Human cytomegalovirus infection in pregnant women and neonates: A new risk factor for cardiovascular disease?

John A. Blaho,++

Virology Division. Molecular Diagnostic Laboratories, LLC 2439 Kuser Road, Hamilton, NJ 08690-3303. Financial support: This work was supported by MDL.

*Correspondence: John A. Blaho Virology Division MDL Company
+Present address: Simons Center for Systems Biology Institute for Advanced Study Princeton, NJ 08540 Email: blaho@ias.edu

Abstract

Human cytomegalovirus (HCMV) is a member of the herpes virus family which may cause significant morbidity in immunocompromised patients, including neonates. No vaccine exists for HCMV but appropriate hygienic precautions can limit the spread of the virus to mothers and, subsequently, neonates. Neonatal HCMV has been associated with congenital birth defects while HCMV infection stimulates the expression of cellular angiogenesis genes, as well as increasing production of cytokines and growth factors [8]. It now appears that HCMV infection induces the differentiation and migration of monocytes [9], which are likely the major cell type harboring reactivation of latent HCMV. These, and presumably other, modifications to the vasculature as a consequence of HCMV likely impact the pathophysiology of vascular disease. HCMV infection and high blood pressure. The direct mechanism through which viruses might cause pulmonary hypertension remains unknown. It is conceivable that the anti-viral inflammatory response against HCMV plays an important role in the process. In fact, inflammation-dependent hypertension has been validated in a mouse animal model system [10]. A recent analysis utilizing murine CMV (MCMV) in mice demonstrated that viral infection led to increased arterial blood pressure [11]. Coincident with MCMV replication was increased expression of proinflammatory cytokines. The significance of these studies is their implication that management of CMV infection may limit development of atherosclerosis and hypertension in humans.

Introduction

Human cytomegalovirus (HCMV) is a member of the Herpesvirideae family of large enveloped DNA viruses. There are eight herpesviruses that are known to infect and cause morbidity and mortality in humans. The definitive characteristic of the herpesvirus family is the ability of these viruses to cause both acute lytic infections, as well as long term persistent latent infections. Thus, once an individual has been infected by HCMV, they remain infected with the virus for the remainder of their life. Throughout the course of an infected individual’s life, the virus may “reactivate” to generate productively replicating virus particles, which may be spread to other, noninfected individuals. Since many HCMV infections are asymptomatic or “silent,” infected individuals may not know that they pose a risk for transmission to others. It is for this reason that asymptomatic HCMV infections in pregnant mothers pose a significant risk to fetuses and neonates. The consequence of such infections on the coronary heart health of children is the focus of this Commentary.

HCMV and vascular cell proliferation. One of the initial correlates of HCMV with vascular disease was the finding of increased HCMV-specific antibodies in atherosclerosis patients who required surgery compared to those who did not [1]. Subsequently, HCMV DNA was detected in atherosclerotic coronary arteries [2]. Perhaps most importantly, anti-HCMV ganciclovir therapy was shown to lower atherosclerosis following heart transplants [3]. It should be noted that these early associations were not universally accepted [4, 5]. Since that time, it has been realized that most clinical HCMV isolates replicate in cultured cells derived from the vasculature, including epithelial, endothelial, smooth muscle, and monocyte-derived macrophage cells [6, 7]. A recently developed rat heart transplant model provided data consistent with HCMV infection stimulating the expression of cellular angiogenesis genes, as well as increasing production of cytokines and growth factors [8]. It now appears that HCMV infection induces the differentiation and migration of monocytes [9], which are likely the major cell type harboring reactivation of latent HCMV. These, and presumably other, modifications to the vasculature as a consequence of HCMV likely impact the pathophysiology of vascular disease.

Mechanisms of transmission. HCMV infections are found in all socioeconomic groups throughout all geographic locations in the world. It has been estimated by the United States Centers for Disease Control (CDC) that between 50 and 80% of the adult population in the United States is seropositive for HCMV [13]. While seroprevalence increases with age, the majority of these infections occur prior to puberty. In most cases, transmission of HCMV occur person to person by close physical interaction, which involves contact with secretion and excretion of bodily fluids including saliva, blood, urine, tears, semen, vaginal fluid, and breast milk. Another source of HCMV transmission is receipt of solid organ or hematopoietic stem cell transplantation from an infected donor. HCMV is a member of the TORCHES group of pathogens that can cross the placenta so it also spreads by vertical transmission from mother to child.
HCMV infection during pregnancy. Most HCMV infections, including late-gestational in utero and neonatal, are subclinical. However, HCMV is the most common virus transmitted from infected pregnant mother to child. Approximately one-third of women who have a primary HCMV infection during pregnancy pass the virus on to the neonate [13]. Thus, approximately one in 150 children are born with congenital HCMV infections. Congenital HCMV infection is defined by detection of the virus in the newborn's urine, blood, or saliva within three weeks of birth. Children with congenital HCMV present with small body size, jaundice, petechiae, hypotonia, and hepatosplenomegaly. They may also be prone to lethargy and seizures. Women who are planning to become pregnant may receive an HCMV blood test, which detects the presence of immunoglobulin molecules directed against the virus. If the test is positive for HCMV, it is unlikely that the baby will be at risk for congenital HCMV. Seronegative mothers must take hygienic precautions (listed above).

