

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

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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 of healthy adults may cause a mild mononucleosis. Recent evidence suggests that HCMV infection may be associated with vascular cell proliferation and increased arterial blood pressure. This commentary questions whether neonatal HCMV infection is a new risk factor for heart disease.

Introduction

Human cytomegalovirus (HCMV) is a member of the Herpesviridae 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.

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.

Cardiovascular disease risk in children. Since 1988, the incidence of hypertension among persons twenty years of age and older has been steadily increasing. According to the 2003-2004 National Health and Nutrition Examination Survey, obesity plays a major role. Approximately seventeen percent of individuals aged between two and nineteen years of age are overweight. In light of this growing childhood obesity epidemic, it may be time now to consider the implications of congenital HCMV in the development of cardiovascular disease. Neonatal arterial thrombosis due to severe congenital HCMV infection has been reported [12]. Thus, HCMV exposure during gestation may turn out to be an important additional cardiovascular risk factor.

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 seroprevalance 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 regime 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 tonsillopharyngitis, pneumonitis, myocarditis, 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.

Referencias

1. Adam E, Melnick JL, Probstfield JL, Petrie BL, Burek J, Bailey KR, McCollum CH, DeBakey ME (1987) High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis. *Lancet* 2:291-293.
2. Wu TC, Hruban RH, Ambinder RF, Pizzorno M, Cameron DE, et al. (1992) Demonstration of cytomegalovirus nucleic acids in the coronary arteries of transplanted hearts. *Am J Pathol* 140:739-747.
3. Valantine HA, Gao SZ, Menon SG, Renlund DG, et al. (1999) Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis: a post hoc analysis of a randomized, placebo-controlled study. *Circulation* 100:61-66.
4. Daus H, Ozbek C, Saage D, Scheller B, Schieffer H, et al. (1998) Lack of evidence for a pathogenic role of *Chlamydia pneumoniae* and cytomegalovirus infection in coronary atheroma formation. *Cardiology* 90:83-88.
5. Adler SP, Hur JK, Wang JB, Vetrovec GW (1998) Prior infection with cytomegalovirus is not a major risk factor for angiographically demonstrated coronary artery atherosclerosis. *J Infect Dis* 177:209-212.
6. Gerna G, Zipeto D, Percivalle E, Parea M, Revello MG, et al. (1992) Human cytomegalovirus infection of the major leukocyte subpopulations and evidence for initial viral replication in polymorphonuclear leukocytes from viremic patients. *J Infect Dis* 166:1236-1244.
7. Ryckman BJ, Rainish BL, Chase MC, Borton JA, Nelson JA, et al. (2008) Characterization of the human cytomegalovirus gH/gL/UL128-131 complex that mediates entry into epithelial and endothelial cells. *J Virol* 82:60-70.
8. Streblov DN, van Cleef KW, Kreklywich CN, Meyer C, Smith P, et al. (2007) Rat cytomegalovirus gene expression in cardiac allograft recipients is tissue specific and does not parallel the profiles detected in vitro. *J Virol* 81:3816-3826.
9. Smith MS, Bentz GL, Alexander JS, Yurochko AD (2004) Human cytomegalovirus induces monocyte differentiation and migration as a strategy for dissemination and persistence. *J Virol* 78:4444-4453.
10. Daley E, Emson C, Guignabert C, de Waal Malefyt R, Louten J, et al. (2008) Pulmonary arterial remodeling induced by a Th2 immune response. *J Exp Med* 205:361-372.
11. Cheng J, Ke Q, Jin Z, Wang H, Kocher O, et al. (2009) Cytomegalovirus infection causes an increase of arterial blood pressure. *PLoS Pathog* 5:e1000427.
12. Lanari M, Lazzarotto T, Papa I, Venturi V, Bronzetti G, et al. (2001) Neonatal aortic arch thrombosis as a result of congenital cytomegalovirus infection. *Pediatrics* 108:E114.
13. (2008) Knowledge and practices of obstetricians and gynecologists regarding cytomegalovirus infection during pregnancy--United States, 2007. *MMWR Morb Mortal Wkly Rep* 57:65-68.
14. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, et al. (2005) Breastfeeding and the use of human milk. *Pediatrics* 115:496-506.
15. Tortorella D, Gewurz BE, Furman MH, Schust DJ, Ploegh HL (2000) Viral subversion of the immune system. *Annu Rev Immunol* 18:861-926.
16. Fernandez-Ruiz M, Munoz-Codoceo C, Lopez-Medrano F, Fare-Garcia R, Carbonell-Porras A, et al. (2008) Cytomegalovirus myopericarditis and hepatitis in an immunocompetent adult: successful treatment with oral valganciclovir. *Intern Med* 47:1963-1966.
17. Gandhi MK, Khanna R (2004) Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. *Lancet Infect Dis* 4:725-738.
18. Sitbon O, Lascoux-Combe C, Delfraissy JF, Yeni PG, Raffi F, et al. (2008) Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *Am J Respir Crit Care Med* 177:108-113.

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