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[Review Article] Cytomegalovirus Infection

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Abstract

Cytomegalovirus (CMV) is a common viral pathogen. Most people who have acute CMV will have an undetectable infection. It is known that cytomegalovirus (CMV) is the most prevalent congenital viral infection in individuals and a significant factor in morbidity and mortality in immunosuppressed hosts, as well as a significant factor in neurodevelopmental disabilities and sensorineural hearing loss. In order to screen for congenital CMV infection, PCR assays are currently being evaluated.

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Introduction

Structure of CMV

Cytomegalovirus (CMV) belongs to the Herpesviridae family, Beta-herpesvirinae (also called human herpesvirus-5 “HHV5”), and is rather common in adulthood (do Carmo et al., 2014).

The genetic material of CMV exists in an icosahedral capsid containing a linear dsDNA of 236 kb (in length), which is regarded as the longest genome when compared with other viruses and is enclosed by an amorphous proteinaceous layer known as “tegument,” that is surrounded by a lipid bilayer (Tomtishen, 2011), as shown in Figure (1).

The architecture of the CMV genome has a higher G+C content. It includes internal repeat short and long (IRS and IRL), and terminal repeat short and long (TRS and TRL), as well as two unique regions (unique short US & unique long UL), which are its two main structural sections (Dolan et al., 2004; Griffiths et al., 2009).

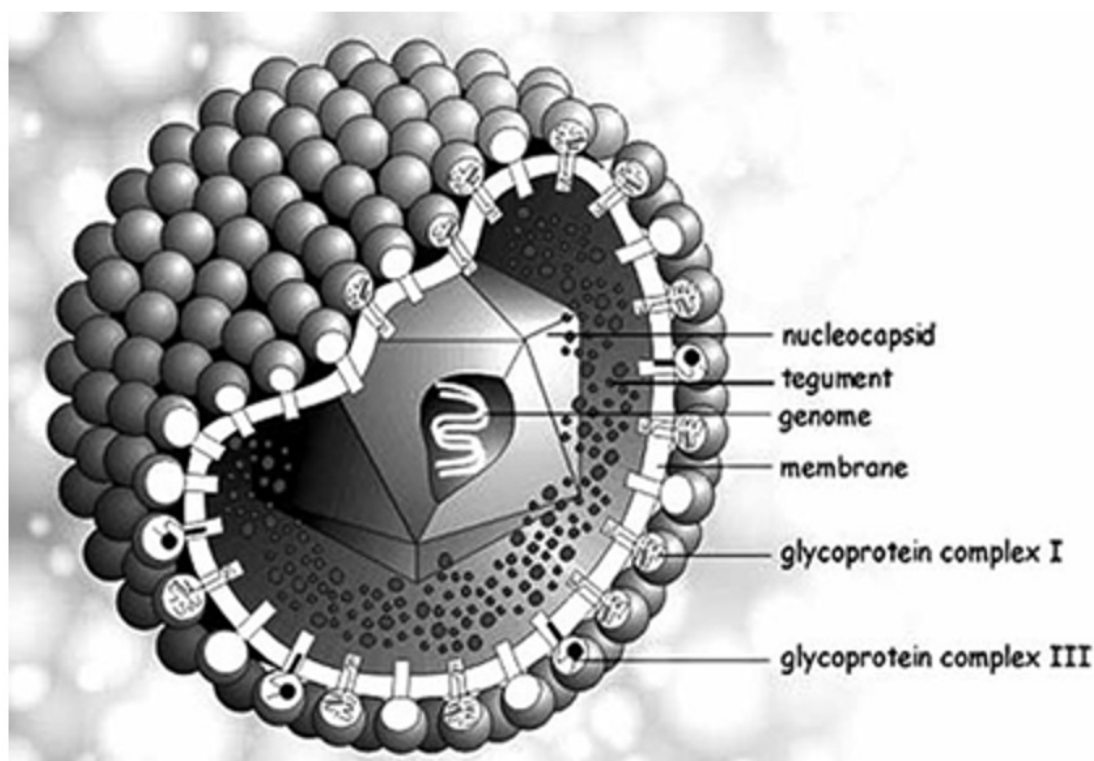


Figure 1. CMV Structure (Courtesy of Marko Reschke and Markus Eickmann, Institute for Virology, Marburg, Germany, 2007).

