IN BRIEF

Congenital Cytomegalovirus

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Congenital cytomegalovirus (cCMV) is the commonest congenital infection and cause of birth defects worldwide. Globally, approximately 1 in 150 live-born infants (0.7%) are affected, with approximately 40,000 cases per year in the United States, 5,000 of whom manifest permanent sequelae. Despite the magnitude of the problem as well as evidence for efficacy of preventive actions, awareness among women of childbearing potential is low, questions regarding optimal diagnostic methods remain, treatment options are limited, and an effective vaccine is yet to become available.

CMV is a double-stranded DNA virus of the *Herpesviridae* family. After infection, the virus persists in leukocytes and tissue cells with intermittent shedding in urine, saliva, and genital secretions. Vertical transmission most commonly occurs in utero, but infection can be acquired at the time of birth or via human milk. Clinical manifestations are evident at birth in only 10% of infected infants and run the gamut from isolated sensorineural hearing loss (SNHL) to more severe disease comprising growth restriction, thrombocytopenia, direct hyperbilirubinemia, hepatosplenomegaly, microcephaly, periventricular calcifications, chorioretinitis, and neurodevelopmental delay. Life-threatening complications include sepsislike illness, myocarditis, hemophagocytic lymphohistiocytosis, and other end-organ involvement, with death estimated to occur in 3% to 10% of infants symptomatic at birth. In US children, cCMV is the leading nongenetic cause of SNHL, its most common sequela. Importantly, approximately 40% of children who experience SNHL as a result of cCMV do not have detectable hearing loss within the first month of life, meaning that targeted testing of infants who fail the newborn hearing screen misses a significant proportion of those at risk.

Close contact with children younger than 2 years, especially those who attend child care centers, is a particular risk factor for maternal infection. Racial and socioeconomic disparities are stark, with poverty identified as a race-independent predictor of both higher CMV seroprevalence in pregnancy and infant hearing loss, and with the highest prevalence of infection occurring in Black infants, likely the effect of social determinants of health. Rates are increased in the infants of women who are immunocompromised, including those with human immunodeficiency virus infection. The greatest risk of infection to the fetus comes with primary CMV infection of a pregnant woman, with severe sequelae most likely following infection during the first and second trimesters. However, transmission can also follow reactivation during pregnancy of an old infection, or if the mother is reinfected by a different strain of CMV. Indeed, it is estimated that 75% of cCMV in the United States affects infants born to women

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with previous infection, and increasing evidence suggests that the risk of congenital infection becoming symptomatic, particularly with SNHL, is comparable after either primary or nonprimary maternal infection. In the less common instance when an infant becomes infected at birth or postnatally, prematurity and low birthweight have been identified as risk factors for developing symptomatic disease. Most infants who acquire CMV from human milk do not develop clinical manifestations or complications, likely protected by passive transfer of maternal antibody.

Regarding testing during pregnancy, early universal screening to identify seronegative women who would be at risk for primary infection is not currently recommended. Rather, when maternal CMV infection is suspected clinically, or when fetal imaging shows suggestive findings, serology tests should be offered. When the mother is known to have previously tested CMV seronegative, diagnosis of infection may be based on the detection of CMV-specific immunoglobulin (Ig) G in the serum. If the immune status before pregnancy is unknown, the diagnosis of maternal primary CMV infection is made with the detection of both CMV IgM and low- to moderate-avidity CMV IgG. Although a recently published randomized controlled trial concluded that valacyclovir is effective in reducing the rate of cCMV from maternal first-trimester primary infection, the use of this drug during pregnancy to prevent cCMV remains investigational.

For the fetus, testing is offered when there is confirmed maternal primary infection during the pregnancy, or when fetal imaging has findings consistent with cCMV. Diagnosis of fetal infection is made via amniocentesis and testing of amniotic fluid using nucleic acid test assays, such as real-time polymerase chain reaction (PCR). Confirmation of infection can be made when fetal urination is well-established after 20 to 21 weeks' gestation and at least 6 weeks after the time of maternal infection.

