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Recent insights into viral infections as a trigger and accelerator in alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which only symptomatic medication is available, except for the recently FDA-approved aducanumab. This lack of effective treatment urges us to investigate alternative paths that might contribute to disease development. In light of the recent SARS-CoV-2 pandemic and the disturbing neurological complications seen in some patients, it is desirable to (re)investigate the viability of the viral infection theory claiming that a microbe could affect AD initiation and/or progression. Here, we review the most important evidence for this theory with a special focus on two viruses, namely HSV-1 and SARS-CoV-2. Moreover, we discuss the possible involvement of extracellular vesicles (EVs). This overview will contribute to a more rational approach of potential treatment strategies for AD patients.

Keywords: Alzheimer's disease; Viral infection theory; Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; Herpes simplex virus; HSV

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Introduction

Alzheimer's disease (AD; see Glossary) is an age-related neurodegenerative disease that was discovered in 1907 by Alois Alzheimer.[1] It is the most common form of dementia, affecting > 50 million people today worldwide and this number is set to increase in the coming decades.[2,3] Patients are characterized by progressive and disabling deficits in cognitive function, ultimately leading to impairment in daily life quality.[4] Pathologically, AD brains are marked by the deposition of amyloid-beta (Aβ) protein in senile plaques outside neurons and the formation of neurofibrillary tangles (NFT) composed of hyperphosphorylated Tau (p-Tau) protein inside neurons. This results in the loss of synapses and neurodegeneration which ultimately leads to symptoms associated with AD.[5] Although the effects of the disease are similar, there are two main types of AD: early-onset AD (EOAD) usually starting before the age of 65 and late-onset AD (LOAD) developing after the age of 65. EOAD forms the minority (5 %) of all AD cases and has an autosomal-dominant inheritance linked to three genes: amyloid protein precursor (*APP*), presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*).[6] By contrast, researchers have not found a specific gene that directly causes LOAD and several hypotheses are proposed as the underlying cause. Today, the three most common hypothesis are the Aβ cascade hypothesis, the Tau hypothesis and the neuroinflammation hypothesis.[7] Consequently, research has so far mainly focused on the evaluation of therapies aiming to reduce pathological aggregates of either Aβ or p-Tau or aiming to lower neuroinflammation. Unfortunately, except for the recently FDA-approved aducanumab for which the therapeutic effect is not yet conclusively proven, only symptomatic medication that is effective for some AD patients is available.[8–13] Owing to the absence of disease-modifying therapeutics and the increasing number of AD patients, we urgently need to investigate other hypotheses that could also contribute to the development of AD.

In light of the coronavirus disease 19 (COVID-19) pandemic and the associated neurologic complications in some patients, one of the more controversial hypothesis has gained increasing attention, namely the viral infection hypothesis.[14–16] The idea that a viral infection can affect the development of AD goes back to 1982 when Ball *et al.* proposed the idea that recurrent infection with human herpesvirus (HSV)-1 plays a part in AD development and/or progression.[17] Over the years, this idea was further supported by post-mortem brain studies,[18] epidemiological studies,[19–23] genetic data[24–27] and preclinical studies,[28–33] as discussed later in this review.

Mechanisms underlying viral pathogenesis in AD might include a direct or indirect viral effect. According to the 'direct infection theory', the virus enters the brain and causes neuronal death or activates antiviral responses. This leads to neuroinflammation and AD pathology. In most cases, reactivation of the virus or periodical reinfection are supposed to correspond to the cumulative damage observed in AD patients.[24] In contrast to the direct hypothesis, the 'indirect infection hypothesis' assumes that the virus does not need to enter the brain to cause AD pathology and the effect is mediated via virus-induced systemic inflammation. Of note, it became increasingly clear that inflammation, peripheral and central, are important (and often early) events in AD progression.[34,35] In agreement with this, our recent publication entangles different mechanisms behind the interplay between peripheral inflammation and AD brain pathology.[36] Recently, we also reviewed the current understanding of how systemic inflammatory processes can affect brain pathology.[37] Next to the direct and indirect forms of the viral infection hypothesis, other possible mechanisms behind a viral infection and the development of AD are also under investigation. For example, as the involvement of extracellular vesicles (EVs) in viral infections and AD is becoming increasingly clear, the idea that viruses affect the development and progression of AD by interfering with EV pathways presents itself. EVs are nano-sized membrane vesicles that are secreted by a wide variety of cell types. EVs ferry biological cargos as proteins, lipids and nucleic acids from the mother cell to adjacent and distant cells. Studies have demonstrated that EVs can serve as vectors to transfer misfolded proteins such as Aβ and Tau between cells.[38] Because viruses can interfere with biogenesis pathways of EVs, viruses can affect the production of EVs and in this way contribute to the progression or development of AD.[39,40] Later in this review, we elaborate further on the different ways a viral infection can affect AD development.

Throughout history, several viruses have been proposed to be associated with the development of AD, mainly human herpesviruses and now recently also human coronaviruses.[2,21–23,31,41] Both virus families infect a large part of the population. In 2016, 67 % of the global population under the age of 50 was HSV-1 positive, whereas at present, according to the world health organization, >267 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[42,43] From this point of view, it is important not to ignore the potential interplay between a viral infection and the development of AD. If viruses are indeed able to induce or accelerate AD this will result in a strong increase in AD patients over the next 10–15 years owing to the COVID-19 epidemic today. This increase in AD patients will put enormous pressure on our healthcare system and, in that case, will also result in an enormous economic burden. Consequently, it is important to now reconsider the viability of the viral infection hypothesis to develop appropriate antiviral treatments for these patients.

