

Cytomegalovirus in Children

Lerine Bahy El-Din

Pediatrics Department, Faculty of Medicine, Ain Shams University

Corresponding Author:

Lerine Bahy El-Din

E-mail: kswidan@yahoo.com

Cytomegalovirus, or CMV, is a common virus that infects most people worldwide. CMV infection is usually harmless and rarely causes illness. A healthy immune system can hold the virus in check. However, if a person's immune system is seriously weakened in any way, the virus can become active and cause CMV disease.¹

Cytomegalovirus (CMV) is a member of Betaherpesvirinae in the subfamily Herpesviridae. The other Betaherpesvirinae species include human herpesvirus (HHV)-6 and HHV-7, which share common clinical characteristics with CMV.²

CMV is a lytic virus that causes a cytopathic effect *in vitro* and *in vivo*. The pathologic hallmark of CMV infection is an enlarged cell with viral inclusion bodies. Cells that exhibit cytomegaly are also seen in infections caused by other Betaherpesvirinae. The microscopic description given to these cells is most commonly an «owl's eye». Although considered diagnostic, such histological findings may be minimal or absent in infected organs.²

Little is known about the molecular mechanisms responsible for the pathogenesis of tissue damage caused by CMV, particularly for congenital CMV infection. Although the CNS is the ma-

ior target organ for tissue damage in the developing fetus, culturing CMV from the cerebrospinal fluid of symptomatic congenitally infected infants is surprisingly difficult. Because CMV can infect endothelial cells, some authors have postulated that a viral angitis may be responsible for perfusion failure of developing brain with resultant maldevelopment. Others have postulated a direct teratogenic effect of CMV on the developing fetus. Observation of CMV-induced alternations in the cell cycle and CMV-induced damage to chromosomes supports this speculation; however, this hypothesis has been difficult to verify experimentally.³

Immunity to CMV is complex and involves humoral and cell-mediated responses. Several CMV gene products are of particular importance in CMV immunity. The outer envelope of the virus, which is derived from the host cell nuclear membrane, contains multiple virally encoded glycoproteins. Glycoprotein B (gB) and glycoprotein H (gH) appear to be the major determinants of protective humoral immunity. Antibody to these proteins is capable of neutralizing virus, and gB and gH are targets of investigational CMV subunit vaccines; however, although humoral responses are important in control of severe disease, they are clearly inadequate in preventing transplacental infection, which

can occur even in women who are CMV-seropositive. The generation of cytotoxic T-cell (CTL) responses against CMV may be a more important host immune response in control of infection. In general, these CTLs involve major histocompatibility complex (MHC) class I restricted CD8+ responses.^{3,4}

FREQUENCY

In developing countries, most children acquire CMV infection early in life, with adult seroprevalence approaching 100% by early adulthood. In contrast, in developed countries, the seroprevalence of CMV approximates 50% in young adults of middle-upper socioeconomic status. This observation has important implications for congenital CMV epidemiology because CMV-seronegative women of childbearing age are at major risk of giving birth to infants with symptomatic congenital infection if primary infection is acquired during pregnancy.⁵

MODES OF INFECTION

Infectious CMV may be shed in the bodily fluids of any previously infected person, and thus may be found in urine, saliva, blood, tears, semen, and breast milk. The shedding of virus may take place intermittently, without any detectable signs, and without causing symptoms.⁶

The route of congenital infection is presumed to be transplacental. CMV also may be transmitted perinatally, both by aspiration of cervicovaginal secretions in the birth canal and by breastfeeding. Infants who are not infected congenitally or perinatally with CMV are at high risk to acquire infection in day

care centers. In adulthood, sexual activity is probably the most important route of acquisition of CMV, other important routes of transmission include blood transfusion and solid organ transplantation.⁷

Spread of CMV is from person to person. Infection requires close contact with a person excreting the virus in their saliva, urine, or other bodily fluids. CMV can be sexually transmitted. It can also be transmitted via breast milk, transplanted organs and, rarely, blood transfusions. Although the virus is not highly contagious, it has been shown to spread in households and among young children in day care centers.⁸

Transmission of the virus is often preventable because it is most often transmitted through infected bodily fluids that come in contact with hands and then are absorbed through the nose or mouth of a susceptible person. Therefore, care should be taken when handling children and items like diapers. Simple hand washing with soap and water is effective in removing the virus from the hands.

