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REVIEW

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Alzheimer's disease and herpes viruses: Current events and perspectives

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Abstract

Alzheimer's disease (AD) is a real and current scientific and societal challenge. Alzheimer's disease is characterised by a neurodegenerative neuroinflammatory process, but the etiopathogenetic mechanisms are still unclear. The possible infectious aetiology and potential involvement of Herpes viruses as triggers for the formation of extracellular deposits of amyloid beta (Aβ) peptide (amyloid plaques) and intraneuronal aggregates of hyperphosphorylated and misfold could be a possible explanation. In fact, the possible genetic interference of Herpes viruses with the genome of the host neuronal cell or the stimulation of the infection to a continuous immune response with a consequent chronic inflammation could constitute those mechanisms underlying the development of AD, with possible implications in the understanding and management of the disease. Herpes viruses could be significantly involved in the pathogenesis of AD and in particular, their ability to reactivate in particular conditions such as immunocompromise and immunosenescence, could explain the neurological damage characteristic of AD. Our review aims to evaluate the state of the art of knowledge and perspectives regarding the potential relationship between Herpes viruses and AD, in order to be able to identify the possible etiopathogenetic mechanisms and the possible therapeutic implications.

KEYWORDS
Alzheimer's disease, CMV, EBV, herpes viruses, HHV-6, HHV-7, HSV-1, HSV-2, VZV

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative brain disorder that affects 20 million people worldwide and the incidence is expected to rise. Alzheimer's disease is the main form of dementia among older people, being divided into two forms, sporadic Alzheimer's disease (sAD) and familial Alzheimer's disease, the latter characterised by an autosomal dominant inheritance, due to mutations in Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) or Amyloid Precursors Protein|Amyloid Precursor Protein (APP) genes.[1–3] Alzheimer's disease is characterised by extracellular deposits of amyloid beta (Aβ) peptide (amyloid plaques) and intraneuronal aggregates of hyperphosphorylated and misfolded tau (tangles or neurofibrillary aggregates). These amyloid plaques and neurofibrillary tangles are responsible for the cerebral atrophy and neuroinflammation process typical of AD.[4,5] Patients with AD are characterised by progressive neurocognitive decline with loss

Abbreviations: AD, Alzheimer's disease; HSV-1, Herpes Simplex Virus-1; HSV-2, Herpes Simplex Virus-2; VZV, Varicella–Zoster Virus; EBV, Epstein Barr Virus; CMV, cytomegalovirus; HHV-6, Human Herpesvirus 6; HHV-7, Human Herpesvirus 7.

of abstract thinking, understanding, communication and memory skills. Underlying this clinical neurocognitive decline is a neuroinflammatory process characterised by a progressive loss of neurons and synapses that lead to reduced neural plasticity.[5]

The actual etiopathogenetic mechanism of this condition, or rather of the formation of these amyloid plaques and neurofibrillary tangles, is not clear and several hypotheses have been put forward. In particular, the hypothesis of an infectious aetiology as a trigger seems to be a potential and possible explanation, as viruses with their need and ability to integrate with the genome of the host cell, could induce genetic alterations such as to achieve in the development of AD.[6,7] The AD pathogen hypothesis states that pathogens act as triggers, interacting with genetic factors to initiate the accumulation and/or formation of Aβ, hyperphosphorylated tau proteins, and inflammation in the AD brain.[8–11]

A rapidly growing body of evidence indicates that neuroinflammation has emerged as an important component of AD pathology, and a vast amount of experimental and clinical data indicates the crucial role of activation of the innate immune system in the disease promotion and symptoms progression. Persistent formation and deposition of Aβ aggregates give rise to chronic activation of the immune system. Interactions between activated glia and neurons around Aβ plaques maintain a chronic self-sustaining inflammatory state in the affected brain. Some authors suggest that infectious factors such as viruses or bacteria can lead to cytokine dysregulation and brain injury through a variety of mechanisms, including altered neurotransmission, apoptosis and activation of microglia and astrocytes. Postmortem study of AD brains demonstrated the presence of acute-phase inflammatory reactants and many investigators suggest that AD is an infectious disease or infectious agents constitute a risk factor for AD.[10–14]

