically, severe hepatic disease presents before the age of 6 months and if not treated, the patient may expire^[12]. With no treatment, frequent neurologic crisis with mental status changes, abdominal pain, peripheral neuropathy and respiratory insufficiency that would need mechanical respiration, will occur. The prevalence rate is 1 in 100,000 to 200,000 births, but because of variable manifestations of the disease, only 50% of patients who survive would be diagnosed^[12]. Differential diagnosis includes neonatal cholestasis and tryrosinemia. Urine should be tested for succinyl acetone and blood for tyrosine levels.

Increase in α -fetoprotein is seen (on average increases over 160,000 ngr/cc (normal value is less than 1000 ngr/cc for the ages from 1 to 3 months and less than 12 for ages from 3 months to 18 years). PT and PTT are prolonged and would not be corrected by vitamin K and Transaminases and bilirubin are elevated, usually^[12].

All findings mentioned above did exist in our patient but tests could not prove acidosis and proximal RTA. Probability of type I tyrosinemia is decreased if α -fetoprotein, PT and PTT are normal^[13]. These infants have the smell of boiled cabbage or rotten mushroom;

multiple fractures of ribs in these infants may be due to rickets.

Epidemiologically, accompaniment of tyrosinemia and any specific infectious disease is not common, and simultaneous incidence of tyrosinemia and CMV infection is very rare and is not reported.

Conclusion

Although coexistence of two causes for cholestasis is very rare, it is sometimes necessary to study more to rule out other entities like metabolic disease including tyrosinemia (if any symptoms exist). In addition it is necessary to search cytomegalovirus in the other twin if one of the twins is infected.

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