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Herpes Simplex Virus Neurovirulence Across the Human Lifespan

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The ability of herpes simplex virus (HSV) to establish lifelong latency in sensory neurons makes it one of the most pervasive viruses worldwide. Although most HSV infections are asymptomatic or cause limited cutaneous symptoms, some give rise to serious central nervous system (CNS) manifestations. Both primary HSV infection and subsequent reactivation events can cause viral replication and spread within the brain, ultimately leading to pathologic inflammation and direct CNS damage. In addition to fulminant presentations of HSV encephalitis, subclinical HSV CNS infections have been implicated in neurodevelopmental, cognitive, and neurodegenerative impairment. Here, we review the pathogenesis of HSV infection and resulting CNS manifestations across the human lifespan. Identifying the mechanisms of HSV-induced CNS damage, and therefore the populations at highest risk for neurological morbidity, may provide a better understanding of the role viruses play in neurological diseases and inform novel approaches to treatment.

Keywords. herpes simplex virus; HSV-1; HSV-2; neurovirulence; encephalitis.

Herpes simplex viruses (HSVs) are neurotropic, double-stranded DNA viruses infecting more than two-thirds of the global population [1]. In general, HSV type 1 (HSV-1) infections are more prevalent than HSV type 2 (HSV-2) infections, and the rate of seropositivity for any HSV infection increases by age [2]. The World Health Organization estimates that >3.8 billion people aged <50 years are infected with HSV-1 and 519.5 million people between the ages of 15 and 49 years are infected with HSV-2 [3]. Together, high rates of viral transmission and the ability of the virus to establish lifelong infection make HSV one of the most common viral infections worldwide.

Primary infection with HSV is acquired at mucosal sites such as the lips and genitals, through contact with infected hosts (Figure 1). Classically, oral lesions are caused by HSV-1, and genital lesions by HSV-2. However, HSV-1 has recently become a more common cause of incident genital infection than HSV-2 in certain populations [4–6]. Genital infection with either virus can result in mother-to-child transmission at birth. Lytic replication at sites of infection followed by retrograde viral transport along innervating sensory nerves results in viral spread from mucosal surfaces to peripheral nervous system ganglia [7]. At sensory neuron nuclei, HSV establishes lifelong latency through repression of viral gene expression by histone modification [8]. Periodically, fever or other stressors may cause HSV to reactivate and spread back to peripheral mucosal sites through anterograde transport along sensory neuron axons, resulting in skin lesions [9]. Less commonly, HSV may access the central nervous system (CNS) following primary infection or reactivation via the same axonal pathways [10, 11]. Antiviral drugs halt viral replication and reduce reactivation events but do not eradicate HSV from the host [12].

The most serious symptoms associated with HSV infection occur following viral invasion of the CNS. Herpes simplex encephalitis (HSE) remains the most detrimental consequence of HSV CNS invasion, resulting in high rates of mortality without treatment, and the potential for lifelong neurological morbidity [13, 14]. However, data are now accumulating to suggest that even low-level, subclinical HSV CNS infections may contribute to lasting neurodevelopmental, neurocognitive, and neurodegenerative impairment [15, 16]. Here, we review the virus–host interactions that contribute to HSV neurovirulence, as well as the expanding set of possible neurological consequences of HSV infection throughout the human lifespan.

PATHOGENESIS OF HSV CNS INFECTION

HSV typically enters the CNS via sensory nerve pathways following primary infection, or reactivation of latent viral

