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Literature Review

# Dormant No More: The Neurogical Impact of Herpes Simplex Virus Reactivation Following Traumatic Brain Injury

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**Abstract**

Herpes simplex viruses (HSV), including HSV-1 and HSV-2, are neurotropic viruses capable of establishing lifelong latency in sensory ganglia and reactivating under various triggers, including traumatic brain injury (TBI). TBI induces secondary injury cascades such as neuroinflammation, excitotoxicity, and blood-brain barrier disruption, which create a conducive environment for HSV reactivation. The reactivation of HSV after TBI, particularly HSV-1 and HSV-2, can lead to significant neurological consequences, including encephalitis, cognitive decline, and the development of neurodegenerative diseases like Alzheimer's disease and Chronic Traumatic Encephalopathy. Current therapeutic approaches focus on antiviral agents like acyclovir and valacyclovir, which manage acute HSV infection but are less effective in preventing long-term neurological damage. Emerging research highlights the potential of anti-inflammatory and neuroprotective strategies to complement antiviral therapies, aiming to reduce the neuronal damage caused by viral reactivation and inflammation. However, gaps remain in understanding the precise mechanisms linking TBI-induced neuroinflammation to HSV reactivation and its long-term impact on neurological health. This review synthesizes the current literature on the pathophysiology of HSV reactivation following TBI, and their contributions to acute and chronic neurological outcomes.

**Keywords**: Herpes simplex virus, traumatic brain injury, neuroinflammation, HSV reactivation

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## Introduction

Herpes simplex viruses (HSV), including HSV-1 and HSV-2, are neurotropic viruses capable of establishing lifelong latency in sensory ganglia and reactivating under specific triggers such as trauma, stress, or immunosuppression. While HSV-1 is widely acknowledged as the primary cause of viral encephalitis in developed nations, HSV-2 is commonly linked to meningitis and problems in immunocompromised persons. They are among the most serious viral infections of the brain; if HSV encephalitis is treated promptly with intravenous acyclovir, the untreated fatality rate drops to 15% from over 70%.[1] Significant neurological effects have been shown by both HSV-1 and HSV-2, which are frequently connected to tissue damage, central nervous system (CNS) inflammation, and long-term consequences including epilepsy or cognitive decline.[2,3] Traumatic brain injury (TBI), a leading cause of neurological morbidity worldwide, is known to initiate secondary injury cascades that promote neuroinflammation, excitotoxicity, and blood-brain barrier (BBB) disruption. These pathogenic processes are thought to promote HSV reactivation, resulting in a vicious cycle of inflammation and virus proliferation inside the central nervous system.[3] For example, there is new emerging evidence that TBI-induced

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immunological dysregulation exacerbates tau and amyloid beta pathologies, and HSV-1 reactivation has been connected to neurodegenerative diseases such as Alzheimer's disease.[4] Moreover, HSV-2 reactivation following traumatic brain injury has also been noted in clinical case reports, which has been linked to acute neurological disorders including meningoencephalitis.[2] There are some clinical findings support the hypothesis that TBI creates an environment conducive to HSV reactivation, but there is still no experimental findings covering this area. Despite these findings, the precise mechanisms linking TBI-induced neuroinflammation to HSV reactivation and subsequent neurological injury remain poorly understood. The objective of this literature review is to synthesize emerging evidence on the relationship between TBI, the reactivation of herpes simplex viruses, and their contributions to acute and chronic neurological outcomes.

**Pathophysiology of HSV Reactivation**

HSV-1 and HSV-2 establish lifelong latency in sensory neurons, particularly within the dorsal root ganglia and trigeminal ganglia. Following primary infection, the viral genome persists in a dormant state, primarily expressing latency-associated transcripts (LATs). LATs are critical in maintaining latency by inhibiting apoptosis and minimizing immune detection of infected neurons. This latent state allows the virus to evade the host's immune system and persist indefinitely within the host. Numerous triggers, including as immunosuppression, mechanical damage, and physiological stress, can cause latent HSV to reactivate. Viral reactivation can occur when immunological processes are suppressed by elevated cortisol levels during stress. Furthermore, the virus may emerge from latency if the cellular environment is altered by alterations in neuronal activity or damage.[1,4]