In this review, we summarize the supporting evidence and elaborate on the current understanding of possible underlying mechanisms of the viral infection theory, including new insights regarding the role of EVs and how viruses can contribute to AD pathology spread. Next, we highlight the current knowledge of the two viruses currently seen as risk factors for AD development, namely HSV-1 and SARS-CoV-2. Finally, we outline the use of antiviral therapies as AD treatments.

Evidence for the viral infection theory

Post-mortem studies

The concept that infectious agents can be the cause of AD is not new and dates back to 1982. The first evidence was provided by a post-mortem study that noted that areas affected by HSV-1 coincided with Aβ plaques and p-Tau tangles in the brain of patients in the early stage of AD.[17] A few years later, this theory was affirmed by Gannicliffe *et al.* suggesting that reactivation of

HSV-1 in the elderly might result in neuropsychiatric diseases.[18] Moreover, Baker's group showed an induction of Aβ plaques in marmosets 6–7 years after intracerebral injection of human post-mortem AD brain tissue. This result led to the speculation that a transmissible component must be present in the post-mortem brains of AD patients.[44] In addition, this transmissibility was also observed by injecting post-mortem AD brain extracts in the cerebrum of AD transgenic mice.[45].

Epidemiological studies

Next to the post-mortem studies described above, epidemiological studies present a second batch of evidence for the viral infection theory. Recently, three population cohort studies investigated the relation between anti-HSV immunoglobulin (Ig) titers and the development of AD.[21–23] Two of these studies showed an association between the detection of anti-HSV IgM and a higher risk for AD development.[22,23] In the third study, the number of persons positive for anti-HSV IgM was too small to detect any possible association.[21] By contrast, AD development was not significantly associated with the presence of anti-HSV IgG in all these studies.[22,23] However, Lövheim *et al.*, the third cohort study, did see an association between AD development and anti-HSV IgG levels when blood samples were taken at least 6 years before AD diagnosis.[21] The discrepancy between these epidemiological studies can be explained by the fact that the study of Lövheim *et al.* was a controlled nested case cohort study with a smaller number of included AD patients (36 patients) whereas the two other cohort studies included a larger number of AD patients (50 and 130 AD patients) lowering the risk for inclusion of a bias. Next, a retrospective cohort study of 2018 in Taiwan found that treatment of HSV-infected patients with anti-herpetic medication resulted in a reduced risk for the development of dementia.[19] Upon anti-herpetic treatment only 5.8 % HSV-1 and HSV-2 infected patients developed dementia, whereas dementia was observed in 28.3 % of the untreated HSV-infected patients during the next ten years.[19] Similarly, a cohort study in Sweden conducted between 2005 and 2017 showed that antiviral treatment of varicella zoster virus (VZV) or HSV-positive patients was associated with a reduced risk of dementia.[20].

Genome-wide association studies (GWAS)

Genetic data suggest an association between viral infections and AD pathophysiology. First, the apolipoprotein E (*APOε*) 4 allele, known as a genetic risk factor for AD, appears to also determine the susceptibility of a cell to viral infections.[24] For example, Burt *et al.* demonstrated that this *APOε4* allele augments the cell fusion of the human immunodeficiency virus (HIV) *in vitro*. Moreover, according to an epidemiological study, HIV-positive *APOε4* homozygote patients are characterized by a faster disease progression and death compared with *APOε3* homozygote patients.[46] In addition, the presence of the *APOε4* allele is considered as a risk factor to suffer from herpes labialis upon HSV-1 infection. Recently, *APOε4* homozygote patients have also been associated with an increased risk for the development of severe COVID-19.[47] Beside the *APOε* gene, genes related to viral entry [e.g., clusterin and phosphatidylinositol binding clathrin assembly protein (*PICALM*)] and genes involved in the complement pathways (e.g., complement protein C3) are considered as AD susceptibility genes.[25] The complement system is part of the innate immune system from which the activation is triggered by most viral infections. Once activated, the complement contributes to the clearance of the virus via opsonization, aggregation, recruitment of phagocytic cells and lysis of infected cells mediated by the insertion of a membrane attack complex.[48] In addition, infection with human herpes virus (HHV) 6A led to an increase in the expression of genes involved in the processing of APP.[27] Examples include beta-secretase 1 (*BACE1*) and *PSEN1*, which respectively code for β-secretase and a component of γ-secretase, two enzymes involved in the amyloidogenic pathway that cleave APP sequentially into Aβ.[27] Lastly, Hemmat *et al.* looked at differentially expressed genes (DEG) in the grey matter between AD patients and controls and observed that 58 of these downregulated DEG are targets of HSV-1 microRNAs.[26].

