CONGENITAL CYTOMEGALOVIRUS INFECTION

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Cytomegalovirus (CMV) is the most common congenital infection in humans. Congenital CMV infection can follow either a primary or recurrent maternal infection, but the likelihood of fetal infection and the risk of associated damage is higher after a primary infection. Approximately 90% of congenitally infected infants are asymptomatic at birth. Jaundice, petechiae, and hepatosplenomegaly are the most frequently noted clinical triad in symptomatic infants. More frequent and more severe sequelae occur in symptomatic infants, notably psychomotor hearing loss and retardation. Congenital CMV infection can be diagnosed by isolation of the virus from the urine or saliva within the first three weeks of life. Rapid diagnosis can be accomplished by detection of CMV DNA by DNA amplification or hybridization techniques. (*J Natl Med Assoc.* 2003;95:213-218.)

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Cytomegalovirus (CMV) infection is the most frequent congenital infection worldwide and is diverse in its clinical manifestations.[1] The fetus can be infected by either a newly acquired (primary) maternal infection or a recurrent (reactivated) maternal infection.[2] The likelihood of fetal infection and the risk of associated damage and sequelae is higher after a primary infection.[3] Although most congenitally infected infants are asymptomatic at birth, congenital CMV infection is a leading cause of sensorineural hearing loss, mental retardation, and neurologic deficits.[4]

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DESCRIPTION OF THE VIRUS

CMV is the largest and most complex member of the *Herpesviridae* family of DNA viruses.[5] The genome is composed of a linear double-stranded DNA, approximately 240 kilobases in size ($150x10^6$ daltons), and is capable of isomerization.[5,6] The genome has been completely sequenced and shown to contain non-overlapping open-reading frames for more than 200 potentially immunologic proteins.[1] The genome is surrounded by an icosahedral capsid composed of 162 capsomeres.[5] The capsid is surrounded by a poorly defined amorphous tegment which is itself surrounded by lipid envelope, giv-

ing the complete and mature viral particle a diameter of about 200 n.[5,7] The virus lacks the enzyme thymidine kinase, which renders it resistant to those antiviral agents that depend on this enzyme for their action.

The virus is named for the intranuclear and intracytoplasmic inclusions seen with symptomatic disease, cytomegalic inclusion disease.[8] CMV is highly species specific, and humans are the only known reservoir for disease among humans.[8]

EPIDEMIOLOGY

Congenital CMV infection occurs in approximately 0.2%-2.5% of all live births; infection is more prevalent in underdeveloped countries and among lower socioeconomic groups in developed countries, where crowding is more common.[4,5,7,9,10] Both primary and recurrent infections in the mother during pregnancy may result in congenital CMV infection. On average, 1-4% of susceptible women acquire primary CMV infection during their pregnancy.[10,11] Approximately 10% of sero-positive pregnant women have reactivation of CMV infection during their pregnancy.[10] The transmission rate after primary infection is about 40%, whereas the transmission rate after recurrent infection is about 1-3%.[12-14]

PATHOGENESIS AND PATHOLOGY

Congenital CMV infection results from transplacental transmission of the virus during maternal viremia.[15] Maternal viremia is more likely to occur with primary than with recurrent infection. After transplacental transmission, the virus spreads through the fetus by a hematogenous route. Infection at an earlier gestational age often correlates with a less favorable outcome.[13,14,16]

Infants born to mothers with primary CMV infection during pregnancy are more likely to have symptoms at birth. The presence of maternal antibody to CMV before conception provides substantial protection against intrauterine transmission of the virus and severe fetal infections.[17] The protection, however, is incomplete, and congenital CMV infection may follow recurrent maternal infection.[17,18] More recent studies suggest symptomatic congenital CMV infection after a recurrent maternal infection occurs more frequently than previously documented.[17,19,20]

Although CMV affects most cell types, it has a special affinity for epithelial cells, ependymal cells lining the ventricles, the organ of Corti, and the neurons of the eighth cranial nerve.[6] The characteristic pathologic features include cytomegaly, intranuclear inclusions ("owl's eye" appearance), intracytoplasmic inclusions, and multinucleated giant cells.

CLINICAL MANIFESTATIONS

About 90% of congenitally infected infants are asymptomatic at birth.[2,5] Jaundice (62%), petechiae (58%), and hepatosplenomegaly (50%) are the most frequently noted classical triad (Figure 1).[10] Other clinical manifestations include oligohydramnios, polyhydramnios, prematurity, intrauterine growth retardation, nonimmune hydrops, fetal ascites, hypotonia, poor feeding, lethargy, thermal instability, cerebral ventriculomegaly, microcephaly, intracranial calcifications usually periventricular in distribution, "blueberry muffin" spots, and chorioretinitis.[5,10,21-23] Sensorineural hearing loss develops in 30% of symptomatic infants at birth.[2] Infants with symptomatic CMV infection may be at increased risk for congenital malformations such as inguinal hernia in males, high-arched palate, defective enamelization of the deciduous teeth, hydrocephalus, clasp thumb deformity, and clubfoot.[24] Some affected infants may develop hepatitis, pneumonia, osteitis, and intracranial hemorrhage.[25]

