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Human Cytomegalovirus Infection: Biological Features, Transmission, Symptoms, Diagnosis, and Treatment

Şule Gökçe

Abstract

Human cytomegalovirus (CMV), a member of the human herpesviruses, is a deoxyribonucleic acid virus that is ubiquitous in the world. After primary infection, CMV develops a latent state; however, when the defense of the immune system decreases in a host, it can reactivate. Human cytomegalovirus infections are acquired via several ways. CMV is spread through contact with infected bodily fluids in humans, whereas it occurs in pregnant women through close contact with young children or through sexual transmission. The clinical manifestations consist of non-specific symptoms or clinical findings. However, the patients with acute CMV infections are generally asymptomatic. Congenital CMV infection (present at birth) occurs via intrauterine transmission of the virus that is thought to be transferred to the developing fetus. The common clinical manifestations of congenital CMV infection are sensorineural hearing loss, petechiae, jaundice at birth, and hepatosplenomegaly. The vast majority of healthy children and adolescents infected with CMV infections are most often asymptomatic. Treatment is recommended to initiate to the infants who have a symptomatic infection or primary immunodeficiency or asymptomatic infection with an isolated hearing loss. The diagnosis of congenital CMV infections should be considered when it is detected in the newborns with signs and symptoms consistent with congenital CMV disease or with abnormal neuroimaging consistent with CMV or newborns who have documented sensorineural hearing loss.

Keywords: human cytomegalovirus, transmission, symptoms, diagnosis

1. Introduction

Human cytomegalovirus (CMV), an infectious agent that is ubiquitous in the world population, is a member of human herpesvirus family including viruses such as Epstein-Barr virus, herpes simplex virus, and varicella zoster. CMV is the largest virus of the herpes family with a size of 190 nm. The structure of the virus includes a complex envelope composed of host cell-derived membrane studded and an icosahedral capsid that contains the virion DNA. The tegument layer which describes an amorphous area between the envelope and the capsid induces strong adaptive immune responses including CMV-specific CD8⁺ cytotoxic T lymphocytes that are believed to

play a fundamental role in controlling CMV replication in the infected host. Humans are the only source of cytomegalovirus, and it might infect all races, ages, and genders.

Human cytomegalovirus, an opportunistic pathogen, is transmitted through solid organ/bone transplantation, placental pathway, sexual intercourse, blood transfusion, and in close contact with virus-spreading people. Similar to other herpesviruses, it leads to primary infection, secondary infection, latent infection, and reactivation or reinfection. In immunocompromised patients, CMV is responsible for serious clinical symptoms. After primary infection, the viral genome forms an episomal circular form in myeloid progenitors and endothelial cells. Via TNF-alpha and type II interferon (IFN), latent CMV alter to active CMV and migrate to inflamed tissue where they further propagate during an inflammatory process and a context of immune activation. CMV is a viral agent that also causes intrauterine infections and brings about deafness and neurological anomalies in newborns. Cytomegalovirus has been associated with variable seroprevalence from 45 to 100% in women of reproductive age and is never cleared from the host [1]. In immunocompetent adults, primary CMV infections are usually asymptomatic. Less commonly, fever, lymphadenopathy, and mononucleosis-like syndrome coexist with peripheral lymphocytosis. When people with impaired immune function are not treated, it can lead to infections with high mortality [2].

2. Epidemiology

Human cytomegalovirus infections are acquired via several ways. CMV is generally transmitted by infected fluids (e.g., saliva, breast milk, blood products) contact at home and nursery schools as community exposure. It is also thought that the contaminated urine contact might be a role of cytomegalovirus transmission [3]. Among the postnatal contaminations, breastfeeding is the most common course of CMV infection in young infants particularly in populations with high CMV seroprevalence and high rates of breastfeeding from seropositive women during the first 6 months of breastfeeding, peaking at 4–8 weeks after delivery, but the risk continues for the duration of breastfeeding. Even though it is thought that a local reactivation in the mammary glands of the mothers with latent CMV infection can cause the transmission to baby, but the transmission mechanism has not been clearly defined yet [4]. As a reservoir of virus, these infants excrete virus in the saliva and urine for prolonged periods to other infants, children, and adults. The preschool children with CMV can disseminate through stool, and they might infect their parents and teachers in baby care centers. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. Due to the fact that the virus is present in seminal and cervical fluids, it can also be transmitted by sexual way.