CMV is mainly a problem for certain high-risk groups, including:

- unborn babies whose mothers become infected with CMV during the pregnancy.
- children or adults whose immune systems have been weakened by disease or drug treatment, such as organ transplant recipients or people infected with HIV.^{8,9}

The likelihood of congenital infection and the extent of disease in the newborn depend on maternal immune status. If

primary maternal infection occurs during pregnancy, the average rate of transmission to the fetus is 40%; most of these infants have clinical disease at birth. With recurrent maternal infection (ie, CMV infection that occurs in the context of preconceptual immunity), the risk of transmission to the fetus is lower, ranging from 0.5-1.5%; most of these infants appear normal at birth (ie, silent infection). Hence, congenital infection may be classified as symptomatic or asymptomatic in nature.¹⁰

CLINICALLY

1- Congenital CMV infection:

Symptomatic congenital CMV: Approximately 10% of congenitally infected infants have clinical evidence of disease at birth. The most severe form of congenital CMV infection is referred to as cytomegalic inclusion disease (CID). CID almost always occurs in women who have primary CMV infection during pregnancy, although rare cases are described in women with preexisting immunity who presumably have reactivation of infection during pregnancy. CID is characterized by intrauterine growth retardation, hepatosplenomegaly, hematological abnormalities (Particularly thrombocytopenia), and a variety of cutaneous manifestations, including petechiae and purpura (ie, blueberry muffin baby). However, the most significant manifestations of CID are those involving the central nervous system. Microcephaly, ventriculomegaly, cerebral atrophy, chorioretinitis, and sensorineural hearing loss are the most common neurological consequences of CID.^{11,12}

Asymptomatic congenital CMV: Most infants with congenital CMV infection are born to women who have preexist-

ing immunity to CMV. These infants appear clinically normal at birth; however, even though infants with congenital CMV infection appear well, they may have subtle growth retardation compared to uninfected infants. Although asymptomatic at birth, these infants, nevertheless, are at risk for neurodevelopmental sequelae.¹²

2- Acquired CMV infection:

Perinatal infection: Most infections are asymptomatic. Some infants who acquire CMV infection perinatally may have signs and symptoms of disease, including lymphadenopathy, hepatitis, and pneumonitis, which may be severe on occasion. Interestingly, these infections do not appear to carry any risk of neurological or neurodevelopmental sequelae.¹³

CMV mononucleosis: When first infected (Primary CMV), some adults may have symptoms similar to mononucleosis. Signs and symptoms of primary CMV include: Fatigue, Weakness, Night sweats, Prolonged fever, Swollen glands or sore throat, or both, Loss of appetite or weight loss or both, Muscle aches or joint pain or stiffness, General feeling of illness or discomfort. Rarer manifestations of CMV in immunocompetent individuals include Guillain-Barré syndrome, meningoencephalitis, pericarditis, myocarditis, thrombocytopenia, and hemolytic anemia. Rubelliform or maculopapular rashes are observed with and without the administration of ampicillin. Gastrointestinal ulceration may be found in acute CMV infection in immunocompetent patients, although this finding is much more likely in immunocompromised patients.¹⁴

Transfusion-acquired CMV infection: Posttransfusion CMV infection has a

presentation similar to that of CMV mononucleosis. Incubation periods range from 20-60 days.¹⁴

CMV infections in immunocompromised children: CMV causes a variety of clinical syndromes in immunocompromised patients. Disease manifestations vary in severity depending on the degree of host immunosuppression. Infection may occur because of reactivation of latent viral infection or may be newly acquired via organ or bone marrow transplant from a seropositive donor. Infections may also be mixed in nature, with donor and recipient isolates both present. Viral dissemination leads to multiple organ system involvement, with the most important clinical manifestations consisting of pneumonitis, gastrointestinal disease, and retinitis.¹⁵