Additional evidence

In addition to the post-mortem studies, epidemiological studies and GWAS, one of the most crucial discoveries supporting the infectious disease hypothesis was provided in 2010 by Tanzi and his colleagues.[49] The authors proved that Aβ has an antimicrobial activity with a similar or even greater potency of LL37, a well-known human antimicrobial peptide (AMP).[49] White's group, among other groups, supported this finding by showing that Aβ inhibits the *in vitro* replication of H3N2 and H1N1 influenza viruses and might help clear the infection by stimulating uptake of infected cells by neutrophils and monocytes.[50] Moreover, a mouse experiment showed that Aβ can almost totally prevent viral infections when administered intracerebrally.[51] In 2017, Bode and colleagues demonstrated that $A\beta_{42}$ was able to form pores in cellular membranes and consequently kill bacteria, fungi and enveloped viruses.[52] In view of this second role of Aβ, a new assessment was also made for senile plaques. It is suggested that plaques in the brain form a kind of biofilm.[1,53,54] In this way, the pathogen can protect itself from antimicrobials, toxic substances, among others, and ensures its own survival. However, as mentioned by Folup and colleagues, this is contradictory to the antimicrobial properties of Aβ. Nevertheless, the same authors state that this can be the case if microbes are able to inactivate the antimicrobial properties of Aβ when Aβ is incorporated into the biofilm.[1] Important to note, this latter statement is purely speculative and not yet proven.

Despite all evidence provided above, the viral infectious hypothesis remained in the background during the past decades. Up to 2019, only 0.5 % of all AD-related clinical trials tested the viral hypothesis, whereas > 22 % of the trials focused on the amyloid hypothesis.[55] According to Professor Ithzaki, one of the reasons for this is a lack of virological knowledge and the incorrect perception that viruses can only cause acute diseases.[24] In addition, it should be noted that, in the past, most research was focused on HSV-1 whereas other viruses were addressed to a lesser extent.

The mechanisms behind the viral infection theory

In short, the viral infection theory states that a viral infection can ultimately cause AD pathology.[7] Different mechanisms are pro-

posed to explain this causal relationship. Here, we discuss the two established theories, namely the direct (Fig. 1) and indirect causal relationship; but also a recent proposed mechanism involving EVs.

Direct viral infection of the brain and the effect on AD pathology

Potential mechanisms of direct entry of the virus into the brain. The direct infection theory states that viruses can cause AD by directly invading and infecting the brain. Currently, four different infection routes are proposed: via the brain barriers, the circumventricular organs (CVOs), the olfactory bulb and the peripheral nerves. First, some viruses are believed to gain access to the brain by crossing or infecting the blood–brain barrier (BBB) or blood–cerebrospinal-fluid barrier (BCSFB). The BBB consists of endothelial cells, astrocytes and pericytes, and protects the central nerve system (CNS). The BCSFB consists of a monolayer of choroid plexus (CP) epithelial cells that are firmly interconnected by tight junctions and are situated at the interface between the blood and the CSF containing ventricular cavities. Viruses can cross these brain barriers by transcellular and paracellular migration or via the 'Trojan horse' strategy. According to the latter, the virus traverses the barrier within infected phagocytes.[56] Second, viral entrance can occur via CVOs.[57,58] CVOs are regions in the brain lacking a proper barrier and where no tight junctions are present between capillary endothelial cells.[59] By consequence, viruses present in the bloodstream can easily enter the brain parenchyma via these CVOs.[37] Third, the olfac-

