Clinical Experience with Ganciclovir and Anti-Cytomegalovirus Immunoglobulin Treatment for a Severe Case of Congenital Cytomegalovirus Infection

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We report on a female neonate with severe onset of congenital cytomegalovirus (CMV) infection. She was noted to have cerebral ventriculomegaly on antenatal ultrasound, and presented with petechia after birth. Laboratory tests revealed severe thrombocytopenia (platelet count, 11,000/mm^3) and hypoglycemia (serum glucose level, 5 mg/dl). Hepatosplenomegaly with elevated hepatic enzymes, retinitis, conjugated hyperbilirubinemia, and diffuse brainstem anomaly were also found in subsequent examinations. The diagnosis was confirmed by positive CMV-IgM from serum and the isolation of CMV from a urine sample. The patient received intravenous ganciclovir and human anti-CMV immunoglobulin during admission. She was discharged at the age of 61 days and followed-up monthly at our clinics. Symptoms and signs subsided except for mild cerebral ventriculomegaly at her last visit. We demonstrate a successful treatment with the combined use of ganciclovir and anti-CMV immunoglobulin. *(Chang Gung Med J 2003;26:128-32)*

Key words: **congenital CMV infection, cytomegalovirus, ganciclovir.**

Cytomegalovirus (CMV) is the most frequent cause of congenital infections in humans.[1] Most congenital CMV infections are asymptomatic during the neonatal period. However congenital CMV infection is still the leading viral cause of congenital malformations in the developed world. Congenital CMV infections cause illnesses ranging from asymptomatic infection to prematurity, encephalitis, deafness, and hematological disorders, and even death. Approximately 90% of infected infants are asymptomatic at birth. About half of infants delivered to mothers with primary CMV have congenital infections.[2] If recurrent or reactivated CMV infections develop during pregnancy, the risk of serious fetal injury is very low. Herein, we report on a case of congenital CMV infection with the classic presentations. Although CMV infection is common in Taiwan,[3] such classic presentations are rare and can serve as a good demonstration for physicians to learn about congenital CMV infection.

CASE REPORT

A female baby was born to a G2P1AA1 mother vaginally at the gestational age of 37 weeks with Apgar scores of 8 at 1 min and 9 at 5 min. Her birth weight and head circumference were 2160 g (20th percentile) and 30 cm (less than the 10th percentile). Decreased fetal weight gain was noted by a local obstetrician at the third trimester. Then her mother was referred to our clinics for further evaluation. Cerebral ventriculomegaly was noted by ultrasound

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10 days before the delivery. After birth, petechiae were observed over the face, trunk, and extremities. Her serum glucose level was only 5 mg/dl at 1 hour after birth. Other abnormal laboratory data included thrombocytopenia (a platelet count of 11,000 cells/mm^3) with coagulopathy (a prothrombin time of more than 100 s and an activated partial thromboplastin time of 56.3 s) at 1 hour of life, and conjugated hyperbilirubinemia (direct/total bilirubin of 90.6/194.9 μmol/l or 5.3/11.4 mg/dl) with elevated aspartate aminotransferase (AST, 233 U/l) at 24 hours of life. The ophthalmic fundoscopic examination showed retinitis (Fig. 1), and the ultrasound examination showed hepatosplenomegaly and cerebral ventriculomegaly. Brainstem auditory evoked potential (BAEP) revealed bilateral delay of the central conduction. Positive serum CMV IgM and isolation of CMV collected on the second day of age from urine confirmed the diagnosis. A viral culture of cerebrospinal fluid was negative. Ganciclovir, at 5 mg/kg every 8 hours for 3 weeks, was started intravenously, and human anti-CMV immunoglobulin (Cytotect®), at 400 mg/kg every other day for 10 doses, was also given. Hypoglycemia resolved after the infusion of intravenous glucose, and the serum glucose level was stable on the second day of life. Before discharge, her platelet count was 148,000 cells/mm^3. She was followed-up monthly at our clinics. Mild cerebral ventriculomegaly was still observed at the first visit, although retinitis was not found, and the platelet count was 186,000 cells/mm^3. The serum direct/total bilirubin was 5.13/6.84 μmol/l (0.3/0.4 mg/dl), and AST was 27 U/l at her third visit. The report of BAEP was normal, and no evidence of neuromotor problems was observed at the age of 5 months.

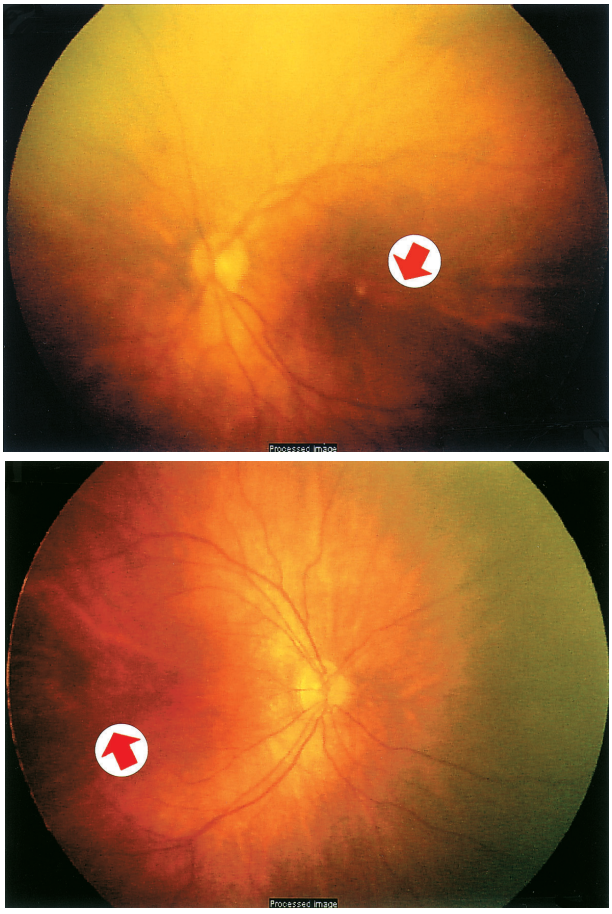

Fig. 1 Eye fundi with bilateral retinitis (arrows). Upper: left eye; Lower: right eye.

