

Review Article

Herpes Simplex Virus and Alzheimer's Disease: The Present State of Clinical Evidence

Stephanie Toscano Kasabkojian^{*}, Gabriela Pacheco de Oliveira, Francine Papaiordanou, Analia Luiza Porto Viana, Antonio Carlos Amedeo Vattimo, Andrea Bauer Bannach, Stevin Zung

Medical Department, Aché Pharmaceuticals Laboratories S. A., São Paulo, Brazil

Email address:

stephanie.kasabkojian@ache.com.br (S. T. Kasabkojian)

^{*}Corresponding author

To cite this article:

Stephanie Toscano Kasabkojian, Gabriela Pacheco de Oliveira, Francine Papaiordanou, Analia Luiza Porto Viana, Antonio Carlos Amedeo Vattimo, Andrea Bauer Bannach, Stevin Zung. Herpes Simplex Virus and Alzheimer's Disease: The Present State of Clinical Evidence.

Clinical Medicine Research. Vol. 10, No. 4, 2021, pp. 121-128. doi: 10.11648/j.cmr.20211004.13

Received: June 10, 2021; **Accepted:** July 1, 2021; **Published:** July 9, 2021

Abstract: Alzheimer's disease (AD) and dementia have a probably multifactorial pathogenesis and, accordingly to several studies, human herpes simplex virus type 1 (HSV-1) infection may be related. The purpose of this review is to assess the updated clinical evidence towards the association between herpes infection and AD. We performed a PubMed/MEDLINE database research and included in this review randomized clinical trials on the subject of antivirals effectiveness and AD, and observational case-control studies and observational cohort studies regarding AD diagnosis (using clinical and/or histological methods) and HSV-1 detection (using molecular biology or immunohistochemical techniques). A total of 23 case-control and 3 cohort studies met the predetermined inclusion criteria. The results showed that AD was associated with HSV-1 in 22 of the 26 included studies, with most of them confirming that herpes infection is more prevalent in AD patients, when compared to control patients. A possible link between HSV-1 and AD was discussed and many different interpretations and hypothesis were considered. Evidence from observational studies suggests a possible relationship between the two conditions, but the role of HSV-1 infection in the pathogenesis of AD is not completely understood yet. Well-designed and large clinical trials are necessary to endorse this hypothesis and to consider the use of antiviral drugs as a potential alternative for prevention or reduction in the progression rate of AD in the future.

Keywords: Alzheimer's Disease, Herpes Simplex, HSV-1, Antiviral, Review

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive impairment in memory, cognitive performance, daily function and independence [1]. The prevalence of AD increases with advancing age, and the global burden of this disease is significant [2].

The most important pathological characteristic changes in AD are intracellular neurofibrillary tangles (formed by the hyperphosphorylation and aggregation of tau protein), extracellular plaques (composed of amyloid beta peptide deposits) and neuronal loss [3, 4].

The etiopathogenesis of AD remains unclear, but a combination of environmental and genetic factors is believed

to be involved in the development of the disease [5]. Among the genetic risk factors, the $\epsilon 4$ allele of the apolipoprotein E gene (APOE- $\epsilon 4$) is known to increase sporadic and late-onset AD susceptibility [6]. Regarding environmental factors, it is suspected that some infections could contribute to the development of the disease through the interaction between pathogens and genetic/immunologic factors and initiate neuropathological changes [4]. In this context, several studies indicate that human herpes simplex virus type 1 (HSV-1) infection may play a role in the development of Alzheimer's disease.

Herpes simplex viruses are among the most ubiquitous

human infections [11]. Infection by HSV-1 causes several diseases, ranging from cutaneous, oral and genital infections to fatal encephalitis [12].

HSV infections are among the most common infections in humans, with seropositivity in 50% to 90% of the adult population [7, 8]. Approximately 15% of those who are sexually active are infected by HSV-2 [7, 8]. Most commonly, virus replication is limited to the epithelia and establishes latency in enervating sensory neurons, reactivating periodically to produce recurrent lesions [7].

HSV-1 is a DNA neurotropic virus, and after primary infection, it may remain latent in the sensory ganglia of the peripheral nervous system and can spread throughout the nervous system [4]. The reactivation of the virus can occur and is commonly inferred by the avidity index of anti-HSV1 immunoglobulin G (IgG) antibodies [9]. IgG neutralizes virus activity, but HSV-1 can avoid this neutralization by binding the Fc portion of IgG₁, IgG₂ and IgG₄, that is, all IgG subclasses except for IgG₃ [10].