History of Cytomegalovirus

CMV infections are frequently asymptomatic or subclinical in nature. The German doctor Ribbert discovered the virus for the first time in 1881 when he revealed giant intracellular inclusion bodies in the kidney of a stillborn infant (Reddehase and Lemmermann, 2006). He was unable to explain his findings until he understood Jesionek and Kiolemenoglou's publication (Jesionek and Kiolemenoglou, 1904), which described the discovery of identical inclusion bodies in the liver, kidney, and lung of stillborn neonates 23 years earlier. Enders, Robbins, and Weller isolated CMV for the first time in 1954. The term "cytomegalovirus" was proposed because of CMV's activity as a cytopathic effect (large intracellular inclusion bodies).

Transmission of CMV

Blood products (transfusions, organ transplants), saliva, urine, breastfeeding, semen, perinatally, vertical transmission (transplacental), and sexual transmission are just a few of the ways that CMV can be transmitted. Patients who develop immunosuppression may experience reactivation, which is linked to higher morbidity and mortality (Zheng et al., 2019). Daycare centers aid in the spread of this infection by increasing close contact between kids, many of whom are excreting CMV. According to Pass et al. (1982), toddlers, in particular, represent a major source of CMV infection.

The predominance of HCMV depends on numerous risk factors; for instance, age, working environment, ethnicity, sexual

habits, geographical area, and socioeconomic status (Manicklal et al., 2013).

Pathogenesis

The usual history of CMV infection is complicated, as there are three distinct kinds of infection. An individual with no immunity to this virus develops a primary infection when they contract it for the first time. This virus can then reactivate from latency (the second infection form). The third category of infection, known as reinfection, occurs when a person who has previously been infected comes into contact with an infectious person and is additionally infected despite possessing natural immunity. HCMV is a frequent cause of congenital CMV disease, and all of the above infection types can complicate pregnancy. Both hematopoietic stem cell transplantation (SCT) and solid organ transplantation (SOT) remain the most prevalent and dangerous opportunistic infections, and it is still a significant opportunistic infection in HIV patients (Cannon & Davis, 2005; Atabani et al., 2012).

The common opportunistic pathogen known as human cytomegalovirus (CMV) infects people. The virus remains dormant in the individual's body for the remainder of their lives after infection. Initially, CMV infection is frequently asymptomatic, followed by an extended period of undetectable infectivity in which CMV remains in mononuclear cells but does not manifest as clinical sickness or observable damage (Gardella, 2008).

Following initial infection, CMV persists dormant in both dendritic cells and myeloid progenitors. Upon reactivation of the infection, the antigen-presenting cells may permit virus transfer to the uterine endothelium, urinary tract epithelium, salivary glands, and endothelial cells (Jones, 2003).

Clinical Manifestations

The clinical findings of CMV infection include myalgia, fever, malaise, headache, and fatigue, followed by atypical lymphocytes and abnormal hepatic function tests. Additionally, uncommon manifestations are pharyngitis, adenopathy, rash, splenomegaly, and hepatomegaly (Mocarski et al., 2007). Immunocompetent individuals with HCMV only have mild to no symptoms, yet the virus is never completely eradicated and leaves its host with a latent infection for life (Reeves and Sinclair, 2008).

Approximately 90% of primary CMV infections in individuals who are immunocompetent, according to studies, are asymptomatic; nonetheless, primary infections can occasionally result in mononucleosis, which is a self-limited illness that lasts between 3 to 4 weeks, although it may last anywhere from 19 to 20 weeks. There have been a few isolated reports of severe primary HCMV infections in immunocompetent patients that affect several organ systems. Immunocompromised patients can experience many complications such as hemolytic anemia, enteritis, transverse myelitis, colitis, thrombocytopenia, and encephalitis. HCMV infection is worst during the initial two months following transplantation or when AIDS patients' CD4 counts fall below 50 cells/ μ L, but in immunosuppressed individuals, the severity of this infection may vary depending on the level of immunosuppression (Griffiths et al., 2009).

Patients undergoing solid organ transplantation (SOT), recipients of hematopoietic stem cell transplantation (SCT), as well as people living with HIV are three patient groups which all have impaired immune systems. Studies in pathology and epidemiology point to a direct connection between CMV and atherosclerosis. Congenital HCMV in children can include complications such as jaundice, small bodies, hypotonia, petechiae, and hepatosplenomegaly at birth (Blaho, 2010; Saffert *et al.*, 2010).

The most frequent cause of intrauterine infection-induced congenital abnormalities in persons that result in abortion or stillbirth is thought to be congenital HCMV infection. Visual abnormalities, epilepsy, mental retardation, microcephaly, intellectual disability, as well as sensorineural hearing loss (SNHL) are other congenital infection findings. In addition, congenital CMV infection is the most prevalent acquired cause of hearing loss, vision loss, and neurological disorders in children. In children and adults in good health, HCMV infection is often mild, if not asymptomatic, although the virus accounts for around 10% of cases of infectious mononucleosis (Fowler *et al.*, 1997; Nassetta *et al.*, 2009; Halwachs-Baumann, 2011).

