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Herpes Simplex Virus Type 1 at the Central Nervous System

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Abstract

Herpes simplex virus type 1 (HSV-1) is a ubiquitous and neurotropic pathogen and is the most common cause of acute sporadic encephalitis in humans. This virus is characterized by establishing a persistent latent infection in neurons of its hosts for life. The pathogenic mechanisms of HSV-1 at the central nervous system (CNS) are not completely elucidated. Besides, evidences suggest that HSV-1 establish latency in the CNS in humans and that this condition would not be harmless, especially in people whose immune system is declined. This trait has been strongly suggested as a risk factor for the development of neurodegenerative pathologies such as Alzheimer's disease. Currently, it is unclear whether a neuron, which undergoes viral reactivation and produces infectious particles, survives and resumes latency, loses functionality, or is killed. These data highlight the need for more studies at cellular and molecular levels to understand the strategies used by the virus and the host cells during both productive and latent infection. The present chapter discusses the current investigations about HSV-1 infection at the CNS and the potential risk of neuronal dysfunction and chronic neurological diseases.

Keywords: HSV-1, AD, CNS infections, Neurovirulence, neuronal dysfunction, neuroepithelium

1. Introduction to herpes simplex virus

Human herpes viruses belong to the family *Herpesviridae* and are characterized by having a linear double-stranded DNA genome, an icosahedral capsid surrounded by a tegument—an

amorphous layer of proteins that surround the capsid—and an envelope formed by polyamines, lipids, and glycoproteins. Herpes simplex virus (HSV) is distributed worldwide and has the ability to infect epithelial and neuronal cells establishing a latent persistent infection at the nervous system [1, 2].

HSV infection typically occurs during childhood, by direct inoculation of infected droplets from orolabial or nasal secretions onto susceptible mucosal surfaces or abraded skin, and infections mostly are asymptomatic and only 1–6% of primary infections are clinically recognized [3]. Initial infection typically occurs in the lip, but can also happen in the mucous membranes of the eyes or nose [1, 4].

In the productive infection, HSV expresses its genome, which is organized as immediate early, early and late genes producing viral particles progeny. For herpes simplex virus 1 (HSV-1), the initial step in the sequential viral gene expression is directed by VP16, a viral tegumental protein that enters into the nucleus associated to the capsids during infection (**Figure 1**). VP16 recruits the following transcription factors to the promoters of viral immediately early genes and several host proteins: host cell factor 1 (HCF1), octamer-binding protein 1 (Oct1), and lysine-specific demethylase 1 (LSD1). The immediate early genes are then transcribed, and among them the infected cell protein 0 (ICP0) is a key regulatory protein that commands different functions and regulates the expression of early and late viral genes [1, 5, 6].

Subsequently, during initial productive infection with HSV-1 on epithelial cells (see **Figure 1**), the viral progeny reaches the cell bodies of the sensory and sympathetic neurons in the trigeminal ganglia through retrograde transport, establishing latent infection, a characteristic of all herpes viruses.

In latent state, episomal HSV-1 DNA remains inside the nucleus of the peripheral neurons of the infected host, without production of infectious progeny lifelong. During latency, the latency-associated transcript (LAT) is abundantly transcribed in infected neurons in mice, rabbits, and humans and is predominantly detected in the nucleus, but can also be detected in the cytoplasm [7]. Splicing of the primary 8.3-kb LAT yields an abundant poly(A) and uncapped stable 2-kb LAT intron, which is necessary for the establishment and maintenance of latency [8]. In [9], the authors concluded that LAT is an miRNA precursor that encodes six miRNAs, one of these, miR-H6, downregulates immediate early ICP4 and ICP0 protein levels, which are involved in the initiation of productive HSV-1 infection or reactivation episodes.

Currently, it has been hypothesized that the establishment of latent state in neurons happens because HCF1 accumulates in the cytoplasm and is transported into the nuclei only in response to stress [5, 6, 10]. In addition, viral capsids, but not VP16, reach the nuclear pore through retrograde transport. Finally, in the absence of nuclear HCF1 and VP16, the immediately early HSV-1 genes are not expressed and the viral genome is fully silenced, except for LATs and miRNAs [1, 5, 6, 9–12].