Regarding the possible infectious aetiology, several viruses have been involved in the possible etiopathogenic mechanism, in particular herpesviruses, flaviviruses, human immunodeficiency virus, hepatitis viruses and influenza A virus.[12]

Herpesviruses are among the main potential protagonists accused in the possible etiopathogenetic mechanism of AD. In fact, all herpesviruses, except Human HerpesViruses-8 (HHV-8), have been involved in the possible etiopathogenesis of AD.[12] At present, as many as 8 Herpesviruses are known, Herpes Simplex Virus-1 (HSV-1), Herpes Simplex Virus-2 (HSV-2), Varicella-Zoster Virus (VZV), Epstein–Barr Virus (EBV), Cytomegalovirus (CMV), Human Herpes Virus-6 (HHV-6), Human Herpes Virus-7 (human herpesvirus 7 (HHV-7)), Human Herpes Virus-8 (HHV-8). In general, herpesviruses are responsible for an active infection phase, characterised by a reproductive and lytic phase, and a latency phase. Following the primary infection, Herpesviruses subsequently undergo the latency phase, however, following states of immunocompromise and/or immunostress, a phase of reactivation of these viruses can occur, with a new phase of replication.[9] Herpes viruses are among the main causative agents that have been attributed and are potentially considered to be involved. Herpes viruses can infect the brain, evade the host immune response, and are highly prevalent in the AD brain. In recent years, several studies have evaluated the possible relationship between Herpes viruses infection and AD.[13] The hypothesis of the viral role in AD was proposed for the first time in 1982 by Ball.[14] and in 1986 by Gannicliffe and colleagues.[15] This hypothesis was also advancedin 1907 by Oskar Fischer and in 1991 for the first time Jamieson and colleagues highlighted traces of HSV-DNA in the brain tissue of Alzheimer's patients.[16] It was noted that damage of the brain tissue in the early stages of the disease includes the same areas, that are affected by the inflammation of the brain caused by Human Herpes Virus-1 (HHV-1).[16] It is also worth to noticing that other viruses of the Herpesviridae family, such as Human Herpes Virus-2 (HHV-2), VZV, EBV, Citomegalovirus (CMV), Human Herpes Virus-6 (HHV-6) and Human Herpes Virus-7 (HHV-7) can also infect nerve cells and pass into latent infection (Figure 1). There are very few studies in this regard (Table 1).[17]

Our review aims to evaluate the state of the art of knowledge and perspectives regarding the potential relationship between Herpes viruses and AD, to be able to identify the possible etiopathogenetic mechanisms and the possible therapeutic implications.

2 | HERPES SIMPLEX VIRUS-1 (HSV-1)

It is estimated that about 80% of the world's population has encountered HSV-1 in their lifetime.[18] HHV-1 acts directly, causing the cell machinery to produce viral proteins and indirectly via an inflammatory process.[19] It is worth mentioning that (APOE ε4) has been found to modulate the severity of disease of microbial cause or susceptibility to infection, including HHV-1 and HHV-2 (Human herpesvirus 2). Reactivation of HHV-1 infection may induce AD-relevant cellular changes that is, formation of Aβ plaques and accumulation of tau protein (NFT), which has been demonstrated in studies with neural cells infected with this virus.[20] Additionally, studies on the distribution of HHV-1 DNA in human brains revealed that viral DNA was found within senile plaques. Many autopsies conducted on AD patients have found the presence of HHV-1-DNA on brain tissue corresponding to brain disease areas.[21,22] Moreover, HHV-1 DNA was present with high frequency in elderly brains in contrast to the brains of young people and children.[23]

The probable involvement of Herpesviridae in old age could be attributable to the phenomenon of immunosenescence, that is, the condition in which in old age the immune system undergoes a dysfunction that could explain the reactivation of herpes viruses.