Congenital CMV infection (present at birth) occurs via intrauterine transmission of the virus that is thought to be transferred to the developing fetus in approximately 30% of women undergoing primary infection during pregnancy or by reactivation in women previously immune for CMV rate on the order of 1–2% (vertical road). In the USA, Canada, Western Europe, and Australia, it is a common infection that is estimated to occur in about 5–7 per 1000 live births [5]. Rates as the highest with 2% in Asia and Africa have been described. Congenital CMV infection contributes to permanent disabilities such as hearing loss, vision loss, cerebral palsy, and/or cognitive impairment in children. Approximately 90% of newborn with congenital CMV are asymptomatic; however, the newborns are also at risk for CMV-associated disabilities [6].

Nosocomial infections with CMV emerge from exposure to blood products containing CMV. Transfusion-acquired CMV infections often caused symptomatic

illness including hepatitis and thrombocytopenia on children and adults. Fatal infections might be developed in newborns who are being born from women without immunity of CMV due to lacking antibodies of CMV. Severe infection can also present in immunocompromised patients who received blood with CMV. Recently, using blood products from CMV-seronegative donors, the incidence of transfusion-associated CMV infections has greatly decreased. Infections arising from CMV transferred in the allograft are major causes of morbidity in the early and late period after transplantation. Even if the antiviral therapy is applied, CMV infection causes long-term graft dysfunction and graft loss, particularly in cardiac and lung transplant recipients [7].

3. Clinical manifestations

The clinical manifestations consist of non-specific symptoms or clinical findings. However, the patients with acute CMV infections are generally asymptomatic. During the intrauterine period, babies infected with CMV usually do not expose symptoms at birth. However, 10–15% of them exhibit symptoms and become symptomatic at a later stage of their infancy. The common clinical manifestations of congenital CMV infection are sensorineural hearing loss, petechiae, jaundice at birth, hepatosplenomegaly, small size for gestational age, microcephaly, lethargy and/or hypotonia, poor suck, chorioretinitis, seizures, hemolytic anemia, and pneumonia [8]. The sensorineural hearing loss may be detectable at birth; however, approximately 30% of the cases have delayed onset. **Table 1** shows clinical manifestations, treatment, and outcome of congenital CMV infections. Congenital CMV associated with hearing loss is bilateral in 71% of children. Eye examination of symptomatic congenital CMV includes chorioretinitis that is the most common ocular abnormality, retinal scars, optic atrophy, central vision loss, and strabismus. The endocrinologic manifestations consist of Graves' disease and diabetes insipidus and renal disease, such as nephrotic syndrome. Congenital CMV infections are the leading cause of other long-term neurodevelopmental disabilities and can also affect other organ systems such as gastrointestinal system including Menetrier disease. Ascites, myocarditis, cardiomyopathy, ventricular trabeculations, and enterocolitis are also seen among manifestations of the congenital CMV in symptomatic neonates [9]. Despite the fact that the overall mortality rate among infants with congenital CMV infection is approximately 4–8% within the first year of life, congenital CMV infection might be associated with mortality in premature infants and infants with primary immune disorders of T cells or natural killer cells. Rarely, many infants without underlying disease

	Clinical manifestations	Treatment	Outcome
Congenital CMV infections	At birth, 90% of cases are asymptomatic Petechiae, jaundice at birth, hepatosplenomegaly, petechial rash, small size for gestational age, thrombocytopenia, microcephaly, intracranial calcifications, polymicrogyria, ventriculomegaly, sensorineural hearing loss, chorioretinitis, seizures	Asymptomatic infants do not require antiviral treatment Ganciclovir or valganciclovir for symptomatic infections	Overall mortality rate is 4–8% Mortality rate with severe fulminant disease is as high as 30%. Long-term sequelae include hearing loss, cerebral palsy, intellectual disability, vision impairment, and seizures

Table 1.
Clinical manifestations, treatment, and outcome of congenital CMV infections.

have the risk of mortality as high as 30% caused by a fulminant course. Death is usually caused by viral-associated hemophagocytic syndrome or severe end-organ disease of the liver, lungs, bone marrow, or central nervous system. Even if the infants with a life-threatening disease associated with congenital CMV are able to live, neurological sequelae might persist for a lifetime (e.g., microcephaly, intellectual disability, cerebral palsy, and hearing disorders) [10, 11]. Pneumonitis, signs of viral sepsis, thrombocytopenia, and coinfections are more likely to have existed in premature infants than term neonates [7]. Additionally, preterm infants can also present with a classical triad of apneas, bradycardia, and gray pallor describing CMV sepsis-like syndrome [12]. The cases with perinatal infections which are generally not associated with any clinical manifestations can be acquired during birth or ingestion of CMV-containing breast milk. Disseminated infections associated with end-organ disease and death might be seen in extremely premature infants or infants born to nonimmune women.