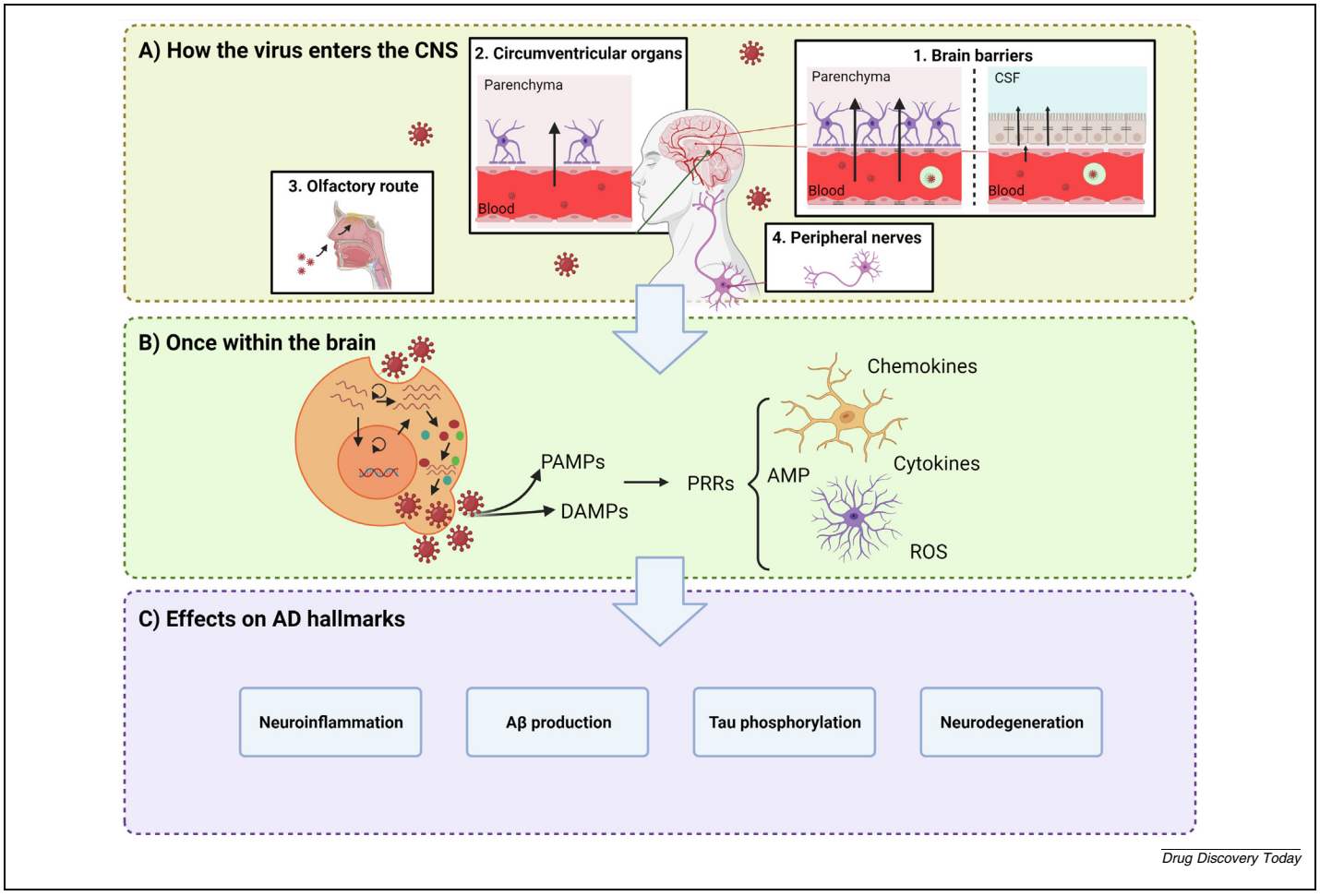

FIG. 1

The direct viral infection theory. The viral infection theory states that Alzheimer's disease (AD) can be caused by a direct viral infection of the brain. **(a)** First, the virus enters the brain. This can occur through different routes, namely: (1) via the brain barriers including the blood–brain barrier (BBB, left) and the blood–cerebrospinal fluid barrier (BCSFB, right). Viruses can cross these barriers by transcellular and paracellular migration or the 'Trojan horse' strategy. (2) By crossing the circumventricular organs which lack a BBB. (3) Via the olfactory route by infecting sensory neurons lining in the epithelial membrane and (4) via the peripheral nerve that innervate peripheral organs. **(b)** Once the virus reaches the brain it starts to replicate which causes the release of PAMPs and DAMPs. These are recognized by PRRs which leads to the release of inflammatory mediators (e.g., cytokines, chemokines, AMP and reactive oxygen species). Ultimately, a whole repertoire of immune responses is generated against the virus characterized by an inflammatory response and the activation of microglial cells and astrocytes. This immune response is needed to get rid of the virus. However, a persistent inflammatory response that becomes chronic or multiple viral challenges that occur during lifetime might result in AD hallmarks such as neuroinflammation, Aβ deposition, Tau phosphorylation and neurodegeneration. Abbreviations: CNS, central nerve system; CSF, cerebrospinal fluid; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRR, pathogen recognition receptor; AMP, antimicrobial peptides; ROS, reactive oxygen species; Aβ, amyloid beta. Created with BioRender.com.

tory system can serve as an entry gate to the brain. Viruses, like HHV, can infect the olfactory sensory neurons lining in the epithelial membrane. By retrograde axonal transport, viruses can reach the olfactory bulb and in this way gain access to the CNS. Lastly, also peripheral nerves which innervate peripheral organs can serve as entry points. This is mediated by the expression of viral receptors on either sensory or motor neurons. Once entered, the virus hijacks the axonal transport system to reach the CNS.[60] Once in the brain, the virus begins to replicate leading to the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Upon binding of these patterns with their corresponding pattern recognition receptor (PRR), inflammatory mediators are produced [e.g., cytokines, chemokines, AMP and reactive oxygen species (ROS)]. Besides, recognition by cytosolic PRR results in the assembly of the inflammasome which induces pyroptotic cell death of the infected cells. Ultimately, a whole repertoire of immune responses is generated against the virus characterized by an inflammatory response and the activation of microglial cells and astrocytes. Despite that this is a desired host response to get rid of the virus, a persistent inflammatory response that becomes chronic or multiple viral challenges occurring during a lifetime can ultimately lead to AD development.[6,7,61].

Direct viral effects on neuroinflammation. Neuroinflammation is caused by the production of proinflammatory cytokines mainly released by microglia and astrocytes. Microglia remain quiescent, unable to perform effector and antigen presentation functions until activated by infection. Upon activation, microglia migrate to the site of infection and induce an innate immune response resulting in the release of inflammatory cytokines, oxidative and nitrative compounds.[37,62] Chronic or recurrent activation of microglia and the associated release of proinflammatory and neurotoxic mediators can induce either direct or indirect neuronal death, suppress axonal transport and neurogenesis. In addition, such sustained activated microglia are less able to remodel synapses.[37] Next, activated microglia can also activate astrocytes that on their terms contribute to further neuronal injury by the release of proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin (IL)-1β.[62].

Direct viral effects on Aβ aggregates. Proinflammatory mediators produced upon viral infection increase the expression of β- and γ-secretase – enzymes necessary for the cleavage of APP into Aβ.[63] Regulation of the expression of β-secretase seemed to occur via glycogen synthase kinase (GSK)-3β, whereas γ-secretase activity is, among other things, regulated by interferon (IFN)-induced transmembrane protein 3 (IFITM3).[64,65] This latter transmembrane protein is produced upon viral infection and is known to be part of the innate immune system. More precisely, it acts as a viral entry restriction factor against, for example, the human coronaviruses.[66,67] Using transgenic 5xFAD mice and *in vitro* studies, Hur *et al*. demonstrated that proinflammatory cytokines induce the expression of *Ifitm3* in neurons and astrocytes and that this is accompanied with higher levels of $A\beta_{40}$ and $A\beta_{42}$. Moreover, their research revealed that this occurs by the binding of IFITM3 near the active site of γ-secretase which upregulates the activity of this enzyme.[65] Therefore, prolonged proinflammatory mediator production could result in increased Aβ deposition and plaque formation. However, normally, the accumulation of Aβ is prevented by clearance, phagocytosis and degradation by astrocytes and microglia. If the proinflammatory status persists and Aβ keeps accumulating, altered microglial function and astrocytic dysfunction occur leading to a decreased expression of phagocytosis receptors on microglial cells.[63,68] Potentially, this will be further enhanced by the altered function of the astrocytes.