In addition, elevated levels of pro-inflammatory cytokines are consistently found in the brains of AD patients. Infection by HSV-1 induces expression of cytokines and pro-inflammatory molecules, this promotes neurodegenerative processes found in AD.[24]

HSV appears to be a risk factor for the development of AD, in fact, the systematic review and meta-analysis by Wu D. et al. showed that HSV-1 infection is a risk factor of AD. Wu D. et al.'s meta-analysis of 21 studies involving 3566 participants showed that HSV-1 infection is associated with risk of AD: pooled odds ratio|odd ratio (OR) 1.40 (95% CI: 1.13–1.75; $I^2 = 3\%$, $p = 0.42$).[25,26]

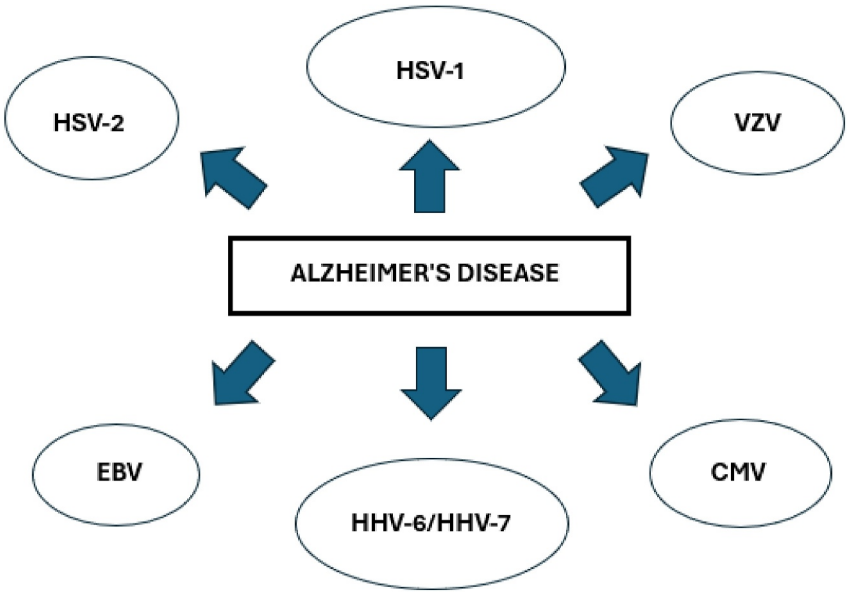

FIGURE 1 Alzheimer's disease and herpes viruses.

TABLE 1 Selected publications investigating the possible role of Herpes viruses in Alzheimer's disease.

Pathogen	Number of references
HSV-1	17
HSV-2	2
VZV	10
EBV	7
CMV	11
HHV-6	7
HHV-7	2

Abbreviations: CMV, Cytomegalovirus; EBV, Epstein Barr Virus; HHV-6, Human Herpesvirus-6; HSV-1, Herpes Simplex Virus-1; VZV, Varicella-Zoster Virus.

The review by Zhang L.N. et al. also highlighted how the reactivation of HSV-1 could be related to an increased risk of developing AD. They highlighted how HSV-1 and APOlipoprotein E ε4 (APOEε4) increase the risk of AD and relate to abnormal autophagy, higher concentrations of HSV-1 DNA in AD, and formation of Aβ plaques and neurofibrillary tangles.[27]

It is described a positive correlation between high titres of HSV-1-specific antibodies and the volumes of brain regions typically affected in disease. A possible connection is further supported by studies demonstrating the detection of HSV-1 within brain tissue from patients with AD and specifically within amyloid plaques, and by the finding that HSV1 infection can induce amyloid beta production and tau hyperphosphorylation in cultured neural cell types. This may indicate a role of HSV in early AD development.[12,28]