Diverse nonspecific events (fever, stroke, hormonal cycle, physical or emotional stress, etc.), including immune system imbalance, can trigger HSV-1 reactivation. It has been suggested that in these situations, nuclear translocation of HCF1 is the triggering event involved in HSV-1 reactivation. Reactivated virus is transported back to the body surface to cause recurrent

lesions manifested as cold sores (herpes labialis) [1, 13]. In some cases, HSV-1 invades the central nervous system (CNS), where it replicates in neuronal cells [1, 10–15] causing devastating herpes simplex encephalitis (HSE) [1, 2], or providing a reservoir for virus production and shedding lifelong.
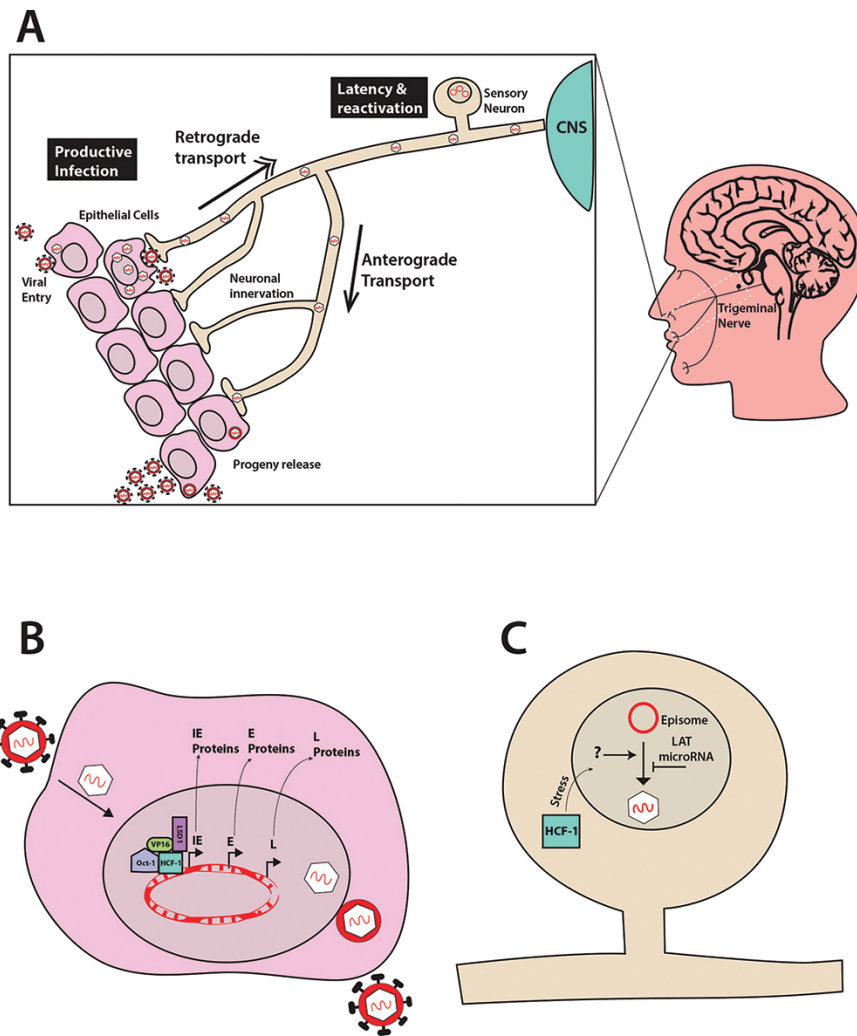

Figure 1. Productive infection and latency/reactivation of HSV-1 cycle. (A) The scheme shows that the viral progeny of HSV-1 productive infection at epithelial cells enters the axons that innerve this site of infection. Then, capsids travel by retrograde transport reaching the nucleus, located in the soma of the neuron at the trigeminal ganglia. At this place, HSV-1 genome enters the nucleus and remains as an episome in a latent state. Under stress conditions, HSV-1 reactivates expressing its genome, and initiating a controlled productive infection in neurons. Then, capsids travel back by anterograde transport reaching the initial site of infection at epithelial cells. The progeny released initiates a new productive infection at this place. **(B)** During productive infection, the initial step in the sequential viral gene expression program is directed by VP16, a viral tegumental protein that enters into the nucleus associated to the capsids during infection. VP16 recruits the following transcription factors to the promoters of viral immediately early genes and several host proteins: host cell factor 1 (HCF1), octamer-binding protein 1 (Oct1), and lysine-specific demethylase 1 (LSD1). The immediate early genes are then transcribed, and among them the infected cell protein 0 (ICP0) is a key regulatory protein that commands different functions and regulates the expression of early and late viral genes. **(C)** In neurons, HSV-1 latency transcripts (LATs and miRNA) silence the viral genome establishing a latent persistent infection. In this state, there is no production of viral particles. Nevertheless, under stressful conditions, the HSV-1 genome is reactivated by a mechanism that is suggested to involve the nuclear translocation of HCF1.