The acquisition of HSV by an infant during the peripartum or postpartum period results in neonatal HSV disease, a rare but significant infection that can be associated with severe morbidity and mortality, especially if there is dissemination or central nervous system involvement [13].

Historically, HSV-1 was associated with mouth and eye infections, whereas HSV-2 was attributed specifically to genital herpes. However, currently, it is more widely known that there is a significant overlap in the sites of HSV infection, with an ever-increasing proportion of genital herpes caused by HSV-1 [14].

Despite the availability of antiviral therapies, their efficacies are limited, and new cases of resistant strains have arisen, mainly in immunocompromised patients but also recently reported in immunocompetent patients [12].

An increasing amount of experimental and epidemiological evidence suggests the presence of herpesviruses in the brains of elderly subjects with and without Alzheimer's disease (AD). In addition, the fact that HSV-1 infection of neuronal and glial cells induces the phosphorylation of the tau protein [14] and similarities between the central nervous system regions affected in AD and HSV-1 encephalitis (temporal cortex, frontal cortex and hippocampus) seem to strengthen the hypothesis that the presence of the APOE-ε4 allele and HSV infection increases the risk of AD [14-16].

Oxidative stress is believed to be one of the possible mechanisms by which HSV-1 causes cell damage: oxidative stress via reactive oxygen species (ROS) and reactive nitrogen species is a well-known consequence of HSV-1 infection. Oxidative damage to DNA by ROS results in DNA lesions that might promote AD progression [17]. Another possible mechanism is the action of HSV-1 on telomeres, accumulating foci of DNA damage; a meta-analysis showed that shorter telomeres are consistently found in patients with AD [18, 19].

Neurofibrillary tangles and plaques in the brain are formed by direct cytotoxicity and inflammatory damage, which are related to the reactivation of the virus, and possibly increase the risk of developing AD in subjects who are genetically predisposed.

In these circumstances, an association between AD and herpes infection was evaluated in the present review, based on updated clinical evidence.

2. Methods

2.1. Literature Search

The PubMed/MEDLINE database was searched using the terms "herpes" AND "Alzheimer" without imposing time limitations. The databases were searched from their inception to July 31, 2020.

The final search string was ("herpes"[All Fields] OR "herps"[All Fields]) AND (((("alzheimer s"[All Fields] OR "alzheimer disease"[MeSH Terms]) OR ("alzheimer"[All Fields] AND "disease"[All Fields])) OR "alzheimer disease"[All Fields]) OR "alzheimer"[All Fields]) OR "alzheimers"[All Fields]) OR "alzheimer s"[All Fields]) OR "alzheimers s"[All Fields]). Filters were used to limit the search to human and English language studies.

2.2. Eligibility Criteria

Studies that met the following inclusion criteria were included in this review, aiming to select the clinical data regarding the relationship between herpes infection and AD:

- 1) Randomized clinical trials evaluating the effectiveness of antivirals in AD.
- 2) Observational cohort studies with clinical and/or histological AD diagnosis and HSV-1 detection by immunohistochemical or molecular biology techniques.
- 3) Observational case-control studies with a clinical and/or histological AD diagnosis and HSV-1 detection by immunohistochemical or molecular biology techniques.

2.3. Exclusion Criteria

Reviews and editorials were excluded to avoid repeated information already considered in the original screened studies. *In vitro* studies were excluded since the objective of this review was to evaluate clinical evidence. Studies with no clinical and/or histological AD diagnosis and/or no HSV-1 detection by immunohistochemical or molecular biological techniques were also excluded since these points were considered inclusion criteria. Unrelated studies of herpes and/or AD screened in the literature search were also disregarded.

2.4. Study Evaluation

The selection phase involved a review by the authors of the abstracts and full texts based on the eligibility and exclusion criteria described above.

3. Results

23 case-control and 3 cohort studies met the predetermined inclusion criteria. We found no randomized controlled trials. In total, there were 39,835 subjects enrolled in the included studies (figure 1).

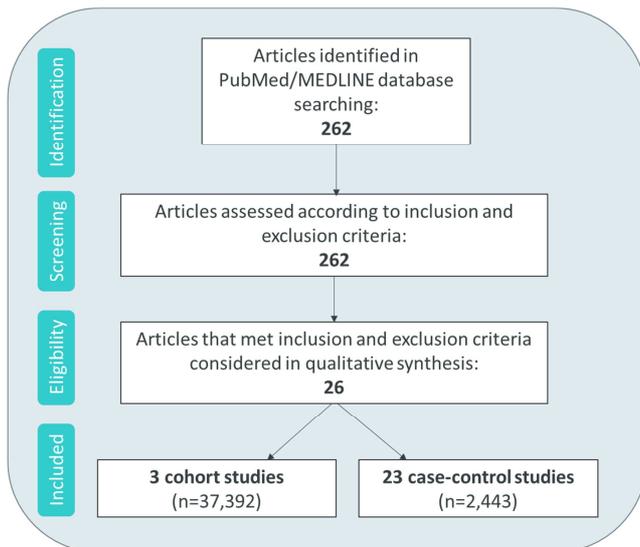


Figure 1. Article identification, assessment, and selection.

