Case report

Treatment of symptomatic congenital cytomegalovirus infection with ganciclovir

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Abstract

Cytomegalovirus (CMV) is the most common cause of congenital infections in humans and it produces considerable morbidity in newborns. There has been insufficient attention given to congenital CMV infection in the developing world and the exact prevalence in Sudan is not known. The classical triad of congenital CMV infection is composed of jaundice, petechiae and hepatosplenomegaly. We report a Sudanese baby born with the typical symptomatology of congenital Cytomegalovirus infection and positive serological test who was treated with Ganciclovir for six weeks with complete resolution of hepatic cholestasis and normal hearing. Currently he has global developmental delay and abnormal CNS examination, his initial CT brain and follow up MRI brain scan were grossly abnormal which was a predictor of severe intellectual impairment.

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Introduction

Human cytomegalovirus (CMV) is one of eight human herpesviruses. It is a member of the beta-herpes virus subfamily (1). CMV is a major cause of morbidity and occasional mortality in newborn infants. In recent years, it has become evident that CMV is the most important cause of congenital infection in the developed world, and that it frequently leads to mental retardation and developmental disability (2). CMV is transmitted by close contact between individuals, through contamination from urine, saliva, semen, cervical secretions and breast milk, while droplet contamination is thought to be less important (3). The risk of intrauterine transmission is highest when primary infection occurs during pregnancy, with a significantly increased risk of adverse fetal effects if fetal infection occurs during the first half of pregnancy (4).

The prevalence of CMV at birth, worldwide, is about 0.64% (5), with 10%–15% of congenitally infected infants being symptomatic at birth. In symptomatic infants, mortality is as high as 30% and late-onset sequelae occur in 35%–100%. In infants who are asymptomatic at birth, neurodevelopmental sequelae occur in 13.5%, with hearing loss occurring in 12% (6).

Ganciclovir (GCV) is the drug of choice for the treatment of CMV infection. When given intravenously for 6 weeks, it has been demonstrated to significantly prevent hearing deterioration and developmental delays in infants with congenital CMV infection (7, 8).

There has been insufficient attention given to congenital CMV infection in the developing world, but the limited data available suggests that CMV may also represent a significant public health concern in these populations (9).

We report a Sudanese baby with congenital CMV infection who was treated successfully with GCV with definitive improvement in hepatic cholestasis and hearing outcome, however the long-term neurodevelopment remains guarded.

Case history

A male baby was born in February 2014 by normal spontaneous vaginal delivery with no resuscitation
required at birth. Birth weight was 2.8 KG and head circumference was 34 Cm (normal). The mother was para 5+0; she did not have any fever or rash in her first trimester. The first antenatal ultrasound was done in the second trimester, which showed foetal ascites that resolved on follow up ultrasound, however hepatosplenomegaly was detected. TORCH screening for the mother showed positive results for Rubella and CMV.

At birth the baby was deeply jaundiced with no dysmorphic features, the abdomen was distended with hepatosplenomegaly and the skin revealed a petechial rash. The initial complete blood count showed normal Hb and WCC, however the platelet count was low (43,000/cmm). Liver function test showed high serum bilirubin (14.1 mg/dl) which was mainly direct (8.5 mg/dl), AST was 245 U/l, ALT was 67 U/l and alkaline phosphatase 203 U/l. Renal function test and coagulation profile were entirely normal.

TORCH screening for the baby showed positive IgM for CMV and was negative for all other viruses. The diagnosis of congenital CMV infection was made based on the above result and the clinical findings. Further investigations were done, abdominal U/S showed hepatosplenomegaly, ophthalmological examination was normal and hearing assessment which was done by otoacoustic emission test, was normal. CT brain showed hypodensity of the white matter, multiple periventricular calcific foci and colpocephaly, all were consistent with congenital CMV infection, figure 1. Repeat liver function tests showed more cholestasis and the serum bilirubin reached 34.5 mg/dl with direct of 28 mg/dl. AST, ALT and alkaline phosphatase remained high. The baby was commenced on GCV in a dose of 6 mg/Kg, twice daily for 6 weeks; he was also put on liver support mainly fat-soluble vitamins, Ursodeoxycholic acid, multivitamin syrup and Zinc sulphate.