In animal models, there is evidence indicating that HSV-1 infection suppresses the hypothalamic-pituitary-adrenal axis during primary infection, suggesting that this stress-induced suppression has a role in virus reactivation [16].

HSV-1 is an endemic worldwide infection, with a population prevalence of 31% in children aged 6–14, 49% in people aged 14–49, and 80–90% in the population over 65 years old [4]. However, only 20–40% of infected people develop symptoms [17]. In spite of this, in [18], the authors showed that close to 35% of asymptomatic subjects were positive for HSV in eye and mouth swabs, showing higher HSV-1 genome copy numbers in saliva than in tears. Healthy humans are reservoirs of herpes viruses, and asymptomatic shedding is a major factor in the spread of the HSV-1.

2. Herpes simplex virus type 1 tropism

HSV attachment and entry are regulated by surface glycoproteins gC, gB, gD, and gH-gL. Attachment is a two-step process involving the primary interaction of gC and/or gB with heparan sulfate proteoglycans (HSPGs) present at cellular surfaces, followed by the secondary gD-mediated binding to its receptors, such as HVEM (herpes virus entry mediator), nectin-1, or 3-O-sulfated heparan sulfate. This interaction triggers the activation of gH-gL and gB, which leads to the fusion of viral envelope and plasma membrane of the host cell either at the surface or in endosomes [19]. The viral glycoprotein gD determines HSV tropism, and the conformational changes in gD upon binding to its receptors are critical in triggering an activation cascade [19]. HSV capsids are then delivered directly to the cytosol at the periphery of these cells, completing the entry process.

Several cell receptors for viral entry have been described, but numerous observations suggest that more receptors for HSV-1 might exist. In [20], a novel role for the proteolipid protein (PLP) in HSV-1 entry into the human oligodendrocytic cell line human oligodendroglioma (HOG) has been proposed. Oligodendrocytes (OLs) are the glial cells that produce myelin, the electrically insulating layer that surrounds axons in the CNS [21]. Proteolipid proteins, together with DM20, a smaller isoform generated by alternative splicing, are the most abundant proteins in the CNS myelin, comprising around 50% of total myelin proteins [22]. In addition, when PLP is transfected in cells infected with mutant virus unable to replicate, there is an increase in viral signal compared to cells without PLP. Additionally, a mouse monoclonal antibody against PLP drastically inhibited HSV-1 entry into HOG cells. Moreover, PLP and virions were shown to colocalize by confocal and electron microscopy analyses, suggesting that PLP might be involved in HSV-1 entry in human oligodendrocytes [20].

Viruses depend on cells for their replication and can differentially affect various signaling pathways during the course of infection [23]. Several gene products of HSV have been demonstrated to highjack signaling pathways such as protein kinase A (PKA), nuclear factor kappa B (NF-κB), PI3K/Akt, and mitogen-activated protein kinase (MAPK) [24–26]. Among them, the tegumental US3 protein kinase was shown to protect cells from apoptosis induced by a number of exogenous agents and stress [24, 27]. Although the precise mechanisms are

still unclear [28–31], it has been proposed that US3 has a similar substrate range and specificity than protein kinase A [26]. More importantly, HSV-1 US3 plays a crucial role in the ability of the virus to invade the brain from the eyes and therefore constitutes a significant neuroinvasiveness factor in vivo [32]. In addition, US3 of the swine pseudorabies virus induces rearrangements in the actin cytoskeleton via activation of the PAK family of kinases, which leads to disassembly of actin stress fibers and induction of cellular protrusions [29].