The mother could recall having no illness during pregnancy, and her laboratory data were normal. Antibodies of her sera were positive for CMV IgG and negative for CMV IgM in the third trimester.

DISCUSSION

CMV is known as the most common cause of intrauterine infection. Congenital CMV infection is a multisystem disease occurring mainly upon primary infection.[4] Occasionally, recurrent CMV infection leads to congenital infection. Although the majority of infected fetuses are asymptomatic at birth, some are irreversibly damaged by the congenital infection leading to long-term neurological sequelae. In symptomatic newborns, the most common clinical manifestations are petechia, hepatosplenomegaly, microcephaly, and ventriculomegaly.[5] The most common long-term sequelae in childhood are sensorineural hearing loss and learning disabilities.

In this baby, severe hypoglycemia was another manifestation of congenital CMV infection. Hypoglycemia is not a common sign in infants infected by CMV. It is still unclear how congenital CMV infection causes hypoglycemia. Fetal hypoglycemia with hypoinsulinemia has been reported as one of the consequences in congenital CMV infection.[6] Therefore, it is important to routinely monitor the serum glucose level to prevent permanent brain damage caused by hypoglycemia in newborns with

Table 1. Symptoms and Signs of Congenital CMV Infection before and after the Use of Gancyclovir and Human Anti-cytomegalovirus Immunoglobulin

Symptom/sign	Before treatment	After treatment
Skin	petechia	no petechia*
Platelets (cells/mm^3)	11,000	186,000†
Serum glucose (mg/dl)	5	80~150
Brain ultrasound	ventriculomegaly	mild ventriculomegaly†
Abdominal ultrasound	hepatosplenomegaly	no hepatosplenomegaly†
AST (U/l)	233	27‡
Bilirubin direct/total (μmol/l)	90.6/194.9	5.13/6.84‡
Eye ground	retinitis	no retinitis†
BAEP	bilateral prolonged central conduction	normal‡

* Before discharge (2 months old).

† At the first visit to our clinics (3 months old).

‡ At the third visit at our clinics (5 months old).

Abbreviations: AST, aspartate aminotransferase; BAEP, brainstem auditory evoked potential.

suspected congenital CMV infection.

A CMV infection had been suspected before labor in our patient; however the serum CMV IgM of the mother was negative. Several methods for prenatal diagnosis of congenital CMV disease have been reported, but the sensitivity varied. Although IgM tests and IgG avidity determination can identify most women at risk of transmitting CMV, some researchers have reported that diagnostic serology of the mother is not always definitive.[7] Polymerase chain reaction and virus culture of amniotic fluid or of fetal blood obtained by cord puncture showed a better detection rate than traditional serological methods.[8,9]

Our patient received intravenous ganciclovir and anti-CMV immunoglobulin to eradicate CMV.[10,11] Thrombocytopenia and abnormal liver function gradually improved after treatment and had became normal by the age of 5 months. Although ganciclovir has been documented as effective management for alleviation of clinical symptoms and signs of congenital CMV infection,[12] there has been no definite proof of whether the combined use of ganciclovir and anti-CMV immunoglobulin is more efficient. We summarize the symptoms and signs of our patient before and after treatment in Table 1. The thrombocytopenia, liver function, and BAEP study became normal in this patient. Therefore, treatment with ganciclovir and anti-CMV immunoglobulin seemed to be effective for improving the symptoms and signs caused by CMV infection. Furthermore, we observed no obvious adverse effects of ganciclovir and anti-CMV immunoglobulin.

The presence of microcephaly at birth is the most specific predictor of poor cognitive outcome with congenital CMV infection, whereas children with normal findings on head CT and head circumference exhibit good cognitive outcomes.[13] Retinitis, cerebral ventriculomegaly, and microcephaly were poor prognostic indices for the intellectual and neurodevelopmental outcome in this patient.[14] However, we have observed no abnormal neurodevelopmental problems to the present. Although sensorineural hearing loss and visual impairment are the most common complications of congenital CMV infection, they are not likely to occur in our patient because her auditory and visual examinations were normal.

We report this case in order to raise physicians' awareness of congenital CMV infection. In spite of advances in prenatal screening for congenital CMV disease, prevention of this disease is still unsatisfactory. An attenuated, live vaccine has been extensively studied, and an improved strain may result from genetic manipulation. The development of a vaccine against CMV is the primary work for preventing congenital CMV disease in the future.[15]

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合併使用Ganciclovir及Anti-CMV Immunoglobulin 治療先天性巨細胞病毒感染

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我們報告一例先天性巨細胞病毒感染，以產前檢查出腦室擴大、出生後全身性的小出血點及重度的低血糖來表現，同時合併有肝脾腫大、直接型的高膽紅素血症、視網膜炎及血小板低下。病患的血清巨細胞病毒IgM爲陽性，同時尿液巨細胞病毒培養亦爲陽性，在接受ganciclovir及anti-CMV immunoglobulin治療後，該病患除了輕微的腦室擴大外，其它的症狀皆完全改善。(長庚醫誌 2003;26:128-32)

關鍵字：先天性巨細胞病毒感染、巨細胞病毒、ganciclovir。

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