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Cytomegalovirus Infection in the Fetus and Neonate

Elizabeth K. Stehel, MD,* Pablo J. Sánchez, MD*

Objectives After completing this article, readers should be able to:

1. Describe the transmission of cytomegalovirus (CMV) to the fetus and newborn and the differences between congenital, natal, and postnatal infection with CMV.
2. Delineate the clinical manifestations and sequelae of congenital, natal, and postnatal infection with CMV.
3. Know how to diagnose CMV infection in the fetus and newborn.
4. Describe potential treatment options for neonatal CMV infections.

Introduction

Human CMV is a DNA virus of the herpesvirus group. CMV infection was described first in the early 1900s in pathologic specimens from an infant who died of presumed congenital syphilis. The virus initially was named salivary gland virus due to the characteristic pathologic changes seen in the salivary glands. It was isolated in tissue culture in 1956, and in the early 1960s, the more descriptive name cytomegalovirus was adopted. CMV infection of host cells results in a characteristic massive enlargement of the affected cells that contain intranuclear and cytoplasmic inclusions (Fig. 1).

Infection of the fetus and neonate with CMV is an important health problem worldwide. In the United States, CMV is the most common congenital viral infection, affecting 0.2% to 2.5% of all live births. Of the 40,000 infants born each year with congenital CMV infection, more than 8,000 develop mental retardation, cerebral palsy, or, most commonly, hearing impairment.

Epidemiology

Infection with CMV is ubiquitous, occurring in all populations and socioeconomic groups throughout the year without any seasonal variation. Person-to-person transmission of CMV occurs by close contact with infected body fluids and secretions. CMV can be isolated from body tissues and fluids such as tears, saliva, human milk, urine, stool, semen, cervical secretions, amniotic fluid, blood, and transplanted organs. In addition, infected secretions on plastic surfaces and toys can harbor the virus for hours, and these fomites play a major role in CMV transmission in child care centers. Viruria occurs in as many as 70% of infected children ages 2 to 3 years. Serologic studies demonstrate a 30% seroconversion rate among parents whose children shed CMV compared with no seroconversions among parents whose children do not excrete the virus. Transmission of CMV from a child in out-of-home child care to his or her mother and her fetus has been confirmed. Young children in child care centers and infected sexual partners are the most likely sources of primary CMV infection for pregnant women in the United States.

In developed countries, CMV seroprevalence varies inversely with socioeconomic status. Approximately 40% to 60% of adults in middle and upper socioeconomic groups have evidence of CMV infection compared with 80% of adults in lower socioeconomic groups. In the United States, approximately 40% to 85% of women in their childbearing years have serologic evidence of CMV infection. Infection of the fetus and newborn occurs despite the presence of maternal antibody. In developing countries, CMV is acquired in early infancy, usually from breastfeeding, and adults almost universally are infected.

After an active replication stage, CMV enters a latent stage in leukocytes and other tissues. Like other herpesviruses, CMV has the ability to reactivate during periods of...
relative immunocompromise, such as pregnancy, and can result in asymptomatic viral excretion. Viral excretion persists for years after congenital and perinatal infections and following primary infection in older children and adults; recurrent infection results in intermittent excretion.

Transmission
CMV can be transmitted to a fetus or newborn following maternal primary infection, recurrent or reactivated infection, or reinfection with a different CMV strain than that which had infected the mother previously. Based on the time of acquisition of CMV infection by the fetus or neonate, transmission is classified as prenatal, natal, or postnatal. Prenatal or congenital infection occurs in utero by a transplacental route from hematogenous spread to the fetus during maternal viremia (Fig. 2). Alternatively, in utero infection occurs rarely by an ascending route following rupture of fetal membranes in a mother who has infected cervical secretions. Natal infection occurs intrapartum after exposure to infected cervical and vaginal secretions during delivery. Postnatally, the infant can become infected with CMV by contact with infected body fluids such as human milk or saliva or by receipt of blood transfusions from CMV antibody-positive donors. Horizontal transmission of CMV in a neonatal intensive care unit has been documented, but is rare.