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for CMV infection depends on the disease category, age of the patient, and epidemiologic considerations. In the neonate with congenital infection, the differential diagnosis includes any of the TORCH agents. Congenital toxoplasmosis may mimic congenital CMV infection but is much less common in the United States; however, in parts of Europe, particularly France and Belgium, congenital toxoplasmosis is a common and significant problem. In contrast to congenital CMV, the intracranial calcifications observed in congenital toxoplasmosis tend to be scattered diffusely throughout the brain and not in the classic periventricular distribution of CMV, which may be an important clue. Other congenital infections to be considered include lymphocytic choriomeningitis virus (LCMV) infection, HSV infec-

tion, syphilis, enteroviral disease, HIV infection, and rubella.¹⁶

In older patients, differentiating CMV infection from EBV infection may be clinically difficult. EBV is a more common cause of mononucleosis syndrome than CMV, and the heterophile antibody test (ie, Monospot) is generally positive, allowing for ready differentiation of the 2 diseases.¹⁷

In immunocompromised patients, disease syndromes that are caused by CMV may be difficult to differentiate from other opportunistic infections. For example, CMV pneumonitis following bone marrow transplantation must be differentiated from *Pneumocystis carinii* infection and other viral infections, such as adenovirus and human herpesvirus 6 (HHV-6) infection. Appropriate diagnostic specimens obtained by studies such as bronchoalveolar lavage are indicated.¹⁷

DIAGNOSIS

Serologic Testing:

The enzyme-linked immunosorbent assay (Or ELISA) is the most commonly available serologic test for measuring antibody to CMV. The result can be used to determine if acute infection, prior infection, or passively acquired maternal antibody in an infant is present. Other tests include various fluorescence assays, indirect hemagglutination, and latex agglutination.¹⁸

An ELISA technique for CMV-specific IgM is available, but may give false-positive results unless steps are taken to remove rheumatoid factor or most of the IgG antibody before the serum sample is tested. Because CMV-specif-

ic IgM may be produced in low levels in reactivated CMV infection, its presence is not always indicative of primary infection. If serologic tests detect a positive or high titer of IgG, this result should not automatically be interpreted to mean that active CMV infection is present. However, if antibody tests of paired serum samples show a fourfold rise in IgG antibody and a significant level of IgM antibody, meaning equal to at least 30% of the IgG value, or virus is cultured from a urine or throat specimen, the findings indicate that an active CMV infection is present.^{18,19}

Virus Isolation:

Urine, saliva, blood and biopsy samples can be used for virus isolation, cell culture: the most important diagnostic study in the evaluation of suspected CMV disease. The specimen is inoculated onto human cells (Usually human foreskin fibroblasts). CMV produces a typical focal cytopathic effect. Shell vial assay: This technique can be processed in 24 to 48 hours, unlike the conventional culture; the shell-vial assay technique does not depend upon the development of a cytopathic effect in tissue culture. Instead, a fluorescence tagged monoclonal antibody is used to detect a CMV antigen that is expressed early in viral replication. Tissue immunofluorescence: Infected lung and liver cells may be stained by specific anti-CMV antibodies. CMV antigenaemia test: Detection of pp65, a structural protein expressed on the surface of infected polymorphonuclear leucocytes. The number of infected leucocytes correlates with the severity of infection, very rapid and used especially in the monitoring of transplant recipients. Detection of CMV DNA by PCR: The use of PCR in the diagnosis of CMV in-

fection had been widely studied. PCR offers the advantages of being rapid and sensitive. However, its inherent sensitivity poses a problem since latent CMV genomes, which are present in practically all seropositive individuals, may be detected.^{20,21}

Imaging Studies:

The diagnosis of CMV pneumonia can be suggested by chest radiograph findings, but these findings cannot be used to differentiate between other common causes for pneumonia in the immunocompromised host. CT scan is more sensitive for the identification of infiltrate. It has been valuable in patients presenting with hypoxia and no infiltrate visible on chest roentgenogram. The most important study in the diagnostic evaluation of the congenitally infected infant with CMV is a CT scan of the head. A CT scan of the head is required for infants with microcephaly or when congenital CMV infection is suspected because abnormalities in this study, particularly the presence of calcifications, have a strong positive predictive value and can aid in identifying children who need ongoing neurodevelopmental evaluation and therapy. Infants with congenital CMV infection may also require abdominal imaging studies (eg, ultrasound, CT scan) for documentation and monitoring of organomegaly.²¹

HISTOLOGICAL FINDINGS

The hallmark of CMV infection is the finding of intranuclear inclusions consistent with herpesvirus infection. CMV infection may be confirmed using in situ hybridization or direct or indirect staining of intranuclear inclusions using CMV-specific antibodies linked

to an indicator system (eg, horseradish peroxidase, fluorescein). However, viral culture, serology, antigenemia, and nucleic acid detection systems (eg, PCR) generally have much better sensitivity for the diagnosis of CMV-associated diseases.²¹

TREATMENT

No treatment is generally necessary for CMV infection in the healthy individual since the majority of infections resolve on their own. Desirable characteristics of CMV drugs are: high potency, orally bioavailable, safe for long-term use, no drug interactions, prevent indirect effects, broad-spectrum anti-herpes (Cost benefit). Nucleosides are the only true antiviral agents active against CMV, Immunoglobulins may provide some antiviral effect, particularly in combination with these agents, they share a common molecular target, namely, the viral DNA polymerase. Ganciclovir (GCV) and foscarnet are antiviral medications that have been used to treat patients with weak immune systems who develop a serious illness from CMV (Including retinitis and pneumonitis). Research is still being done to try to find useful drugs to treat newborn babies suffering from congenital infection with CMV. Antiviral drugs are not used to treat CMV infection in otherwise healthy patients because the drugs have significant side effects that outweigh their benefits.²²

GCV is commonly used as preemptive therapy in transplant recipients at high risk of developing disease (e.g., a CMV seronegative recipient of an organ transplant from a CMV-seropositive donor), and as prophylactic in others (CMV seropositive recipient of an or-

gan transplant from a CMV-seropositive donor).²²

Relatively little information exists concerning the use of GCV in the setting of congenital CMV infection. Some studies show that intravenous GCV led to improvement or stabilization of hearing in 6-month-old infants. Case reports have suggested the efficacy of GCV for acutely ill neonates with life-threatening CMV disease (eg, pneumonia, retinitis, evidence of CNS involvement). Ganciclovir, administered in a 6mg/kg dose intravenously as a 1-hour infusion every 12 hours for up to 6 weeks. It is unknown whether this early and intensive administration of ganciclovir will hasten resolution of acute disease?, beneficially influence growth and development?, decrease auditory and visual impairments?, or improve intellectual outcome in these infants?.²³

It is recommended that ganciclovir not be routinely used to treat infants with congenital CMV disease. Adverse effects of ganciclovir include leukopenia, thrombocytopenia, anemia, infusion site reactions, renal toxicity, hepatocellular dysfunction, hemolysis, nausea, diarrhea and photosensitization. Oral ganciclovir may be useful for maintenance therapy in patients treated with intravenous ganciclovir who are identified to be at increased risk for recurrent CMV.²⁴

The long term outcome of infants with CMV hepatitis is unpredictable. Central pontine myelinolysis secondary to CMV hepatitis can occur, some patients have persistent liver injury despite ganciclovir therapy and ganciclovir therapy did not prevent chronic liver disease.²⁴

Less experience with the use of foscarnet for treatment of CMV disease in organ transplantation and congenital infections, it does not need to be phosphorylated. It is given in a dose of 60 mg/kg three times daily IV 14-21d. Its main side effects are nephrotoxicity, anemia, electrolyte imbalance, nausea, vomiting, and seizures.^{24,25}

