Congenital cytomegalovirus: pathophysiological mechanisms of viral neurotropism and its consequences on fetal brain development.

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ABSTRACT

Congenital infections constitute an important group of teratogenic agents capable of interfering with fetal development through inflammatory, vascular, and cytopathic mechanisms. Among them, congenital cytomegalovirus infection stands out as one of the main infectious causes of central nervous system impairment. This article aims to review the transmission mechanisms, pathophysiology, clinical manifestations, and diagnostic methods of congenital cytomegalovirus (CMV) infection, with emphasis on neurological and neurodevelopmental alterations. Fetal transmission occurs mainly transplacentally after primary or non-primary maternal infection. CMV exhibits tropism for neural progenitor cells, promoting cell death, inflammation, and neuronal migration disorders, which can result in microcephaly, ventriculomegaly, periventricular calcifications, cerebellar hypoplasia, and cortical malformations. In addition to the central nervous system, the infection can affect the retina, cochlea, liver, spleen, bone marrow, and placenta, contributing to manifestations such as chorioretinitis, sensorineural hearing loss, intrauterine growth restriction, hepatosplenomegaly, anemia, and thrombocytopenia. Diagnosis involves maternal serological evaluation, fetal and neonatal molecular tests, and imaging methods. It is concluded that understanding the pathophysiological mechanisms of congenital cytomegalovirus infection is fundamental for early diagnosis, multidisciplinary follow-up, and a better understanding of the structural and functional alterations associated with fetal development. This is a literature review on Cytomegalovirus infection, addressing its pathophysiology, teratogenesis, and diagnosis.

Keywords: Cytomegalovirus; congenital infection; teratogenic agents; microcephaly; cortical defects.

1. INTRODUCTION

Congenital infections are a group of infections transmitted from the pregnant woman to the fetus. Infections are one of the main types of teratogenic agents, agents that influence the formation of deformities during fetal development. In this article, we will discuss cytomegalovirus, one of the main congenital infections affecting the central nervous system.

Cytomegalovirus (CMV) is a virus belonging to the Herpesviridae family. Transmission occurs through organ transplantation and exposure to bodily secretions, including semen, saliva, blood, tears, urine, and breast milk. Cases of indirect transmission through contaminated inert materials have also been described (*Maria Augusta Montenegro et al.*, 2010). Fetal infection occurs through vertical transmission, whereby the virus reaches the fetal bloodstream via the placenta. Pregnant women may acquire CMV infection for the first time (primary infection) or may experience a non-primary infection resulting from reactivation or reinfection (*Um Khalil et al.*, 2025).

Primary CMV infection is generally asymptomatic or presents as a mild syndrome resembling influenza or infectious mononucleosis, characterized by fever, lymphadenopathy, and arthralgia. In immunocompromised patients, such as those infected with HIV/AIDS, cytomegalalovirus infection may cause pneumonia, hepatitis, encephalitis, and ocular infections. Organ transplant rejection may also occur in immunocompromised individuals (*Andrew D. Nguyen & Mahmoud Shorman,* 2025).

MATERIALS AND METHODS

A review of the medical literature on congenital cytomegalovirus was conducted, covering articles and books published between 2010 and 2025 in the fields of pediatric neurology, infectious diseases, ophthalmology, and otorhinolaryngology. To locate references, the primary search terms used on PubMed and Google Scholar were "Cytomegalovirus," "Congenital infection," "microcephaly due to congenital infection," and "hearing loss due to cytomegalovirus"; additionally, Chapter 7 ("Congenital Infection") from the Brazilian book *Neuropediatria Ilustrada* (Illustrated Pediatric Neurology), edited by Maria Augusta Montenegro and Carlos Eduardo Baccin, was consulted.

PATHOPHYSIOLOGY

Congenital cytomegalovirus infection may be associated with fetal necrotizing encephalitis, ventriculomegaly, lenticulostriate vasculopathy, subependymal cysts, cerebral hypoplasia, fetal chorioretinitis, intrauterine growth restriction, hepatosplenomegaly, hepatitis, hyperechogenic bowel, hemolytic anemia, thrombocytopenia, and placentomegaly (*Kenji Tanimura et al*, 2023).