HCMV and breastfeeding. HCMV may be transmitted through breast milk. The newborn population most at risk includes extremely immature (preterm) neonates. The rate of HCMV reactivation in the mother coincides with the seroprevalence of HCMV in the mother so maternal serology is important. Accordingly, the current recommendation of the American Academy of Pediatrics is for breastfeeding of both term and preterm infants [14].

Consequences of congenital HCMV in neonates. In the United States, between 1 and 4% of seronegative mothers get a primary HCMV infection during their pregnancy [13]. If this infection results in HCMV transmission to the unborn child in utero during the first trimester, it may lead to birth defects. The most common consequence is HCMV chronic infection. In extreme cases, there may be central nervous system / perceptual defects or ocular/auditory damage. Approximately one in 750 children in the United States are born with or develop permanent disabilities due to HCMV. This translates into approximately 8,000 children a year. Permanent birth defects associated with congenital HCMV include small head size, lack of coordination, mental disability, and lack of hearing and/or vision. In extreme cases, congenital HCMV may result in death of the neonate. At this time, no tracking exists for the correlation of heart disease development with congenital HCMV infection.

HCMV treatment and prevention. There is currently no vaccine available to prevent HCMV. Because the HCMV virus has evolved to possess an elaborate system of immune evasion strategies [15], current efforts to develop HCMV vaccines must focus on stimulating both the innate and adaptive immune system in order to be successful.

The antiviral treatment of choice for HCMV is the nucleoside analog ganciclovir and it is given to all transplant patients. While ganciclovir may prevent hearing loss in children, it may have side effects. Another nucleoside drug, cidofovir, is also available but is less prominent in use. Both of these drugs have been associated with the emergence to resistant viral strains. A new anti-HCMV drug, maribavir, is currently in clinical trials. Of interest are findings that an oral ganciclovir regimen reduces myocarditis in immune competent adults in certain cases [16]. The best way to prevent HCMV transmission is through behavior modification which emphasizes hygiene. Accordingly, women who are pregnant or who may become pregnant are recommended by the CDC to take the following precautions [13]: (i) wash hands often, especially after contact with saliva or diapers of young children, (ii) never kiss children below the age of six years of age on the mouth or cheek, and (ii) do not share food, drinks, or utensils with young children.

HCMV pathogenesis in adults. Primary HCMV infection in an immunocompetent individual is usually subclinical, rarely causing illness. However, large scale infection can cause an HCMV infectious mononucleosis that has a clinical presentation very similar to that caused by Epstein Barr virus. HCMV “mono” may involve fever, myalgia, lymphadenopathy, splenomegaly, and hepatomegaly [17]. Other rare symptoms of HCMV include tonsillolaryngitis, pneumonitis, myocardiitis, arthritis, ulcerative colitis, and meningitis. Transplant patients may also present with retinitis, esophagitis, and gastritis. HCMV infection in transplant patients also predisposes them to infection by other opportunistic pathogens. As noted above, recent evidence indicates that HCMV infection is also a likely risk factor for heart disease in transplant patients.

HCMV infection in immunocompromised individuals. While neonates and newborns may be considered immunocompromised individuals, HCMV remains the major pathogen of risk for solid organ transplant patients. More than half of all transplant cases show evidence of HCMV infection. The associated morbidity of these infections is a major cause of rejection. For this reason, anti-HCMV drugs must be administered throughout solid organ transplants. While HCMV infection of solid organ transplant recipients are usually acute primary infections, CMV infection following stem cell transplants are frequently due to reactivation of latent virus.

HCMV is a high risk pathogen for individuals who have an impaired adaptive immune response, which is why neonates and newborns are at such high risk. Prior to the establishment of highly active anti-retroviral therapy (HAART), HCMV infections in human immunodeficiency virus (HIV) positive patients were a serious opportunistic infection. At that time, retinitis caused by HCMV was the primary cause of blindness in AIDS patients. Today, patients with chronic HIV infection may develop pulmonary arterial hypertension [18], though the impact of HAART on its incidence remains controversial. The role that HCMV might play in this process is unknown at this time. However, the progressive loss of CD4+ T cells renders these individuals at risk for opportunistic infections, such as new or reactivating HCMV.

Perspective. HCMV is a major human pathogen which places both the mother and child at risk. Once infected, the individual remains infected for life and may spread the virus to others. Although effective antiviral drugs exist for HCMV, the problem is that most infections are asymptomatic. Existing research efforts are focusing on the development of an HCMV vaccine. Currently, the best way to prevent HCMV infection is to limit exposure to bodily fluids. Importantly, HCMV is associated with congenital birth defects. Recent evidence supports a molecular basis for the role of HCMV in vascular cell proliferation and arterial hypertension. It may now be the time to consider coronary heart disease as another potential congenital consequence of neonatal HCMV infection.


