

Congenital and perinatal cytomegalovirus infection

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= Abstract =

Cytomegalovirus (CMV) is currently the most common agent of congenital infection and the leading infectious cause of brain damage and hearing loss in children. Symptomatic congenital CMV infections usually result from maternal primary infection during early pregnancy. One half of symptomatic infants have cytomegalic inclusion disease (CID), which is characterized by involvement of multiple organs, in particular, the reticuloendothelial and central nervous system (CNS). Moreover, such involvement may or may not include ocular and auditory damage. Approximately 90% of infants with congenital infection are asymptomatic at birth. Preterm infants with perinatal CMV infection can have symptomatic diseases such as pneumonia, hepatitis, and thrombocytopenia. Microcephaly and abnormal neuroradiologic imaging are associated with a poor prognosis. Hearing loss may occur in both symptomatic and asymptomatic infants with congenital infection and may progress through childhood. Congenital infection is defined by the isolation of CMV from infants within the first 3 weeks of life. Ganciclovir therapy can be considered for infants with symptomatic congenital CMV infection involving the CNS. Pregnant women of seronegative state should be counseled on the importance of good hand washing and other control measures to prevent CMV infection. Heat treatment of infected breast milk at 72°C for 5 seconds can eliminate CMV completely. (*Korean J Pediatr* 2010;53:14-20)

Key Words: Cytomegalovirus, Congenital, Perinatal, Hearing loss

Introduction

Human cytomegalovirus (CMV) is a member of the *Herpesviridae* family of DNA viruses and ubiquitous in the general population. Most CMV infections are inapparent, but the virus can cause a wide range of diseases in neonates and immunocompromised patients. CMV is the most common cause of congenital infection worldwide, affecting 0.2% to 2.4% of all live births¹⁻⁴. CMV is now the most common viral cause of mental retardation and hearing deficit of children in developed countries⁵⁻⁷.

CMV causes deformation of preformed tissues rather than malformation of developing organs⁸, so CMV can affect fetuses beyond the first trimester, although earlier infection is usually more severe⁸⁻¹⁰. Primary maternal infection is most likely to cause severe symptomatic congenital infection¹¹, but recurrent infection may also rarely do so. Peri-

natal CMV infection is usually not associated with clinical illness in term babies, but may also cause serious problems in preterm infants¹²⁻¹⁵.

Transmission

Transmission of CMV occurs from person to person through body fluids, and requires close contact with contaminated secretions because the virus is not very contagious. CMV can be found in blood, urine, semen, cervical secretions, saliva, breast milk and transplanted organs, all these sites intermittently excrete viruses^{1,12}. Viral excretion is particularly prolonged after primary infection over years but also occurs with reactivation of infection^{1,5}.

Transmission of CMV to fetuses and newborn infants occurs in one of following modes^{12, 15-18}: (1) in utero by transplacental passage from hematogenous spread to the fetus during maternal viremia; (2) at birth by intrapartum passage after exposure to infected cervical and vaginal secretions; (3) postnatally by ingestion of CMV-positive breast milk or infected blood transfusion.

Received : 2 December 2009, Accepted : 6 December 2009

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Epidemiology

CMV infection is endemic and lacking in seasonal variation. Congenital CMV infection can result from maternal primary or reactivated infection during pregnancy^{1, 5}. And also maternal reinfection of different strains of CMV can rarely lead to congenital symptomatic infection^{19, 20}. The prevalence of congenital CMV infection varies between 0.2–2.4% in different countries^{1–4}. In developed countries, around 50–60% of pregnant, middle to high class women have antibodies to CMV, compared with around 70–85% of those from lower socioeconomic groups^{3, 4}. Overall, 1–4% of susceptible women are affected with primary CMV infection during pregnancy, and around 30–40% of the fetus are transplacentally infected, and also about 10% infants manifest clinical signs and symptoms at birth^{1–5}. Approximately 1–3% of infants born of women with preexisting antibody to CMV are infected in utero, but they have rarely symptomatic illnesses at birth (less than 1%)^{5, 19}. It has been known that the risk of symptomatic infections at birth or the baby who will develop subsequent sequelae is higher if maternal infection occurs during the first half of pregnancy, and also most of severe congenital infection is caused by primary rather than recurrent infection of pregnant women^{5, 10, 11}. A suggested schema of congenital CMV infection and its outcome may be a possible scenario in the commu-

nity (Fig. 1).