Direct viral effects on NFT. Viruses were also showed to induce the formation of NFT. Kitazawa *et al*. and Quintanilla *et al*. reported that proinflammatory cytokines led to Tau phosphorylation by increasing the activity of Tau kinases.[69,70] Besides, phosphorylation of Tau is enhanced by quinolinic acid (QA)[35] – a downstream metabolite of tryptophan that is formed by the kynurenine pathway involving the enzyme indoleamine-2,3-oxygenase (IDO). The activity of IDO and the level of QA appear to be elevated in AD patients.[71] This could be owing to viral infection, because IDO activity in immune cells is increased upon inflammation.[35].

Direct viral effects on neurodegeneration. Finally, viruses can also induce neurodegeneration by the elevated expression of QA. This compound activates the *N*-methyl-D-aspartate receptor leading to QA-induced excitotoxin properties by increasing the cytosolic Ca^{2+} concentration, depleting ATP and forming free radicals.[71,72] Besides, the pyrin-domain-containing protein 3 (NLRP3) inflammasome can be activated as a part of the antiviral response, either by the virus itself or by DAMPs released by infected cells. Upon NLRP3 activation, pro-caspase-1 is cleaved to its active form that in turn mediates the proteolytic cleavage of pro-IL-1β, pro-IL-18 and gasdermin D. This ultimately leads to pyroptosis – a lytic cell death pathway in which a lot of proinflammatory cytokines and DAMPs are released, including IL-1β and IL-18.[73,74] Moreover, Heneka *et al*. demonstrated that caspase-1 (CASP1) is more highly expressed in the brain of AD patients and patients with mild cognitive impairment and NLRP3 and CASP1 deficiency improved memory deficits and increased Aβ clearance in APP/PS1 mice.[75] Altogether, knowing that viruses seem to be able to induce all the AD hallmarks, a persistent response, viral reactivation or viral reinfection could lead to cumulative damage and ultimately the development of AD.

Peripheral viral infection without brain entry of the virus and the effect on AD pathology

The indirect viral infection theory states that viruses can lead to the development of AD without effectively entering the brain but by the induction of peripheral inflammation. Recently, we comprehensively reviewed how peripheral inflammation can contribute to the development of AD.[37] Consequently, we will only shortly discuss this in the current review.

Potential mechanisms of how peripheral inflammation affects the brain. The communication between the periphery and the brain can occur via two main pathways, namely the neuronal and humoral route, and was recently extensively reviewed by Xie and co-workers.[37] Following the neuronal route, an infection induces the production of inflammatory signals in the thoracic and abdominal cavities that stimulate the afferent vagal nerve. Upon stimulation, the inflammatory signal can be transmitted to the medulla, reaching the hypothalamus.[76,77] In the case of the humoral route, infection-induced proinflammatory

cytokines and immune cells circulate in the blood and can signal to the CNS via the CVOs, across brain barriers or by acting on vascular cells at brain barriers.[78] In addition, inflammatory mediators and immune cells can reach the brain parenchyma by active transport or by disruption of the brain barriers owing to systemic inflammation.[79] Finally, transmission of inflammation can also occur via the activation of signaling pathways in vascular cells, resulting in the release of prostaglandins.[80] In relation to the BCSFB, research shows that systemic inflammation can also induce the release of EVs containing proinflammatory microRNA. Via the CSF, these EVs can enter the brain parenchyma and can be taken up by astrocytes and microglia, transferring the proinflammatory signal.[80].

Preclinical studies related to indirect effects of a peripheral viral infection on AD hallmarks. Over the years, an increasing body of evidence from preclinical and clinical studies links the effect of systemic inflammation with the development of neurodegenerative disease. Preclinical studies assessing the role of systemic inflammation on AD mostly use the immune-stimulating molecule lipopolysaccharides (LPS) to induce systemic inflammation.[81–85] Our group recently demonstrated that low-grade peripheral inflammation induced by LPS injection in an AD murine model, namely $APP^{NL\text{-}G\text{-}F}$ mice, induces peripheral immune cell infiltration into the brain, BBB integrity loss, sustained microglial activation, neuronal dysfunction and higher Aβ deposition compared with PBS-treated $APP^{NL\text{-}G\text{-}F}$ mice. These results are in agreement with previous studies looking into the effect of a LPS treatment in AD transgenic mice.[36] However, because systemic inflammation induced by peripheral injection of LPS represents a bacterial peripheral infection, polyriboinosinic-poly ribocytidilic acid (poly I:C) might be a better ligand to mimic viral systemic inflammation. In contrast to LPS, poly I:C triggers Toll-like receptor (TLR) 3 instead of TLR4.[86] Unfortunately, studies using poly I:C are performed to a lesser extent compared with studies using LPS as the stimulus. Anyhow, Krstic *et al.* demonstrated that acute intravenous poly I:C injection in 4-month-old AD mice results in increased Aβ deposition and altered Tau phosphorylation later in life. Similar results were obtained upon prenatal injection of poly I:C in WT mice in which increased APP levels, Tau phosphorylation and memory deficits were observed later in life.[87].