It was possible to correlate the occurrence of an association between HSV 1 infection and the presence of AD in 22 of the 26 selected studies, in which, infection was more frequent among patients with AD than among controls (figure 2).

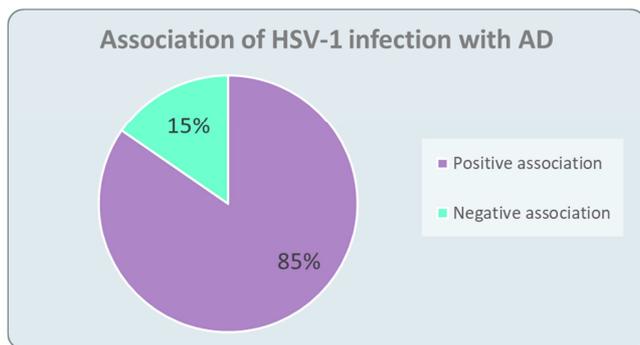


Figure 2. Association of HSV-1 infection with AD observed in the included studies.

A total of 4 studies found no evidence of an association between HSV-1 and AD. Roberts and colleagues (1986) found no HSV antigenicity in the temporal lobe in 25 Alzheimer's disease cases or in 32 controls without neurological disease [20]. Walker and coworkers (1989), in a small case-control study using an *in situ* hybridization technique to detect HSV-1 nucleic acids, found no hybridization signal in the brain sections of 4 AD individuals and 2 controls [21]. Renvoize *et al.* (1987) found no statistically significant differences in HSV-1 serum antibody titers between 33 AD individuals and 28 controls (psychiatric patients without AD) [22]. Finally, Ounanian and colleagues (1990) searched for antibody activity against different viruses and found a higher total IgG mean level in sera from 19 AD patients than in sera from 21 age-matched controls, but HSV-1 antibody titers were significantly lower in AD patients than in controls, suggesting that there is no relationship between AD and herpesvirus [23].

On the other hand, the hypothesis of the involvement of

HSV-1 in the etiopathogenesis of AD was suggested in a case-control study conducted by Jamieson and colleagues (1991) using polymerase chain reaction (PCR). In this study, HSV-1 DNA (specifically the viral thymidine kinase gene) was found in temporal and hippocampal regions of brain samples from individuals with and without AD, suggesting the hypothesis that elements such as the expression of viral genes and host vulnerability might be related to the occurrence of AD [11]. In 1992, the same author assumed the occurrence of deleterious effects of the virus in periods of its reactivation [24].

The association between virus reactivation in the brain and the presence of at least one APOE- $\epsilon 4$ allele was considered an important risk factor for AD by some researchers [16, 25, 26]. Lin and colleagues (1996) found a higher risk of developing AD in individuals with the presence of HSV-1 detected by PCR in the brain and in individuals who had an apolipoprotein E allele $\epsilon 4$ than in individuals with only one of these factors [26].

Similarly, Deatly *et al.* (1990) found latent HSV-1 RNA at a statistically significantly higher frequency in the trigeminal ganglia of AD patients (17/21 = 81.00%) than in age-matched individuals without evidence of neuropsychiatric illness or with non-Alzheimer's dementia (9/19 = 47.40%). Analyzing these results, the authors hypothesized that there is a more frequent establishment of HSV-1 latent infections in AD patients [27].

HSV-1 DNA (specifically the HSV-1 glycoprotein D gene) has also been detected by PCR in the brain samples (mainly frontal and temporal cortex) of individuals with the least common form of AD (familial AD), in which the disease starts earlier. In a study conducted by Mori and coworkers (2004), the occurrence of HSV-1 was linked to beta-amyloid deposition in the cerebral cortex. This suggests that HSV-1 reactivation in the brains of patients with familial AD is associated with beta-amyloid deposition, pointing to the possible involvement of HSV-1 and genetic factors in the pathogenesis of familial Alzheimer's disease [28].