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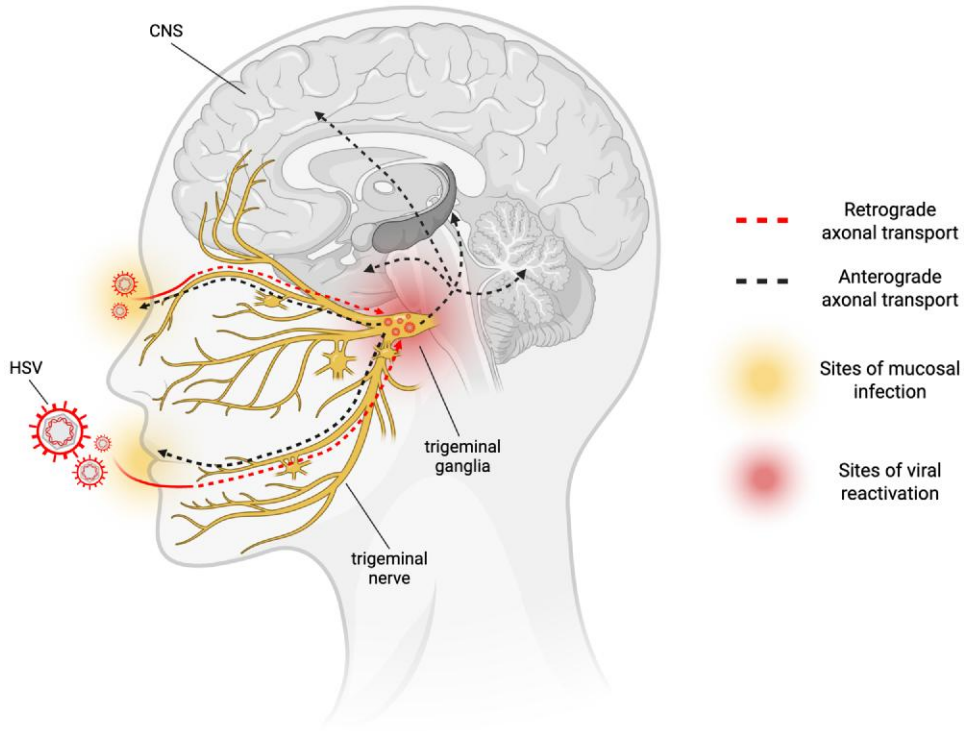

Figure 1. Herpes simplex virus (HSV) access to the central nervous system (CNS). This figure was created with BioRender.com.

genomes from peripheral nervous system ganglia. In the case of neonatal infection, the hematogenous route may also be used. Once in the brain, virus infects and replicates within neurons causing damage. Replicating virus is also recognized by pattern recognition receptors including Toll-like receptors on astrocytes and microglia [17, 18], leading to cytokine release [19]. Proinflammatory cytokines suppress viral replication and limit spread. However, a prolonged or exaggerated innate immune response exacerbates damage to the CNS and contributes to HSV-induced pathogenesis [20]. Recent work has highlighted contributions of the host response and viral virulence to the pathogenesis of HSV infection, implicating each in a complex interplay between virus and host that ultimately determines the outcome of infection (Figure 2).

Host Control of HSV Neurovirulence

The type I interferon (IFN) response is critical to controlling CNS infection, as shown by discovery of single-gene mutations in patients with HSE. In 2006, mutations in UNC93B, a protein involved in TLR3 trafficking, were first identified in 2 children with HSE [21]. TLR3 is a double-stranded RNA sensor that induces antiviral type I IFN production when activated by RNA byproducts of HSV replication [22, 23]. Subsequently, numerous other mutations have been described in patients with HSE, including at least 10 proteins in the TLR3–type I IFN pathway [24]. Together, these mutations explain only a small percentage of total HSE cases but demonstrate the importance of host innate immunity in controlling viral CNS replication. Interestingly, almost all HSE-associated mutations in the TLR3 pathway have been described in children. While this may simply be an epidemiologic association, it is intriguing to speculate whether innate antiviral immunity plays a unique role in the pediatric population. Ex vivo studies of human monocytes have revealed that stimulation of TLR3 in neonatal cells preferentially induces the expression of interleukin 6 (IL-6), while adult-derived monocytes preferentially express tumor necrosis factor α [25]. Furthermore, in neonatal mice, several components of the type I IFN response are expressed in the brain at lower levels than in adult mice. Treatment of neonatal mice with IFN-β restores anti-HSV immunity to adult levels during experimental infection [26]. These observations, along with epidemiologic data showing a disproportionate effect of severe HSV infection on the neonatal population, highlight the relationship between age, immunity, and infection, and suggest a possible role for immunotherapies to augment treatment of HSE.