Pneumonia, retinitis, myelitis, hepatitis, esophagitis, neurological (meningoencephalitis), and gastrointestinal (colitis) diseases are all risk factors for CMV infection in individuals with impaired immune systems. This virus is intermittently secreted during reactivation from vaginal fluids, saliva, breast milk, and urine (LEE *et al.*, 2017).

Diagnosis

The diagnosis of CMV infection is unreliable because it is asymptomatic in many people, and medical symptoms may not be specific. Any individual with a CMV infection will develop antiviral antibodies that remain in the body for the duration of the person's life (Chakravarti *et al.*, 2009).

Diagnostic procedures for cytomegalovirus (CMV) infection include cytology, quantitative nucleic acid testing, serology, histopathology, and immunologic assays. IgM must be present for a diagnosis to be made, and urine and saliva samples with low IgG avidity are utilized to identify acute maternal HCMV infection. Amniotic fluid and viral culture of saliva and urine by polymerase chain reaction (PCR) technique are frequently used to confirm fetal infection (Dahl *et al.*, 2013).

1-Viral isolation and detection

In systemic HCMV infections, the polymerase chain reaction (PCR) technique is considered the gold standard for the detection of CMV in blood samples. Recognition of CMV by PCR technique in saliva and urine samples is favored for diagnostic procedures. Detection of CMV in urine and/or saliva is extremely sensitive for the recognition of congenital CMV infection (Lazzarotto *et al.*, 2008; Dahl *et al.*, 2013).

Additionally, CMV is regarded as a fastidious virus that grows only in cultures of primary embryonic fibroblasts or primary foreskin fibroblasts monolayers. The unique cytopathic effect (CPE) of CMV infection in cell culture is characterized by the characteristic enlargement of infected cells (cytomegaly) and the production of typical intranuclear inclusion bodies, often

known as “owl’s eyes.” Isolation and culture of CMV are usually from specimens of semen, urine, and bronchial wash (Reddehase, 2002).

2-Serology

Simple methods for assisting in the identification of CMV infection include serological methods. Although complement fixation is simple to perform, it is not very sensitive. Indirect hemagglutination is more sensitive, although less reproducible. Latex agglutination and ELISA are the two most prevalent techniques utilized. IgM must be present for a diagnosis to be made, and urine and saliva samples with low IgG avidity are utilized to identify acute maternal HCMV infection (Dahl et al., 2013).

Enzyme-linked immunosorbent assays (ELISA) or several methods for enzyme immunoassay have mainly replaced biological testing for CMV antibodies, for instance, the fluorescent antibody test, neutralizing antibody assays, and complement fixation test. These assays can be utilized to identify and distinguish immunoglobulin G (IgG) or immunoglobulin M (IgM) antibodies in cerebrospinal fluid, serum, blood, and plasma, or they can be used to detect total HCMV antibody in blood. According to Saldan et al. (2017), the existence of IgM and low avidity IgG is typically utilized in laboratories for diagnosing primary infection.

Treatment & Prevention

There are three main medications frequently used to decrease the risk and severity of primary infection with CMV: oral valganciclovir, intravenous ganciclovir, and oral ganciclovir (nucleoside analogs). Both drugs that are secondary options, foscarnet and cidofovir (which inhibit the viral polymerase over the polymerases of the cells), are extremely infrequently utilized for basic preventative measures, due to their toxicities and the requirement for careful medical management. Also, valacyclovir and acyclovir, which are used for the prevention of CMV, have decreased activity against CMV and are not recommended as first-line treatments in modern guidelines (Torre-Cisneros et al., 2011). Newer antiviral drugs, such as maribavir—an effective anti-HCMV medication that is taken orally and works by targeting the viral kinase—and letermovir, leflunomide, and artesunate (MARTY et al., 2017; Ligat et al., 2018), are also available.

Prevention strategies include washing one’s hands after coming into contact with a child’s bodily fluids, either directly or indirectly (through toys, for example), staying away from close contact with CMV patients (such as sharing a bed or kissing them on the mouth or cheeks), and not sharing towels, food, utensils, or drinks with them (Revello et al., 2015).

Conclusion

For both children and adults, the herpesvirus cytomegalovirus (CMV) can be a serious infection. Human CMV is persistent and can lead to recurring infections. Children with a congenital condition are substantially more likely to have hearing deficits. As a result, many nations, including Iraq, call for additional information and global guidelines on controlling CMV

infection.

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