Random donor IVIG appears to be equal in efficacy to CMV hyper immunoglobulin suggests that the benefit may be derived from an immunomodulatory effect unrelated to virus neutralization.²⁵

PREVENTION

For those who have close contact with children, especially pregnant women or women who might become pregnant, hand washing is effective at reducing the risk of infection from exposure to CMV. Not sharing eating utensils with young children and avoiding kissing or intimate contact with CMV-positive individuals is also important.²⁶

A mother who has CMV infection shouldn't stop breastfeeding, as the benefits of breastfeeding are believed to outweigh the risks of passing CMV to the infant, and the infant is unlikely to develop any symptoms if infected.²⁶

For organ-transplant patients who are at risk of getting CMV from a transplanted organ, preventive therapies are available. Blood banks have certain screening and processing procedures that help to prevent CMV from being passed in blood products.²⁷

IMMUNIZATION

The major target population for a CMV vaccine is women of childbearing age. A vaccine can also be useful in controlling CMV disease in organ transplant recipients. Three forms of the vaccine are under trial, a live attenuated vaccine, the Towne vaccine, showed promise for prevention of CMV disease in studies involving renal transplant recipients reported in the 1980s, recombinant chimeric viruses that represent genetic hybrids between Towne virus and a low-passage clinical isolate, the Toledo strain and the subunit vaccine of the major immunogenic CMV envelope protein, gB.²⁸

EVALUATION OF THE NEONATE WITH CMV

Clinical: Height, weight, and head circumference; measure liver/spleen size; ophthalmologic examination.

Laboratory: Complete blood count and peripheral smear; platelet count; liver transaminase levels; bilirubin levels (Direct and indirect); urine CMV culture; cerebrospinal fluid for cell count, protein and glucose levels, CMV DNA if available.

Others: Unenhanced CT scan of brain; hearing assessment by brain stem-evoked responses.^{29,30}

REFERENCES

1. Griffiths PD. Cytomegalovirus. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths P, Schoub B, editors. Prin-

- ciples and practice of clinical virology. 5th ed.: Wiley; 2004: 85-122.
2. Ryan KJ, Ray CG. Sherris medical microbiology. 4th ed.: McGraw-Hill; 2004.
 3. Bennekov T, Spector D, Langhoff E. Induction of immunity against human cytomegalovirus. Mt.Sinai J. Med. 2004; 71 (2): 86-93.
 4. Adler SP. Congenital cytomegalovirus screening. *Pediatr.Infect.Dis. J.* 2005; 24 (12): 1105-6.
 5. Onorato IM, Morens DM, Martone WJ, Stansfield SK. Epidemiology of cytomegaloviral infections: Recommendations for prevention and control. *Rev. Infect. Dis.* 1985; 7 (4): 479-97.
 6. Adler SP. Cytomegalovirus and child day care: Risk factors for maternal infection. *Pediatr.Infect. Dis.J.* 1991; 10 (8): 590-4.
 7. Brown HL, Abernathy MP. Cytomegalovirus infection. *Semin. Perinatol.* 1998; 22 (4): 260-6.
 8. Alford CA, Stagno S, Pass RF, Britt WJ. Congenital and perinatal cytomegalovirus infections. *Rev. Infect. Dis.* 1990; 12 Suppl 7: S745-53.
 9. Vancikova Z, Dvorak P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals--a review. *Curr.Drug Targets Immune Endocr Metabol. Disord.* 2001; 1 (2): 179-87.
 10. Fowler KB, Pass RF. Risk factors for congenital cytomegalovirus infection in the offspring of young women: Exposure to young children and recent onset of sexual activity. *Pediatrics* 2006;118 (2): e286-92.
 11. Cannon MJ, Pellett PE. Risk of congenital cytomegalovirus infection. *Clin. Infect.Dis.* 2005 1; 40 (11): 1701, 2; author reply 1702-3.
 12. Ross DS, Dollard SC, Victor M, Sumartojo E, Cannon MJ. The epidemiology and prevention of congenital cytomegalovirus infection and disease: Activities of the Centers for Disease Control and Prevention Workgroup. *J. Womens Health. (Larchmt)* 2006; 15 (3): 224-9.
 13. Samileh N, Ahmad S, Mohammad F, Framarz M, Azardokht T, Jomeht E. Role of cytomegalovirus in sensorineural hearing loss of children: A case -control study Tehran, Iran. *Int. J. Pediatr. Otorhinolaryngol.* 2008; 72 (2): 203-8.
 14. Arnar DO, Gudmundsson G, Theodors A, Valtysson G, Sigfusson A, Jonasson JG. Primary cytomegalovirus infection and gastric ulcers in normal host. *Dig. Dis. Sci.* 1991; 36 (1): 108-11.
 15. Zanghellini F, Boppana SB, Emery VC, Griffiths PD, Pass RF. Asymptomatic primary cytomegalovirus infection: Virologic and immunologic features. *J. Infect. Dis.* 1999; 180 (3): 702-7.
 16. Yow MD, Demmler GJ. Congenital cytomegalovirus disease--20 years is long enough. *N. Engl. J. Med.* 1992 5; 326 (10): 702-3.
 17. Fowler KB, Stagno S, Pass RF. Maternal age and congenital cytomegalovirus infection: Screening of two diverse