Wozniak *et al.* (2009) studied the presence of HSV-1 DNA by brain PCR in 6 AD patients and 5 healthy controls and the proximity between this DNA and amyloid plaques by *in situ* PCR. The results showed that HSV-1 DNA was found in almost all the samples studied and in nearly all amyloid plaques. In both AD patients and aged individuals without the disease, few plaques lacked HSV1 DNA, suggesting that almost all were caused by the virus. The proportion of HSV1 DNA associated with plaques was lower in aged normal brains than in AD brains, which could indicate a possible relationship between the virus and plaque formation. The findings also suggested that the virus enters the brains of elderly individuals due to a decline in immunity and can reactivate and infect cells, which can then die and release amyloid aggregates, which can form amyloid plaques. Apparently, in APOE- $\epsilon 4$ carriers, AD develops either because of HSV1-induced plaque accumulation or as a direct consequence of virus-induced cell death or inflammation [29]. In another study, Wozniak

also found HSV-1 activity in the brains of individuals with and without AD [30].

A commonly adopted method to study the possible relationship between HSV-1 and AD is the analysis of anti-HSV antibodies in AD individuals compared to controls without AD. In this context, Lövheim and coworkers (2014) evaluated the presence of anti-HSV antibodies in plasma samples obtained from 360 AD patients and 360 sex- and age-matched controls without dementia. An increased risk for AD was found in individuals with the presence of anti-HSV IgG antibodies in their plasma, with a follow-up time of 6.6 years or more between plasma sampling and AD diagnosis. This result indicates the possible participation of HSV infection in the early development of AD. This study is particularly important due to its robustness, based on the large number of individuals evaluated and the diagnostic reliability of AD cases [16].

Mancuso and colleagues (2014) investigated associations between HSV-1 humoral responses and cortical gray matter volumes in AD individuals using MRI. They found that a significantly higher proportion of AD patients compared to sex- and age-matched healthy controls presented with elevated antiviral Ab titers. Additionally, temporal and orbitofrontal cortices were more preserved in AD patients in whom higher HSV-1-specific Ab titers were detected. The authors concluded that HSV-1-specific-Abs could possibly play a protective role in the early stages of AD [15].

In a large population-based cohort study, 512 aged individuals without dementia were followed for 14 years, and during that period, 77 of them developed AD. IgM-positive subjects (controlled for known risk factors for AD - age, educational level and APOE4 status) showed a significantly higher risk of developing AD. In IgG-positive subjects, no significantly increased risk was observed. It was concluded that the reactivation of HSV seropositivity is highly correlated with incident AD and that HSV chronic infection may contribute to progressive brain damage in AD [31]. In another large epidemiological cohort that enrolled 3432 study subjects with a mean follow-up time of 11.3 years, a total of 245 subjects were diagnosed with AD over time. An association between anti-HSV IgM, which possibly indicates reactivated infection, and increased risk for AD was also observed. Positivity for anti-HSV IgM was found to almost double the risk for AD in this study [32].

Kobayashi and coworkers (2013), in a case-control study, evaluated the possible association between HSV-1 reactivation and cognitive symptoms in AD by avidity index analysis of anti-HSV-1 IgG antibodies—a recognized indicator of HSV-1 reactivation. This avidity index was higher in individuals with amnesic mild cognitive impairment (MCI), a condition that can predispose individuals to AD, than in AD subjects or controls, suggesting that HSV-1 reactivation occurs from the stage of amnesic MCI and that the anti-HSV-1 IgG antibody avidity index might be a convenient biomarker for the early diagnosis of amnesic MCI as well as AD. It was also suggested that antiviral medication for HSV-1 could play a

role in preventing the onset of AD [10].

Smaller observational studies also found an association between HSV-1 infection and AD, corroborating these findings. Agostini and colleagues found a higher proportion of individuals with MCI presenting HSV-1 IgG₃ in the serum than AD individuals and sex- and age-matched healthy controls. However, the neutralizing capacity of AD patients seemed to be reduced even in the presence of elevated amounts of IgG₃. These data may suggest that in MCI individuals, there is an attempt to reduce HSV-1 reactivation by increasing the expression of IgG₃, but the counteracting activity of AD serum is impaired regardless of its IgG₃ quantity [33]. The same authors, in another study, analyzed the possible relationship between HSV-1-specific humoral immunity and a polymorphism (an arginine-to-glycine substitution at position 78) in paired immunoglobulin-like type 2 receptor alpha (PILRA, a cell surface receptor used by HSV-1 to infect cells) in MCI, AD and healthy controls. They observed that patients with the “protective” PILRA R78 (AA) rs1859788 genotype had higher HSV-1-specific IgG₁ titers, indicating a possible interaction between distinct genetic and environmental risk factors involved in the pathogenesis of AD [33].