Similar data are also presented by the study by Letenneur et al., which showed that reactivation of HSV seropositivity was highly correlated with incident AD and HSV chronic infection might therefore be contributove to the progressive brain damage characteristic of AD. IgM-positive subjects showed a significant higher risk of developing AD (hazard ratio [HR] = 2.55; 95% confidence interval [CI] [1.38–4.72]), although no significant increased risk was observed in IgG-positive subjects (HR = 1.67; 95% CI [0.75–3.73]).[29]

De Chiara G et al. demonstrated that recurrent HSV-1 infections in the central nervous system produced an AD-like phenotype, suggesting that they are a risk factor for AD. Through a model of recurrent HSV-1 infection in mice undergoing repeated cycles of viral reactivation they showed accumulation of AD hallmarks including amyloid-β protein, tau hyperphosphorylation, and neuroinflammation markers.[30]

In this regard and for what has been observed, it could be hypothesised that HSV-1 in its lytic phase or in its latent phase may on the one hand interfere at the gene level, in particular it may interfere with Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) or APP genes, or on the other hand induce an immune response with a consequent chronic inflammatory response, potential etiopathogenetic mechanisms underlying the formation of Aβ plaques.[31–33]

However, Tran et al. pointed out that HSV-1 infection in the lytic phase was not correlated with an increased risk of aberrant amyloid formation β and phosphorylated tau expression.[34]

With regard to what has been reported and the potential etiopathogenetic correlation between HSV-1 and AD, it can be said that there are several studies that support this hypothesis. In particular, the presence of HSV-DNA found in the brain areas affected by the disease, the increased risk of developing this neurological disease in those who have had HSV-1 infection and the evidence that HSV-1 reactivations may increase the risk of AD, highlight how HSV-1 infection may be a trigger in the etiopathogenesis of AD. In this regard, it would be interesting to demonstrate whether active infection could play a decisive role and at the same time antiviral and/or anti-inflammatory therapy could be a possible therapeutic option.

3 | HERPES SIMPLEX VIRUS-2 (HSV-2)

There are not much data to support the involvement of HSV-2 in AD. Particular attention should be paid to the report by Kristen H. et al., who highlighted how HSV-2 infection in human neuroblastoma cells induced alterations similar to AD, in particular HSV-2 infection in human neuroblastoma cells alters the tau phosphorylation state, APP processing, and autophagic process in human neuroblastoma cells, that is, AD-like neurodegeneration markers.[35]

Instead, Bergström P. et al. showed that HSV-2 was mainly involved in forms of meningitis.[36]

Unlike HSV-1, in the case of HSV-2 there are no clear and obvious studies to support the potential correlation between HSV-2 and AD. Unfortunately, there is only some evidence of brain areas affected by the two types of pathology. However, it would be interesting to investigate HSV-2 as HSV-1 has been investigated in order to be able to clarify the potential role of HSV-2. In fact, in this regard, it would be useful to search for HSV-2-DNA on brain tissue, CerebroSpinal fluid (CSF) and blood.

4 | VARICELLA-ZOSTER VIRUS

It is known that the VZV can be responsible for two types of infection, namely, the primary infection known as Chickenpox and the reactivation, known as Shingles. Varicella-Zoster Virus can remain latent in the neurons of the cranial nerve ganglia, dorsal root ganglia and enteric and autonomic ganglia.[37]

Zoster predominantly affects people over the age of 50 and immunocompromised individuals. It has been observed that VZV is responsible for vasculopathies.In view of this possible etiopathogenetic mechanism and characteristic vasculopathies in Alzheimer's patients, it has been hypothesised that VZV may be related to the risk of developing AD.[38–41]