Further work has implicated polymorphisms in apolipoprotein ϵ4 (APOE4) as a possible mediator of HSV neurovirulence. APOE encodes a glycoprotein involved in lipid metabolism that can be found in the bloodstream as part of a large lipoprotein molecule [27]. In humans, APOE can exist as 3 isoforms: APOE2, APOE3, and APOE4 [28]. Carriers of the APOE4 allele

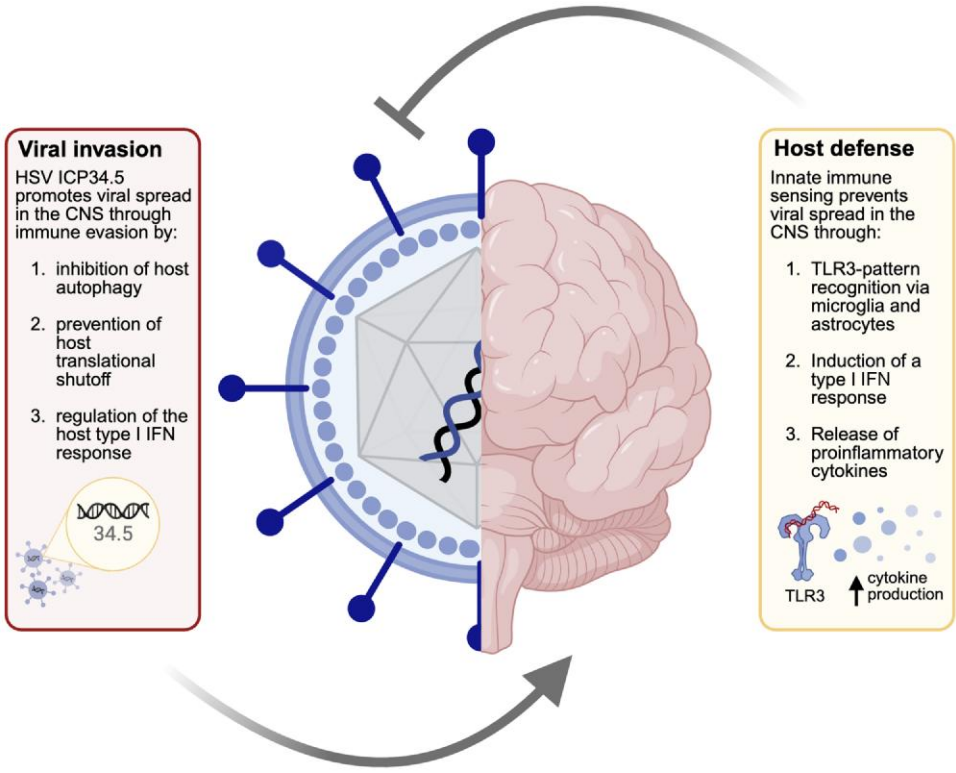

Figure 2. Host and viral factors mediating herpes simplex virus central nervous system infection. This figure was created with BioRender.com. Abbreviations: CNS, central nervous system; HSV, herpes simplex virus; ICP34.5, infected cell protein 34.5; IFN, interferon; TLR3, Toll-like receptor 3.

show more frequent cutaneous HSV symptoms than noncarriers [29], and mouse models of the APOE4 genotype show that APOE4 expression facilitates HSV invasion and establishment of latency in the CNS [30, 31]. Although APOE4 expression has not been implicated in HSE pathogenesis in humans, there are increasing clinical studies showing a relationship between APOE4 status, HSV infection, and Alzheimer's disease [32, 33] (see "HSV and Dementia").