Clinical studies related to indirect effects of a peripheral viral infection on AD hallmarks. Next to preclinical studies, clinical studies also underscore a link between peripheral inflammation and AD development. For example, a prospective cohort study revealed that an increase in inflammatory markers during midlife is associated with memory decline and reduced brain volume 20 years after inflammatory marker measurement.[88,89] Moreover, AD patients and persons with mild cognitive impairment are characterized by elevated proinflammatory cytokine levels and inflammatory signals in their blood.[35] Interesting in the light of the viral infection hypothesis is the nested case-control study performed by Dunn and co-workers.[90] This study demonstrates a positive association between infectious episodes, from which the amount was counted starting 4 years before dementia diagnosis, and the risk of dementia in elderly.[90]

EVs as a novel emerging mechanism behind the viral infection hypothesis

EVs are nanosized membranous vesicles composed of a lipid bilayer and are secreted by all cell types.[91] They act as carriers to protect macromolecules such as proteins, RNA, among others, from enzymatic degradation and ferry these macromolecules between different cells, from neighboring cells to more-distant cells or immune cells. Moreover, it has been shown that specific EVs are able to cross the brain barriers such as the BBB.[92]

EVs and AD. It is shown that Aβ and Tau can associate with EVs and that this can contribute to the spread of AD traits.[38] However, compared with the total secretion of both proteins, the association with EVs is rather limited. Of all secreted Aβ, <1% is associated with EVs, whereas for Tau this is 2 %.[93,94] Nevertheless, EVs seem to be important in the spreading of AD pathology as prevention of EV secretion is associated with a reduction in Aβ plaques in 5XFAD mice[95] and protects against AβO-induced cognitive decline.[96] However, EVs seem to play a dual part in AD[97] and some studies show an association between EV secretion and neuroprotective effects.[98,99] For example, in the study of Yuyama *et al.*, EVs derived from neurons were associated with an increased microglial Aβ uptake and a reduction in extracellular Aβ levels.[98] Besides, EVs derived from neuronal stem cells appear to increase the resistance of synapses to Aβ oligomers and prevent memory deficits in mice. The secretion of neuronal stem-cell-derived EVs can give an explanation about why a direct correlation can be found between the number of neuronal stem cells in the *gyrus dentatus* and preserved cognitive function in individuals with AD neuropathology.[100].

EVs and viruses. It is shown that viruses can influence EV secretion and composition. Moreover, EVs can carry viral particles, viral proteins and viral nucleic acids.[92] Examples of viral proteins that have been detected in EVs are the spike (S) protein, the M and E proteins of coronaviruses and the Tat and gp120 proteins of HIV-1.[101,102] With the help of EVs, the virus attempts to circumvent or manipulate the immune response and extend viral tropism. In addition, a virus can use EVs to infiltrate into the CNS via the 'Trojan horse' method.[92] Taking the role of EVs in viral infections and AD into account, viruses can affect the development and progression of AD by interfering with EV pathways. Below, we propose different mechanisms which play a part in the direct and/or indirect viral infection hypothesis via viral proteins and cytokines in EVs and via an effect on Tau-containing EV secretion and transfer efficiency.

Viral proteins in EVs. In this first proposed mechanism, the virus uses EVs to enter the CNS or to transfer viral proteins or viral nucleic acids across the BBB.[92] In accordance with this idea, Zhou *et al.* showed that EVs containing Langat virus RNA cross the endothelial brain barrier and subsequently infect neuronal cells. Moreover, these neurons also release EVs after infection, which causes further neuronal spreading of the virus.[103] Once inside the brain parenchyma, the direct infection hypothesis can be applied. Next, it is also proposed that this mechanism plays a part in HIV-1 associated dementia. With the help of EVs, HIV-1 viral proteins such as Tat can be transferred from the periphery into the brain. Once in the brain parenchyma,

the Tat proteins contribute to Aβ accumulation, memory deficits and neurodegeneration.[104–108].

Cytokines in EVs. This second mechanism could play a part in the indirect infection hypothesis. Studies show that EVs can carry various proinflammatory mediators produced upon peripheral viral infection. Because EVs can cross the BBB, they can transmit proinflammatory signals from the periphery to the brain and in this way induce neuroinflammation.[109] Evidence is provided by Li *et al*., among others, who showed that LPS treatment of mice induces serum-derived EVs in which proinflammatory microRNAs are significantly upregulated. Moreover, when these EVs are peripherally injected into recipient mice, an increase of proinflammatory cytokines, activated astrocytes and activated microglia is seen in the CNS.[110] Besides, peripheral infections can increase the release of proinflammatory EVs by CP cells that form the BCSFB into the CSF and these EVs can enter the brain parenchyma, eventually inducing neuroinflammation as discussed in the indirect infection theory.[80].