Prenatal Infection
Both the incidence and severity of prenatal infection varies with the type of maternal infection during pregnancy. Fetal infection is more likely to occur and is more severe after maternal primary infection than after reactivation of latent infection in the mother. The incidence of primary CMV infection acquired during pregnancy is 1% to 4%, and its occurrence is associated with a 40% risk of congenital infection. Although maternal infection in the first half of pregnancy leads to more severe fetal disease, transmission can occur at any time during gestation. Overall, only 10% to 15% of infected infants manifest clinical signs at birth, that is, are “symptomatic.” Approximately 0.2% to 2.0% of infants born to women who are seropositive before becoming pregnant are infected in utero, but they rarely have clinically apparent disease at birth. Recent evidence also suggests that maternal reinfection with a different CMV strain can result in symptomatic congenital disease; the frequency of this occurrence currently is not known. Although the transmission rate of infection to the fetus is lower among seropositive women, reactivation and reinfection probably account for more cases of prenatal infection than does primary maternal infection. However, there is concern that maternal coinfection with human immunodeficiency virus and CMV may promote perinatal transmission of CMV and result in clinically apparent CMV disease in the newborn, even among infants born to mothers who have recurrent infection.

Natal Infection
About 2% to 28% of seropositive pregnant women shed CMV in cervical and vaginal secretions during delivery. Approximately 50% of exposed infants become infected.
and develop clinical signs of CMV disease at about 4 to 6 weeks of age.

Postnatal Infection
In the postpartum period, maternal-to-infant transmission of CMV occurs during breastfeeding because 9% to 88% of seropositive women shed CMV into their milk. Approximately 50% to 60% of infants fed human milk that contains CMV become infected. Because CMV excretion in human milk usually is the result of reactivation of CMV infection in a seropositive mother, most infants develop no clinical signs of disease due to the presence of maternally derived, transplacental CMV immunoglobulin (Ig)G antibodies. Among preterm infants who lack sufficient quantities of these antibodies, transmission of CMV through human milk has resulted in symptomatic infection.

An important iatrogenic source of CMV infection is transfusion of blood that has not been treated to remove viable CMV from a seropositive donor to a seronegative infant. Under such conditions, the incidence of infection is about 15% and usually occurs in infants who weigh less than 1,300 g. The risk of infection is related to the volume of transfused blood, number of donors, and elevated complement fixation titers to CMV in donor blood.

Clinical Manifestations
Congenital Infection
Antenatal ultrasonography has documented CMV-associated fetal abnormalities such as hepatosplenomegaly, echogenic bowel, ventriculomegaly, and intracranial calcifications (Fig. 3). Umbilical blood sampling in infected fetuses has demonstrated thrombocytopenia, anemia, or elevated liver enzymes.

Most infants infected with CMV have no clinical signs of disease at birth or in the neonatal period and are classified as being “asymptomatic.” Among those who manifest clinical, laboratory, or radiographic abnormalities, the most typical and severe include intrauterine growth restriction, hepatosplenomegaly, jaundice, petechiae or purpura, “blueberry muffin” spots, microcephaly, chorioretinitis, sensorineural hearing loss, and cerebral calcifications (Table) (Fig. 4). “Blueberry muffin” lesions of the skin are palpable, discrete, well-circumscribed, bluish-purple lesions on jaundiced skin. Often mistaken for purpura, they represent dermal hematopoeisis in the more severely affected infants. The

Table. Clinical Findings in Infants Who Have Congenital CMV Infection

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<tr>
<th>Physical Examination Findings</th>
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<tr>
<td>Nonimmune hydrops fetalis</td>
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<td>Prematurity</td>
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<td>Intrauterine growth restriction</td>
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<tr>
<td>Jaundice*</td>
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<td>Hepatosplenomegaly*</td>
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<td>Petechiae*</td>
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<td>Purpura</td>
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<tr>
<td>Blueberry muffin spots</td>
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<tr>
<td>Chorioretinitis</td>
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<td>Microcephaly*</td>
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<td>Lethargy</td>
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<td>Poor feeding</td>
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<td>Hypotonia</td>
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<td>Seizures</td>
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<td>Inguinal hernia (males)</td>
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<th>Laboratory Findings</th>
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<tr>
<td>Anemia*</td>
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<td>Thrombocytopenia*</td>
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<tr>
<td>Elevated liver enzymes</td>
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<tr>
<td>Hyperbilirubinemia (direct and indirect)*</td>
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<td>Elevated cerebrospinal fluid protein content</td>
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<th>Radiographic Findings</th>
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<tr>
<td>Pneumonia</td>
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<td>Neuroimaging</td>
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<tr>
<td>— Calcifications (periventricular, thalamic, cortical)*</td>
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<td>— Ventriculomegaly</td>
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<td>— Cortical dysplasia</td>
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| Hearing Impairment* |

*Prominent feature
presence of these features in newborns is termed cytomegalic inclusion disease, a syndrome characterized by multiorgan involvement, with the reticuloendothelial and central nervous systems most frequently and severely affected. More commonly, infected infants exhibit only one or a few of these manifestations. Isolated microcephaly, splenomegaly, thrombocytopenia, or hearing deficit is relatively common and should prompt diagnostic evaluation for CMV infection.