Viral Factors

HSV has evolved sophisticated mechanisms of evading the host immune response. Both HSV-1 and HSV-2 express infected cell protein 34.5 (ICP34.5)—a neurovirulence protein that counteracts host cell antiviral defense via multiple mechanisms including inhibition of host cell autophagy, disruption of type I IFN signaling, and prevention of host translational shutoff [34]. HSV-1 ICP34.5 binds beclin to inhibit host cell autophagy, thereby moderating viral antigen presentation and reducing the adaptive immune response to infected cells [35–37]. HSV-1 ICP34.5 also counteracts the type I IFN response by prohibiting the interaction between TANK-binding kinase 1 and IRF3; however, the relevance of the TANK-binding domain in regulating IFN expression in vivo has been questioned [38, 39]. Finally, HSV-1 ICP34.5 prevents host translational shutoff by recruiting the host protein phosphatase 1 to the eukaryotic initiation factor 2α [40]. These observations highlight the systematic nature of innate and adaptive CNS defenses following HSV-1 infection, as well as the advanced nature of viral countermeasures. Importantly, HSV-1 ICP34.5 deletion mutants have been safely used as oncolytic viral vectors in clinical trials, demonstrating that ICP34.5 is important for human CNS pathogenesis [40, 41].

As a double-stranded DNA virus with proofreading capabilities, the HSV genome has been thought to be relatively invariant, and differences in clinical outcomes have largely been attributed to host factors. However, recent comparative analyses of HSV-2 clinical isolates from neonates with a wide spectrum of disease outcomes suggest that viral genetic variation plays a larger role in HSV clinical presentation than previously thought [42–44]. Further research will determine the contribution of specific viral variations to neurologic disease, and its mechanisms.

ACUTE AND INSIDIOUS CONSEQUENCES OF HSV CNS INFECTION

Following invasion of the CNS, HSV has the potential to cause severe acute disease (HSE) both through direct virus-induced neuronal damage and indirect immunopathology. Growing evidence suggests that HSV CNS infection may also insidiously