Besides, some HSV-1 proteins control nuclear transcription to favor viral replication and immune evasion, where the immediately early viral protein ICP0 is the major HSV-1 protein dedicated to defeating host responses to infection [6]. Previous studies have demonstrated that ICP0 plays a key role in regulating the balance between lytic and latent infection. ICP0 has a zinc-stabilized RING finger domain that confers E3 ubiquitin ligase activity. This domain is essential for the core functions of ICP0 and its activity mediates the ubiquitination and proteasome-dependent degradation of several cellular proteins that are modified by the small ubiquitin-like SUMO family of proteins. Some of these proteins are involved in cellular defenses that restrict viral infection [33–37]. During the first 5 h after infection, ICP0 localizes and performs multiple functions in the nucleus. Nevertheless, after 7 h post infection, ICP0 accumulates in the cytoplasm where it modulates cell signaling [1]. Several functions of ICP0 linked to physical interactions with cytoplasmic proteins have been described. Thus, ICP0 interacts with EF-1δ and enhances translation efficiency and with CIN85 to recruit Cbl, which are involved in endocytosis and negative regulation of numerous receptor tyrosine kinases, depleting these receptors from the cell surface [38].

3. Herpes simplex virus type 1 at the central nervous system

Numerous and consistent reports note that there is a high percentage of the worldwide population with HSV-1 genetic material at the central nervous system [39–44]. However, the invasion mechanism used by this pathogen and its preference for infecting certain neuronal areas is not completely elucidated [8, 42, 45, 46]. Accordingly, the route of entry chosen by the virus to the brain could define the localization, distribution, and establishment of viral latency in certain areas of CNS. Faced with the above, the evidence points to the use of three different routes of viral entry: (1) through the trigeminal ganglia, (2) through vomeronasal system, and (3) the hematogenous route. In this way, HSV-1 travels centripetally from the trigeminal nerve to the meninges, finally reaching the temporal lobe. It also could use the neuronal flow provided by the vomeronasal system (olfactory nerve) and then be distributed in the hippocampus [47]; alternatively, it could travel through the hematogenous route in the presence of protein factors that can facilitate its entry into the brain [43, 44, 48].

The evidence on the latency at the CNS showed that 15.5% of olfactory bulbs [46, 49], and 72.5% of trigeminal nerves from human corpses at forensic post-mortem, and 35% of 40 autopsied human brains contained HSV-1 DNA [48]. At brain level, latent HSV-1 DNA was found in the olfactory bulbs, amygdala, hippocampus, brain stem, and trigeminal ganglia, even though, it is not known by which route HSV-1 entered the olfactory bulbs and brain. Nevertheless,

olfactory bulb HSV-1 infection in mice [48] leads to virus migration into the brain amygdala and hippocampus via the olfactory nerve and locus coeruleus. Other herpes viruses, such as the human herpes virus 6 (HHV-6), also present high frequency of viral DNA in the olfactory bulb/tract region compared to the other brain regions examined in human autopsies, making it a possible route for CNS entrance [50]. The presence of HHV-6 in the nasal cavity and saliva was also a frequent observation, suggesting that both could represent in vivo reservoirs for the virus.

Most evidences are in favor of the olfactory route for neuroinvasion in humans. In this regard, HSV-1 antigens were detected in patients who died of HSE. The antigens were found in the olfactory tract and olfactory cortex, as well as in the limbic system, lower and middle temporal lobe, hippocampus, amygdala, insula, and cingulate gyrus, but not in regions related to the potential trigeminal invasion pathway [51–54]. Additionally, the presence of HSV-related histopathological alterations have been demonstrated in the olfactory neuroepithelium, olfactory nerve, and olfactory bulb [52, 53, 55], but not in the trigeminal ganglion [56]. The evidence supports that HSV-1 is able to establish a latent infection in the olfactory bulb and a particular set of limbic structures. This indicates that HSV reactivation may originate in the olfactory bulb as well as in limbic structures [47].

Furthermore, the information suggests that both primary infection and reactivation of latent virus in the brain may lead to damage of neurons involved in memory, learning, and behavior, as observed in infected mice models [55].

Independent of the route used by the virus, the infection at the CNS level can be localized or diffused and can cause acute neurological disorders as HSE or mild encephalitis, the latter being often imperceptible due to minimal symptoms [17]. Nevertheless, in most cases, the infectious process is asymptomatic, probably indicating that the virus establishes a latent infection in the CNS. This condition would not be harmless, especially in people whose immune system is compromised [55, 57].

Previously, HSV-1 DNA was detected in 1–30% of neurons of latently infected mouse ganglia [16, 58]. In addition, the latent HSV-1 DNA copy number in humans ranges from less than 300 copies/10^5 cells to over 10,000 copies/10^5 cells (in trigeminal ganglia) [16, 59]. Furthermore, another study found that the median HSV genome copy number per 10^5 cells for each ganglion was as follows: vestibular 83222 (4453–890217), geniculate 4307 (311–79518), cochlear 306 (86–32864), and trigeminal 111 (30– 20257) [16, 60].

