Journal of Clinical Infectious Diseases & Practice

Research Article Open Access

Infection on the Brain: Understanding Neuroinvasion and Inflammation in Viral Central Nervous System Infections

Chasapis Christos*

Paediatric Infectious Diseases, Department of Pediatrics, Medical Faculty Mannheim, Heidelberg University, Germany

Abstract

Viral infections affecting the central nervous system (CNS) pose a significant threat to human health, often leading to severe neurological complications. One of the key mechanisms by which these viruses cause damage is through neuroinvasion, the process by which viruses enter and spread within the CNS. Once inside the CNS, viral replication and subsequent immune responses can trigger inflammation, further contributing to the pathology of the infection. In this article, we explore the intricate relationship between neuroinvasion, inflammation, and viral CNS infections, highlighting the mechanisms involved and the consequences for affected individuals.

The complex balance of pro-inflammatory and antiviral immune responses to viral neuroinvasion and pathology is also discussed, especially in the context of the hypothesised Trojan horse mechanism of neuroinvasion. A greater understanding of the routes and mechanisms of arboviral neuroinvasion, and how they differ between viruses, will aid in predictive assessments of the neuroinvasive potential of new and emerging arboviruses, and may provide opportunity for attenuation, development of novel intervention strategies and rational vaccine design for highly neurovirulent arboviruses.

Introduction

Viral central nervous system infections can be classified depending on the anatomical site of the inflammation and the entry site of viral pathogens. An infection of the meninges is referred to as meningitis, of the brain as encephalitis, and of the spinal cord as myelitis [1]. When a combination of regions is affected, the terms meningoencephalitis or encephalomyelitis are applied. Despite an often mild acute phase, fatal outcomes are possible, while the long term impact of viral CNS infections has not been elucidated in detail yet.

Haematogenous neuroinvasion

Following replication at peripheral sites, such as the skin and draining lymph nodes, many arboviruses enter the blood, resulting in acute viraemia. This allows for systemic spread of infection, bringing the virus into close contact with organs distant from the initial vector bite site, including the CNS. The CNS is an immune-privileged site protected from blood-borne pathogens by physical barriers such as the blood–brain barrier. The BBB is a selective semipermeable border consisting of brain microvascular endothelial cells [2], joined by a continuous line of tight junctions and adherens junctions, ensheathed by astrocytes and pericytes. BMECs exhibit minimal vesicular transcytosis, limiting passage by a transcellular route, whilst the tight cell–cell interactions at the inter-endothelial cleft acts to limit paracellular transport. The endothelial luminal glycocalyx layer, a villiform layer of proteoglycans and glycosaminoglycans, also plays a role in vascular permeability by acting as both a physical and electrostatic charge barrier. The BBB is implicated as an important interfaces for neuroinvasion via the haematogenous route, but research into other potential interfaces of haematogenous invasion, such as via the cerebrospinal fluid across the choroid plexus, is lacking [3]. The endothelium of the choroid plexus does not exhibit a strict barrier function, instead the epithelial cells form tight junctions to inhibit paracellular diffusion of water-soluble molecules into the cerebrospinal fluid, establishing a blood-CSF barrier. Viral traverse of haematogenous barriers during viremia may occur via transcellular transport of virions through infected cells or via paracellular transport through the intercellular space between cells.

Models to Study Viral CNS Infection Several in vitro models, both static and under flow conditions, as well as in vivo models, mainly murine, exist to study the pathogenesis of viral CNS infection. Application of in vitro models can facilitate easier handling and may increase the spectrum of potential investigations in comparison to a complex experimental in vivo setup. However, in in vitro setup, it is barely possible to mimic the extremely complex and interrelated structures of the CNS [4]. In vitro models of the BBB can be grouped into two major set ups: (1) single culture models with brain microvascular endothelial cells and (2) coculture models with, for example, BMEC, astrocytes, and pericytes and/or glia cells. A commonly used single culture BBB model to study CNS infection is based on human brain microvascular endothelial cells [5].

Neuroinvasion: Gateway to the central nervous system

Neuroinvasion refers to the ability of viruses to breach the protective barriers of the CNS, such as the blood-brain barrier (BBB), and gain access to the brain and spinal cord. Several routes exist for neuroinvasion, including hematogenous spread, neuronal retrograde transport, and direct infection of CNS-resident cells. Hematogenous spread occurs when viruses in the bloodstream cross the BBB, often facilitated by disruptions in the barrier's integrity during inflammation or viral-induced alterations. Neuronal retrograde transport involves viruses exploiting nerve terminals to travel from peripheral sites to the CNS [6]. Lastly, direct infection of CNS cells can occur when viruses breach the BBB in regions with fenestrated capillaries, such as the circumventricular organs.

***Corresponding author:** Chasapis Christos, Paediatric Infectious Diseases, Department of Pediatrics, Medical Faculty Mannheim, Heidelberg University, Germany, E-mail: Christoschasapis@gmail.com

Received: 02-May-2023, Manuscript No: jcidp-23-99919, **Editor assigned:** 05-May-2023, Pre-QC No: jcidp-23-99919 (PQ), **Reviewed:** 19-May-2023, QC No: jcidp-23-99919, **Revised:** 24-May-2023, Manuscript No: jcidp-23-99919 (R) **Published:** 31-May-2023, DOI: 10.4172/2476-213X.1000184

Citation: Christos C (2023) Infection on the Brain: Understanding Neuroinvasion and Inflammation in Viral Central Nervous System Infections. J Clin Infect Dis Pract, 8: 184.