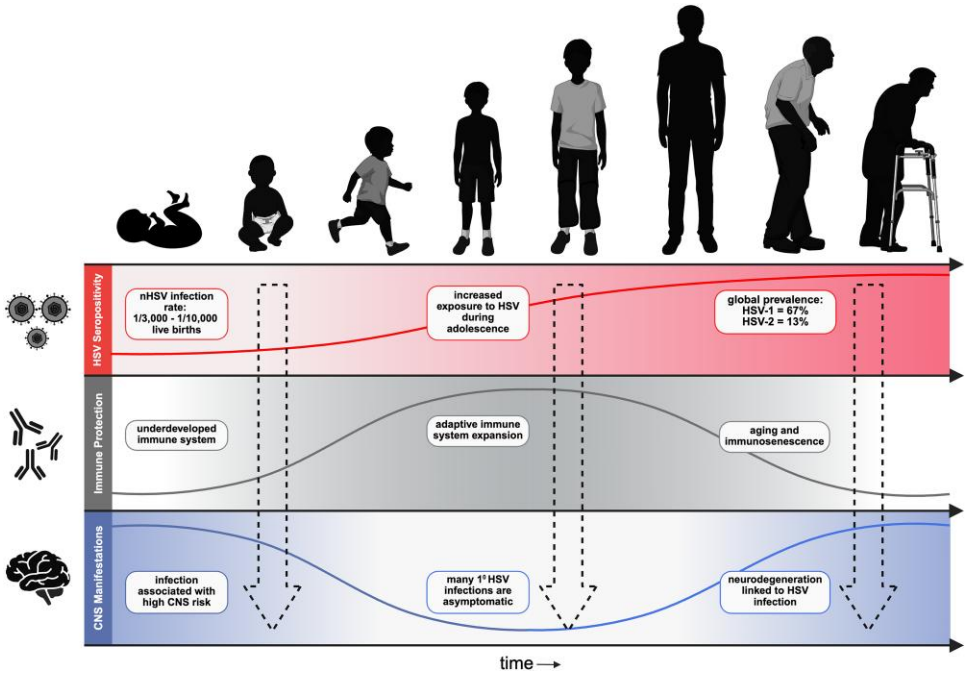

Figure 3. Herpes simplex virus central nervous system manifestations across the human lifespan. This figure was created with BioRender.com. Abbreviations: CNS, central nervous system; HSV, herpes simplex virus; nHSV, neonatal herpes simplex virus.

contribute to neurodevelopmental, cognitive, and neurodegenerative changes. Here, we review the lifelong neurological impact of fulminant HSE and subclinical HSV infection (Figure 3).

Herpes Simplex Encephalitis

Herpes simplex encephalitis is a rare manifestation of HSV infection in adults and children outside of the neonatal period with an approximate incidence of 1 case per 250 000–500 000 individuals per year [45]. Although uncommon, HSE is the most frequent cause of sporadic, fatal encephalitis, accounting for 13.8% of encephalitis hospitalizations from 2000 to 2010 [46]. HSE is almost always caused by HSV-1 and follows a bimodal age distribution with 30% of cases occurring in children between 6 months and 20 years, and one-half occurring in adults >50 years of age [45]. Patients with HSE typically present with acute onset of fever and headache in addition to focal neurological symptoms [45]. Magnetic resonance imaging (MRI) most commonly shows focal encephalitis with associated mass effect in the temporal lobe, insula, and frontal lobe [47, 48]. Cerebrospinal fluid analysis reveals a lymphocyte-predominant pleocytosis and the presence of HSV DNA [49]. Treatment for HSE includes intravenous antivirals, seizure control if needed, and supportive care. Antiviral therapy has decreased the mortality rate from 70% to 10%, however, 30%–50% of survivors contend with lasting neurological impairment including seizure disorders and neurocognitive sequelae [14, 50].

Neonatal HSE and HSV-Induced Neurodevelopmental Delay

Neonatal HSV (nHSV) infection with either HSV-1 or HSV-2 leads to encephalitis in 30% of cases [51]. Mortality associated with nHSV encephalitis has been reduced from 60% prior to the advent of antiviral therapy to <10% today [52]. Despite this reduction in mortality, neurological morbidity associated with infection remains high [14]. In a United States–based longitudinal cohort study of neonates with HSV CNS infection between 1997 and 2008, 31% demonstrated neurological impairment at 12 months of age [53]. In a Swedish study of nHSV survivors, 51% showed signs of neurodevelopmental delay 1 to 15 years postdiagnosis [54]. Finally, an Australian study evaluating survivors of both neonatal and childhood HSV CNS infection reported long-term neurologic impairment in 74% of children [55]. Although this study was small, inclusion of older children with HSV CNS infections showed that HSV infection beyond the neonatal period can cause neurodevelopmental delay.

The neurological outcomes described for HSE, both within the neonatal period and for older children and adults, suggest that better therapies are needed. Ongoing work evaluates the effectiveness of therapies that enhance or suppress specific aspects of immunity as adjunctive therapy to treat HSE and potentially reduce HSE-associated neurologic sequelae [56, 57]. However, until the pathophysiology is better understood, early administration of antivirals remains the standard of care for HSE patients. Notably, long-term administration of antivirals has been shown to improve neurocognitive outcomes for neonates with HSE [53]. Six months of oral acyclovir

suppression (following 21 days of intravenous acyclovir treatment) significantly improved cognitive development scores at 12 months. This suggests that neurodevelopment may be negatively affected by low-level HSV replication in early life. Interestingly, a similar study evaluating prolonged antiviral treatment in adult survivors of HSE showed no benefit [58]. Additional studies are needed to identify populations most at risk for developing neonatal HSE and lasting neurological impairment following HSV CNS infection over the lifespan, as well as the mechanisms underlying pathogenesis.