Bu XL et al (2015) hypothesized that infection by 4 to 5 pathogens (HSV-1, cytomegalovirus, *Borrelia burgdorferi*, *Chlamydomydia pneumoniae*, *Helicobacter pylori*) may play a role in the development of AD and found higher levels of serum inflammatory cytokines (tumor necrosis factor α and interleukin-6) in these individuals than in those exposed to up to 3 pathogens. Despite the theory about a strong association between inflammation and cognitive decline, the exact mechanism for the possible correlation between infectious burden and AD remains unclear [34].

IFN- λ is another key cytokine in antiviral activity against HSV-1 infection, and single nucleotide polymorphisms in the genes that regulate its expression were observed in AD patients. An allelic discrimination analysis was performed in 79 AD patients, 57 patients with MCI and 81 healthy controls who were HSV-1 positive to determine the correlation of IFN- λ serum concentration with anti-HSV-1 antibody titers. The results suggested that the IFNL3 rs12979860 and IRF7 rs6598008 polymorphisms modulate immune responses against HSV-1 through their effect on the IFN- λ pathway. It was concluded that polymorphisms in genes involved in antiviral mechanisms may play a role in modulating the pathogenesis of AD, supporting the hypothesis of a possible relation between viral infections and dementia [4].

The importance of the discussion about the relationship between HSV-1 and AD can be evidenced by studies evaluating dementia risk reduction with the use of antiherpetic medications. In this context, a retrospective cohort study involving a Taiwanese population found an association between the use of antiherpetic medications to treat HSV infections and a reduced risk of dementia, including AD [35].

Table 1 summarizes the main characteristics of the included studies.

Table 1. Summary of included studies.

Author, year	Title	Design	n (disease)	n (control)	Possible association between HSV and AD (Y/N)
Agostini, 2019	The PILRA G78R Variant Correlates with Higher HSV-1-Specific IgG Titers in Alzheimer's Disease	Case-Control	61 (AD)/48 (MCI)	57	Y
Agostini, 2018	HSV-1-Specific IgG Subclasses Distribution and Serum Neutralizing Activity in Alzheimer's Disease and in Mild Cognitive Impairment	Case-Control	67 (AD)/58 (MCI)	61	Y
Tzeng, 2018	Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan	Prospective Cohort	8362 (HSV)	25086	Y
Costa, 2017	Modulation of Immune Responses to Herpes Simplex Virus Type 1 by IFNL3 and IRF7 Polymorphisms: A Study in Alzheimer's Disease.	Case-Control	79 (AD)/57 (MCI)	81	Y
Lovheim, 2015	Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study.	Case-Control	360 (AD)	360	Y
Lovheim, 2015	Reactivated herpes simplex infection increases the risk of Alzheimer's disease.	Prospective Cohort	NA	3432	Y
Bu, 2015	A study on the association between infectious burden and Alzheimer's disease	Case-Control	128 (AD)	135	Y
Mancuso, 2014	Titers of Herpes Simplex Virus Type 1 Antibodies Positively Correlate with Grey Matter Volumes in Alzheimer's Disease	Case-Control	83 (AD)	51	Y
Kobayashi, 2013	Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnesic mild cognitive impairment and Alzheimer's disease.	Case-Control	85 (AD)/34 (MCI)	28	Y
Letenneur, 2008	Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study.	Prospective Cohort	NA	512	Y
Wozniak, 2009	Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques.	Case-Control	6 (AD)	5	Y
Wozniak, 2005	Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients.	Case-Control	27 (AD)	13	Y
Mori, 2004	Reactivation of HSV-1 in the brain of patients with familial Alzheimer's disease.	Case-Control	5 (AD)	6	Y
Mori, 2004	PCR Search for the Herpes Simplex Virus Type 1 Genome in Brain Sections of Patients with Familial Alzheimer's Disease	Case-Control	5 (AD)	6	Y
Itabashi, 1997	Herpes simplex virus and risk of Alzheimer's disease.	Case-Control	46 (AD)	23	Y
Itzhaki, 1997	Herpes simplex virus type 1 in brain and risk of Alzheimer's disease.	Case-Control	46 (AD)	44	Y
Lin, 1996	Neurotropic viruses and Alzheimer disease. Interaction of herpes simplex type 1 virus and apolipoprotein E in the etiology of the disease.	Case-Control	36 (AD)	36	Y
Lin, 1995	Alzheimer's disease, herpes simplex virus type 1, cold sores and apolipoprotein E4.	Case-Control	26 (AD)	26	Y
Jamieson, 1991	Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains.	Case-Control	8 (AD)	6	Y*
Jamieson, 1991	Detection of herpes simplex virus type 1 DNA sequences in normal and Alzheimer's disease brain using polymerase chain reaction	Case-Control	8 (AD)	5	Y
Jamieson, 1992	Herpes simplex virus type 1 DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type.	Case-Control	14 (AD)	9	Y
Ounanian, 1990	Antibodies to viral antigens, xenoantigens, and autoantigens in Alzheimer's disease.	Case-Control	19 (AD)	21	N
Deatly, 1990	Human herpes virus infections and Alzheimer's disease.	Case-Control	21 (AD)	19	Y
Walker, 1989	In situ hybridization analysis for herpes simplex virus nucleic acids in Alzheimer disease.	Case-Control	4 (AD)	2	N
Renvoize, 1987	A sero-epidemiological study of conventional infectious agents in Alzheimer's disease.	Case-Control	33 (AD)	28	N
Roberts, 1986	Herpes simplex virus: a role in the aetiology of Alzheimer's disease?	Case-Control	25 (AD)	32	N