Periodic but limited reactivation cycles in peripheral sensory neurons might facilitate invasion at CNS level. In this sense, in [47], the results showed that HSV-1 might suppress the apoptotic induction after a reactivation at the peripheral nervous system (PNS) (olfactory neuroepithelium and trigeminal ganglia) enhancing viral neuroinvasion. Besides, HSV-1 US3 has been shown to play a crucial role in the ability of the virus to block apoptosis, facilitating the brain invasion from the eyes and therefore constitutes a significant neuroinvasiveness factor in vivo [32].

Olfactory receptor neurons constitute a bipolar olfactory system, which has dendrites in the olfactory epithelium at the roof of the nasal-pharyngeal cavity. In addition, the olfactory nerve

innervates the olfactory epithelium and the olfactory bulb ends in CNS. This system connects the environment with the nervous system, being a gateway to various pathogens to the CNS. Nevertheless, thanks to the presence of mucus- and pathogen-recognition receptors, the olfactory epithelium is protected from the most common infections [61, 62]. However, in laboratory models, olfactory portal can be used by several viruses (HSV-1, vesicular stomatitis virus, Borna disease virus, rabies virus, influenza A virus, parainfluenza viruses), and prions, to enter the CNS [47, 63]. Advances in the knowledge of the mechanisms involved in pathogen-host relationships, such as the route of entry and spread in the CNS, will provide tools for the development of more effective therapies and prevention programs. In addition, these studies will be very relevant in the case of new outbreaks of emerging zoonotic infections, involving pathogens that could use similar mechanisms to invade the CNS [62].

4. HSV-1 and risk of neurological diseases

HSV infection of the CNS can take place in newborns causing encephalitis, spread infection, or keratoconjunctivitis mostly associated to the genital herpes virus HSV-2 [2, 16, 64]. In adults and children older than 6 months, HSV-1 infection is the most common cause of sporadic and nonepidemic acute encephalitis by herpes simplex (HSE), followed by HHV-6 [65–67]. It is considered a devastating disease of the CNS causing fatal sporadic acute encephalitis, usually localized and with an incidence in the United States of two to four cases/million inhabitants per year [65–67]. This estimation is similar for the rest of the countries, and it affects equally both genders and its onset is likely to occur at any age but with two incidence peaks (under 20 and over 50 years old). Even under antiviral treatment, the mortality associated with HSE is 50–60%, and survivors show significant neuropsychological and neurobehavioral sequelae, which afflict patients for life even if they have been treated very early and have made a good recovery [2, 39, 67, 68]. A previous study demonstrated that HSV load in CSF was not associated with poor outcome in patients with HSE [69].

Neuroimaging findings in HSE patients showed abnormality on T2-weighted spin echo and T2-weighted FLAIR images, involving cortex and underlying white matter with predilection for the temporal and inferior frontal lobes, as well as the insular and cingulate cortexes. In early stages of HSE, these abnormalities are generally unilateral; however, they may progress to bilateral involvement, which can be asymmetric. Patchy areas of diffusion restriction indicating cytotoxic injury, particularly of cortex and deep-gray matter structures, are usually present and are key features of viral encephalitis [70]. The HSE-damaged regions of the CNS are related to the limbic system, which are associated with memory, cognitive and affective processes, and personality. The presence of HSV-1 viral antigens has been found in brains of patients dying of HSE, concentrated mainly in the inferior and middle temporal lobes, hippocampus, amygdala, olfactory cortex, insula, and cingulate gyrus [14, 65, 67].

Additionally, several studies suggest that the cellular damage and dysfunction due to repeated cycles of reactivation of HSV-1 may contribute to the development of chronic and degenerative neurological conditions, such as chronic psychiatric illness, epilepsy [71], dementia [17],

Alzheimer's disease (AD) [71–75], schizophrenia (SZ), bipolar disorder, multiple sclerosis [41], and Parkinson's disease [76]. This idea is mainly based on the evidence demonstrating the presence of HSV-1 genome in brain regions associated with such pathologies [77–82]. Concerning other herpes viruses, HHV-6 is frequently associated with neurologic diseases, including multiple sclerosis, mesial temporal lobe epilepsy (MTLE), encephalitis, and febrile illness [50].

