CASE REPORT

Congenital Cytomegalovirus Infection in Monozygotic Twins with Twin-to-twin Transfusion Syndrome

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Background: Symptoms of congenital cytomegalovirus infection remains unclear. **Case characteristics**: Extremely low birth weight twins with twin-to-twin transfusion syndrome were infected with cytomegalovirus congenitally.**Observation**: The donor showed neuronal impairment, whereas the recipient showed hepatic dysfunction. **Message**: Intrauterine hemodynamics may be important in pathophysiology of congenital cytomegalovirus infection.

Keywords: *Intrauterine infection; Outcome, TORCH infection.*

The symptoms of congenital cytomegalovirus (CMV) infection vary widely and include liver dysfunction, neuronal impairment, skin manifestations, and ophthalmological complications [1]. The precise pathophysiology of these manifestations remain unclear. Twin-to-twin transfusion syndrome is a severe complication of monochorionic twins that is attributed to transanastomotic transfusion between twins, resulting in hemodynamic imbalance [2]. twin-to-twin transfusion complicated with congenital cytomyalovirus infection, showing different manifestations.

CASE REPORT

A 34-year-old healthy woman, with one previous child birth, who spontaneously conceived diamniotic–monochorionic twins, was referred to us for polyhydramnios and threatened premature delivery at 20 weeks of pregnancy. At the time of referral (20 weeks + 5 days of pregnancy), reversed umbilical artery diastolic flow was observed. Stage III twin-to-twin transfusion was diagnosed ultrasonographically, and she was treated with amniocentesis on the same day. The results of screening for toxoplasma, rubella, varicella, human immunodeficiency virus, syphilis, hepatits B, and hepatitis C were negative. As screening tests for CMV are not routinely performed at our institute, and she had no episode suggesting infection during pregnancy, she was not evaluated for CMV. Antenatal betamethasone was administered at 23 weeks of gestational age. Emergency cesarean section was performed at 24 weeks (+3 days) of pregnancy owing to premature rupture of the membranes and fetal distress. After the resuscitation procedure, including intubation, the twins were admitted to the neonatal intensive care unit.

The first twin was a 587 g female (appropriate for gestational age) with Apgar scores of 5 at 1 and 5 min, and this score was elevated to 7 (10 min) after intubation 5 min after birth. Her head circumference was 21 cm (0.58 SD). She was diagnosed as a donor out of twin-to-twin transfusion because of her smaller body size. Physical assessment showed no abnormalities, except for a cleft soft palate. Cranial ultrasonography on admission revealed bilateral general cerebral dysplasia. At birth, hepatic enzymes were unremarkable. Total bilirubin, direct bilirubin, total IgM levels, and the platelet count were 2.30 mg/dL, 0.38 mg/dL, 180 mg/dL, and 89×10^9/L, respectively. She was treated with artificial ventilation; central venous nutrition; inotropes and sedatives; indomethacin for patent ductus arteriosus; glucose–insulin therapy for hyperkalemia; transfusion of red blood cells, fresh frozen plasma and albumin; and intravenous gammaglobulin, hydrocortisone, and antibiotics. Congenital CMV infection was suspected because of structural abnormality of the central nervous system. Serum CMV IgM (enzyme immunoassay) and urine CMV polymerase chain reaction (PCR) (qualitative analysis), performed on days 11 and 16 after birth, were positive. CMV-specific therapy was not given considering her prematurity and general unstable condition. She was extubated on day 62 and discharged on day 179. An ophthalmological examination at 2 months showed stage 3 retinopathy of prematurity (ROP), while CMV-related findings were not observed. Computed tomography (CT) and magnetic resonance imaging (MRI) of head, performed at 4 months of age, showed brain hypoplasia with calcification in the right temporal lobe, and delayed myelination (***Fig.* 1**). Bilateral sensorineural hearing loss was diagnosed by an auditory brain stem response at 9 months of age.

The second twin weighed 631 g (appropriate for date) at birth, with Apgar scores of 1 (1 min) and 2 (5 min), and this score was elevated to 7 (10 min) after intubation at 8 min after birth. Her head circumference was 20.5 cm (0.95 SD). She was the recipient owing to her larger body size and anasarca. At birth, petechiae were recognized on the trunk and lower limbs, whereas hepatosplenomegaly was not apparent. A cleft soft palate was also found. Ultrasonography after birth showed normal intracranial structures. Echocardiography showed pulmonary stenosis. AST, ALT, total bilirubin, direct bilirubin and total IgM levels, and the platelet count were within normal limits. She was treated similarly to her twin, but more careful and extended treatment was needed for stabilization of the circulation. She received inotropes until day 6. After her general condition stabilized, her oxygen saturation was 95-100% (room air), and cyanosis was not observed. She attained adequate oral intake. Serum CMV IgM and urine CMV PCR on day 15 were positive. The specific therapy for CMV infection was not performed as for Case 1. AST and ALT levels were elevated to 2584 and 220 U/L on day 2, and maintained at 80-100 U/L (AST) and 30-40 U/L (ALT) until discharge. She was extubated on day 57 and discharged on day 179. An ophthalmological examination at 2 months showed only stage 3 ROP, which was treated with laser therapy. Her brain CT, brain MRI, and an auditory brain stem response at 4 months showed no abnormalities.

