Congenital cytomegalovirus infection in twin pregnancy

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SUMMARY

Cytomegalovirus (CMV) infection is one of the preeminent congenital viral infections, and despite its potential morbidity, uncertainty about its physiopathology, prevention and treatment remains until now. We report a case of a dichorionic and diamniotic twin pregnancy in which only one of the fetus had signs of being affected. The first twin had prenatal diagnosis of intrauterine growth restriction and hyperechogenic bowel, attributable to CMV infection, while there was no evidence of infection of the second one. Prenatal treatment was done with maternal administration of valacyclovir and postnatal treatment of the infected newborn with oral valganciclovir with normal neurodevelopment assessment at 12 months corrected age. In this case, maternal CMV infection was not equally transmitted to both fetuses, suggesting that there may be intrinsic fetal and placental factors influencing both transmission and the clinical features of the infection.

BACKGROUND

Cytomegalovirus (CMV) infection is the main cause of congenital viral infection, and it remains the main infectious cause of sensorineural hearing loss and intellectual disability in children. Prevalence ranges from 0.2% to 2.0%,[1–3] directly dependent on CMV infection prevalence in the population. Infection during pregnancy can be primary or secondary, with vertical transmission rates of 30% and 0.2%–8%, respectively.[1] Despite its potential morbidity, CMV congenital infection is still underdiagnosed,[4] and both universal maternal screening and prenatal treatment of infection are not carried out systematically during pregnancy.[2 5] Congenital CMV-infected neonates might be asymptomatic or symptomatic at birth, and severity of long-term adverse outcomes varies substantially,[2] even between twins. Maternal diagnosis of CMV infection is still a challenge because usually mothers have no symptoms,[2] and when CMV immune status before pregnancy is unknown and prenatal serological screening is not performed, seroconversion is rarely identified.[2] The management of a pregnant woman at risk of transmitting CMV (ie, after diagnosis of maternal primary infection) includes close ultrasound evaluation, with the most common abnormalities being intrauterine growth restriction (IUGR), hyperechogenic bowel, hepatosplenomegaly, liver calcifications, microcephaly, hydrocephaly, ventriculomegaly, increased periventricular echogenicity and periventricular pseudocysts.[2 5 6] In practical terms, prenatal diagnosis of fetal CMV infection needs confirmation by invasive measures,[7] through detection of viral DNA by PCR in amniotic fluid. This procedure can be proposed when there is a maternal primary CMV infection during pregnancy or when there are abnormalities on ultrasound compatible with fetal CMV infection.[2 5] Higher CMV DNA loads and thrombocytopenia in fetal blood are significantly associated with a symptomatic status at birth.[5] Fetal treatment with maternal administration of valacyclovir produces therapeutic concentrations in the blood of infected fetuses and is effective in reducing both fetal viral load and thrombocytopenia.[3 7] In this sense, prenatal treatment of infected fetuses with valacyclovir may almost double the proportion of asymptomatic neonates,[3] improving prognosis. No significant adverse effects have been reported. However, randomised controlled studies are needed to further support this approach.[5 6]

CASE PRESENTATION

We report the case of a dichorionic and diamniotic twin pregnancy with prenatal diagnosis of IUGR and hyperechogenic bowel of the first fetus and hydronephrosis of the second. In the case of IUGR, the investigation revealed negative first trimester screening for aneuploidies, normal echocardiogram and negative maternal serology for other TORCH infections (which includes toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella and herpes infections). Maternal serology for CMV was IgG positive and IgM negative, so taking into account the ultrasound changes, it was decided to perform amniocentesis at 23 weeks' gestation. PCR on the amniotic fluid was positive for CMV infection in first fetus and negative in the second. The pregnant woman was started on valacyclovir in high doses (8 g/ day) at 24 weeks of gestation until the end of pregnancy, and no side effects were reported. At about 31 weeks of pregnancy, a fetal neurosonography was performed, which confirmed severe IUGR, with particular repercussions on the cephalic pole of the first fetus. A fetal MRI was then performed and confirmed biparietal and frontoccipital diameters below the 10th percentile, without evidence of other brain abnormalities in fetus 1, and normal overall appreciation in fetus 2. Due to the worsening of the biophysical profile of fetus 1 with signs of acute fetal distress (oligo/anhydramnios and abnormal Doppler waveform from the umbilical arteries), an urgent caesarean section was performed at 34 weeks. The first female fetus was born with Apgar score 8/9/10, 880 g (<P3), 36.5 cm

of length (<P3) and 21.8 cm of head circumference (<P3), while the second female fetus was born with Apgar score 10/10, with 2125 g (P10–50), 42.5 cm in long (P10–50) and 31.5 cm of head circumference (P50–90).

INVESTIGATIONS

The histopathology of the placentas revealed involution changes and calcium deposits, particularly that on the first fetus, where it was also evident diffuse parenchymal infiltration by fibrin and increased numbers of trophoblastic syncytial knots, but no morphological changes were directly related to CMV inclusions.

