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PERINATAL/NEONATAL CASE PRESENATION

Severe postnatal cytomegalovirus infection with multisystem involvement in an extremely low birth weight infant

E Okulu[1], İM Akin[1], B Atasay[1], E Çiftçi[2], S Arsan[1] and T Türmen[1]

[1]Division of Neonatology, Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey and [2]Division of Infectious Diseases, Department of Pediatrics, Ankara University School of Medicine, Ankara, Turkey

Cytomegalovirus (CMV) infection is the most common intrauterine and perinatal viral infection. Postnatal CMV infection is acquired mainly from breast milk and may cause severe illness in preterm infants. We report an extremely low birth weight infant who presented with a sepsis-like syndrome and multiple organ involvement, notably hepatitis and pneumonitis, and treated with ganciclovir without adverse effect or relapse.
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Introduction

Acquisitiıon of cytomegalovirus (CMV) may occur by either prenatal infection *in utero*, resulting in congenital CMV infection, or by perinatal acquisition, during either the labor and delivery process, via blood transfusion or by breast milk. There is considerable evidence showing that the shedding of the virus into breast milk is the main source of postnatal CMV infection in infants.[1,2] Most acquired CMV infections in term infants are asymptomatic or manifest as a self-limited disease. In premature neonates, postnatal CMV infection can lead potentially life-threatening problems. Only few cases of postnatal CMV multisystem infection with severe course have been reported.[3,4] Treatment of the postnatal CMV infection of the premature neonate and therapeutic options remain controversial. We report an extremely low birth weight infant with postnatal CMV infection presented with sepsis-like symptoms, hepatitis, pneumonitis, and showed recovery under antiviral treatment.

Case

A 24-year-old mother was admitted to the hospital with premature rupture of membranes and chorioamnionitis. At 28 gestation weeks, a male infant weighing 880 g was delivered by cesarean section. The baby received surfactant replacement, high-frequency oscillation ventilation for refractory respiratory failure. Enteral feeding with breast milk was initiated at day of life (DOL) 1. On DOL 35, he was still on nasal continuous positive airway pressure, and his respiratory condition deteriorated with the increase of tracheal secretions. He had also distended abdomen with hepatomegaly, diminished activity and gray pallor of the skin. Laboratory analysis showed pancytopenia, increased C-reactive protein, direct bilirubin (15.8 mg dl^{-1} at the highest) and liver enzymes levels (aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase levels were 354, 148 and 236 U l^{-1} at the highest, respectively). Chest X-ray revealed new alveolar infiltrations. Broad-spectrum antibiotics were initiated after obtaining cultures from blood, cerebrospinal fluid, tracheal aspirate and urine. CMV immunoglobulin M and immunoglobulin G were positive. By the quantitative PCR analysis of CMV DNA copy numbers in plasma, urine and tracheal aspiration samples were 2×10^6, 1.7×10^6 and 3.7×10^6 copies ml^{-1}, respectively. Cerebrospinal fluid was negative for CMV DNA. PCR testing for CMV on specimen of blood in Guthrie card taken on DOL 8 for neonatal screening was negative. The mother was CMV immunoglobulin G seropositive. The CMV DNA copy number in breast milk was 1.6×10^6 copies ml^{-1}. His eye examination was negative for chorioretinitis, and head ultrasound was normal. The patient had previously received irradiated, leukocyte filtered erythrocyte suspension seven times, 10 mg kg^{-1} per each transfusion. All cultures before initiation of antibiotic treatment were found to be sterile. As the clinical deterioration and the laboratory abnormalities persisted, and acquired CMV infection was confirmed, antiviral therapy with intravenous ganciclovir was started on DOL 42 (12 mg kg^{-1} body weight in two daily doses for 5 weeks). Respiratory symptoms and pancytopenia resolved rapidly in a week, direct bilirubin levels and liver function tests became to normal levels in 2 weeks. On day of 25 of the treatment, CMV DNA was undetectable in plasma, tracheal aspirate and urine samples. The auditory brain stem response showed normal response. Neither any side effect due to ganciclovir nor relapse of the infection after treatment was observed in this patient.

Correspondence: Dr E Okulu, Department of Pediatrics, Ankara University School of Medicine, 06000 Cebeci-Ankara, Turkey.
E-mail: emelderelli@hotmail.com
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Discussion

Postnatal CMV infection is most often transmitted through breastfeeding. The other sources of postnatal infection include exposure to infected genital secretions in the birth canal, infection through transfusion of contaminated blood products and horizontal transmission by close contact. In our patient intrauterine transmission was unlikely, because of the absence of CMV DNA in Guthrie card.

Transmission of CMV by the breast milk of seropositive mothers is well described.[5–7] In premature infants, the transmission of protective maternal antibodies starting within the 29th gestational week is missing, which puts them at high risk for symptomatic infection transmitted via breast milk.[8] In a study of CMV-seropositive mothers, in 87% of the cases, virus was detectable in breast milk with transmission occurring in 22,8% premature infants and leading symptomatic disease in 0–34.5% of them.[7] Studies have shown that 'Holder' pasteurization (pasteurization for 30 min at 62.5 °C) or freezing breast milk at −20 °C may reduce CMV viral titers and infectivity.[5] However, in our unit, fresh breast milk was exclusively used for feeding. Because the high seroprevelance of CMV in our population,[9] and the use of filtered and irradiated blood products, our patient seems to acquire CMV from his mother's breast milk which has high CMV DNA copy.

In recent years, there has been increased awareness of morbidities that result from congenital CMV infection, which has led to study more on the antiviral agents. Ganciclovir and its prodrug valganciclovir, foscarnet and cidofovir are the agents that are active against CMV. Experience with these agents in the setting of congenital and postnatal CMV infection is limited.[10,11] Positive effects of ganciclovir treatment have been described in cases with postnatal infection.[4,12] Commonly reported side effects of ganciclovir include myelosuppression, technical problems with venous access and long-term side effects as gonadal toxicity. Recent clinical studies of valganciclovir in neonates with congenital infection are quite promising. The effectiveness and safety of foscarnet and cidofovir in premature infants is unproven. Type specific immunoglobulin has been used for postnatal infection, but not seem to be a valuable approach.[10,13] Finally, CMV vaccines may hold the greatest promise in reducing the neurodevelopmental consequences of congenital infection, although the immune correlates of protection of the fetus incompletely defined.[14] In our patient, the clinical condition remained critical under broad-spectrum antibiotic therapy and intensive care, we opted for starting intravenous ganciclovir-based antiviral therapy. We observed a rapidly clinical and laboratory improvement with treatment. No adverse effect of drug that requires the cessation of the treatment has been encountered. There was no relapse of the infection after treatment.

Limited data are available on long-term outcome of postnatal CMV infection in preterm infants. In outcome analysis studies revealed that postnatal acquired CMV infection via breast milk does not have negative effects on neurodevelopment and hearing.[15,16] So careful and long-term neurodevelopmental follow-up with auditory monitoring, should be offered. In our patient, cranial ultrasound examination was normal, and auditory test showed normal response.

Postnatally acquired CMV infection may cause severe and possibly life-threatening disease in premature infants. Our patient is among the few cases with a severe postnatal CMV infection, most likely due to breast milk, treated successfully with intravenous ganciclovir. We propose that antiviral treatment should be considered in the very sick preterm infants. Because CMV-seropositive women can transmit infection via breast feeding, interventions to screen breast milk, or to attempt to render non-infectious breast milk through treatments may be warranted in high-risk premature infants.

Conflict of interest

The authors declare no conflict of interest.

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