Viral effect on Tau-containing EV secretion and transfer efficiency. Next to the use of EVs as cargo for inflammatory signals and viral components, viruses themself might affect EV secretion and transfer efficiency. This was demonstrated by the study of Lui *et al*. and concerns the influence of viral glycoproteins on secretion and transfer efficiency of Tau and cytosolic prions.[39] Glycoproteins reside on the surface of virions and mediate or support the adhesion and fusion with the membrane of the target cell. However, it is shown that glycoproteins such as the vesicular stomatitis virus glycoprotein (VSV-G) can also decorate EVs and in this way enhance cargo delivery. Keeping this in mind, Lui *et al*. raised the question of whether the presence of these viral glycoproteins on EVs also facilitates proteopathic transfer of, for example, Tau via EVs. Using *in vitro* studies, the researchers showed that the presence of the S protein of SARS-CoV-2 and VSV-G on Tau containing EVs leads to an increase in Tau and induction of cytosolic aggregates by supporting the fusion of EVs to recipient cells. Via this mechanism, viruses can accelerate the spreading of Tau and cytosolic prions. Moreover, beside enhancing the interaction, VSV-G also enhances seed-containing EV secretion, which can result in an even greater effect on Tau pathology. However, because this effect was not observed for the S protein of SARS-CoV-2, the occurrence of increased secretion owing to the presence of glycoproteins cannot be extended so far.[39] Nevertheless, further research is needed to have a more clear view on the effect of EVs decorated with viral glycoproteins and the development or progression of AD.

Viruses involved in AD pathology

Today, most research is focused on the involvement of HSV-1 in the development and progression of AD. In addition, in light of the SARS-COV-2 pandemic and the fact that several COVID-19 patients suffer from neurological symptoms, we will also elaborate on the possible involvement of SARS-CoV-2 in AD development and progression.

HSV-1

HSV-1 is a neurotropic virus and based on serological tests ~ 80 % of the human population is infected with this virus.[7] Infection usually starts at the mucosal epithelium and spreads via peripheral nerves. More precisely, the virus travels from the terminal end of a neuronal axon toward the centrosome via dynein motor proteins. When reaching the centrosome, HSV-1 deposits its viral DNA through nuclear pores into the nucleus of the neurons. Surprisingly, this process occurs with the help of kinesin motor proteins of epithelial cells incorporated in the viral particle and carried along by the virus. Once in the nucleus, the viral DNA integrates in the genome and forces the infected cells to make new viral copies.[111] HSV-1 is a virus that stays in a latent phase in sensory neurons of the trigeminal ganglia (TG) and reactivation can occur.[6] Because it has been shown that HSV-1 is able to reach the CNS, cause encephalitis and HSV-1 DNA is observed in post-mortem brains,[112–115] it is suggested that HSV-1 can also become latent in the brain. This was demonstrated by Lewandowski *et al*., among others, who showed that, after primary labial HSV-1 infection, latency was established in the brain and TG of cotton rats and mice.[116] These observations led to the investigation of the effects of HSV-1 infection on AD development and an overview can be found in Table 1.

Effect of HSV-1 infection on neuroinflammation. Intranasal infection of BALB/c mice with HSV-1 induces viral latency from 30 days post-infection (dpi) onward. At 60 dpi, these mice were characterized by a persistent neuroinflammatory process that potentially corresponds with viral reactivation.[28] This study is not the only one observing induction of lasting neuroinflammation upon HSV-1 infection. Using labial infected BALB/c mice and thermal stress to reactivate the virus periodically, De Chiara *et al*. showed a significant increase in IL-6 and IL-1β levels in the brain and astroglyosis.[29] Finally, these finding were further supported by Toscana *et al*. who observed upregulation of proinflammatory signals such as IL-1β and IL-6 and downregulation of anti-inflammatory signals such as IL-10 in HSV-1-infected C57BL/6 mice.[30] However, the results of this latter study need to be interpreted with caution because HSV-1 was injected intracranially.

Effect of HSV-1 infection on Aβ accumulation. Labial infection of mice with HSV-1 and periodic reactivation of the virus by thermal stress progressively increased Aβ accumulation.[29] Moreover, according to another study, $A\beta_{42}$ deposition can already be observed after primary HSV-1 infection.[31] Different explanations for this direct relationship between HSV-1 and Aβ levels are proposed. First, HSV-1 could stimulate the amyloidogenic pathway and $A\beta_{42}$ accumulation which can occur via stimulating the expression of β-secretase and nicastrin, a component of γ-secretase,[31] or via inducing Ca^{2+}.[117] The latter process can occur by the activation of GSK3 that phosphorylates APP at Thr668.[118] Important to note is that the involvement of Ca^{2+} levels in AD pathology is supported by the observation of increased Ca^{2+} levels in neurons of AD mice.[119,120] Second, HSV-1 could inhibit or interfere with Aβ degradation. For example, an *in vitro* study showed that HSV-1 interferes with the autophagic response by preventing autophagosomes to deliver Aβ for Aβ lysosomal degradation.[32] Moreover, genetic analysis revealed that miR-H1, the first discovered HSV-1 microRNA, silences E3 ubiquitin protein ligase UBR1 which is involved in the degradation of, among others, Aβ.[121] Next, Benboudjema *et al*. demonstrated that Us11, a viral phosphoprotein, binds to PAT1 which causes

TABLE 1

Overview of preclinical studies on the effect of HSV-1 infection on Alzheimer's disease pathology.