Recently, it has been proposed that during reactivation, HSV-1 might affect neighboring neurons of PNS or CNS, through neuroinflammation or direct neuronal damage [4, 28, 82].

Additional findings established that cognitive functioning in individuals with schizophrenia is associated both with serological evidence of HSV-1 infection and with activated immune system, evidenced by elevated C-reactive protein (CRP) levels [83]. CRP is a pentameric protein generated in the liver, which plays a central role in the inflammatory process in humans. A previous study of 413 individuals with schizophrenia [84] found that those who had levels of CRP above 5.0 μg/ml had significantly lower cognitive scores than patients who did not have elevated CRP levels [84].

Genome-wide association studies (GWASs) have implicated single nucleotide polymorphisms (SNPs) on the human leukocyte antigen (HLA) region of chromosome 6p21.3-22.1, as common risk factors for schizophrenia [85]. Although studies indicate that exposure to HSV-1 is associated with impairment in specific cognitive domains among SZ patients and community-based control individuals [86], an association between HSV-1 exposure and SZ risk per se has not been convincingly demonstrated [85].

Given that the demonstration of the viruses in the host target tissues is difficult, the exposure to the infectious agent is measured indirectly using antibody titers in the serum, and serological assays indicate the infectious exposure, but do not reveal when it occurred. The timing of the exposure may be a critical determinant of viral effects on neurodevelopment thought to be relevant for SZ pathogenesis [86]. In [86], the authors suggested ominous effects of persistent infection that are particularly notable in SZ patients exposed to HSV-1: (1) structural damage in the cortical gray matter, (2) cognitive impairment, and (3) cognitive deterioration over time [86].

In addition, findings have established that limbic structures affected by HSE are the same as that affected in AD, hypothesizing that HSV-1 might be involved in the pathogenesis of this disease [75]. Two main pathological features in the brain characterize AD: senile plaques and neurofibrillary tangles (NFTs). Senile plaques are extracellular deposits of amyloid-β (Aβ) peptide, which are generated by amyloid-β protein precursor (APP) cleavage. Neurofibrillary tangles are intracellular clusters of abnormally phosphorylated tau protein, which is normally associated with microtubules in neurons, and contributes to AD pathology in its hyperphosphorylated state [87].

The loss of synapses and dying-back of axons are among the earliest detectable features in neurodegenerative diseases, which are accompanied by a decay of intracellular transport that correlates with the incipient loss of memory and brain functions [88]. In this regard, several

triggering events such as oxidative stress, inflammatory cytokines, lack of growth factors, and Aβ peptide have been implicated in axonal and/or neuronal decay.

Additional support to the idea that HSV-1 could be a risk factor to AD comes from several studies, which have detected the viral genome inside neurons or in senile plaques and intranuclear inclusion bodies in astrocytes obtained from the brains of deceased persons from AD [68, 74, 75, 79, 88, 89]. Also, anti-HSV-1 antibodies have been found in cerebrospinal fluid (CSF) in 70% of people over age 50, but not in CSF of children under 7 years [72], suggesting that HSV-1 can cause neurological damage in these individuals [90]. A prospective population study showed that there is a significant risk of AD in older patients presenting IgM antibodies against HSV-1. Furthermore, an additional evidence for HSV-1 in AD involves the type-4 allele of the apolipoprotein E gene, known as APOE-ε4 or APOE4 [90, 91]. Currently, the APOE gene (located on chromosome 19) is the only gene identified related to the late onset of AD (LOAD). APOE at the molecular level is the gene that encodes for apolipoprotein E, which is a cholesterol carrier in the brain, helping to reduce amyloid aggregation and the clearing of deposits from the parenchyma of the brain. Thus, in the absence of function of this gene, excessive beta-amyloid deposits occur in the brain, which is one of the findings in patients with LOAD [91–93].

Interestingly, a significantly increased risk for sporadic AD is associated with the presence of both HSV-1 in brain and carriage of the APOE-ε4 allele [94]. In studies of AD post-mortem brains, neither HSV-1 nor the APOE-4 allele alone was found to be risky for AD; nevertheless, the virus with the allele APOE-4 together increased the risk for AD [95].