Perinatal CMV infection can result from exposure to infected secretions of maternal genital tract at delivery or breast milk that contains the virus. Around 2–28% of seropositive mothers shed CMV in cervical and vaginal secretions during delivery, and approximately 50% of exposed infants are infected¹⁵. Around 9–88% of seropositive women shed CMV into their milk, and approximately 50–60% of infants fed breast milk that contains the virus become infected^{15, 21}.

Transfusion-acquired perinatal CMV infection occurs in infants of seronegative mothers who are exposed to blood products that contain the virus. The incidence of infection is about 10–30% and occurs usually preterm infants with a birth weight of less than 1,500 g^{1, 22}. The risk of infection is related the volume of transfused blood or number of donors, and the titer of CMV in donor blood¹⁵.

Clinical manifestation

1. Congenital infection

Approximately 10% of infants with congenital CMV infection have signs and symptoms at birth, and only one half of these babies have the fulminant illness; cytomegalic inclusion disease (CID)^{13, 15}. Another 5% of these infants show mild and atypical involvement, and 90% are born with

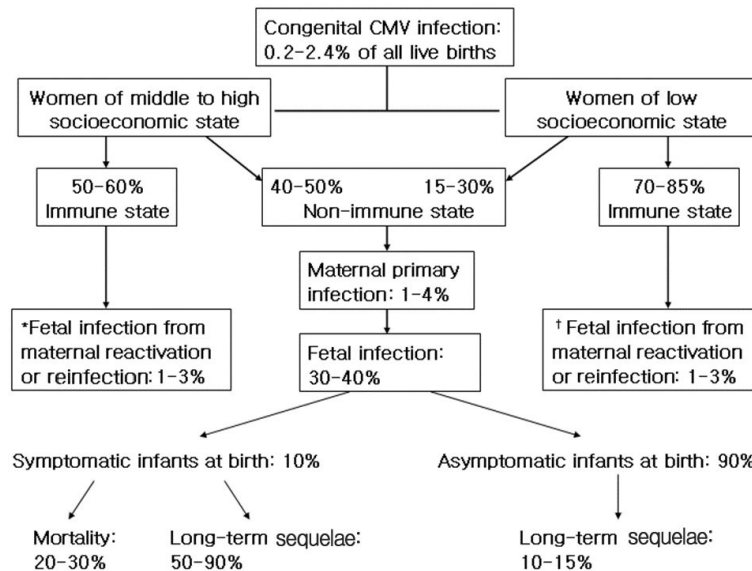


Fig. 1. A schema of congenital cytomegalovirus infection and its outcome. *†The rate of symptomatic infection at birth is less than 1%. The suggested incidence rate reflects data reported in the pediatric literature^{1–6, 8, 9}.

subclinical but chronic infection^{2, 15}). The symptomatic infection of infants usually results from primary infection of the mother^{5, 9}. And it appears that the risk is greater, the earlier in gestation the infection occurs^{5, 11}.

Infants with CID typically have a purpuric rash due to thrombocytopenia (usually with petechiae), intrauterine growth retardation (IUGR), hepatosplenomegaly, jaundice, hearing loss, microcephaly, chorioretinitis and intracerebral calcification. More commonly, infected infants may exhibit a wide spectrum of disease with only one or a few of these manifestations¹⁵ (Table 1). Premature infants or babies who are small for gestational age with hepatosplenomegaly and abnormal liver function are most common findings of symptomatic congenital CMV infection⁴. Hyperbilirubinemia may be transient with a rise in the direct component. Thrombocytopenia is developed one third of infants with congenital infection, and may persist for weeks⁵. There may also be a Coombs-negative hemolytic anemia^{5, 11}. Pneumonia