Other findings include poor feeding, pneumonia, lethargy, hypotonia, seizures, and inguinal hernia in males. Laboratory abnormalities include Coombs-negative hemolytic anemia, elevated liver enzymes, and elevated cerebrospinal fluid (CSF) protein concentrations. Central nervous system infection can result in cortical dysplasia and encephalitis with resultant ex vacuo ventriculomegaly (Fig. 5). Arrested brain growth results in microcephaly, and obstruction of the fourth ventricle may result in hydrocephalus. Defective enamelization of the deciduous teeth occurs in 40% of symptomatic newborns and in 5% of infants who have asymptomatic infection at birth.

Sensorineural hearing loss is the most common abnormality seen in congenital CMV infection, occurring in about 30% to 65% of symptomatic infants and 5% to 15% of asymptomatic infants. Most hearing impairment from congenital CMV infection develops after the newborn period in both symptomatic and asymptomatic infants, and it tends to be progressive. Approximately 50% of infected infants have further hearing deterioration throughout childhood and into adolescence. Cochlear implantation has been used successfully as early as 1 year of age for children who have bilateral profound hearing loss.

**Natal Infection**

After an incubation period of 4 to 12 weeks (mean, 8 wk), CMV infection acquired at delivery may result in an afebrile pneumonia in approximately 50% of exposed infants. Rarely, hepatitis or encephalitis may occur. The disease tends to be mild in term infants due to the presence of maternally derived CMV IgG antibodies, and it does not result in late neurologic sequelae or sensorineural hearing loss. Among preterm infants whose birthweights are less than 1,500 g, natally acquired CMV infection may be more severe. CMV pneumonitis in these infants has been associated with development or exacerbation of bronchopulmonary dysplasia (BPD). Administration of postnatal steroids for BPD in CMV-infected preterm infants has been associated with progression of the CMV disease.

**Postnatal Infection**

Among term infants, CMV infection acquired by breast-feeding is a common, benign, and asymptomatic infection because the infants possess maternal CMV IgG antibody. CMV infection acquired through administration of infected human milk to preterm very low-birthweight infants also may result in asymptomatic infection. However, as many as 15% to 25% of infected preterm infants may develop a sepsislike illness that includes apnea, bradycardia, hepatosplenomegaly, distended bowel, pallor, neutropenia, thrombocytopenia, and elevated liver function tests. It is not known if such infants develop long-term neurologic sequelae. Transfusion-acquired CMV infection in low-birthweight infants may be severe and is characterized by a gray ashen pallor, respiratory distress, pneumonia, hepatosplenomegaly, hepatitis, atypical lymphocytosis, thrombocytopenia, and hemolytic anemia; it has a 10% mortality.
Diagnosis

Congenital CMV infection is diagnosed best by identification of virus from urine or saliva before 3 weeks of age. Isolation of CMV from amniotic fluid has been used to document in utero infection. Among infants infected with CMV natally, viruria and pharyngeal shedding appear after an incubation period of 4 to 12 weeks. Therefore, after 3 weeks of age, it is impossible to differentiate among prenatal, natal, or postnatal acquisition of CMV unless the infant previously has had a negative CMV culture. This distinction is important because prenatal infection has been associated with long-term sequelae such as hearing impairment.

CMV is identified in body fluids and tissues via the shell-vial culture assay, a technique in which a monoclonal antibody is used to detect early CMV antigen after the specimen is incubated in tissue culture for 24 to 48 hours. Use of the shell-vial assay allows rapid identification of infected neonates. On routine viral culture, characteristic cytopathologic changes occur after about 2 weeks of inoculation of the specimen onto a human fibroblast monolayer. Sensitivity is optimized by transporting the clinical specimen to the virology laboratory as soon as possible or maintaining the specimen refrigerated at 4°C or on wet ice during transport.