LABORATORY DIAGNOSIS

Congenital CMV infection can be diagnosed by isolation of the virus from the urine or saliva within the first three weeks of life.[1,14] This can be accomplished by traditional virus culture methods which may take one to two weeks to obtain a result

or rapid culture methods ("shell vial assay") using centrifugation to enhance infectivity and monoclonal antibody to detect early antigens in infected tissue culture cells which may yield results in 24 hours.[4,20,26] Rapid diagnosis of CMV can also be accomplished by detection of CMV DNA by DNA amplification techniques via the polymerase chain reaction (PCR) or DNA hybridization techniques.[26,27] Culture, however, maintains a slight advantage over PCR in terms of specificity.[28]

The presence of CMV-specific IgM in cord blood or in the infant's blood within the first three weeks of life suggests the diagnosis of congenital CMV infection.[10,14] However, CMV-specific IgM can only be detected in about 70% of congenitally infected newborn infants.[10,14] On the other hand, a negative CMV-specific IgG titer in cord blood excludes the diagnosis of congenital CMV infection whereas its presence may merely imply passive transfer from the mother or may indicate a congenital infection.[10]

Prenatal detection of fetal infection can be established by isolation of the virus from the amniotic fluid obtained by amniocentesis.[26] A negative culture does not exclude fetal infection especially if the amniocentesis is carried out too early with respect to the maternal infection.[7,28] Diagnosis of a primary maternal CMV infection can be established by the demonstration of an IgG seroconversion during pregnancy, especially if accomplished by the detection of CMV-specific IgM antibodies in the maternal blood.[5,29] Fetal abnormalities detected by prenatal ultrasonography generally indicate more severe fetal disease.

In symptomatic infants, anemia, thrombocytopenia, hyperbilirubinemia, atypical lymphocytosis, elevated serum transaminases, and elevated cerebrospinal fluid protein may be found. Skull radiographs, CT scan, and MRI may

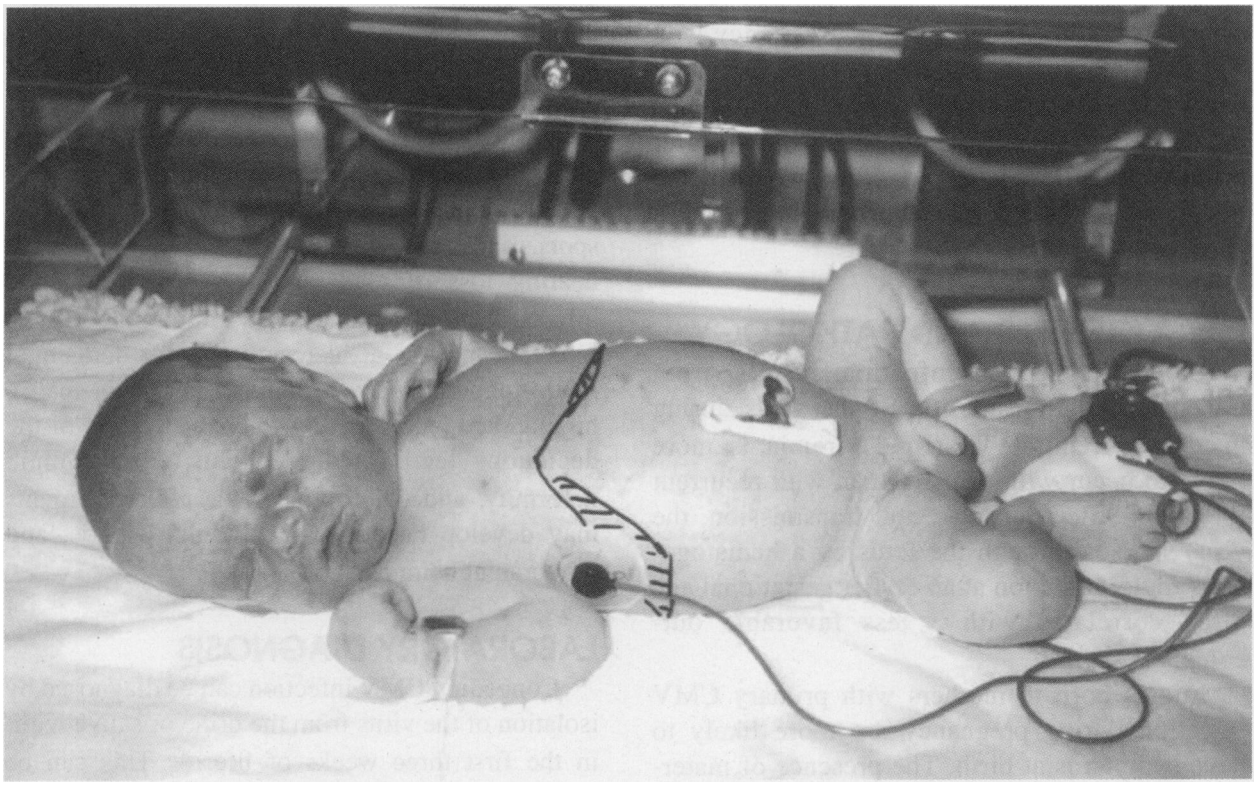

Figure 1. A newborn infant with symptomatic congenital CMV infection presenting with petechiae, jaundice, and hepatosplenomegaly.

