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Short review

Chronic fatigue syndrome related to herpes simplex viruses infection – a narrative review

Authors:

1) Kuba Bieńkowski – Students Scientific Association at Department and Clinic of Infectious Diseases, Medical University of Lublin, ul. Staszica 16, 20-081 Lublin, ORCID 0009-0007-0589-2035
2) Albert Bielaska - Students Scientific Association at Department and Clinic of Infectious Diseases, Medical University of Lublin, ul. Staszica 16, 20-081 Lublin, ORCID 0009-0000-0976-1445
3) Ewelina Wesołek-Bielaska – Students Scientific Association at Department and Clinic of Gastroenterology, Hepatology and Internal Diseases with Endoscopy Unit, ul. Jaczewskiego 9, 20-090 Lublin, ORCID 0000-0001-7819-2661
4) Wojciech Kołodziej - Students Scientific Association at Department and Clinic of Infectious Diseases, Medical University of Lublin, ul. Staszica 16, 20-081 Lublin

5) Jakub Krzysztof Gałązka – Students Scientific Association at Department and Clinic of Infectious Diseases, Medical University of Lublin, ul. Staszica 16, 20-081 Lublin, ORCID 0000-0003-3128-773X, e-mail: jakubgalazka2@wp.pl (corresponding author)
6) Magdalena Greszta – Institute of Health Sciences, Catholic University of Lublin John Paul II, ul. Konstantynów 1H, 20-708 Lublin

Abstract

This article reviews the potential impact of herpes simplex viruses (HSV) on chronic fatigue syndrome (CFS). HSV-1 and HSV-2 are prevalent pathogens, with HSV-1 acquired early in life and HSV-2 typically transmitted sexually. Studies have shown an association between HSV and CFS, with HSV-1 detected in saliva and cerebrospinal fluid of CFS patients and elevated HSV-2 antibodies found in CFS patients. Immunological abnormalities, including increased pro-inflammatory cytokines and chemokines, suggest immune dysregulation in CFS patients infected with HSV. HSV infections can also disrupt the hypothalamic-pituitary-adrenal axis and autonomic nervous system, impacting energy metabolism regulation and contributing to CFS fatigue. Neuroinflammation, indicated by increased translocator protein binding in CFS patients' brains, may play a role in CFS symptoms. However, the mechanisms linking HSV to CFS and the contribution of viral-induced neuroinflammation are still unclear. Despite the evidence, understanding the complex interactions between HSV, immune responses, and other factors in CFS remains challenging. In conclusion, HSV, particularly HSV-1 and HSV-2, may contribute to CFS development. Further research is needed to unravel the mechanisms involved and identify potential therapeutic interventions.

Keywords: chronic fatigue syndrome, herpes simples viruses, neurology, infectious diseases, neuroinflammatory

Introduction

HSV is a member of a family of viruses whose genomes consist of a single large double-stranded DNA molecule. To initiate infection, HSV must attach to cell-surface receptors, fuse its envelope to the plasma membrane, and allow the developed capsid to be transported to the nuclear pores. The DNA is released into the nucleus at the core. Viral surface glycoproteins mediate attachment and penetration of the virus into cells. They also elicit host immune responses to the virus [1] . After the initial infection, the HSV ascends through the periaxonal sheath of sensory nerves to the sacral ganglia of the hosts nervous system, where the virus replicates and persists in a dormant state[2].

Herpes simplex virus type 1 (HSV-1), and HSV-2 are highly prevalent human pathogens with worldwide prevalence levels of about 67% and 13%, respectively. Transmission of both HSV-1 and HSV-2 occurs through close contact and results in a lifelong infection. Most people acquire HSV-1 early in life through the orolabial mucosa, while HSV-2 infections occur later, normally through sexual transmission. Infection with one HSV type normally induces immunity to prevent re-infections with the same serotype, but not with the other. The outcome of infection with HSV-1 and HSV-2 is mostly mild and self-resolving, but can also be life-threatening or asymptomatic. The interaction between HSV and the host, in particular with the immune system, determines the outcome of infection. Diseases caused by HSV include cold sores, genital herpes, herpes stromal keratitis, eczema herpeticum, disseminated disease in the neonate, meningitis and herpes simplex encephalitis[3].