HSV-1 and HSV-2 have different transmission pathways but share fundamental mechanisms of latency and reactivation. While HSV-1 is generally spread through direct contact with contaminated saliva or other body secretions, HSV-2 is mainly distributed through sexual contact during viral shedding. Both viruses start their replication at mucocutaneous infection sites, like the vaginal or oral epithelium, and then proceed retrogradely to their respective neural ganglia via sensory axons. HSV-1 usually develops latency in the trigeminal ganglia, whereas HSV-2 favours the lumbosacral ganglia. Until it is reactivated by particular conditions, the virus stays dormant and persists as episomal DNA within neuronal nuclei.[5,6]

The latency of HSV-1 and HSV-2 is characterized by a lack of full viral gene expression, enabling the virus to evade immune surveillance. HSV-1's capacity to obstruct antigen presentation is a crucial aspect of its immune evasion. The virus prevents natural killer T (NKT) cell activation by causing CD1d molecules to be intracellularly sequestered within antigen-presenting cells (APCs). The immune response is weakened by this alteration in antigen presentation, which permits the virus to continue living inside the host. To further maintain its latent condition, HSV-1 also uses additional mechanisms to suppress cytokine production and hinder T-cell and dendritic cell activation.[5]

HSV-2, while employing similar pathways of immune evasion, demonstrates a preference for latency within the sensory ganglia associated with the lower spine. Following the initial infection, the virus withdraws to these ganglia, where the host's immune system regulates its multiplication. Within the peri-axonal sheath of sensory neurons, the virus stays latent. When the immune system is compromised, the virus reactivates and moves anterogradely along sensory neurons to the surface of the epithelium. At the dermatological site innervated by the afflicted neuron, HSV-2 multiplies and produces distinctive vesicular lesions.[6] The latency condition of HSV-1 can be disrupted by mechanical damage or surgical manipulation of the trigeminal nerve, which promotes viral proliferation and reactivation. Similarly, after localized damage, like that brought on by friction or other mechanical stress in mucocutaneous regions, or systemic immunological dysregulation, HSV-2 may reactivate. Cellular stress and neuroinflammatory cues are necessary

for the viruses to transition from latency to the lytic phase, when full viral replication resumes.[4–6] Clinically, reactivation of HSV-1 is often associated with orolabial herpes or herpes simplex encephalitis (HSE) in severe cases. This is particularly concerning following neurosurgical procedures, where manipulation of cranial nerves or systemic immunosuppression may serve as triggers.[3,7] HSV-2 reactivation is predominantly linked to recurrent genital herpes, although in immunocompromised individuals, it can lead to complications such as aseptic meningitis or disseminated infection.[8] The fundamental mechanisms of latency, immune evasion, and reactivation for HSV-1 and HSV-2 underscore the viruses' common capacity to take advantage of immunological and neural weaknesses, although variations in clinical presentation.

## Correlation Between HSV Reactivation and TBI

TBI provides a unique environment for these triggers, initiating an acute inflammatory response characterized by the release of cytokines such as IL-1β, TNF-α, and IL-6. By interfering with immune surveillance systems and neural homeostasis, these cytokines foster an environment that is favourable to HSV reactivation. Experimental studies have shown that mechanical injury to sensory neurons, such as in controlled cortical impact (CCI) and closed head injury (CHI), significantly disrupts the latency state, promoting the transition to viral replication. By weakening the host's antiviral defenses, immunosuppressive conditions—whether brought on by systemic stress or corticosteroid medication frequently used after TBI—further aggravate this reactivation process.[4] TBI triggers a series of secondary pathophysiological processes that are linked to HSV reactivation, such as neuroinflammation, oxidative stress, excitotoxicity, and disruption of the BBB.