In the newborn, further diagnostic testing is indicated with suspected or confirmed maternal or fetal infection or when there are signs, symptoms, or suggestive laboratory or imaging findings. Typical laboratory abnormalities include elevated liver transaminase levels, direct hyperbilirubinemia, and thrombocytopenia. Common findings on neuroimaging include periventricular calcifications, lenticulostriate vasculopathy, white matter disease, and ventriculomegaly. Definitive diagnosis of cCMV infection requires a positive PCR in urine, saliva, blood, or cerebrospinal fluid within the first 3 weeks after birth: a positive result beyond 3 weeks could reflect postnatal acquisition. Saliva is the preferred sample for PCR testing, having been shown to be greater than 95% sensitive for the identification of cCMV, but a positive result may require confirmation with testing of urine because of potential contamination of saliva with CMV in human milk. Additional considerations for testing in neonates may include screening by PCR for infants who fail the newborn hearing screen, are small for gestational age, or are born to mothers with human immunodeficiency virus infection or other immunocompromising conditions. Advocacy groups have recommended that universal CMV screening be included in state newborn screening panels.

A positive PCR result should prompt an evaluation of the infant with a complete blood cell count, liver function tests, and neuroimaging, as well as audiologic and ophthalmologic assessments. After evaluation, the infected newborn can be classified as having asymptomatic cCMV infection, asymptomatic cCMV infection with isolated SNHL, mildly symptomatic cCMV (1 or 2 isolated manifestations that are mild and transient), or moderately to severely symptomatic cCMV (multiple manifestations and/or central nervous system involvement). Neonates with moderately to severely symptomatic cCMV demonstrate improved audiologic and neurodevelopmental outcomes at 2 years of age when treated with oral valganciclovir or intravenous ganciclovir for 6 months. Significant neutropenia occurs in 20% of infants treated with valganciclovir and in 66% treated with ganciclovir; absolute neutrophil count as well as serum transaminase levels should be monitored over the course of treatment. Additional potential long-term risks of treatment include gonadal dysgenesis and carcinogenicity. In view of known toxicities, and with a lack of data suggesting benefit in infected neonates with mildly symptomatic disease or isolated SNHL, at this time treatment is not recommended for such infants. All patients with cCMV should have frequent audiologic assessments throughout early childhood.

Current control strategies focus most strongly on prevention of maternal infection. Effective measures involve meticulous hand hygiene, along with avoidance of the bodily secretions of young children. Health-care providers should be educated about cCMV and, in turn, provide education to pregnant women. Hopefully we can look forward to the introduction of an effective CMV vaccine, either as part of the routine childhood schedule or for adolescent girls and women of childbearing age. Approximately 50% efficacy has been achieved in phase II trials of recombinant glycoprotein B vaccines, and a phase III mRNA vaccine trial in women of childbearing age is presently being planned.

COMMENTS: Unfortunately, CMV is both ubiquitous and genetically diverse—a bad combination. After primary infection, viral shedding in a variety of bodily fluids can occur throughout life, making person-to-person transmission a persistent threat. Young children, before toilet training and with their proclivity for drooling, put their pregnant mothers and female child care providers at particular risk for infection, leading then to vertical transmission to fetuses and newborns—a vicious cycle. CMV can also be thought of as a sexually transmitted infection among adolescents and adults through contaminated seminal and cervical fluids. With most infections remaining asymptomatic but still harboring live virus in white blood cells and body tissues, transfusions and transplants (both organ and stem cell) pose a threat to their recipients. Although currently available antiviral agents can mitigate symptomatic disease, they do not eliminate the underlying infection, which remains lifelong, and thus the ongoing risk for transmission.

Our best hope, as has so often been the case with insidious infections, is for an effective vaccine. If we can develop one, it will, of course, be truly effective only if people take it!

–Henry M. Adam, MD
Associate Editor, *In Brief*