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HUMAN CYTOMEGALOVIRUS AND THE CNS: IMMUNITY AND INFLAMMATION

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ABSTRACT

Human cytomegalovirus (HCMV) is a highly widespread β-herpes virus that affects all age groups and is largely asymptomatic. The virus is transmitted through contact with bodily fluids and affects the central nervous system (CNS), causing neuropsychiatric disorders and contributing to immune activation and inflammation. HCMV infection can cause significant morbidity and be life-threatening for immunocompromised individuals and those taking immunosuppressant drugs. The virus can cause viral encephalitis in the immunocompromised, frequently resulting in brain damage. In addition, HCMV can cause serious infections affecting newborns with severe symptoms. In newborns, the virus can cross the blood-brain barrier (BBB), infecting brain cells and cerebrospinal fluid. Furthermore, HCMV can infect microglia, immune cells of the CNS with functions similar to macrophages, by activating toll-like receptors (TLRs) with the release of pro-inflammatory cytokines, including IL-1, TNF, and IL-6. This process leads to inflammation and neuropathic pain, which can be reduced by inhibiting these cytokines. Infection can also affect neurons and contribute to glioma and other brain pathologies. Here, the pathogenesis of HCMV infection involving the immune system and the effects on the CNS will be reported.

KEYWORDS: *cytomegalovirus, CNS, immunity, inflammation, microglia, infection*

INTRODUCTION

Human cytomegalovirus (HCMV) is a β-herpes virus that is widespread worldwide and primarily asymptomatic since the immune system contains it. HCMV is a virus that can affect any age group, with an incidence of about 50%-60% in developed countries (1,2), contributing to immune activation and inflammation (3). In addition, HCMV can affect the central nervous system (CNS), causing neuropsychiatric disorders (4) and the immune system, particularly in immunocompromised individuals and those taking immunosuppressant drugs (5,6).

The virus is transmitted from an infected individual to a healthy individual through contact with body fluids, including breast milk, saliva, urine, blood, sperm, tears, wounds, and pus. (7). HCMV infection can remain permanently latent, and its reactivation in subjects with immune pathologies can cause serious damage to vital organs (8). HCMV infection appears to affect immunodeficient patients but can also affect individuals with an efficient immune system. Therefore, HCMV infections can have different degrees of severity. It is one of the most frequent serious infections affecting

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newborns, estimated to be the leading cause of congenital infection in developed countries with an incidence between 0,3% and 2,3% of all births, presenting with cranial bone changes, mental retardation, microcephaly, jaundice, hearing loss, skin lesions, impaired neurodevelopment, and other symptoms (9,~~10~~). This infection most commonly affects children with Down syndrome (trisomy 21). HCMV is also transmitted in bodily fluids from infected but symptom-free individuals (10). Most newborns can render the infection asymptomatic, and the severity of the disease depends on the individual immune response. HCMV infections can be lethal, especially in immunosuppressed patients with impaired T lymphocyte response. In the most severe pathological cases, the CNS and the hematopoietic and respiratory systems can be altered, especially in the first months of the newborn's life (11).

HCMV Immunity and Inflammation

HCMV, present in body fluids, is primarily transported by myeloid cells and mainly affects certain types of cells, such as endothelial, epithelial, smooth muscle, and fibroblast cells (12). HCMV is transmitted from mother to child across the placenta, passes to the fetus, enters the bloodstream, and reaches the brain (13); the infection mainly affects newborns, while adults show a higher resistance. Since the newborn blood-brain barrier (BBB) is not yet formed, the virus can infect the brain cells and cerebrospinal fluid (14). The virus initially targets and replicates in astrocytes, cells important in synapse formation and supporting the BBB (11).

HCMV can cause viral encephalitis, a very common disease after brain infection, responsible for permanent CNS damage, which can even lead to patient death (15). Viral encephalitis can be caused by various infections mediated by the immune cells responsible for the inflammation. HCMV encephalitis affects most patients with compromised immune systems, and the disease can be diagnosed by polymerase chain reaction (PCR) analysis. Brain damage caused by HCMV is relatively frequent and, in certain circumstances, can cause IL-1beta-mediated fever, chills, fatigue syndrome, myalgia, motor deficits with paraplegia, hypoesthesia, paraesthesia, dysesthesia, anaesthesia, disorientation, brain fog, bilateral visual loss, urinary retention, constipation, and coma (Table I).

Table I. *Infections caused by HCMV.*

Most frequent manifestations:	• Colitis	• Encephalitis
	• Meningitis	• Myelitis
Pathological states of other organs:	• Hemolytic anemia	• Thrombocytopenia
	• Venous and/or arterial vascular thrombosis	• Uveitis
	• Pneumonia	• Splenic rupture
	• Coagulation	• Pancytopenia
	• Myelodysplastic changes	• Abdominal pain
	• Headache	• Jaundice

Microglia are long-lived immune cells in the brain that viruses, including HCMV, can activate. The innate immune defense of these cells protects against infection in the CNS, although in the case of HCMV, microglia are not the primary target. Microglia perform a function similar to peripheral blood monocytes in the CNS, protecting the brain from infection and inducing inflammation by releasing inflammatory mediators (16). Therefore, these cells appear to be not easily infected by HCMV. However, the virus can infect microglia by activating toll-like receptors (TLRs) involved in glial activation (17). It binds to TLR4, activating pro-inflammatory cytokines such as IL-1 beta, TNF-alpha and IL-6, causing inflammation and neuropathic pain (18,19) (Fig.1). These cytokines generated primarily by microglia, are the most studied inflammatory mediators in CNS insults, as several activators including viruses upregulate them. Their inhibition significantly reduces the inflammatory and neuropathic pain induced by pathogenic viruses. However, the exact mechanism(s) remain to be confirmed (20).

Neurons, which have little possibility of replication, can be weakly infected by viruses which exploit neuronal metabolism to replicate and induce apoptosis (21). In addition, neuronal stem cells are also resistant to HCMV infection. However, the ependymal glial cells of the CNS have cilia that move the cerebrospinal fluid of the CNS and are easily infected by the virus (11).

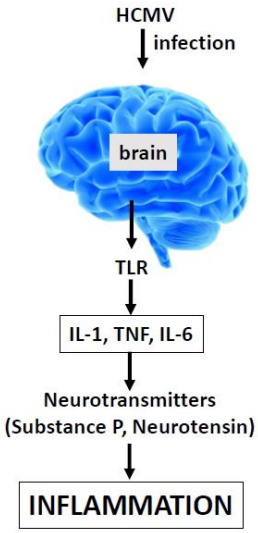

Fig. 1. *Here, we depict inflammation induced by HCMV in the brain, which provokes the generation of inflammatory cytokines and neurotransmitters such as substances P and neurotensin, leading to inflammation.*

An immunodeficiency involving CD8+ and/or CD4+ T cells is important for the reactivation of HCMV infection, an effect to be confirmed by future studies (22). Infection with HCMV can also promote the onset of tumors such as glioma and other brain pathologies (23). In addition, virus infection in the brain attracts T cells, exhibiting an immune and inflammatory effect. In some cases, specific antivirals can relieve symptoms, including systemic inflammation, and avoid death. (24,25).

However, the pathogenesis of HCMV infection is still unclear, and therefore, future studies, especially involving the immune system, are needed to unravel the many obscure points that arise in the CNS.

Conflict of interest

The authors declare that they have no conflict of interest.

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