Polymerase chain reaction (PCR) has been used successfully for identification of CMV DNA in such clinical specimens as amniotic fluid, urine, blood, and cerebrospinal fluid. PCR is the preferred method for detection of CMV in the CSF. Among symptomatic infants, a positive CSF CMV PCR result has been associated with a more severe neurologic outcome. PCR also is preferred for detection of CMV in blood specimens, in which the finding of CMV DNA in blood is supportive of active infection. A positive blood CMV PCR result has been associated with development of hearing loss in infants who have congenital CMV infection. At present, blood PCR is not recommended in newborns who already have been diagnosed with congenital CMV infection by standard culture methods. The best utility of blood CMV PCR in neonates may be in diagnosis of CMV disease acquired nataly or postnatally. CMV PCR also has been performed on dried blood spot samples obtained by heel stick from newborns. This ultimately may offer the opportunity for screening of all newborns for congenital CMV infection.

Detection of pp65 antigen in white blood cells has been used to detect active infection in immunocompromised hosts, but its requirement for a large quantity of blood has limited its use in neonates.

Serologic assays that measure CMV IgG or IgM are not recommended for the diagnosis of CMV infection in neonates. A positive CMV IgG antibody test reflects transplacentally acquired maternal IgG antibody and does not diagnose neonatal infection. Maternal IgG antibody can persist for up to 18 months of age. Persistence of CMV IgG antibody beyond this time cannot differentiate between congenital, natal, or postnatal infections. Both false-positive and false-negative test results occur with CMV IgM assays. A negative maternal IgG antibody test at the time that an infant presents with clinical signs of possible congenital infection rules out the diagnosis, but with the availability and sensitivity of CMV culture and PCR performed on newborns, this is not a necessary or recommended method of evaluation for congenital CMV infection.

Treatment

Management of infants who have congenital CMV infection consists primarily of supportive care in the newborn nursery or neonatal intensive care unit. Breastfeeding is encouraged. Affected infants often require phototherapy
for hyperbilirubinemia and red blood cell or platelet transfusions for severe anemia and thrombocytopenia. Evaluation should include head ultrasonography or computed tomography to ascertain central nervous system involvement as well as audiometric and ophthalmologic evaluations.

Ganciclovir (6 mg/kg intravenously every 12 h) has been used to treat infants who have congenital CMV infection. Ganciclovir inhibits viral DNA polymerase, thereby acting as a chain terminator during elongation of newly synthesized viral DNA. In laboratory animals, ganciclovir is a teratogen and carcinogen and is associated with gonadal atrophy and decreased spermatogenesis. The most common adverse effect in neonates is neutropenia, which occurs in as many as 60% of recipients.

A phase III, multicenter, randomized study of ganciclovir therapy for infants who had congenital CMV infection involving the central nervous system was performed by the Collaborative Antiviral Study Group from 1991 to 1999. The investigators evaluated the safety and efficacy of intravenous ganciclovir for 6 weeks versus no therapy in 100 CMV-infected neonates (≥32 weeks of gestation, birthweight of ≥1,200 g). Among only 47 evaluable infants, those who received ganciclovir were significantly more likely to have either improved or normal hearing at 6 months than untreated infants, and none of the ganciclovir-treated infants had worse hearing. At 1 or more years of age, those who received ganciclovir also were significantly less likely to have worse hearing than the untreated group. Other beneficial effects of ganciclovir therapy included a significant decrease in median time to normalization of the alanine aminotransferase concentration as well as improved weight gain and head circumference after 6 weeks of therapy, but no change in mortality. Neurodevelopmental assessments were not performed, and it is not known if ganciclovir therapy affects the long-term prognosis in these infants. Based on this study, ganciclovir therapy may be offered to CMV-infected neonates who manifest central nervous system disease for prevention of hearing impairment. Extrapolating from the effects on hearing, in which ganciclovir was most effective in preventing hearing deterioration rather than improving hearing function, the beneficial effects of ganciclovir may be in prevention of further damage to the central nervous system. Ganciclovir is not likely to be beneficial for infants who manifest severe brain injury that occurred in utero. Another possible indication for ganciclovir therapy is chorioretinitis that involves the macula and may result in blindness.

A 10- to 14-day course of ganciclovir may be beneficial in mostly preterm, critically ill infants who acquire the infection natally or postnatally. Such infants have life-threatening CMV disease manifested by pneumonitis, hepatitis, or encephalitis. Ganciclovir also has been used in steroid-associated CMV disease in preterm infants with and without hyperimmune CMV globulin. Ganciclovir prophylaxis should be considered in CMV-infected preterm infants who require steroid therapy for severe BPD. Further studies in these areas are needed.

Neither standard nor CMV-hyperimmune intravenous immune globulin is indicated for treatment of congenital CMV infection. A phase I/II pharmacokinetic evaluation of oral valganciclovir in neonates who have symptomatic CMV infection is ongoing.