The baby showed gradual improvement in liver cholestasis with complete resolution by 2 months of age, the platelet count also returned to normal. At 6 months follow up the baby showed mild developmental delay and hypotonia and was commenced on physiotherapy. An MRI brain scan was done at the age of one year, which showed bilateral cystic encephalomalacia, colpocephaly and hypoplastic corpus callosum figure 2. Repeat ophthalmological assessment was normal and hearing assessment, which was done by brain stem auditory responses, was normal. The baby was seen recently at the age of 16 months, the head circumference was 43 Cm (below the third percentile for age and sex), neurological assessment revealed increased tone peripherally, central hypotonia and global developmental delay.
Figure 2. MRI brain scan showing bilateral cystic encephalomalacia, colpocephaly and thinned corpus callosum

Discussion

CMV is the most common cause of congenital infections in humans and it produces considerable morbidity in newborns. There has been insufficient attention given to congenital CMV infection in the developing world and the exact prevalence in Sudan is not known. The effects of race and genetics on clinical manifestations of CMV infection are not well understood. In some studies in the United States, the prevalence of congenital CMV infection appears to be higher in infants born to black women.

The diagnosis of congenital CMV infection in a neonate is based on demonstration of the virus by isolation from urine, by identification of CMV-DNA by polymerase chain reaction in body fluids or the demonstration of CMV IgM in the newborn, which is indicative of congenital CMV infection. Our case had the typical symptomatology at birth in addition to positive CMV IgM.

The majority of infants born with congenital CMV infection are asymptomatic at birth and only about 10% have clinical evidence of the disease at birth. The classical triad of congenital CMV infection is composed of jaundice, which is present in 62%, petechiae in 58%, and hepatosplenomegaly in 50%. All these classical symptoms were present at birth in our case, which confirmed the diagnosis of congenital CMV infection.

GCV is the drug of choice for the treatment of neonates or infants with congenital CMV disease. This drug is active only after phosphorylation to Ganciclovir triphosphate, which is recognized as guanosine triphosphate by the viral DNA polymerase, with consequent inhibition of CMV replication. GCV is active only in infected cells. Potential adverse effects of GCV in neonates include transient neutropenia, which may necessitate dose adjustment or interruption of therapy.

Our case did not show any adverse effects of the drug and the Neutrophil count was carefully monitored. Sensorineural hearing loss is the most frequent long-term consequence of congenital CMV infection and is not manifest invariably at birth or in the neonatal period but in many cases may fluctuate and be progressive in nature. In our case GCV treatment was instituted very early in the course of the disease with no deterioration in hearing on follow up visits compared to base line test, this is actually consistent with many studies in this area. One collaborative prospective study did demonstrate a benefit of intravenous GCV in infants with symptomatic congenital CMV infection. Antiviral treatment in this study led to improvement or stabilization of hearing.

Our case has alarming CNS findings, both clinically and by imaging studies. An MRI brain scan done at one year of age showed bilateral cystic encephalomalacia, colpocephaly and hypoplastic corpus callosum, these findings are quite consistent with the expected CNS findings in congenital CMV infection that were reported before. Despite definitive improvement in hepatic cholestasis with GCV therapy and supportive treatment, GCV did not seem to have influenced the course of CNS deterioration despite early institution. Normal neuro-imaging at birth in symptomatic congenital
CMV infection predicts a good long-term neurological outcome (19). Our case had an abnormal CT brain at birth which is consistent with the finding that intracranial lesions on neuroimaging at birth are associated with severe intellectual impairment in more than 80% of cases later on in life (19).

**Conclusion**

CMV is the most common cause of congenital infections in humans and it produces considerable morbidity in newborns. The classical triad of congenital CMV infection is composed of jaundice, petechiae and hepatosplenomegaly. Early treatment with GCV leads to improvement in hepatic cholestasis and hearing outcome. However, abnormal neuro-imaging at birth might predict severe intellectual impairment later on in life.

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**References**


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