A Neonate with Reduced Cytomegalovirus DNA Copy Number and Marked Improvement of Hearing in the Treatment of Congenital Cytomegalovirus Infection

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Abstract

Congenital cytomegalovirus (CMV) infection can cause severe permanent disabilities. A mother who is seronegative before conception but acquires infection during pregnancy is a risk factor for congenital infection. We describe a neonate in whom congenital CMV infection was diagnosed at birth and confirmed with DNA quantitation by means of the polymerase chain reaction, was accompanied by cerebral ventriculomegaly and severe hearing loss, and was treated with ganciclovir/valganciclovir for 6 weeks. Initially, cerebral ventriculomegaly and calcification were also found with computed tomography, and severe hearing loss was detected with auditory brainstem response testing. After treatment, CMV DNA decreased in copy number and became undetectable. No marked side effects occurred after treatment. Surprisingly, 1 year after treatment, neurological and motor development was equivalent to that in a healthy infant. Audiometry indicated that auditory ability would improve with rehabilitation, speech and language therapy, and cochlear implantation. Single-photon emission computed tomography showed marked improvement 6 months after treatment. This case provides compelling evidence that a reliable diagnosis of congenital CMV infections coupled with a prompt and appropriate treatment program can prevent permanent disability. It is, therefore, important to establish a more effective strategy for the management of congenital CMV infection.


Key words: congenital cytomegalovirus infection, ganciclovir, valganciclovir, hearing loss, auditory brainstem response
**Introduction**

Cytomegalovirus (CMV) is a common congenital infection that can cause permanent childhood disabilities, such as sensorineural hearing loss, visual deficits, epilepsy, developmental delay, and pervasive developmental disorders. Approximately 14% of children with congenital CMV infections will have permanent hearing loss\(^1\), but about half of these cases cannot be detected with screening techniques designed for newborns and are manifested only later\(^2\). The pathogenesis of hearing loss in CMV infection is poorly understood; however, both direct cytopathic effects and localized inflammatory responses seem to play important roles. Ganciclovir is reported to be effective for treating symptomatic congenital CMV infections\(^3\) and, especially, for preventing the progression of hearing loss\(^4\).

Here we report the successful use of ganciclovir/valganciclovir to treat congenital CMV infection in a male neonate. Although he might require cochlear implantation and rehabilitation to restore hearing ability, he has so far exhibited age-appropriate neurological and motor development.

**Case Description**

A male neonate was born through cesarean section, because of chorioamnionitis, at 39 weeks' gestation and had no neonatal asphyxia. There were no manifestations of CMV infection in the mother; however, there had been no opportunity to check for such an infection during the pregnancy. The birth weight and height were 2.64 kg and 48 cm, respectively. No hepatosplenomegaly was observed. Thirty hours after birth, a fever of 39°C developed. When the patient was referred to our clinic, the white cell count was 17,100/μL, serum C-reactive protein was 6.7 mg/dL, and the cerebrospinal fluid was pleocytotic (33/3). The serum immunoglobulin M level was 22 mg/dL, which we attributed to an intraterine infection during pregnancy. Therefore, antibiotic treatment was started, and the patient's condition improved over the following 48 hours. Although there were no abnormal neurologic findings, computed tomography of the head revealed cerebral ventriculomegaly and periventricular calcification in the anterior ventricle 5 days after birth (Fig. 1(a)).

Infection with CMV was diagnosed on the basis of CMV DNA found in both the serum and urine 5 days after birth. The patient received intravenous ganciclovir at a dose of 6 mg/kg twice a day for 2 weeks, followed by valganciclovir at a dose of 16 mg/kg twice a day for 4 weeks. No side effects were observed during treatment. The CMV DNA copy number was measured weekly (Fig. 2). The minimum neutrophil count was 870 cells/μL in the second week, but no side effects were observed during treatment. Although the CMV DNA copy number had decreased to 92 copies/1.0 × 10⁶ cells by 5 weeks, it increased again to 285 copies/1.0 × 10⁶ cells. Thereafter, however, it decreased again, and CMV DNA has remained at undetectable levels since 11 weeks. Single-photon emission computed tomography (with isopropyl-p-[123I]-iodoamphetamine) was also performed at 1 month (before treatment) and at 6 months (after treatment) (Fig. 3). The low accumulation of isopropyl-p-[123I]-iodoamphetamine over the whole cerebrum seen at 1 month was significantly improved after treatment. Follow-up computed tomography 1 year after the initial treatment showed that although the calcification in the anterior ventricle remained, the ventriculomegaly had improved (Fig. 1(b)). The neurological findings, except auditory ability, were normal, and the development was appropriate for a healthy 1-year-old infant.

As for the hearing ability, the auditory brainstem response (ABR) showed profound hearing loss (no response as a loss >90 dB) until 1 month after birth; however, at 4 months after treatment, 80 dB was only barely perceived by the left side. Moreover, at the age of 1 year, the ABR of the right side was obviously improved (Fig. 4). The infant would respond to the sound of his mother's loud call and even started crying when the mother was seated. Thereafter his daily life was without difficulty, sometimes even without a hearing aid. The auditory perceptive performance has achieved open set recognition. The major stages of language...
development were transitional languages and single-word utterances. A cochlear implant is planned to aid in the further development of hearing.