**Prognosis**

More than 90% of infants who have symptomatic congenital CMV infection manifest abnormalities on follow-up evaluations, ranging from hearing impairment to mental retardation and cerebral palsy. Microcephaly, intracranial calcifications, abnormal neuroimaging studies, and a positive CSF CMV DNA PCR result are predictive of a worse long-term outcome (Fig. 5). The most frequent sequela is sensorineural hearing loss, which develops in approximately 50% of symptomatic infants. Cochlear implantation has been performed successfully as early as 1 year of age in children who have profound bilateral hearing loss.

Approximately 90% of infants who have asymptomatic congenital CMV infection have no apparent sequelae and only rarely manifest severe neurologic impairment. About 7% of such children develop hearing impairment.

Infants and children who have congenital CMV infection require close and intense pediatric follow-up. They should be enrolled in early childhood intervention programs that provide physical, occupational, and speech therapy. All require periodic evaluation of hearing throughout childhood and adolescence to detect progressive or late-onset hearing loss. In addition, they should receive periodic ophthalmologic evaluation to assess visual acuity, strabismus, and chorioretinitis. The more severely affected children often have feeding difficulties, with suck and swallow incoordination and laryngeal aspiration that may require gastrostomy tube placement and Nissan fundoplication. Careful assessment of caloric needs is needed to prevent obesity. Sleep disorders and school dysfunction also are common. Family support is an essential component, and decisions regarding resuscitation status need to be discussed.
Prevention

The mainstay of prevention remains avoidance of exposure. Infants who have CMV infection are cared for using standard precautions only. Studies in health care workers demonstrate that hand hygiene prevents acquisition of CMV infection. Because of this and the ubiquitous nature of CMV, pregnant women are not excluded from caring for infants who are infected with CMV. The greater risk to the pregnant health care worker may be the unidentified asymptomatic infant who is excreting CMV.

Routine serologic screening is not recommended for women of childbearing age because no prophylactic or therapeutic interventions are available during pregnancy. Meticulous adherence to standard precautions, especially hand hygiene after exposure to urine or saliva from young infants and toddlers and immunocompromised patients, is the most effective means of preventing primary CMV infection in pregnant women.

Routine screening of all newborns for CMV is not recommended. Because CMV is the most common non-genetic cause of hearing loss, newborns who do not pass their hearing screen may be screened for CMV. Approximately 5% of such infants are infected with CMV and require close audiologic follow-up.

Transfusion-acquired CMV infection is eliminated by administration of CMV antibody-negative blood products, leukofiltration of blood to remove the white blood cell fraction, and use of frozen deglycerolized red blood cells that lack viable leukocytes.

Freezing of expressed human milk at $-20^\circ$C for 3 to 7 days significantly diminishes CMV titers but does not eliminate infectivity completely. Pasteurization ($62.5^\circ$C) is required for complete neutralization of the virus, but this is not routinely done or available. In general, the potential benefits of providing expressed human milk to vulnerable preterm infants far outweigh the potential risk of symptomatic CMV infection.

CMV vaccine ultimately may be the best preventive strategy, but vaccine development remains investigational.

Suggested Reading


NeoReviews Quiz

8. Congenital cytomegalovirus (CMV) infection occurs in utero by the transplacental route from hematogenous spread to the fetus during maternal viremia. Of the following, the most common fetal abnormality seen in congenital CMV infection is:
   A. Chorioretinitis.
   B. Meningoencephalitis.
   C. Myocarditis.
   D. Pneumonia.
   E. Sensorineural hearing loss.

9. A newborn has clinical features of intrauterine growth restriction, microcephaly, hepatosplenomegaly, and petechial skin rash. Head ultrasonography reveals periventricular calcification. Of the following, the preferred method for diagnosing suspected congenital CMV infection in this infant is via:
   A. Detection of pp65 antigen in white blood cells.
   B. Polymerase chain reaction assay of cerebrospinal fluid.
   C. Serologic assay for immunoglobulins G and M.
   D. Shell–vial monoclonal antibody assay of blood.
   E. Viral isolation in urine.

10. The management of newborns who have CMV infection consists primarily of supportive care. Of the following, the only antiviral treatment that has been evaluated in a phase III, randomized trial involving neonates who have congenital CMV infection is:
    A. Acyclovir.
    B. CMV hyperimmune globulin.
    C. Foscarnet.
    D. Ganciclovir.
    E. Valganciclovir.