Subacute Impact of HSV Infection on Cognition

Even in the absence of HSE, lifelong persistence of HSV in the human nervous system may lead to permanent changes to host neurocognition and neuroanatomy. The Tampere Autopsy Study found that 1.9% of brain tissue samples taken from patients without encephalitis were positive for HSV DNA [11]. This suggests that HSV can establish low-level, asymptomatic CNS infection and supports the emerging hypothesis that HSV may have a subacute impact on neurocognitive function. A cohort study in India demonstrated that study participants seropositive for HSV-1 showed reduced emotion discrimination and reduced spatial memory, compared to HSV-1 seronegative participants [59]. While the association between lower socioeconomic status and higher HSV-1 infection rates often confound cross-sectional studies performed in developing nations, studies designed to control for this show similar results. For example, seropositivity for HSV-1 has been associated with reduced neurocognitive performance on the Penn Computerized Neurocognitive Battery in otherwise healthy American adults [60]. These findings highlight the importance of studying the impact of HSV infection on cognition throughout life, even in patients without HSE.

Individuals with severe mental illnesses such as schizophrenia (SZ) and bipolar disorder (BD) may be particularly susceptible to HSV-induced changes to neurocognition [61]. In a study of 1308 patients with SZ, HSV-1 seropositivity was associated with lower neurocognitive performance [62]. HSV-1–seropositive individuals with BD also show decreased cognitive function relative to seronegative individuals with BD [63]. Neuroanatomical changes may underlie differences in cognitive performance as HSV-1–seropositive patients with SZ and BD show reduced gray matter volume by MRI [64–66]. HSV-1–seropositive patients with SZ show neuroanatomical changes in the anterior cingulate cortex [66], cerebellum [66], and the posterior cingulate gyrus [64], relative to seronegative patients with SZ. Seropositive SZ and BD patients share neuroanatomical changes to the left frontal cortex, left precentral cortex, and the left temporal cortex relative to seronegative patients [65]. Although these anatomic findings are specific to individuals with SZ or BD, they highlight a potential connection between HSV infection and lasting changes to neuroanatomy and cognition.

HSV and Dementia

The role of HSV in Alzheimer's disease (AD) has been debated since the 1980s [67, 68]. AD is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and disruption of executive functioning skills in old age. In the United States, approximately 10% of the population >65 years of age carries an AD diagnosis [69]. Although controversial, mounting evidence suggests that HSV-seropositive individuals have a greater risk of developing AD than seronegative individuals. The first studies to explore the relationship between HSV infection and AD found HSV DNA in postmortem brain samples of individuals with AD, primarily in the hippocampus and temporal lobes [67, 70]. Later studies confirmed this observation, demonstrating HSV DNA colocalized with β-amyloid plaques and hyperphosphorylated tau neurofibrillary tangles [71], hallmarks of AD CNS pathology [72].