Inflammation in viral CNS infections

Once inside the CNS, viruses can trigger a cascade of immune responses leading to inflammation. The immune response is primarily orchestrated by resident microglia, the primary immune cells of the CNS, and infiltrating peripheral immune cells, including macrophages and lymphocytes. The recognition of viral components by pattern recognition receptors on these cells leads to the production of pro-inflammatory cytokines [7], such as interleukin-1β, tumor necrosis factor-alpha, and interferons.

While the immune response aims to control viral replication, excessive or dysregulated inflammation can contribute to CNS pathology. The release of pro-inflammatory cytokines can disrupt the BBB, causing further influx of immune cells and potentially exacerbating neuronal damage [8, 9]. Inflammatory mediators can also directly affect neurons and glial cells, leading to oxidative stress, excitotoxicity, and apoptosis. Additionally, the activation of coagulation pathways during inflammation can result in thrombosis, further compromising cerebral blood flow and contributing to tissue damage.

Consequences and complications

Neuroinvasion and inflammation in viral CNS infections can lead to a range of complications and long-term consequences. Acute viral encephalitis, characterized by fever, altered mental status, and neurological deficits, is a common manifestation. Viruses such as herpes simplex virus, West Nile virus and enteroviruses are known to cause encephalitis [10]. In severe cases, viral meningitis, inflammation of the meninges surrounding the brain and spinal cord, can occur.

Treatment

Treatment strategies for viral CNS infections aim to control viral replication, modulate inflammation, and manage associated symptoms. Antiviral drugs can be used to target specific viral pathogens [11], reducing viral load and limiting further damage. Immune-modulating therapies may be employed to modulate excessive inflammation and minimize collateral damage to CNS tissues. Supportive care and rehabilitation are also crucial for managing complications and promoting recovery [12].

Research efforts are ongoing to better understand the mechanisms underlying neuroinvasion and inflammation in viral CNS infections. Improved understanding of these processes will aid in the development of targeted therapies and preventative strategies, such as vaccines, to mitigate the impact of these devastating infections on individuals' neurological health [13].

Conclusion

Neuroinvasion and inflammation play central roles in the pathogenesis of viral CNS infections. The ability of viruses to breach the protective barriers of the CNS and trigger immune responses within the brain and spinal cord contributes to the development of severe neurological complications. Understanding the mechanisms involved in neuroinvasion and inflammation is crucial for devising effective treatment strategies and preventative measures. Further research in this field will undoubtedly pave the way for improved outcomes and better management of viral CNS infections in the future. The complex interactions between different CNS-tropic viruses, inflammatory mediators and leukocytes, and the CNS. However, due to the complex nature of controlled biological processes in humans, the task to identify specific cytokine and chemokine profile for each pathogen is demanding. Adequate models and additional in vitro, in vivo, and clinical studies analyzing CNS inflammation and leukocyte migration in the context of viral CNS infections are warranted. The thorough understanding of the complex and interrelated inflammatory mechanisms as well as identifying universal mediators promoting CNS inflammation is essential for the development of new diagnostic and treatment strategies.

References

1. Smith MA, Seibel NL, Altekruse SF (2010) Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 28: 2625–2634.
2. Soliman H, Agresta SV (2008) Current issues in adolescent and young adult cancer survivorship. Cancer Control 15: 55–62.
3. Meadows AT, Friedman DL, Neglia JP (2009) Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 27: 2356–2362.
4. Schiffman JD, Geller JI, Mundt E (2013) Update on pediatric cancer predisposition syndromes. Pediatr Blood Cancer 60: 1247–1252.
5. Neale RE, Stiller CA, Bunch KJ (2013) Family aggregation of childhood and adult cancer in the Utah geneology. Int J Cancer 133: 2953–2960.
6. Magnusson S, Wiebe T, Kristoffersson U, Jernstrom H, Olsson H, et al. (2012) Increased incidence of childhood, prostate and breast cancers in relatives of childhood cancer patients. Familial Cancer 11: 145–155.
7. Friedman DL, Kadan-Lottick NS, Whitton J (2005) Increased risk of cancer among siblings of long-term childhood cancer survivors: a report from the childhood cancer survivor study. Cancer Epidemiol Biomark Prev 14: 1922–1927.
8. Mitchell ER, Scarcella DL, Rigutto GL (2004) Cancer in adolescents and young adults: treatment and outcome in Victoria. Med J Aust 180: 59– 62.
9. Trott PA (1977) International Classification of Diseases for Oncology. J Clin Pathol 30:782-783.
10. Australian Institute of Health and Welfare (2013) Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Asia Pac J Clin Oncol 23: 929–939.
11. Draper GJ, Sanders BM, Lennox EL, Brownbill PA (1996) Patterns of childhood cancer among siblings. Br J Cancer 74:152–158.
12. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ (2001) Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol 30:1428–1437.
13. Pandolfi F, Cianci R, Pagliari D, Landolfi R, Cammarota G (2009) Cellular mediators of inflammation: Tregs and TH17 cells in gastrointestinal diseases. Mediat Inflamm 13: 245-247.