* the possibility cannot be excluded that the presence of HSV DNA may be irrelevant to AD

4. Discussion

The aging of the world population has led to an increase in the number of cases of AD, the most common type of dementia [30]. Hence, a better understanding of the etiopathogenesis of the disease is imperative.

The presence of the APOE ϵ 4 allele has been implicated as a risk factor for AD, but it is neither sufficient nor indispensable for the development of the illness [16]. As a multifactorial illness, other aspects must play a role in the pathophysiology of AD, and among them, the relation of HSV1 and AD has been studied.

HSV-1 infection is very common, and the virus can be

latent in the peripheral nervous system, especially in the trigeminal ganglia. It is believed that with the decline in immunity with age, HSV-1 can reach the brain in elderly patients [17].

Numerous studies indicate that HSV-1 infection may participate in the development of Alzheimer's disease. HSV-1 infection showed an association with AD in 22 of the 26 selected studies, with most of them indicating that herpes infection is more frequent in AD patients than in controls.

Several interpretations and hypotheses were suggested for the possible connection between HSV-1 and AD, such as [14, 29, 30]:

- a. Similarities between the areas affected in the central nervous system (CNS) in AD and in HSV-1 encephalitis;
- b. The detection of this virus in elderly brain tissue and within amyloid plaques from AD individuals;
- c. The detection of viral DNA plaque-associated;
- d. An increase in beta amyloid intracellular levels triggered by HSV-1 infection of neuronal and glial cells and the induction of the phosphorylation of tau protein.

It is worth mentioning that the association between HSV-1 DNA and amyloid plaques is not indisputable proof of causality between the presence of the virus and the formation of the plaques, having already suggested the possibility that this colocalization may function as an inhibitor of viral replication [16, 28]. On the other hand, other studies propose that HSV-1 can induce cell death or the formation of amyloid plaques. It is hypothesized that HSV-1 affects how beta amyloid is produced through the proteolysis of amyloid precursor protein (APP) and how it is processed within the brain, thus being linked to the occurrence of AD [17, 29].

Based on the results from previous studies, it is reasonable to suppose that the presence of HSV-1 in the brain is not sufficient for the development of AD, since studies have also detected the presence of this virus in brain samples from individuals without AD, and there is probably an influence of factors such as viral expression and the vulnerability of the individual in the pathophysiology of AD. It is possible that factors related to the immunity of the individual are associated with the reactivation of the virus and its dispersion to the central nervous system (association between the expression of viral genes and host vulnerability), since HSV-1 latent infections were more frequent in AD patients with viral spread to the brain [27].

Although no current technique has been able to provide direct evidence of HSV reactivation in the human brain, recurrent viral reactivations can have cumulative damaging effects as they cause cytotoxicity and brain inflammation, eventually becoming related to AD [17]. In another four studies, the risk of developing AD was much greater in subjects who were HSV-1 positive in the brain and who possessed an APOE4 allele. Some studies indicate a higher risk of AD in patients with at least one APOE ϵ 4 allele and the presence of HSV-1, demonstrating that the combination of virus reactivation in the brain and the presence of the APOE ϵ 4 allele can constitute a greater risk factor for AD, together with the hypothesis that APOE- ϵ 4 carriers are more

vulnerable to herpes infection [26]. The mechanism of interaction between HSV1 and APOE- ϵ 4 remains uncertain [17].