The inflammatory response is particularly significant; robust gliosis and arise inflammatory mediators are the results of activating microglia and astrocytes in response to injury. As depicted in Figure 1, the inflammatory response plays a central role, marked by the activation of microglia and astrocytes, which leads to gliosis and the release of pro-inflammatory cytokines such as IL-1β. A new study in 3D human brain tissue models latently infected with HSV-1, CHI has been shown to amplify these inflammatory responses, increasing the likelihood of HSV-1 reactivation. The resulting viral reactivation is associated with the accumulation of pathological markers such as β-amyloid (Aβ) and phosphorylated tau (P-tau), which further exacerbate neurodegeneration and potentially contribute to conditions like

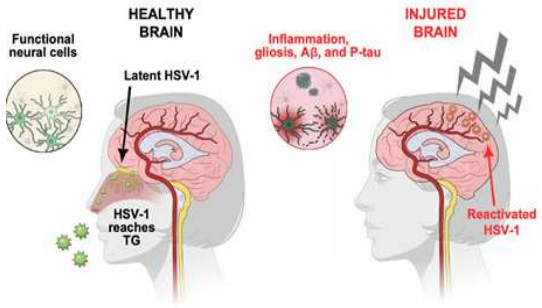


**Figure 1. Suggested mechanism for the neurodegeneration by TBI-induced HSV-1 reactivation.[4]**

Alzheimer's disease (AD). This figure highlights how TBI-induced neuroinflammation serves as a critical driver for HSV-1 reactivation and subsequent neurological damage.[4] Experimental model developments have greatly improved the understanding of the mechanisms behind HSV reactivation after traumatic brain injury. In vitro studies using human-induced neural stem cells (hiNSCs) and 3D brain tissue models have demonstrated the interplay between mechanical injury and viral reactivation.[4] Blocking inflammatory pathways, such as with IL-1β neutralizing antibodies, significantly reduced HSV-1 reactivation and neuroinflammatory markers in these models, underscoring the central role of inflammation in the reactivation process.

Additionally, the extent of reactivation and subsequent neuronal damage was found to be age-dependent, with younger brain tissues showing more severe responses, aligning with clinical observations of chronic traumatic

encephalopathy (CTE) in individuals exposed to repetitive head trauma at an early age.[9–11]

**Neurological Consequences of HSV Reactivation**

Severe neurological deficits, including changed mental status, disorientation, and cognitive dysfunction, can be resulted from HSV reactivation in the initial phase after TBI. According to studies, HSV-1 reactivation, especially in the trigeminal nerve ganglia, is frequently observed following neurosurgical procedures and can also happen after direct traumatic brain injury. Fever, convulsions, and localized neurological impairments are common clinical symptoms. CSF analysis often reveals a lymphocytic pleocytosis, mildly elevated protein levels, and normal glucose, which, when combined with PCR testing for HSV, provides a definitive diagnosis. In cases of post-TBI HSV reactivation, the neurological prognosis is highly dependent on the timing of antiviral treatment. Without early diagnosis and antiviral intervention, the risk of severe complications such as seizures, focal deficits, and increased intracranial pressure becomes elevated, further complicating the management of the patient.[3] The reactivation of HSV-1 also has been linked to excitotoxicity through dysregulated glutamate release. Experimental models show that controlled cortical impact (CCI) and closed head injury (CHI), two paradigms for TBI, both result in elevated extracellular glutamate levels, exacerbating neuronal hyperexcitation and ultimately causing cell death.[4]

Over the long term, the effects of HSV reactivation post-TBI can be profound. Chronic neuroinflammation resulting from repeated viral reactivation is believed to contribute to the pathogenesis of neurodegenerative diseases such as Alzheimer disease (AD) and chronic traumatic encephalopathy (CTE).[9,10] A study stated that in the case of repeated mild TBI, which is common in contact sports and military service, HSV reactivation exacerbates the accumulation of amyloid plaques and tau phosphorylation, both hallmarks of neurodegenerative diseases.[4] This process is particularly exacerbated in individuals with genetic predispositions, such as those carrying the apolipoprotein E epsilon 4 (APOE4) allele, which increases the risk of developing AD following repeated head injuries. Furthermore, in a cross-sectional analysis of brain donors with repetitive head injury, APOE4 was significantly associated with severe CTE and elevated levels of phosphorylated tau in the frontal cortex. Additionally, chronic reactivation aldo can lead to sustained gliosis and neuronal loss, impairing cognitive functions and increasing the susceptibility to further brain damage.[4,12]