Clinical studies have investigated the relationship between HSV seropositivity and later-in-life neurodegeneration using HSV symptoms and antibody status as metrics of HSV exposure, and cognitive performance and clinical diagnoses as metrics of neurodegeneration (Table 1). AD [32, 73–80], generalized dementia [78–82], and cognitive decline [33, 83, 84] were all linked to HSV infection, although the degree to which HSV infection was linked to neurodegeneration risk varied. For example, one study showed that HSV infection was associated with cognitive impairment but not a diagnosis of dementia or AD [83]. Others showed that HSV immunoglobulin M (IgM) [74, 76], HSV immunoglobulin G (IgG) [32, 73, 75, 77, 81–84], and a history of HSV symptoms [78–80], were all risk factors for development of neurodegenerative phenotypes. HSV-associated symptoms and HSV IgM^+ serology are most frequently linked to neurodegeneration phenotypes, while the relationship between HSV IgG^+ serology and neurodegeneration is contested [76]. While these studies suggest an intriguing link between HSV reactivation and progressive neurodegeneration, future studies that control for confounding socioeconomic factors are needed. Finally, as AD is a product of both genetic and environmental factors, some studies investigated the role of genetics in shaping the effect of HSV infection on neurodegeneration outcomes. In some analyses, HSV-seropositive carriers of APOE4 (see "Host Control of HSV Neurovirulence") had the greatest risk of developing AD [32, 33, 67, 73, 75, 77, 84], while other studies have shown an effect of HSV serostatus on neurodegenerative phenotype independent of APOE4 expression [74, 78, 82]. Future studies may benefit from taking genetic background into account and considering multiple markers of HSV infection (IgG seropositivity, IgM seropositivity, and/or HSV-positive symptoms) and neurodegeneration (cognitive decline, mild cognitive impairment diagnosis, and/or AD diagnosis).

Animal and in vitro models support a relationship between HSV and neurodegeneration, demonstrating that HSV infection

Table 1. Selected Clinical Studies Linking Herpes Simplex Virus Infection to Neurodegeneration

Author, Year [Reference]	Country	HSV Detection Method	Associated Risk	Observations	Effect of APOE4?
Cantero et al, 2024 [73]	Spain	Serology	AD	Anti-HSV IgG seropositivity was associated with greater β-amyloid load in cognitively normal adults.	Yes
Letenneur et al, 2008 [74]	France	Serology	AD	Anti-HSV IgM seropositivity was associated with higher AD incidence.	No
Linard et al, 2021 [75]	France	Serology	AD	Anti-HSV IgG seropositivity was associated with a greater risk of AD among APOE4 carriers.	Yes
Linard et al, 2020 [32]	France	Serology	AD	Anti-HSV IgG or anti-HSV IgM levels were associated with an increased risk of AD among APOE4 carriers.	Yes
Lövheim et al, 2015 [76]	Sweden	Serology	AD	Anti-HSV IgM seropositivity was associated with an increased risk of AD.	Not assessed[a]
Lopatko Lindman et al, 2019 [77]	Sweden	Serology	AD	Anti-HSV IgG seropositivity was associated with increased risk for developing AD. Risk was further increased among APOE4 carriers.	Yes
Tzeng et al, 2018 [78]	Taiwan	Symptomatic infection	AD, dementia	Symptomatic HSV infection was associated with an increased risk of dementia, including AD and vascular dementia.	No
Shim et al, 2022 [79]	Korea	Symptomatic infection	AD, dementia	Symptomatic HSV-1 infection was associated with an increased risk of dementia, including AD, vascular dementia, and dementia with Lewy bodies.	Not assessed
Shin et al, 2024 [80]	Korea	Symptomatic infection	AD, dementia	Symptomatic HSV infection was associated with an increased risk of dementia, including AD and vascular dementia.	Not assessed
Mekli et al, 2022 [81]	United Kingdom	Serology	Dementia	Anti-HSV IgG seropositivity was associated with greater dementia risk.	Not assessed
Vestin et al, 2024 [82]	Sweden	Serology	Dementia	Elevated anti-HSV IgG was associated with an increased risk of dementia.	No
Murphy et al, 2021 [83]	The Netherlands	Serology	Cognition	Anti-HSV IgG seropositivity was associated with decreased global cognition.	Not assessed[a]
Weidung et al, 2023 [84]	Sweden	Serology	Cognition	Increased anti-HSV IgG was associated with poorer cognition in seniors aged 75–85 years.	Yes
Lövheim et al, 2019 [33]	Sweden	Serology	Cognition	Anti-HSV IgG seropositivity was associated with declining episodic memory, especially among APOE4 carriers.	Yes

Abbreviations: AD, Alzheimer's disease; APOE4, apolipoprotein ϵ4; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