The APOE-ε4 allele with resultant ApoE4 phenotype influences the pathophysiology of AD by increasing the pathogen load in the brain specifically for HSV-1 and *Chlamydophila pneumoniae*. ApoE4 also interacts with pathogens to enhance the human innate pro-inflammatory response and contributes to the breakdown of the blood-brain barrier (BBB). HSV-1 may be a primary CNS infiltrative pathogen, and a possible treatment of HSV-1 and other pathogens present in AD brains and peripherally may be the most efficacious way to reduce CNS inflammation in the pathophysiology of AD [96].

In addition, an inverse correlation was found between the presence of IgM against HSV-1 and low plasma levels of peptide Aβ (usually generated by an increase in deposits of the peptide in the brain), which can be considered a marker of early risk of dementia [97]. More recent studies showed that an increase in anti HSV-1 IgG during reactivation correlates with cognitive impairment and prodromal phase of AD [96, 98]. Concerning the CSF biomarker profile, the total and phosphorylated (especially at Ser 181) tau proteins were significantly increased in AD and HSV-1 encephalitis compared to bacterial meningitis, human immunodeficiency virus (HIV)-associated dementia, and controls [99]. This evidence of high levels of total and phosphorylated tau proteins reflects cortical axonal degeneration and neurofibrillary pathology, respectively [99, 100].

Similarly, it has been observed that during HSV-1 infection, cellular distribution and processing of amyloid precursor protein (APP) in infected cells is altered, favoring an amyloidogenic cleavage [4, 96, 97, 101].

HSV-1 also enhances Alzheimer-type pro-inflammatory signaling pathways by inducing miRNA146a [102]. An exaggerated cytokine response, including increased tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interferon (IFN)-γ levels, has been detected in CSF from individuals with HSE or AD compared with healthy controls [103]. In addition, astrocytosis represents a fundamental reaction of the CNS to diverse neurological disorders and brain injuries, where glial acidic fibrillary protein (GAFP) is high in CSF [103].

Additionally, it has been demonstrated that in vitro infection of neuronal cultures with HSV-1 generates a deterioration of neuritic processes, altered microtubule dynamics, hyperphosphorylation of tau protein and tau cleavage by active caspase-3, all characteristics associated with early events of neurodegeneration [13, 98, 104].

When brain swells, because of infection or normal damaging processes related to aging, there is a local activation of innate immune system. Contrary to other tissues, the CNS has practically no major histocompatibility complex (MHC) expression and is protected from antibodies, by the BBB [13]. That is why there must be a fast local response by microglial cells, in the detection of pathogen-associated molecular patterns (PAMPs) and toxic debris too (such as Aβ fibrils and other aggregated proteins) through several pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) [105]. Growing evidence indicates that TLRs are pivotal mediating inflammatory responses in CNS pathologies. TLR-mediated intracellular signaling pathways converge to activate NF-κB, and c-Jun N-terminal kinases, which induce the transcription of many genes involved in the onset and/or regulation of this kind of responses, mostly cytokines and chemokines [13].

In this regard, HSV-1 has the ability to induce activation of signaling pathways dependent on Toll-like receptors (TLR2 and 4) in astrocytes [106]. Correspondingly, using an in vivo murine model of infection with HSV-1, we found hyperphosphorylation and cleavage of tau protein by activated caspase 3 during productive and latent infection, alterations that are mainly concentrated in the olfactory bulb and trigeminal nerve, and less extensive in regions of the cerebral cortex. Similarly, during latent infection with HSV-1 it was possible to observe a marked gliosis and increased expression of TLR-4 [55], suggesting repeated neuroinflammatory events that could result in neurodegenerative processes. Moreover, we have recently observed that during infection, the virus modulates differentially the stress sensors AMPK/Sirtuin 1 associated with apoptosis and mitochondrial biogenesis [23].

Even though the evidence reviewed here supports the hypothesis that recurrent infection by HSV-1 at the level of CNS would play a critical role in the development of diseases such as AD, it remains unanswered whether this virus is indeed a causative agent. Nonetheless, age is the main risk factor in the development of chronic and neurodegenerative diseases, coinciding with the decline of the immune system and therefore less restriction on the brain invasion of HSV-1.

In this regard, reports of the World Health Organization (WHO) and the International Federation of the AD (ADI) estimate that in 20 years, the number of people with AD will increase to approximately 66–67 million people and in subsequent years this number will double. Concomitantly, the world population has a greater life expectancy, so it is of great

importance to establish possible genetic, environmental, and pathogenic factors that may have an impact on the development of diseases of the central nervous system, especially related to aging diseases [107].

Acknowledgements

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