CMV PCR assays in urine were positive in newborn 1 and negative in newborn 2. Blood tests performed in newborn 1 revealed normal haemoglobin 166 g/L, leucopenia (white cell count 5.28×10^9/L), neutropenia (neutrophil cell count 1.07×10^9/L), thrombocytopenia (82×10^9/L platelets), unconjugated hyperbilirubinemia (total bilirubin 7.32 mg/dL and conjugated bilirubin 0.54 mg/dL), normal transaminases (aspartate aminotransferase 61 U/L, alanine transaminase 8 U/L) and slight elevation of gamma-glutamil-transferase (236 U/L). CMV PCR assays in blood were positive in this fetus, with a CMV viral load of 776 UI/mL (2.9 log). Newborn 2 had perfectly normal blood tests.

The multiorgan evaluation of possible manifestations of CMV of the newborn 1 included a normal newborn hearing screening, transfontanellar ultrasound appropriate to gestational age, a normal ophthalmological evaluation and normal abdominal ultrasound.

TREATMENT

Considering the symptomatic CMV infection in newborn 1, oral valganciclovir was started with 16 mg/kg per dose two times per day, on the fourth day of life, until 6 months. Blood tests routinely performed revealed normalisation of leukocytes and platelets, and also of bilirubin after 2 days of phototherapy. On the 21st day of valganciclovir, the newborn presented with leucopenia (minimum 3.87×10^9/L) and neutropenia (minimum 0.64×10^9/L), with normalisation 1 week later. No more therapeutic side effects were reported.

OUTCOME AND FOLLOW-UP

Newborn 1 was discharged at 40 weeks and 6 days of corrected age with 1815 g, asymptomatic, with self-feeding and consistent gain weight. She completed 6 months of valganciclovir and maintained frequent follow-up with neonatology, otorhinolaryngology, ophthalmology and physical medicine and rehabilitation. At 3 months of age, she performed a brain MRI that revealed a 'slight dilation and dysmorphic aspect of the temporal horns, a fact that may not be meaningful, but which is also documented in the context of CMV infection'. Additionally, she took a hearing assessment with auditory evoked potentials, audiometry and tympanogram, that revealed normal results. She also continued a multidisciplinary follow-up with appropriate development for her corrected age. With 12 months of corrected age, she had 5995 g (<P3), 70 cm of length (P10) and 42 cm of head circumference (<P3) and she uses the objects intentionally, clapping, doing fine forceps, kitten, sitting without support, standing up alone, supporting the lower limbs with good stability and walking with support.

DISCUSSION

In this case, maternal CMV infection was not equally transmitted to both fetuses, suggesting that there may be intrinsic fetal and placental factors influencing both transmission and the clinical features of the infection. In dichorionic twins, both a concordant and a discordant infection have been described, and among concordant infected fetuses, completely different outcomes may be observed.[8] Therefore, it seems that different fetus react differently to the same maternal influences,[6 9] suggesting that the placenta could have a more important role as a protective factor than maternal immunological reactivity.[6 9 10] Placenta may act either as a portal of entry for the virus, either as a barrier, since even during maternal primary infection, transmission occurs only in 30% of the cases.[5 6] In this case, the histopathology of placenta did not show morphological changes related to CMV inclusions, it showed instead morphological changes that may be related to immune responses to the virus. Knowledge about pathophysiologic mechanisms that affect transplacental transmission of the virus and the virulence of fetal infection is limited,[11] but several studies have been carried out addressing the disclosure of these mechanisms.

Congenital CMV remains a major problem worldwide, with no established effective therapy for pregnant women,[4] no vaccination available and several doubts about physiopathology, prevention and treatment of infection. For now, a high degree of diagnostic suspicion is needed in order to justify prenatal treatment and possible anticipation of postnatal medication. Both prenatal and postnatal treatments apparently reduce the fetal viral load and thrombocytopenia,[12] thus improving child's prognosis. However, even newborns initially asymptomatic may evidence later progressive sensorineural deafness or intellectual disability, challenging the capacity for CMV diagnosis and opportunities for early intervention.[2 5] Universal screening at the first prenatal visit could increase the number of primary maternal CMV infections identified.[11] Nevertheless, it is necessary to improve our knowledge about other factors (maternal, placental and fetal) that contribute to the prognosis of CMV and also prove the effectiveness of existing treatments for prevention of mother/fetus transmission.[11]

Learning points

- Cytomegalovirus infection is the main cause of congenital viral infection and remains responsible for severe morbidity in children over years.
- A high degree of suspicion remains necessary to diagnose and treat cytomegalovirus (CMV) congenital infection, both for prenatal or postnatal treatments.
- The same exposure to the CMV in a twin pregnancy did not cause disease in both fetus, suggesting that there may be others factors than maternal infection influencing both transmission and the clinical features of the infection.
- Knowing these mechanisms can allow us to improve the diagnosis, treatment and even the prevention of CMV infection.

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