Antibodies of other infections (rubella, syphilis, herpes simplex 1, and toxoplasma) were negative in both patients. Chorioretinitis was not observed in either of the patients during hospitalization. Follow-up urine CMV PCR was performed for both patients at 5 months, and the results were negative. At 18 months, the first twin could hold her head up, but not turn over and sit. She smiled but did not speak any meaningful words. No seizures were observed. The second twin could stand holding onto something. She could speak more than three words at 18 months.

DISCUSSION

Most previous reports of congenital CMV infection in twins discussed diamnionic–dichorionic patients whose genetic predisposition, gestational age at infection, and viral load were suggested to be definitive factors in the manifestation of infection [3-7]. In our patients, the former two factors were the same because of their monozygosity and continuous blood exchange. Intrauterine hemodynamics between the donor and recipient was the only difference that could be recognized, and these were considered to be an important factor for the discordant manifestations in our patients. A decrease in circulating blood volume of the twin-to-twin transfusion syndrome donor leads to intracranial hypoperfusion and brain dysplasia [8]. Because hypoperfusion results in damage to neuronal cells and the blood–brain barrier, the central nervous system of the donor may become more susceptible to CMV invasion. Griesmaier, *et al*. [9] reported diamniotic–monochorionic twins complicated with twin-to-twin transfusion syndrome and congenital CMV infection. Their similar finding – that the donor showed more severe neurological manifestations than did the recipient – may bolster the importance of intrauterine hemodynamics in pathogenesis of CMV infection. Blood influx from a donor increases preload and secretion of vasoconstrictors, such as endothelin-1, resulting in an increase in afterload [10]. Increased pre- and after-load place stress on the recipient's heart, resulting in right heart failure. Additionally, the pulmonary stenosis in Case 2, which is a relatively frequent complication of the recipient of twin-to-twin transfusion syndrome, might have further increased right-heart overload [10]. These factors could injure the recipient liver, and the damaged liver might

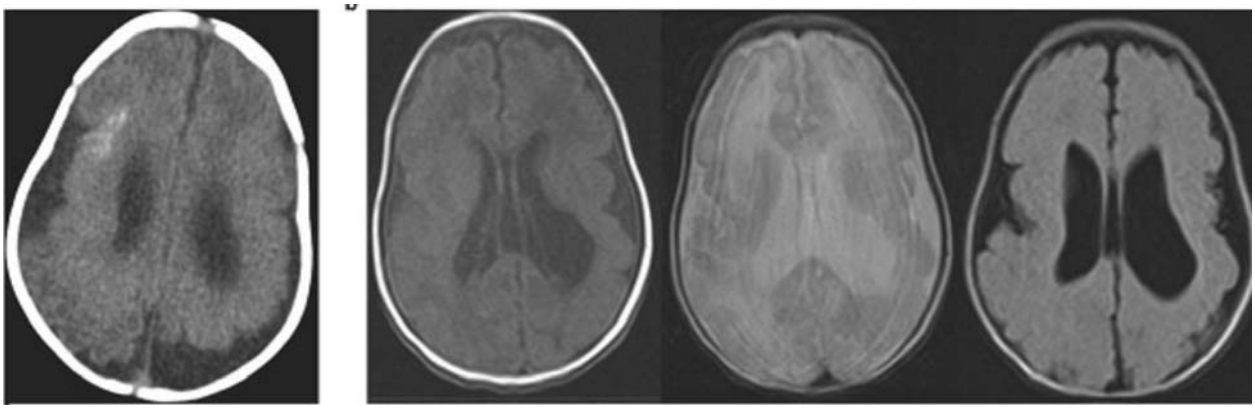

Fig. 1 *Calcification in the right temporal lobe was observed in CT of twin 1 (**a**); Brain MRI of twin 1 shows brain hypoplasia and delayed myelination (**b**).*

increase its susceptibility to CMV. Neither drug-induced liver injury nor right-heart overload after birth alone is sufficient to explain the manifestation of Case 2 because transaminase levels peaked before the weaning of medication and stabilization of the circulation.

The manifestations of our patients suggest the importance of intrauterine hemodynamics in the pathophysiology of congenital CMV infection.

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