In this regard, Tsai MC et al. showed that patients with Herpes Zoster Ophthalmicus (HZO) had a higher risk of developing cerebral dementia than the control group. Tsai et al. conducted a prospective observational study that aimed to assess the risk of developing dementia in HZO patients versus a control group, for a follow-up period of approximately 5 years. Patients with HZO had a 2.83-fold higher risk of developing dementia (HR = 2.83, 95% CI = 1.83–4.37, p-value < 0.001). In addition, this risk was 1.4 times higher in men than in women (HR = 3.35, 95% CI = 1.79–6.28, p-value < 0.001 vs. HR = 2.40, 95% CI = 1.31–4.41, p-value < 0.01).[42]

Bae et al., in a study of 229,594 patients aged ≥50 years, found that patients with shingles had an increased risk of cerebral dementia (adjusted HR, 1.12 [95% CI 1.05–1.19]).[43]

The study by Chen et al. also highlighted the correlation between Herpes Zoster and the risk of developing cerebral dementia. In particular, Chen et al. showed that patients with Herpes Zoster compared to the control group had a higher risk (HR = 1.11; 95% CI, 1.04–1.17).[38]

The study by Cairns et al. highlighted how the infection of VZV in vitro in neuronal cells was not related to a pathological condition similar to AD, but if such infection involved neuronal cells already affected by HSV-1, this infection induced a reactivation of HSV-1 with a pathological condition similar to AD, in particular with Aβ and P-tau accumulation.[44]

While the study by Choi HG et al. showed that HZ infection was not related to an increased risk of neurodegenerative dementia (adjusted OR for HZI was 0.90 (95% CI = 0.84–0.97) in the dementia group).[45]

Schmidt et al.'s study also showed that HZ was not associated with an increased risk of dementia, in particular Schmidt et al. on 247,305 people with zoster and 1,235,890 matched general population comparators observed that dementia was diagnosed in 9.7% of patients with zoster and 10.3% of matched comparators (HR was 0.93 [95% CI 0.90–0.95]).[46]

With regard to VZV, the hypotheses of possible involvement in AD, either directly through the vasculopathic effect or indirectly through the induction of HSV-1 reactivation, are very attractive and interesting, however supporting data are scarce. At the same time, the potential relationship between VZV and the risk of developing brain dementia should prompt and further research into the potential role of VZV in relation to AD. These hypotheses should be investigated with the demonstration of VZV-DNA on brain tissue, CSF, blood and endothelial tissue, with the concomitant search for HSV-1 DNA in patients with AD.

5 | EPSTEIN BARR VIRUS (Epstein–Barr Virus)

EBV is a ubiquitous virus that affects about 90%–95% of the general population and is characterised by two possible states, latent infection and lytic replication.[47,48] Epstein Barr Virus has been linked to several neurological disorders, in particular it has been associated with AD, Parkinson's disease, multiple sclerosis, acute cerebellar ataxia, meningitis, acute disseminated encephalomyelitis, and brain tumours, although the underlying etiopathogenetic mechanisms are not well understood.[49]

Although EBV-related AD data are limited, the virus may be a risk factor for development AD. A compelling hypothesis would see EBV as a possible trigger for that chronic inflammatory state characteristic of AD. Some authors hypothesise that EBV in the latency phase may constitute a continuous and chronic stimulus to an immune system response with a consequent chronic inflammatory response. This condition could underlie a potential etiopathogenetic mechanism of AD.[50]

Carbone et al. showed that EBV infection could be a risk factor for the development of AD, they searched for EBV-DNA on both peripheral blood leucocytes (PBL) and brain samples. The study showed that 45% of PBL samples from AD patients and 31% from controls were positive for EBV (OR = 1.843, 95% CI = 0.976–3.480; p = 0.05), while EBV positivity was 6% in AD brains.[51]

Huang SY et al. also highlighted with a study including 21,982 AD cases and 41,944 controls showed that patients with a history of infectious mononucleosis had an increased risk of developing AD (odds ratio [OR] = 1634, 95% CI = 1092–2446, $p = 0.017$, FDR-corrected $p = 0.034$).[52]

While the study by Torniainen-Holm M et al. did not show any correlation between EBV infection and AD, this study was based only on the assessment of EBV seroprevalence and possible correlation with neurocognitive declines.[53]

Unfortunately, EBV's role in relation to AD has never been properly explored and addressed. In fact, the characteristics of EBV make it potentially one of the main protagonists in this sense, in particular, its ability to constitute a trigger of chronic inflammation could represent a potential explanation of that neurological damage characteristic of AD. In this regard, it would be appropriate to research EBV-DNA on blood, CSF and brain tissue and at the same time to evaluate and quantify the inflammatory response, by means of cytokine assay, in subjects affected by AD.