Table 1. Clinical Manifestation of Congenital Cytomegalovirus Infection

Physical Examination Findings
Nonimmune hydrops fetalis
Prematurity
Intrauterine growth retardation
Jaundice*
Hepatosplenomegaly
Petechiae*
Pupura
Blueberry muffin spots
Chorioretinitis
Microcephaly*
Lethargy
Poor feeding
Hypotonia
Seizures
Inguinal hernia (males)
Laboratory Findings
Anemia*
Thrombocytopenia*
Elevated liver enzymes*
Hyperbilirubinemia (direct and indirect)
Elevated cerebrospinal fluid protein content
Radioogic Findings
Pneumonia
Neuroimaging
Calcifications (periventricular, thalamic, cortical)*
Ventriculomegaly
Cortical dysplasia*
Hearing impairment*

*Prominent features
Data from Stehel EK, et al.¹⁵

may develop as a late findings of congenital CMV infection, usually occurring at 1–4 months of age^{1, 15}. CMV pneumonia in preterm infants has been associated with development or exacerbation of bronchopulmonary dysplasia (BPD)²³. And also postnatal administration of steroid for BPD in CMV-infected perterm infants has been associated with progression of CMV disease¹⁵.

A major important issue in congenital CMV infection is central nervous system (CNS) involvement including meningoencephalitis, calcification, microcephaly, disturbance of neuronal migration, germinal matrix cysts, ventriculomegaly and cerebellar hypoplasia⁶. CNS disease usually results in following symptoms and signs; lethargy, hypotonia, seizure, hearing deficit, or chorioretinitis. Some examples of abnormal magnetic resonance imaging (MRI) findings in infants with congenital CMV infection are suggested (Fig. 2).

Sensorineural hearing deficit (SNHD) may present at birth, either unilateral or bilateral, or can become later in childhood. Some patients have normal hearing for the first 6 years of life, but they can subsequently develop sudden or fluctuating hearing loss. Among children with hearing deficit, further deterioration of hearing occurs in 50%, with the median age of first progression at 18 months of age (range, 2 to 70 months of age)^{8, 24, 25}. Hearing loss apparently result from viral replication in the inner ear²⁶.

Infants with symptomatic congenital CMV infection have a mortality rate of 20–30%^{4, 9}. Death are usually due to hepatic dysfunction, bleeding, disseminated intravascular coagulopathy or secondary bacterial infection⁴.

2. Perinatal infection

The incubation period of perinatal CMV infection ranges between 4 and 12 weeks (mean, 8 weeks)^{1, 15}. The quantity of virus excreted by infants with perinatal infection is less than that developed in congenital infection, but this infection is also chronic, with viral excretion persisting for years¹.

Most term infants with perinatal CMV infection are asymptomatic, because the babies have maternal-transmitted CMV IgG antibody. In contrast, 15–25% of infected preterm infants may develop clinical illnesses such as pneumonia, hepatitis or sepsis-like illness that present with apnea, bradycardia, hepatosplenomegaly, distended bowel, anemia, thrombocytopenia and abnormal hepatic function^{12, 15}. Transfusion-acquired CMV infection in preterm babies with very low birth weight may develop severe symptoms

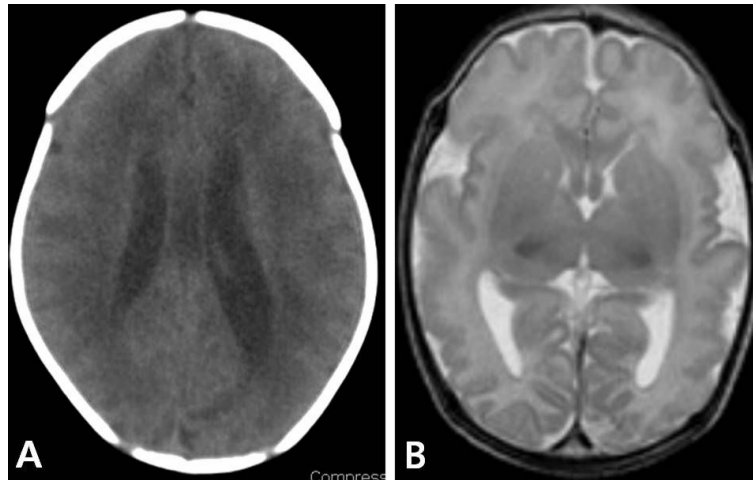


Fig. 2. Some examples of magnetic resonance imaging findings in infants with congenital cytomegalovirus infection. (A) Periventricular calcification and mild ventriculomegaly. (B) Diffuse polymicrogyria of cerebral hemispheres.

that resembled CID¹¹.