**Discussion**

Congenital CMV infection is an important infectious disease in neonates. In Japan, a large statistical analysis was performed for the 11,938 infants born in the Sapporo area from 1999 through 2004; 0.31% of the infants were infected with CMV, but 86.5% of the infected infants were asymptomatic. No large-scale screening of pregnant mothers has been established in Japan; however, the frequency of seropositive CMV cases has recently been decreasing in developed countries (50.4% in United States in 1999–2004) compared with that in developing countries (85% in 1999–2004). Therefore, it is now more important than ever to establish an effective screening system for congenital CMV infections during pregnancy.

The critical time for maternal CMV infection is 12 to 24 weeks’ gestation. Hearing impairment and other cortical abnormalities are caused by cells in the subventricular and ventricular zones being prevented from migrating to their final locations in the cerebral cortex. Neurological disorders, especially hearing loss, resulting from congenital CMV infections seem to be caused by the disturbance of this migration during the second trimester. Therefore, the most important issue regarding CMV infection in neonates is to assess...
Fig. 2  The CMV DNA copy number for $1 \times 10^6$ per cells over 24 weeks. The DNA was obtained from samples of peripheral blood.

Fig. 3  Single-photon emission computed tomography (using isopropyl-p-[123I]-iodoamphetamine) was performed at 1 month (before treatment) (a–c) and 6 months (after treatment) (d–f). (a) and (d) are axial images, (b) and (e) are coronal images, and (c) and (f) are sagittal images.

when infection occurred during pregnancy. Clinical trials of anti-CMV therapy with ganciclovir or a high titer of γ-globulin for fetuses have been performed\(^9\); however, the technique and protocol for these treatments are still being discussed. Another difficulty of diagnosing a congenital CMV infection in neonates is that most are asymptomatic at birth and have symptoms only months or even years later\(^9\). Thus, establishing a routine screening system for congenital infections at birth is necessary.
to avoid late-onset neurodevelopmental sequelae. ABR can be performed easily and routinely to screen for congenital hearing loss in Japanese clinics. About 20% of cases of suspected auditory problems in infants are due to CMV infections; therefore, once problems with hearing are suspected, it is important to measure the level of CMV DNA in the serum or urine and to perform secondary evaluation with imaging studies as soon as possible. A delayed retrospective diagnosis may be too late to address problems with a neonate’s neurological development.

Only high-titer immunoglobulin is permitted as a standard protocol for CMV treatment in Japan. Although ganciclovir seems to be effective, the specific protocol, in terms of dose and duration, is still being discussed. Jacob et al. have reported that orally administered valganciclovir achieves clinical outcomes equivalent to those of ganciclovir and is a safer and easier alternative for the treatment of neonates11. We administered ganciclovir and valganciclovir for 6 weeks and observed no side effects at 1-year follow-up. Recently, Amir et al.
recommended prolonged treatment owing to the persistent effects of the antiviral drug, with no observed deterioration in hearing after treatment was stopped at the age of 1 year. Amir et al have also reported that the initial intravenous treatment resulted in a rapid decline in viral load, in the order of 2 to 3 log, especially during the first week. On the way of the treatment, we found that CMV DNA levels increased again after treatment. Other studies have also reported a similar rebound in CMV DNA levels a few weeks after the end of short-term treatment. Further cases should be accumulated to determine the appropriate duration and dosage of ganciclovir/valganciclovir treatment for neonates with congenital CMV infection.

The present patient’s neurological growth was favorable considering the prognosis based on imaging results at birth. Similarly, with the combination of ganciclovir/valganciclovir and subsequent rehabilitation with hearing aids, the auditory prognosis was extremely favorable. In the absence of treatment, hearing loss tends to become more severe after the first year of life, with further deterioration during the next 3 years of life.

However, the efficacy of cochlear implants for children who are deafened by congenital CMV during early infancy is still being discussed. There have been concerns over the suitability for cochlear implants because of the high incidence of motor-cognitive and central auditory disorders, which may interfere in the learning of spoken language. Moreover, learning or attention disorders are common in children receiving cochlear implants. Despite these problems, the linguistic prognosis following cochlear implantation is usually positive. Thus, speech pathologists or care workers for deaf people with auditory, neurological, and phoniatric expertise should work with CMV-infected infants. It is necessary to implement an early and comprehensive rehabilitation program to address an infant’s audio and cochlear implantation to ensure appropriate perceptive skills, language, and cognitive developmental function.

In conclusion, we observed a favorable outcome following ganciclovir/valganciclovir therapy for the treatment of congenital CMV infection. Prenatal screening for congenital CMV infection and early treatment with ganciclovir/valganciclovir are important to avoid disabilities and to improve quality of life. A vaccine against CMV is now being developed; however, in the meantime, a more sophisticated and appropriate prenatal screening method must be developed to further improve clinical outcomes for infants with congenital CMV infection. Our experience will help raise awareness of congenital CMV infection.

References

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