Other hypotheses for the correlation between HSV-1 and AD have been proposed [4], 10, 15, 33]:

- a. Increased risk of AD following HSV-1 reactivation: several reactivations would lead to progressive damage in parts of the brain that may favor the clinical expression of AD;
- b. Impaired ability of IgG₃ to neutralize the virus in AD subjects;
- c. Polymorphisms in genes involved in antiviral and HSV-1 infection mechanisms may play a role in modulating the pathogenesis of AD;
- d. Accumulative infections and inflammation;
- e. Oxidative stress caused by HSV-1.

One of the studies showed the presence of HSV-1 DNA in brain samples from patients with familial AD, suggesting that preventive and therapeutic measures against HSV-1 should also be taken for familial Alzheimer's disease patients, since repeated reactivation of HSV-1 may promote neurodegeneration [28].

A large proportion of the population carries HSV; therefore, additional factors must be considered modifiers of the AD risk associated with HSV. An individual's humoral immune response to infection might be one such factor, as well as the presence or absence of the APOE-E4 allele.

This review has important limitations. The studies evaluated are heterogeneous; the criteria used for AD diagnosis, methods and endpoints are quite different between the studies; and several of the studies reviewed have methodological limitations, such as a small number of participants and an observational design.

However, the assessment of a possible relationship between HSV-1 and AD is very important, since reactivations of the virus (thought to be a possible cause of progressive brain damage, favoring clinical expression and increasing the risk of AD) can be easily detected with periodic blood tests, and AD prevention strategies could be established. Such reactivations can be inferred by IgM anti-HSV1 antibody levels and the avidity index of anti-HSV-1 IgG antibodies. As inflammation can lead to HSV-1 reactivation, one hypothesis is that the use of anti-inflammatory drugs could reduce the extent of the reactivation in question. Likewise, the use of antivirals could be of great therapeutic value if a relationship between AD and HSV-1 is confirmed [16].

5. Conclusion

Accordingly to observational studies, a possible association between AD and HSV-1 infection (especially in APOE ϵ 4 carriers) could be possible, but the role of the virus in the pathogenesis of AD remains still uncertain. Well-designed and large clinical trials are necessary to confirm this hypothesis and to consider the use of antiviral drugs as a potential alternative for prevention or reduction in the progression rate of AD.

Acknowledgements

This work was supported by Aché Pharmaceuticals Laboratories S. A.