Diagnosis

Congenital CMV infection is diagnosed by isolation of virus from infants within the first 3 weeks of life^{3, 13, 15}. So it is difficult to differentiate whether CMV infection was acquired congenitally or perinatally in infants more than 3 weeks of age, unless clinical features of the former such as chorioretinitis, intracranial calcification, microcephaly and hearing loss, are present^{13, 15}.

CMV is usually isolated from urine and saliva but may be isolated other body fluids including breast milk, cervicovaginal secretions, amniotic fluid, white blood cell, cerebrospinal fluid, stool and biopsy specimens. The best test for diagnosis of congenital or perinatal CMV infection is virus isolation or demonstration of CMV genetic material by polymerase chain reaction (PCR) from urine or saliva of newborn infants^{1, 15}. The sensitivity of PCR with urine specimens is 89%, and the specificity is 96%^{1, 27}. Urine specimens should be refrigerated (4°C) but never frozen or stored at room temperature. The recovery rate of viruses remains at 93% in urine after 7 days of refrigeration, decreasing to 50% after 1 month⁵. Although a fourfold rise in IgG titer in paired sera or a strong positive IgM anti-CMV may be a useful finding suggesting infection, serologic assays are not recommended for diagnosis of CMV infection in neonates. Because IgG anti-CMV detected in newborn infants reflects transplacentally acquired maternal antibody

and that can persist for up to 18 months of age¹⁵. And also IgM assay has both false positive and false negative^{28, 29}. Computed tomography (CT) is most sensitive to detect intracranial calcification. And MRI is particularly valuable for detection of the disorders of neuronal migration and other cerebral parenchymal lesions complicated with congenital CMV infection⁶.

Amniocentesis may be the most valuable single antenatal diagnostic test, and viral culture or PCR test of amniotic fluid are equally specific and sensitive^{2, 5}. Quantitative PCR demonstrating 10^5 genome equivalent per mL of amniotic fluid may be a predictor of symptomatic congenital infection². Ultrasonographic fetal abnormalities in pregnant women with primary or recurrent CMV infection generally indicate symptomatic fetal infection. Reported sonographic abnormalities of the fetus include oligohydroamnios, IUGR, microcephaly, ventriculomegaly, intracranial calcification, hypoplastic corpus callosum, ascites, hepatosplenomegaly, hypoechoic bowel, pleural and pericardial effusion, and hydrops¹⁶.

Treatment

There are now two drugs for systemic treatment of congenital and perinatal CMV infection: ganciclovir and valganciclovir (oral prodrug of ganciclovir).

In a randomized controlled, multicenter, phase III study with ganciclovir (6 mg/kg/dose intravenously every 12 hr for a 6 week course)³⁰, it was carried out to treat newborn

infants who have congenital CMV infection involving the CNS, as defined by microcephaly, intracranial calcification, abnormal findings of cerebrospinal fluid, chorioretinitis and/or hearing deficit. When tested at 6 months, 84% of treated infants maintained normal hearing or improved their hearing, in contrast to 59% of control infants. At 6 months follow-up, none of the treated infants had hearing deterioration, while 41% of control patients did. When tested 1 year of age or beyond 21% of treated and 68% of control infants had hearing deterioration. Primary ganciclovir-related toxicity was neutropenia. 63% of treated infants developed neutropenia, compared with 21% of control infants.

In a pharmacokinetic and pharmacodynamic study of oral valgancyclovir in treatment of infants with congenital CMV infection³¹, it showed that a 6 mg/kg intravenous ganciclovir dose and 16 mg/kg oral valganciclovir provides similar systemic exposure to ganciclovir. In addition, treated patients with a 6 week course decreased in viral load of 0.7 log viral DNA copies/mL in urine. Toxicity of valganciclovir is similar to that of ganciclovir with 38% of subjects developing neutropenia.