Chronic fatigue syndrome (CFS) is a complex and debilitating condition characterized by persistent fatigue that is not alleviated by rest and accompanied by a range of other symptoms. The etiology of CFS remains elusive, but growing evidence suggests that viral infections, including herpes simplex viruses (HSV), may play a role in the development and perpetuation of the syndrome[4].

This article aims to provide an in-depth examination of the potential impact of herpes simplex viruses on chronic fatigue syndrome, exploring the existing literature and research findings in this field.

State of the art

The potential link between herpes simplex viruses and chronic fatigue syndrome has been the subject of extensive research. Several studies have reported an association between HSV-1 and CFS. For instance, researchers have detected HSV-1 in the saliva and cerebrospinal fluid of CFS patients, suggesting a potential role of the virus in the pathogenesis of the syndrome [5–7] . Furthermore, studies have shown an elevated prevalence of HSV-2 antibodies in CFS patients compared to healthy controls, indicating a possible link between HSV-2 infection and the development of CFS [8, 9] . These findings highlight the need for further investigation into the relationship between herpes simplex viruses and CFS.

The involvement of herpes simplex viruses in the pathogenesis of CFS may extend beyond their direct presence in patient samples. Studies have revealed various immunological abnormalities in CFS patients infected with herpes simplex viruses. For example, researchers have observed increased production of pro-inflammatory cytokines and chemokines in CFS patients, suggesting a dysregulated immune response [10, 11] . This dysregulation probably is mediated by T-regulatory cells and may contribute to the development and persistence of CFS symptoms [12] . Additionally, studies have shown that herpesvirus infections, including those caused by HSV-1 and HSV-2, can lead to the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system [9] . Disruption of these systems could potentially interfere with the regulation of energy metabolism and contribute to the fatigue experienced by individuals with CFS.

Neurological involvement is another area of interest in the study of herpes simplex viruses and CFS. Neuroinflammation has been proposed as a potential mechanism linking viral infections to CFS symptoms [13] . Positron emission tomography (PET) studies using radioligands targeting the translocator protein (TSPO), a marker of neuroinflammation, have shown increased TSPO binding in the brains of CFS patients[13]. But on the other hand, other research suggest that various neurological diseases (including CFS) may be an effect of interactions of viral infections with genes polymorphism [14] . Nevertheless, the studies on monozygotic twins infected by viruses linked with CFS did not support this hypothesis [15] . This finding suggests the presence of neuroinflammatory processes in individuals with CFS

and raises the possibility of viral-induced neuroinflammation as a contributing factor to the fatigue and cognitive dysfunction experienced by these patients.

Conclusion

While the existing evidence points to a potential association between herpes simplex viruses and chronic fatigue syndrome, several questions and challenges remain. The mechanisms by which these viruses contribute to the development and perpetuation of CFS are not yet fully understood. It is unclear whether viral reactivation and replication directly trigger CFS symptoms or if other factors, such as immune dysregulation or neuroinflammation, play a more significant role. Additionally, the heterogeneity of CFS and the complex interplay between viral infections, host immune response, and other contributing factors make it challenging to draw definitive conclusions.

In conclusion, herpes simplex viruses may have a role in the pathogenesis of chronic fatigue syndrome. The existing literature suggests a potential association between herpes simplex viruses, particularly HSV-1 and HSV-2, and the development of CFS. Viral presence, immune dysregulation, and neuroinflammation have all been implicated in the pathophysiology of CFS. However, further research is needed to unravel the complex interactions between herpes simplex viruses and CFS, shedding light on the underlying mechanisms and providing potential avenues for therapeutic interventions.

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