References

- [1] Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, Young JZ, et al. Single-cell transcriptomic analysis of Alzheimer's disease. *Nature*. 2019 Jun; 570 (7761): 332-337.
- [2] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013 Jan; 9 (1): 63-75. e2.
- [3] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet*. 2011 Mar 19; 377 (9770): 1019-31.
- [4] Costa AS, Agostini S, Guerini FR, Mancuso R, Zanzottera M, Ripamonti E, et al. Modulation of Immune Responses to Herpes Simplex Virus Type 1 by IFNL3 and IRF7 Polymorphisms: A Study in Alzheimer's Disease. *J Alzheimers Dis*. 2017; 60 (3): 1055-1063.
- [5] Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int J Nanomedicine*. 2019 Jul 19; 14: 5541-5554.
- [6] Castellano JM, Kim J, Stewart FR, Jiang H, DeMattos RB, Patterson BW, et al. Human apoE isoforms differentially regulate brain amyloid- β peptide clearance. *Sci Transl Med*. 2011 Jun 29; 3 (89): 89ra57.
- [7] Whitley R, Baines J. Clinical management of herpes simplex virus infections: past, present, and future. *F1000Res*. 2018 Oct 31; 7: F1000 Faculty Rev-1726.
- [8] Whitley RJ. Herpes Simplex Virus Infections of the Central Nervous System. *Continuum (Minneapolis)*. 2015 Dec; 21 (6 Neuroinfectious Disease): 1704-13.
- [9] Kobayashi N, Nagata T, Shinagawa S, Oka N, Shimada K, Shimizu A, et al. Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnesic mild cognitive impairment and Alzheimer's disease. *Biochem Biophys Res Commun*. 2013 Jan 18; 430 (3): 907-11.
- [10] Agostini S, Mancuso R, Hernis A, Costa AS, Nemni R, Clerici M. HSV-1-Specific IgG Subclasses Distribution and Serum Neutralizing Activity in Alzheimer's Disease and in Mild Cognitive Impairment. *J Alzheimers Dis*. 2018; 63 (1): 131-138.
- [11] Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J Med Virol*. 1991 Apr; 33 (4): 224-7.
- [12] Pires de Mello CP, Bloom DC, Paixão IC. Herpes simplex virus type-1: replication, latency, reactivation and its antiviral targets. *Antivir Ther*. 2016; 21 (4): 277-86.
- [13] James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. *Infect Dis Clin North Am*. 2015 Sep; 29 (3): 391-400.
- [14] Mancuso R, Baglio F, Cabinio M, Calabrese E, Hernis A, Nemni R, et al. Titers of herpes simplex virus type 1 antibodies positively correlate with grey matter volumes in Alzheimer's disease. *J Alzheimers Dis*. 2014; 38 (4): 741-5.
- [15] Lövheim H, Gilthorpe J, Johansson A, Eriksson S, Hallmans G, Elgh F. Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study. *Alzheimers Dement*. 2015 Jun; 11 (6): 587-92.
- [16] Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet*. 1997 Jan 25; 349 (9047): 241-4.
- [17] Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: possible mechanisms and signposts. *FASEB J*. 2017 Aug; 31 (8): 3216-3226.
- [18] Deng Z, Kim ET, Vladimirova O, Dheekollu J, Wang Z, Newhart A, et al. HSV-1 remodels host telomeres to facilitate viral replication. *Cell Rep*. 2014 Dec 24; 9 (6): 2263-78.
- [19] Forero DA, González-Giraldo Y, López-Quintero C, Castro-Vega LJ, Barreto GE, Perry G. Meta-analysis of Telomere Length in Alzheimer's Disease. *J Gerontol A Biol Sci Med Sci*. 2016 Aug; 71 (8): 1069-73.
- [20] Roberts GW, Taylor GR, Carter GI, Johnson JA, Bloxham C, Brown R, et al. Herpes simplex virus: a role in the aetiology of Alzheimer's disease? *J Neurol Neurosurg Psychiatry*. 1986 Feb; 49 (2): 216.
- [21] Walker DG, O'Kusky JR, McGeer PL. In situ hybridization analysis for herpes simplex virus nucleic acids in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1989 Fall; 3 (3): 123-31.
- [22] Renvoize EB, Awad IO, Hambling MH. A sero-epidemiological study of conventional infectious agents in Alzheimer's disease. *Age Ageing*. 1987 Sep; 16 (5): 311-4.
- [23] Ounanian A, Guilbert B, Renversez JC, Seigneurin JM, Avrameas S. Antibodies to viral antigens, xenoantigens, and autoantigens in Alzheimer's disease. *J Clin Lab Anal*. 1990; 4 (5): 367-75.
- [24] Jamieson GA, Maitland NJ, Wilcock GK, Yates CM, Itzhaki RF. Herpes simplex virus type 1 DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type. *J Pathol*. 1992 Aug; 167 (4): 365-8.
- [25] Itabashi S, Arai H, Matsui T, Higuchi S, Sasaki H. Herpes simplex virus and risk of Alzheimer's disease. *Lancet*. 1997 Apr 12; 349 (9058): 1102.
- [26] Lin WR, Shang D, Itzhaki RF. Neurotropic viruses and Alzheimer disease. Interaction of herpes simplex type 1 virus and apolipoprotein E in the etiology of the disease. *Mol Chem Neuropathol*. 1996 May-Aug; 28 (1-3): 135-41.
- [27] Deatly AM, Haase AT, Fewster PH, Lewis E, Ball MJ. Human herpes virus infections and Alzheimer's disease. *Neuropathol Appl Neurobiol*. 1990 Jun; 16 (3): 213-23.
- [28] Mori I, Kimura Y, Naiki H, Matsubara R, Takeuchi T, Yokochi T, et al. Reactivation of HSV-1 in the brain of patients with familial Alzheimer's disease. *J Med Virol*. 2004 Aug; 73 (4): 605-11.
- [29] Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. *J Pathol*. 2009 Jan; 217 (1): 131-8.
- [30] Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF. Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. *J Med Virol*. 2005 Feb; 75 (2): 300-6.

- [31] Letenneur L, Pérès K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. *PLoS One*. 2008; 3 (11): e3637.
- [32] Lövheim H, Gilthorpe J, Adolfsson R, Nilsson LG, Elgh F. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. *Alzheimers Dement*. 2015 Jun; 11 (6): 593-9.
- [33] Agostini S, Costa AS, Mancuso R, Guerini FR, Nemni R, Clerici M. The PILRA G78R Variant Correlates with Higher HSV-1-Specific IgG Titers in Alzheimer's Disease. *Cell Mol Neurobiol*. 2019 Nov; 39 (8): 1217-1221.
- [34] Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, et al. A study on the association between infectious burden and Alzheimer's disease. *Eur J Neurol*. 2015 Dec; 22 (12): 1519-25.
- [35] Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, Huang SY, et al. Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan. *Neurotherapeutics*. 2018 Apr; 15 (2): 417-429.