6 | CYTOMEGALOVIRUS (CMV)

Cytomegalovirus (CMV) is one of the most ubiquitous viruses in the world, affecting up to 90% of the general population. After the primary infection, the virus then tends to stabilise in a latency phase, with possible reactivation in case of immunocompromise and/or immunostress. Advanced age could be a predisposing condition to immune impairment, such as to induce a reactivation of CMV and consequently the possible hypothesis of a correlation between CMV and the risk of developing AD.[54]

Several studies have shown an association between CMV infection and increased risk of both cognitive impairment and development of AD. Aiello et al. found that individuals with higher levels of IgG antibody to CMV at baseline experienced a more rapid rate of cognitive decline over a 4-year study period than those with lower levels. Strandberg et al.[55] and Katan et al. found that CMV was associated with cognitive decline as discussed in the HSV-1 section above.[56] Carbone et al. found baseline CMV IgG antibody levels to be significantly increased in patients who developed clinical AD over a 5-year follow-up period compared to patients who remained cognitively healthy in a group of elderly patients.[51] The probable involvement of Herpesviridae in old age could be attributable to the phenomenon of immunosenescence, that is, the condition in which in old age the immune system undergoes a dysfunction that could explain the reactivation of herpes viruses.

Tarter et al. highlighted that CMV seropositivity was associated with impaired coding speed, impaired middle-aged learning and recall.[57] In contrast, Lin et al. found CMV in a very high proportion of postmortem vascular dementia brains.[58] CMV also seems to be involved in the process of immunosescence, particularly affecting T cells, with a consequent immune dysregulatory process.[59] Stowe et al. suggested that CMV infection may adversely influence the immune response, allowing for increased HSV-1 reactivation. Stowe et al. measured serum CMV and HSV-1 antibody levels in 1454 multiethnic subjects. The results suggest chronic CMV infection can accelerate immunosenescence, leading to immune dysregulation with increased HSV-1 reactivation.[60]

Recent publications suggest that there is an association between CMV infection and risk of AD. In another study it was pointed out that there was not a direct relationship between CMV infection and the development of AD, but an interaction between CMV and HSV1 was found to be associated significantly with AD development. These findings suggest that CMV infection facilitates the development of HSV1-associated AD, possibly via its effects on the immune system.[61]

In this regard, Barnes and colleagues demonstrated that CMV infection is associated with an increased risk of AD and a faster rate of cognitive decline in older different populations, in particular CMV seropositivity was associated with an increased risk of AD (relative risk, 2.15; 95% CI, 1.42–3.27) and a faster rate of decline in global cognition (estimate [±standard error], -0.02 ± 0.01; $p = 0.03$).[62]

In the study by Lurain et al., it was found that subjects with CMV seropositivity had a greater activity of pro-inflammatory cytokines, both on blood and CerebroSpinal fluid (CSF), and that at the same time they had a greater risk of developing AD.[63]

Westman et al. also showed increased activity of pro-inflammatory cytokines in subjects with positive serology for CMV and AD.[64]

While Lovheim et al. did not show a possible correlation between CMV infection and AD, in particular, the presence of anti-CMV IgG antibodies did not increase the risk of AD (odds ratio [OR], 0.857; $p = 0.497$).[61]

However, the same study highlighted a possible correlation between AD and the interaction between CMV and HSV-1, in particular an association between CMV and HSV1 carriage was detected (OR 7.145, $p < 0.001$); in a conditional logistic regression model, the interaction between CMV and HSV1 was associated with AD development (OR 5.662; $p = 0.007$).[61]

This finding is in some respects like the one already highlighted by Cairns et al., regarding the relationship between AD and the VZV and HSV-1 interaction.[44] Therefore, both the Lovheim and Cairns studies could represent the possibility of the hypothesis of an interaction between herpes viruses and the risk of developing AD.