demonstrate periventicular calcifications and venticulomegaly. Radiographs of the long bones many show longitudinal radiolucent streaks ("celery stalk" appearance).

DIFFERENTIAL DIAGNOSIS

Congenital CMV infection should be distinguished from other congenital infections such as toxoplasmosis, rubella, herpes simplex, and syphilis. Such distinction can be done both clinically and serologically. Toxoplasmosis is more likely to be associated with chorioretinitis, microphthalmia, hydrocephalus, and scattered cerebral calcifications. Petechial and purpuric eruptions, which are common in symptomatic congenital CMV infections, are rare in congenital toxoplasmosis; the latter often presents with a maculopapular rash. The presence of congenital heart disease and cataracts points to congenital rubella infection. Vesicular skin lesions or scarring present at birth suggest congenital herpes simplex infection. Rhinitis and radiological evidence of osteochondritis and epiphysitis favor the diagnosis of congenital syphilis. Other differential diagnoses include bacterial sepsis, erythroblastosis fetalis, and metabolic disorders such as galactosemia and tyrosinemia.

PROGNOSIS

Infants with symptomatic congenital CMV infection have a mortality rate of 10-15%.[4] Approximately 50-90% of symptomatic survivors have long-term sequelae such as sensorineural hearing loss, mental retardation, developmental delay, cerebral palsy, epilepsy, ocular abnormality, and microcephaly.[4,9,10,30] The former occurs in up to 50% of affected infants.[4] The worst prognosis occurs in infants born to mothers with primary CMV infection during pregnancy, infants with CMV-specific IgM in the cord blood, and infants symptomatic at birth, particularly those with microcephaly, intracranial calcifications, chorioretinitis, or raised cerebrospinal fluid protein.[5,15,31] Some of the late complications such as hearing loss and central nervous system damage presumably result from ongoing viral replication.[28]

Approximately 7-15% of asymptomatic infants have sensorineural hearing loss.[4,30] Whether these infants are at increased risk of mental retardation is controversial.[32,33] Hanshaw et al compared 44 children with asymptomatic congenital CMV infection with both matched and random controls and found school failure and deafness to be associated with asymptomatic congenital CMV infection.[32] On the other hand, Kashden et al. compared 204 children who had asymptomatic congenital CMV infection with 177 uninfected siblings and found that there was no statistically significant difference between the two groups on intellectual measure.[33]

MANAGEMENT

Ganciclovir, a synthetic acyclic nucleotide analog of guanine, is phosphorylated to a triphosphate within the cell and acts as an inhibitor of viral DNA synthesis. Preliminary data have shown ganciclovir effective in the treatment of symptomatic congenital CMV infection.[34] A phase II study with ganciclovir showed hearing improvement or stabilization in five of 30 infants with symptomatic congenital CMV infection at six months or later.[34] During the treatment period, quantitative excretion of CMV in the urine decreased. However, after cessation of therapy, viruria returned to near pre treatment levels. A phase III randomized trial suggests that ganciclovir may benefit infants with severe congenital CMV infection.[4] Central nervous system damage that has already occurred will not be reversed, but ongoing viral replication causing postnatal damage is controlled campared to untreated CMV-infected controls. The value of ganciclovir for the prevention or treatment of hearing loss in asymptomatic children has not been determined. Side effects of ganciclovir include bone narrow suppression and potential gonadal toxicity.[1] Presently there is insufficient data to justify the

routine use of ganciclovir in the treatment of congenital CMV infection.[35]

Children with congenital CMV infection are at risk for hearing loss, mental retardation, psychomotor delay, cerebral palsy, and impaired vision. This is especially so for the hearing loss, for as many as 80% of cases are of late-onset or progressive.[6] As such, children with congenital CMV infection should have long-term audiologic, neurodevelopmental, and ophthalmic follow-up for early identification of these problems.

PREVENTION

Women of childbearing age should practice meticulous personal hygiene, such as avoidance of contact with urine or saliva of others and proper hand-washing after such contact. Nurses who practice good handwashing do not have increased rates of CMV acquistition, but daycare workers often do, suggesting that barrier precautions are effective in interrupting transmission. Several candidate vaccines are under development. These vaccines are urgently needed and ultimately may be an important preventive measure.[36]

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