The vast majority of healthy children and adolescents infected with CMV infections (acquired CMV infection) are most often asymptomatic (Tables 2 and 3). However, the remaining patients (approximately 10%) could present with several mild or moderate symptoms. A clinical entity named mononucleosis-like syndrome with no heterophile antibody titers or positive monospot tests is characterized by fever, fatigue, pharyngitis, adenopathy (especially cervical adenopathy), and hepatitis. A headache, abdominal pain with diarrhea, arthralgias, and rash can also be observed in mononucleosis-like syndrome in acquired CMV infection. Laboratory findings mimic to EBV-related mononucleosis syndrome like lymphocytosis or lymphopenia with thrombocytopenia and elevated transaminases [13]. Unusual manifestations or complications of acquired CMV infections in healthy individuals consist of pneumonitis, myopericarditis, hemolytic anemia, viral hemophagocytic syndrome, granulomatous hepatitis, Guillain-Barré syndrome, and meningoencephalitis [7].

When a reactivation of the endogenous virus and infection from the transplanted organ or from blood product transfusion take place in immunocompromised children and adolescents, serious CMV disease can be observed which is linked to the underlying disease process responsible for the immunosuppression (Table 4). Non-specific symptoms such as fever, malaise, and leukopenia might be seen in all types of patients. Patients with renal transplant are at graft loss; the liver recipients are most likely to be associated with hepatitis and colitis. Early myocarditis followed by late atherosclerosis is seen in heart transplant recipients. Recipients

	Clinical manifestations	Treatment	Outcome
Early postnatal CMV infection	Term infants: Most infants are asymptomatic Fever, hepatosplenomegaly, mild pneumonitis, abnormal blood counts, abnormal liver function tests Premature and VLBW infants: Infection can be severe and life-threatening Sepsis-like syndrome, hepatosplenomegaly, pneumonitis, hepatitis, NEC, abnormal blood counts	Most term infants and asymptomatic preterm infants do not require antiviral treatment Ganciclovir or valganciclovir for severe symptomatic infections in premature infants	Term infants: no permanent sequelae. Premature and VLBW infants: mortality rate with symptomatic infection is 5–10% There does not appear to be increased risk of hearing loss, cerebral palsy, or other neurodevelopmental disabilities; however, long-term outcomes are not clearly understood

Table 2.
Clinical manifestations, treatment, and outcome of early-postnatal CMV infection.

	Clinical manifestations	Treatment	Outcome
CMV infection in immunocompetent children and adolescents	Most children are asymptomatic Fever, fatigue, pharyngitis, mononucleosis-like syndrome, adenopathy, hepatitis, headache, abdominal pain, diarrhea, arthralgias, rash, lymphocytosis or lymphopenia, thrombocytopenia, abnormal liver function tests, negative monospot test	Antiviral treatment is generally not indicated Supportive care with hydration and fever control	No permanent sequelae

Table 3.
Clinical manifestations, treatment, and outcome of CMV infection in immunocompetent children and adolescents.

	Clinical manifestations	Treatment	Outcome
CMV infection in immunocompromised children and adolescents	Infection can be severe and life-threatening Fever, malaise, leukopenia, hepatitis, pneumonitis, colitis, graft loss (in patients with organ transplant), myocarditis, retinitis, encephalitis/encephalopathy (especially in patients with HIV)	Ganciclovir or valganciclovir	High risk of morbidity and mortality; depends in part on the underlying condition

Table 4.
Clinical manifestations, treatment, and outcome of CMV infection in immunocompromised children and adolescents.

with lung and bone marrow transplant generally show a state of pneumonia. Children with human immunodeficiency virus (HIV) and CMV coinfection tend to have retinitis, colitis, pneumonitis, and encephalitis/encephalopathy [14].