[a]APOE4 carrier status assessed in association with HSV positivity but not in association with dementia or cognitive status.

leads to Alzheimer's-like pathology and cognitive impairment. Although animal and in vitro models of HSV CNS infection have limitations because some aspects of HSV pathogenesis in humans are distinct, they provide further evidence for a possible connection between HSV and neuroimpairment. Our group showed that neonatal HSV infection of mice leads to anxiety-like behavior and cognitive impairment in adulthood [85–87]. De Chiara et al found that multiple rounds of induced HSV reactivation exacerbates cognitive deficits in a mouse model of HSV infection and leads to CNS deposition of neurotoxic peptides such as β-amyloid, hyperphosphorylated tau, interleukin 1β, and IL-6 [88]. Although the exact mechanism of HSV-induced neurotoxicity is still unknown, HSV infection of CNS neurons leads to cellular production of β-amyloid and hyperphosphorylated tau [89, 90]. Qiao et al recapitulated these findings in an induced pleuripotent stem cell cerebral organoid model, showing that HSV infection leads to β-amyloid deposition, neuron loss, reactive gliosis, and neuroinflammation indicative of AD neuropathology [91]. Together, these data suggest a consistent pattern of neurodegeneration following HSV CNS infection in both animal and in vitro models, warranting further research on the mechanism of impairment and risk factors associated with this relationship in humans.

CONCLUSIONS

Herpes simplex virus is a remarkably successful human pathogen, capable of establishing lifelong latent infections in a majority of the population. Mounting evidence suggests a connection between subclinical infection and neuroimpairment across the human lifespan (see Figure 3). Still, several issues remain unknown. First, the role HSV serotype plays in the development of HSV CNS impairment is understudied. HSV infection of the brain in adults or older children (either symptomatic or subclinical) is typically caused by HSV-1 following oral exposure. Unsurprisingly, dementia is also most consistently associated with HSV-1 [92]. However, neonatal HSV infection may be caused by HSV-1 or HSV-2 following maternal genital exposure, with small studies suggesting that HSV-2 may be more neurovirulent [93, 94]. These incongruent observations warrant further study on the differential effects of HSV-1 and HSV-2 infection on CNS manifestations throughout life. Interestingly, increases in genital HSV-1 infection have resulted in a shift in neonatal epidemiology toward HSV-1 infection as well [95]. Future studies will show whether this shift results in decreased overall severity of neonatal HSV encephalitis, and its long-term neurocognitive impact.

Second, the mechanism of CNS damage following HSV infection is yet to be fully characterized. It is likely that both direct HSV cytopathic injury and indirect immunopathology contribute to CNS impairment during both primary infection and viral reactivation. However, the degree to which each mechanism contributes to HSV CNS damage in different disease contexts across life is unknown. Fortunately, an effective treatment for HSV infection already exists and has greatly reduced the mortality and morbidity associated with severe HSE presentations [96], as well as more insidious long-term CNS effects. Studies have found an association between antiviral use and protection from dementia in patients from Sweden [97] and Taiwan [78]. Further work is needed to understand whether targeted immune suppression may provide adjunctive benefit to reduce inflammatory neuropathology. If preventing a lifetime of HSV reactivation is important for reducing the risk of developing neuroimpairment, an effective HSV vaccine would also be critical. Currently, multiple messenger RNA vaccines targeting HSV are under preclinical and clinical investigation [98–100]. We argue that the cumulative cognitive impact of lifelong HSV infection may be greater than originally appreciated and warrants a renewed focus on patient and viral risk factors for CNS infection, mechanisms of HSV pathogenesis, and neuroprotective treatment strategies.

Notes

Author contributions. A. J. D. and C. K. H.: Conceptualization, writing–original draft preparation, writing—reviewing and editing. D. A. L. and L. N. A.: Conceptualization, writing–reviewing and editing.

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