Although there are few studies on the potential relationship between CMV and AD and this potential relationship does not seem to be clear and evident, there are two very interesting points. In particular, CMV could present two potential and possible indirect roles involved in AD: the potential role in the process of immunosenescence and the consequent dysregulated inflammatory response on the one hand, and on the other hand, the possible interaction with HSV-1 and the reactivation of the latter with the consequent neurological damage. In this regard, this hypothesis should be investigated with the search for CMV-DNA on blood, CSF and brain tissue, with the concomitant search for HSV-1 DNA.

7 | HUMAN HERPESVIRUS 6 (HHV-6) AND HUMAN HERPESVIRUS 7 (HHV-7)

HHV-6 and HHV-7 have a marked neurotropic activity and seem to be involved in a series of neurological pathologies with inflammatory etiopathogenesis.[65]

HHV-6 is a neurotropic virus and exists in 2 forms: type A and type B. The HHV-6A variant is considered more neurotropic than type B.[65] HHV-6 can cause meningoencephalitis, and has been associated with multiple sclerosis, seizures, and temporal lobe epilepsy.[65] HHV-6 establishes latency in the brain and can reactivate under conditions of immunosuppression. HHV-6 has been found in the brains of AD patients in various studies using PCR; Lin and collaborators studied 50 postmortem AD brains and found HHV-6 in 72% of frontal and temporal cortex samples versus 40% of age-matched normal brain samples, which was statistically significant.[58] Hemling et al. examined autopsy brain samples from hippocampus, temporal cortex, frontal cortex, and anterior cingulate gyrus, and found HHV-6 in 88% of AD and 87.5% of normal controls, indicating no significant difference between the two groups. However, the number of specimens from the different brain regions tested was not specified.[66]

Few studies have highlighted or attempted to evaluate the potential correlation between AD and HHV-6, among which Huang et al. observed that HHV-6 infection and in particular the extent of viral replication correlated with neurocognitive decline in elderly subjects.[67] The probable involvement of Herpesviridae in old age could be attributable to the phenomenon of immunosenescence, that is, the condition in which in old age the immune system undergoes a dysfunction that could explain the reactivation of herpes viruses.

Readhead et al. showed increased human herpesvirus 6A (HHV-6A) and human herpesvirus 7 (HHV-7) from subjects with AD compared with controls by searching for HHV-6–DNA and HHV-7–DNA on brain tissue.[68]

Eimer et al. also highlighted that active HHV-6 infections in brain might accelerate amyloid deposition and the progression of AD through in vitro studies.[69]

Particularly interesting is also the hypothesis that HHV-6 infection might interfere with autophagy mechanisms and promote neurodegenerative processes typical of AD. Romeo MA et al. showed that HHV-6A infection of astrocytoma cells and primary neurons reduced autophagy, increased Aβ production and activated tau protein hyper-phosphorylation, supporting the hypothesis that HHV-6 infection might play a role in AD.[70]

While Bigley et al. showed that there was no correlation between HHV-6 and HHV-7 infection and possible Aβ plaque formation and AD development. Through a mouse model and the induction of HHV-6 and HHV-7 infection, Bigley et al. showed that a neuroinflammatory process followed the infection, however, this neuroinflammation did not result in the formation of Aβ plaques or possible pathological alterations of Alzheimer's pathology.[71]

Several studies support the hypothesis of the possible and potential involvement of HHV-6 in AD, while there is little data on the potential role of HHV-7. HHV-6 together with HSV-1 appears to be significantly involved in the etiopathogenesis of AD. In fact, several studies have highlighted how HHV-6 infection could be responsible for that inflammation resulting in neurological damage characteristic of AD.