Treatment with ganciclovir of a 6 week course can be considered for symptomatic infants with congenital CMV infection involving the CNS, but can not be routinely recommended¹⁵. A 2 week course of ganciclovir may be beneficial in critically ill infants with symptomatic perinatal CMV infection. And additional 1–2 weeks of ganciclovir can be considered if symptoms and signs have not been resolved¹².

Prognosis

Infection during early pregnancy more often result in more severe sequelae than infection later in pregnancy. Approximately 50–90% of symptomatic survivors have long-term sequelae such as microcephaly, hearing loss, motor deficit (paresis/paralysis), cerebral palsy, mental retardation, seizure, ocular abnormalities (chorioretinitis, optic atrophy), autism and learning disabilities³² (Table 2). In contrast, 10–15% of infant with congenital CMV infection who are asymptomatic at birth have long-term neurodevelopmental injury.

Factors associated with poor cognitive prognosis are microcephaly and abnormalities detected on brain CT^{4, 6}. In contrast, children with normal findings on brain CT and normal head circumference have been revealed to have a

good cognitive outcome³³. So radiologic findings of brain with MRI and CT may be the most specific and sensitive predictors of neurodevelopmental outcomes⁶. Microcephaly dose not always persist, and dose not always result in later handicap. Infants who have microcephaly alone without other neurologic findings have relatively a good prognosis in early childhood³⁴. Chorioretinitis is nearly always indicative significant mental retardation and often lead to optic atrophy. It can also develop on several weeks after birth⁸. SNHD, the most common sequelae of congenital CMV infection may occur in both symptomatic and asymptomatic infected infants. Although about 60% of infants with hearing loss is developed at birth or in neonatal period, at least 40 % may have delayed-onset loss⁶. Additionally progression of hearing loss in patients who had already SNHD has also been observed in about 60% of infants with through childhood and into adolescence^{15, 25, 35}. So all babies with congenital CMV infection should be followed at least school entry, and hearing test regularly performed to detect late deficit^{6, 8}. Patient with disseminated symptomatic infection including petechiae or IUGR at birth and those with higher viral load at birth appear to have an increased risk of hearing loss^{1, 35}.

Premature and ill full-term infants with serious perinatal CMV infection may be an increased risk of neurologic sequelae and psychomotor retardation, even though there dose not appear to be a higher rate of SNHD, microcephaly and chorioretinitis^{1, 2}.

Table 2. Long-term Sequelae of Congenital Cytomegalovirus Infection in Children

Sequelae	Affected children, %	
	Symptomatic	Asymptomatic
Overall incidence	50–90	10–15
Hearing loss	50–60	7–15
Cognitive deficit	50–70	–4
Microcephaly	35–40	–2
Ocular abnormalities	25–50	–3
Seizures	15–20	–1
Motor deficit (mild to moderate)	25–30	<1
Motor deficit (severe)	15–25	<1

*Rates reflect a range of incidence data reported in the pediatric literature.
Data from Schleiss MR³²

Prevention

CMV is usually not very contagious, and its horizontal transmission requires direct contact with infected materials, such as different secretions that contain the virus, and less likely, fomites. So adherence to standard precautions with good hand hygiene is effective to prevent CMV infection^{1, 13)}.

Preexisting maternal immunity to CMV affords significant protection to the fetus. In contrast, with maternal primary infection, the overall risk for delivering a symptomatic neonate is about 5%^{3, 4, 9)}. So women of childbearing age should have CMV serologic tests, especially if they provide care for young children who are potential CMV excretors^{1, 2, 36)}. And pregnant women who are CMV seronegative should be provided with information on prevention measures and reassured that common sense steps such as hand washing and avoiding contact with secretions should prevent this infection^{1, 37)}. Although newborn hearing screening programs may miss the late-onset hearing loss complicated in congenital CMV infection, routine screening of all newborns for CMV is not yet recommended^{38, 39)}.

Pasteurization (72°C for 5 seconds) of breast milk can inactivate CMV completely without affecting nutritional and immunologic properties of milk, although freezing (−20°C for 3–7 days) will significantly decrease viral titers^{12, 40, 41)}. Transfusion-acquired CMV infection is eliminated by administration of CMV antibody-negative blood products and filtration of blood to remove white blood cells¹²⁾.

CMV vaccine ultimately may be an important preventive measure, but are not yet successful.

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