**Current and Emerging Therapeutic Approaches**

Antiviral therapy, especially with drugs like acyclovir and valacyclovir, has long been the first choice of treating HSV reactivation after TBI. These substances stop the herpes virus's replication during its reactivation phase by blocking the production of viral DNA. The gold standard for treating HSV-induced encephalitis is still acyclovir, which can be given orally or intravenously. Improving patient outcomes requires prompt intervention. Research has indicated that when administered as soon as possible after diagnosis, intravenous acyclovir can lower the death rate from HSV encephalitis from 70% to 15%.[2,3] Valacyclovir, a prodrug of acyclovir, has the benefit of increased bioavailability and is frequently prescribed for less serious conditions or in outpatient settings. Acyclovir and valacyclovir, however, are effective against acute HSV infection; nevertheless, they are not very successful in avoiding the long-term neurological effects of viral reactivation, such as neurodegeneration and cognitive loss.[13] Although famciclovir and other antiviral medications have been investigated for their possible advantages in treating HSV reactivation in the central nervous system, they have not yet outperformed acyclovir in this regard. The incapacity of these treatments to target latent viral reservoirs, like those found in the trigeminal ganglia, is a significant drawback that could result in chronic problems and recurrent reactivation.[2]

Emerging research highlights the need of neuroprotective measures in addition to antiviral medicines to lessen the brain damage

brought on by TBI and HSV reactivation. Anti-inflammatory and immunomodulatory therapies are some promising strategies for reducing the overreaction of the immune system brought on by brain damage and viral reactivation. The degree of neuronal damage may be limited by drugs that target pro-inflammatory cytokines, such as IL-1β inhibitors, which may help lower the viral load and the inflammatory response in the central nervous system. Antioxidants which can reduce oxidative stress and shield brain cells from apoptosis brought on by HSV reactivation and the inflammatory milieu after TBI, is another possible neuroprotective approach.[3,4] Moreover, neurotrophic factors like brain-derived neurotrophic factor (BDNF) are being explored for their ability to promote neuronal survival and plasticity following both viral infections and traumatic injuries.[14]

In order to avoid recurrence and lessen long-term brain damage, new research is concentrating on creating more specialized treatments that target the underlying mechanisms of HSV latency and reactivation. The creation of vaccinations targeted at avoiding HSV infection or reducing its capacity to enter latency in the first place is one field of ongoing research. Despite the fact that HSV vaccines are still in the early stages of development, promising candidates have demonstrated the ability to prevent primary infections and reduce viral shedding. Furthermore, new treatments that specifically target the body's viral reservoirs—like the trigeminal ganglia—may aid in the removal of latent HSV or the prevention of its reactivation following trauma. Developments in precision medicine, such as genetic and epigenetic methods, may also result in tailored treatment plans for individuals at risk of HSV reactivation after traumatic brain injury, increasing treatment effectiveness and reducing adverse effects.[2,4,7,13]

## Limitations and Gaps in Current Research

One of the primary gaps in current research is the incomplete understanding of the molecular and cellular mechanisms underlying HSV latency and reactivation, particularly in the context of TBI. HSV is capable of establishing lifelong latency within sensory neurons, notably in the trigeminal ganglia, but the precise factors that trigger reactivation after trauma or stress remain unclear. While it is known that neuroinflammation and immune dysregulation following TBI play a role, the complex interplay between the virus, the host immune system, and the injury-induced environment is not fully elucidated. Additionally, studies on the role these pathways play in long-term neurological consequences like neurodegeneration and cognitive decline are still in their infancy. It is still difficult to create tailored treatments that can stop viral reactivation without impairing regular brain function until these mechanisms are better understood.[2,7,13] Although the neurological effects of HSV reactivation after TBI are becoming more widely acknowledged, there are still important questions that need to be answered regarding the latency and reactivation mechanisms of the virus, the approaching and treatment strategies including antiviral and neuroprotective strategies.

## Conclusion

In conclusion, the reactivation of HSV following TBI presents significant challenges in both acute and chronic neurological outcomes. Neuroinflammation and immune dysregulation, which are exacerbated by TBI, play crucial roles in facilitating HSV reactivation and subsequent neurodegenerative processes such as AD and CTE. Although emerging research points to the potential of novel therapies, including immunomodulatory treatments and vaccines targeting HSV latency, several gaps of the precise mechanisms linking TBI to HSV reactivation remains undiscovered. Further research is essential to uncover these mechanisms and develop effective treatments to mitigate both the acute and long-term neurological consequences of HSV reactivation after TBI.

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