4. Diagnosis

The diagnosis of congenital CMV infections should be considered when it is detected in the newborns with signs and symptoms consistent with congenital CMV disease or with abnormal neuroimaging consistent with CMV or newborns who have documented sensorineural hearing loss (SNHL). Newborns who are possessed by a mother with seroconversion positivity or with positive CMV immunoglobulin G (IgG) and CMV immunoglobulin M (IgM) antibody or with mononucleosis-like illness during pregnancy should also be evaluated for congenital CMV infections. Infants with an abnormal T-cell receptor in newborn screening should be suspected for congenital CMV infections. The reliable diagnosis of congenital CMV infections must be detected through sources of virus and viral nucleic acids from urine, saliva, and blood within the first 3 weeks of life in infants. The newborns with suspected congenital CMV infection should be analyzed by viral culture, modified culture (also called rapid culture or shell vial assay), and polymerase chain reaction (PCR) for diagnosis. Detection of CMV by PCR in blood or plasma samples is more accurate than other diagnostic tests [15]. Due to the fact that the polymerase chain reaction provides quantitative results, urine and saliva that include high levels of CMV DNA are generally evaluated in newborns suspected with CMV.

Primary infection of CMV in nonimmunocompromised individuals requires evidence of an IgM reactivity for CMV in blood. It can persist for months depending on the sensitivity of the particular assay. Due to the fact that the infected

individuals can intermittently shed virus, body fluids such as saliva or urine do not provide the diagnosis of CMV infection. Polymerase chain reaction-based methods are also utilized for diagnosis of urine, saliva, and blood and in tissue specimens obtained at biopsy. A combination with immunofluorescence detection of CMV-encoded and conventional culture of CMV using human dermal fibroblasts remains standard in many institutions. Characteristic nuclear (and cytoplasmic) inclusions (owl's eye inclusions) can be detected by histologic stains in tissue specimens.

5. Treatment

Treatment is recommended to be initiated to the infants who have a symptomatic infection or primary immunodeficiency or asymptomatic infection with an isolated hearing loss for congenital CMV infection within the first month of life. At the first line, ganciclovir through intravenous route and its orally available prodrug, valganciclovir, for treatment of congenital CMV disease are indicated. Randomized clinical trials of the Collaborative Antiviral Study Group suggested that 6 weeks of ganciclovir treatment could confine hearing loss and improve developmental outcome in infants infected symptomatically. In addition, infants with severe perinatal CMV infection caused by breast milk could be treated with ganciclovir [7, 16].

In the normal host and early-postnatal infections in term asymptomatic infants, treatment of acquired CMV infections is not recommended. However, treatment must be implemented in preterm or very-low-birth-weight (VLBW) infants with severe infection.

Immunocompromised hosts are recommended with antiviral therapy with ganciclovir in children with active CMV disease. Even if there are no signs or symptoms of end-organ disease in immunocompromised children, it is also suggested to apply the antiviral therapy due to CMV viremia (e.g., positive or rising quantitative PCR). Treatment of CMV disease in immunocompromised pediatric patients consists of ganciclovir and oral valganciclovir similar to that in adults. Treatment is usually given in the form of intravenous ganciclovir or oral valganciclovir for 4–6 weeks on average [17]. Patients are recommended to seek for antiviral treatment monitoring with white blood cell count, AST, and ALT regularly. In some cases, when the antiviral therapy cannot improve clinical or virologic response within several weeks of treatment with ganciclovir or valganciclovir, foscarnet might be integrated to the treatment. Another specific anti-CMV treatment is cidofovir that may be used in children with careful monitoring of renal function and metabolic condition when antiviral resistance occurs.

6. Prevention

6.1 Passive immunoprophylaxis

Intrauterine disease could be prevented from infection through passive transfer of anti-CMV antibodies. However, this transfer is not successful in allograft recipients. A neonatal transfer is prevented from CMV infection using CMV-seronegative or leukocyte-reduced blood for extremely preterm infants. Freezing/thawing or pasteurization eliminates the risk of transfusion-related CMV infection in breast milk contaminated with CMV, however; it might not be complete. The passive transfer of anti-CMV antibodies is recommended to limit transmission and disease in pregnant women with primary CMV infection.

6.2 Active immunoprophylaxis

A number of different vaccine platforms that will be available for prevention of CMV disease in newborns and immunocompromised patients have been evaluated in clinical trials. However, none are licensed.

7. Final considerations

Cytomegalovirus is a common agent that can be seen all over the world. Although CMV is generally asymptomatic in healthy individuals, it can lead to severe infection in individuals with immune deficiency. During pregnancy, CMV also cause significant disabilities in babies whose mother has CMV. After its primary infection, the virus remains as an inactive form in the host throughout the life. Recurrent CMV infections may occur with the reactivation of the silent virus. Due to the fact that congenital CMV infections are asymptomatic, a hearing test is strongly recommended to the newborns.

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