- newborn populations, 1980-1990. *J. Infect. Dis.* 1993; 168 (3): 552-6.
18. Sharma A, Rasul ES, Hazarika NK. A serological study of cytomegalovirus infection in pregnant and non-pregnant women at Gauhati Medical College and Hospital. *J. Indian Med. Assoc.* 2007; 105 (6): 320, 322-3.
19. Noyola DE, Demmler GJ, Williamson WD, Griesser C, Sellers S, Llorente A, et al. Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. *Congenital CMV Longitudinal Study Group. Pediatr.Infect. Dis. J.* 2000; 19 (6): 505-10.
20. Kearns AM, Turner AJ, Eltringham GJ, Freeman R. Rapid detection and quantification of CMV DNA in urine using LightCycler-based real-time PCR. *J. Clin.Virol.* 2002; 24 (1-2): 131-4.
21. Mattes FM, McLaughlin JE, Emery VC, Clark DA, Griffiths PD. Histopathological detection of owl's eye inclusions is still specific for cytomegalovirus in the era of human herpesviruses 6 and 7. *J. Clin. Pathol.* 2000; 53 (8): 612-4.
22. Noble S, Faulds D. Ganciclovir. An update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 1998; 56 (1): 115-46.
23. Bueno J, Ramil C, Green M. Current management strategies for the prevention and treatment of cytomegalovirus infection in pediatric transplant recipients. *Paediatr.Drugs* 2002; 4 (5): 279-90.
24. Michaels MG, Greenberg DP, Sabo DL, Wald ER. Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr.Infect. Dis. J.* 2003; 22 (6): 504-9.
25. Kerrey BT, Morrow A, Geraghty S, Huey N, Sapsford A, Schleiss MR. Breast milk as a source for acquisition of cytomegalovirus (HCMV) in a premature infant with sepsis syndrome: Detection by real-time PCR. *J. Clin. Virol.* 2006; 35 (3): 313-6.
26. Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. *BMC Public Health* 2005; 5:70.
27. Ahsan N, Holman MJ, Yang HC. Efficacy of oral ganciclovir in prevention of cytomegalovirus infection in post-kidney transplant patients. *Clin. Transplant.* 1997; 11 (6): 633-9.
28. Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N. Engl. J. Med.* 2005 29; 353 (13): 1350-62.
29. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus among pregnant women. *J. Pediatr.* 2004; 145 (4): 485-91.
30. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J. Pediatr.* 1997; 130 (4): 624-30.
-