Magnetic resonance imaging (MRI) and computed tomography (CT) studies have demonstrated a characteristic pattern consisting of leukoencephalopathy associated with subcortical cysts in the temporal lobes, as well as associations with cortical malformations (*Maria Augusta Montenegro et al.*, 2010), including schizencephaly, heterotopia, pachygyria, and microlissencephaly. These abnormalities significantly increase the risk of refractory epilepsy, cerebral palsy, cognitive delays, and intellectual disabilities.

Nervous system

CMV induces cell death and inhibits the division of neural progenitor cells, reducing the overall number of neurons and resulting in a smaller brain volume, thereby causing microcephaly, a condition commonly associated with congenital cytomegalovirus infection and other teratogenic

agents. Furthermore, CMV elicits a severe inflammatory response that disrupts the radial glial scaffolding required for neuronal migration. Without this structural support, the limited number of surviving neurons are unable to migrate appropriately to the cerebral cortex, resulting in neuronal migration disorders such as pachygyria, polymicrogyria, and, in severe cases, lissencephaly. Lissencephaly is characterized by the absence of normal cerebral gyri and sulci; when associated with microcephaly, the condition is referred to as microlissencephaly.

CMV replicates extensively within the cells lining the cerebral ventricles, triggering a severe local inflammatory response known as necrotizing encephalitis. Necrotic tissue subsequently attracts calcium deposits, resulting in the characteristic periventricular calcifications observed in congenital CMV infection. Ventriculomegaly associated with CMV differs from hydrocephalus, as it is not caused by excessive cerebrospinal fluid production. Instead, viral destruction of neurons and surrounding white matter leads to cerebral tissue loss, causing ventricular enlargement through an ex vacuo mechanism. Consequently, ventriculomegaly results from cerebral parenchymal loss and inflammatory obstruction of cerebrospinal fluid circulation.

When CMV infection is associated with cerebellar hypoplasia, as described by *Kenji Tanimura et al.* (2023), affected individuals may present with ataxia, balance disturbances, speech impairments, tremors, and developmental delays. If cerebellar hypoplasia coexists with cortical malformations, neurodevelopmental outcomes tend to be less favorable due to impairment of the cortico-ponto-cerebellar circuitry, leading to more severe motor delays and substantial cognitive deficits. Since the cerebellum also contributes to cognitive and language functions, its involvement in conjunction with cortical abnormalities significantly increases the risk of severe intellectual disability, profound speech delay, and epilepsy.

Vision and Hearing

Sensorineural hearing loss in congenital CMV infection results from viral invasion of the stria vascularis and cochlear hair cells within the inner ear. Viral replication disrupts potassium homeostasis in the endolymph, leading to cellular death and degeneration of the auditory nerve. Hearing impairment associated with CMV will be discussed in greater detail later in this article. Because chronic inflammation and latent viral replication may persist in the inner ear for months or even years after birth, hearing loss is frequently progressive or delayed in onset (*Xinyu Shi et al.*, 2023).

The retina and choroid are extensions of the central nervous system. CMV directly infects retinal vascular endothelial cells and photoreceptors, causing vasculitis, ischemia, retinal necrosis, and subsequent scarring, ultimately leading to permanent visual field defects. Anterior uveitis may also be associated with CMV infection (*Ana Carolina de Lima Lopes Névoa et al*, 2024). In a study conducted by Natacha Teissier et al., cases of infection involving the olfactory bulb were described, potentially resulting in sensorineural dysfunction.

Systemic Findings

Fetal growth restriction associated with CMV infection arises from viral infection of placental trophoblasts, leading to chronic inflammation (chronic villitis) and thrombosis of placental

vessels. These pathological changes significantly impair the transfer of oxygen and nutrients from the mother to the fetus. Hepatosplenomegaly and jaundice result from viral invasion of hepatocytes and Kupffer cells, causing fetal viral hepatitis. The inflammatory process obstructs the intrahepatic biliary ducts (cholestasis), impairing bilirubin excretion and leading to jaundice in both the fetus and newborn. Splenic enlargement results from both direct viral infection and increased destruction of damaged blood cells.