8 | ANTIVIRAL THERAPY

The data regarding the impact of antiviral therapy for herpes viruses on AD are interesting and innovative, although they are scarce. In fact, some studies have shown that antiviral therapies based on acyclovir can reduce the formation of amyloid plaques and neurofibrillary aggregates in the brain.[72–75]

The study by Chen et al. also showed that prescribing antiviral therapy with acyclovir for Herpes Zoster reduced the risk of developing cerebral dementia (HR = 0.55; 95% CI, 0.40–0.77).[38]

The same study by Bae et al. on a group of 34,505 patients with shingles observed that 28,873 (84%) undergoing antiviral treatment showed a lower risk of developing cerebral dementia (HR 0.76; 95% CI 0.65–0.90). Therefore, the use of antiviral therapy for HZ was associated with a lower risk of developing dementia.[43]

In addition, acyclovir inhibits HSV-1-induced abnormal tau phosphorylation in vitro. Acyclovir decreased Aβ by reducing cellular viral spreading and decreased tau phosphorylation by interfering with viral replication. Penciclovir and foscarnet, which also inhibit viral DNA replication, were shown to reduce phosphorylated tau and Aβ, with foscarnet being less effective than acyclovir and penciclovir. The drug would directly target a potential cause of AD, act on infected cells only, and would not affect the normal metabolism of infected neurons.[72]

The study by Tzeng NS et al. also showed that antiviral therapy with acyclovir reduced the risk of developing dementia, in particular with a retrospective cohort study conducted on 33,448 subjects of which 8362 with newly diagnosed HSV infections Tzeng et al. showed that patients with HSV infection who underwent treatment with acyclovir had a reduced risk of developing dementia (HR = 0.092 [95% CI 0.079–0.108], $p < 0.001$).[73]

Preclinical and small clinical studies treating early-stage AD patients with IntraVenous ImmunoGlobulin (IVIG) showed decreases in CSF Aβ levels and increases in serum Aβ levels compared to baseline, with reductions in cognitive decline compared to controls.[74] However, the Gamma Globulin Alzheimer's Partnership study, a large double blind IVIG clinical trial treating mild to moderate AD patients, did not meet primary outcome objectives regarding cognitive function and activities of daily living.[75]

Although the data regarding anti-Herpes Viruses antiviral therapies and their impact on AD are very interesting and promising, however, these are few studies and almost all retrospective, therefore further studies and clinical trials are needed to evaluate this data.

9 | CONCLUSIONS

Alzheimer's disease is a real challenge, both from a management point of view and in the understanding of the etiopathogenetic mechanism, the latter still unknown. The hypothesis of a possible infectious aetiology and in particular the hypothesis of an involvement of Herpes viruses is always more and more concrete and realistic. After all, there are numerous data that highlight the potential correlations between AD and Herpes viruses. In particular, the possible genetic interference of Herpes viruses with the genome of the neuronal host cell or the possible and continuous stimulation of an immune response with consequent chronic inflammatory response, could motivate and explain the formation of those hallmarkers of AD. In fact, the interaction between multiple herpes viruses could also be at the root of this condition. Particularly interesting are also the data on the impact of anti-Herpes viruses antiviral therapy on the evolution of neurocognitive decline.

These data have to be used to encourage further research in this area, in order to better understand and address AD.

AUTHOR CONTRIBUTIONS

Biagio Pinchera: Conceptualisation, writing – original draft, writing – review & editing, supervision; **Isabella Di Filippo:** Investigation, resources, visualisation; **Federica Cuccurullo:** Resources, project administration; **Elena Salvatore:** Data curation, investigation, resources; **Ivan Gentile:** Supervision, writing – review & editing, project administration, visualisation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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Data available on request from the authors.

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Not applicable.

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