CMV may infect hematopoietic progenitor cells within the fetal bone marrow, suppressing the production of erythrocytes and platelets. Additionally, systemic inflammation may induce hemolysis through accelerated destruction of red blood cells. Because the infected fetal bone marrow becomes functionally compromised, hematopoietic insufficiency stimulates compensatory extramedullary hematopoiesis. This process results in the formation of violaceous nodules rich in hematopoietic precursor cells, producing the characteristic “blueberry muffin” lesions. The combination of severe fetal anemia and viral myocarditis predisposes the fetus to high-output congestive heart failure. As cardiac function deteriorates, fluid accumulates within tissues, leading to generalized edema, ascites, and pleural effusion. If placental support ultimately collapses in conjunction with the previously described pathological processes, intrauterine fetal demise may occur.

For this reason, cytomegalovirus infection is considered a teratogenic agent, as it directly contributes to the formation of fetal deformities—primarily affecting the central nervous system—much like other congenital infections such as syphilis, toxoplasmosis, rubella, Zika, and many others.

DIAGNOSIS AND OF CONGENITAL CYTOMEGALOVIRUS INFECTION AND THE USE OF VALACYCLOVIR

Maternal CMV infection during pregnancy is asymptomatic in most cases. When symptoms occur, they are typically nonspecific and may include low-grade fever, asthenia, myalgia, and influenza-like manifestations. Certain laboratory abnormalities may be detected through complete blood count and liver function testing, including lymphocytosis exceeding 40% and elevated hepatic enzyme levels (*Serena Salomé et al*., 2023).

Prenatal diagnosis of fetal CMV infection may be achieved through fetal ultrasonography, fetal magnetic resonance imaging, and fetal computed tomography. Maternal diagnosis is based on CMV-specific IgM and IgG serology, including IgG avidity testing. Fetal diagnosis may be confirmed through amniocentesis and polymerase chain reaction (PCR) testing for CMV. Following birth, neonatal diagnosis is established by PCR analysis of saliva and urine samples.

Comprehensive obstetric follow-up throughout pregnancy is essential for both the mother and fetus. Even after neonatal discharge, affected patients cannot be considered fully free from the consequences of the disease and should remain under long-term follow-up with a pediatric neurologist and other healthcare professionals.

When maternal CMV infection is symptomatic, manifestations may include fever, profound fatigue, sore throat, lymphadenopathy, myalgia, and occasionally skin rash or abnormalities in liver enzyme levels. Valacyclovir hydrochloride

has been shown to reduce the rate of fetal CMV infection following primary maternal infection acquired during early pregnancy. Early treatment of pregnant women with primary CMV infection may prevent pregnancy termination and reduce the incidence of congenital cytomegalovirus infection in newborns (*Keren Shahar-Nissan et al*, 2020).

CONCLUSION

Congenital cytomegalovirus infection remains one of the leading infectious causes of fetal neurological injury and long-term neurodevelopmental disability worldwide. Its marked neurotropism allows viral invasion of neural progenitor cells and other developing fetal tissues, disrupting critical processes involved in neuronal proliferation, migration, differentiation, and cortical organization. These pathogenic mechanisms underlie the wide spectrum of central nervous system abnormalities observed in affected fetuses and newborns, including microcephaly, ventriculomegaly, periventricular calcifications, cerebellar hypoplasia, cortical malformations, sensorineural hearing loss, and visual impairment.

Beyond its neurological effects, congenital CMV infection may compromise multiple organ systems through placental dysfunction, hematological abnormalities, hepatic involvement, and systemic inflammatory responses, contributing to fetal growth restriction, hydrops fetalis, and, in severe cases, intrauterine fetal demise. Advances in prenatal ultrasonography, fetal magnetic resonance imaging, molecular diagnostic techniques, and maternal screening have significantly improved the ability to identify fetal infection and assess disease severity during pregnancy. Early recognition of maternal and fetal CMV infection is essential for appropriate counseling, prenatal surveillance, and timely therapeutic interventions. Furthermore, long-term multidisciplinary follow-up involving pediatric neurologists, audiologists, ophthalmologists, developmental specialists, and rehabilitation professionals remains crucial, as neurological and sensory sequelae may emerge or progress throughout childhood.

A comprehensive understanding of the pathophysiological mechanisms underlying congenital CMV infection is fundamental not only for accurate diagnosis and prognostic assessment but also for the development of preventive strategies and future therapeutic approaches aimed at reducing the substantial burden of this disease on affected children, their families, and healthcare systems. As advances in fetal medicine, neuroimaging, and antiviral therapies continue to evolve, improving the early detection and management of congenital CMV infection remains a critical objective for reducing lifelong neurological morbidity and improving quality of life among affected individuals.

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