Approach	Animal model	Effect on the brain	Refs
Intranasal infection or ear scarification	BALB/c mice	$A\beta_{42}$ ↑	31
Intranasal infection with 10^5 PFU	BALB/c mice 13-week-old	Neuroinflammatory markers ↑ Neurodegenerative markers ↑	28
Labial injection of 10^6 PFU and TS induced reactivation (7 times with intervals of 6–8 weeks)	BALB/c mice 6–8-week-old	Progressive: Aβ ↑ Tau hyperphosphorylation ↑ Cognitive function ↓ Astrogliosis ↑ IL-1β and IL-6 ↑	29
Labial injection of 10^6 PFU and TS induced reactivation (7 times with intervals of 6–8 weeks)	BALB/c mice 6–8-week-old	Oxidative stress ↑	128
Labial injection 10^6 PFU and TS induced reactivation (7 times with intervals of 6–8 weeks)	BALB/c mice 6–8-week-old	Acceleration of neuronal aging	129
Labial injection of 10^6 PFU and TS induced reactivation (6- and 10-weeks post infection)	C57BL/6 and *APP*$^{-/-}$	C57BL/6: Aβ ↑ in neuronal stem cells Stem cell proliferation ↓ Stem cell differentiation ↓ *APP*$^{-/-}$: No effect on neuronal stem cell differentiation and proliferation	130
Intracranial injection of 10^2 PFU	C57BL/6 mice	Hippocampal damage Anti-inflammatory signals ↓ Proinflammatory signals ↑ Presence of: Perivascular inflammatory cells Immune cells Reactive glia cells Neuronal loss ↑ Apoptotic index ↑	30
Bilateral intracranial injection of 10^9 PFU	5XFAD mice 5–6-week-old	Aβ deposition ↑ Time to death ↑	131
Intracranial injection of $2*10^6$ PFU	5XFAD mice 13-week-old	$A\beta_{42}$ ↑	132
Intracranial injection of three different doses of different strains. Doses for 17 syn + include 10^5,10^4,10^3 and 10^4,$5*10^3$ and 10^3 for McKra strains	5XFAD mice 6-week-old	No protection	61

This table summarizes the approach and animal model used. Moreover, the outcome of the study is indicated with a '↓' or '↑' symbol meaning a decrease or an increase of the assessed outcome, respectively. Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; PFU, plaque-forming unit; TS, thermal stress; IL, interleukin.

PAT1 accumulation in the perinuclear region. Normally, PAT1 is expressed in the nucleus where it binds to microtubules and is involved in intracellular transport of APP.[122]

Effect of HSV-1 infection on Tau phosphorylation. An increase of hyperphosphorylation of Tau is observed in HSV-1 BALB/c infected mice after thermal stress reactivation.[29] This phenomenon is also noted in *in vitro* studies of Alvarez *et al.* and Zambrano *et al.* who observed Tau hyperphosphorylation in HSV-1 human neuroblastoma cells and mice neuronal cell cultures, respectively.[33,123] HSV-1 can induce this by activation of caspase-3 which, via cleavage of AKT kinase, causes activation of the GSK3β pathway. In addition, HSV-1 could also stimulate the activity of kinase A.[124,125] Kinase A and AKT kinases are other components that might be involved and with which HSV-1 might interfere.[33,126]

Effect of HSV-1 infection on neurodegeneration. HSV-1 can induce neurodegeneration directly or indirectly through different mechanisms. One mechanism is by inducing DNA damage caused by oxidative stress and impairment of the DNA repair machinery. De Chiara *et al.* showed that HSV-1 induces the accumulation of DNA damage and stimulates the proteasomal degradation of Ku80 in neuronal cells. Ku80 plays a crucial part in the non-homologous end-joining pathway involved in the repair of double-strand DNA breaks. Downregulation of Ku80 in HSV-1-infected neurons therefore results in an accumulation of DNA damage and possibly cell death.[127] Next, an *in vivo* study of Protto *et al.* shows that oxidative stress occurs in mouse brains upon recurrent HSV-1 infection. In this way, not only DNA damage can be induced but the virus can also cause disturbances in energy metabolism, protein folding, degradation and cell structure.[128] Furthermore, HSV-1 can potentially induce neurodegeneration by accelerating neuronal ageing.[129] To complete the story, the virus also seems to be involved in neurogenesis. This could occur through the accumulation of Aβ in the neuronal stem cells of the hippocampus, reducing the proliferation and differentiation of these cells.[130]

Taken together, a combination of these pathological effects induced by HSV-1 infection can eventually lead to AD pathology.

This was also observed in the preclinical study of De Chiara *et al.* in which recurrent HSV-1 infections induce the progressive accumulation of AD hallmarks and also progression in cognitive deficits.[29] Because cumulative effects are observed in recurrent infections, the latent state and the amount of HSV-1 reactivation seemed to be important to explain why some HSV-1-positive patients develop AD and others do not. One of the factors that influences this reactivation is the genetic background of the patients, for example the presence of *APOε4* allele, as discussed above.

SARS-CoV-2

The coronaviruses have caused several epidemic and pandemic outbreaks during the past decades.[134,135] Of these, the SARS-CoV-2 pandemic is the most recent one which started at the end of 2019 in Wuhan and (at time of writing) infected > 267 million people worldwide.[136] To enter host cells, this virus uses the angiotensin-converting enzyme 2 (ACE2) receptor from which expression is, among others, observed in the CNS and more precisely in brain vessels, CP and neocortical neurons.[137–139] This expression pattern suggests that the virus could be able to enter the CNS. In addition, 36.4 % of the hospitalized SARS-CoV-2 patients display neurological symptoms like loss of smell, headache, disturbance of consciousness, seizures and stroke.[140,141] Moreover, the ability of SARS-CoV-2 to enter the CNS is supported by a study on rhesus monkeys.[142] Following intranasal inoculation into these non-human primates, the virus was able to enter the CNS, mainly through the olfactory bulb and spread to functional areas such as the hippocampus. Furthermore, the infection was accompanied with an inflammatory response and pathological damage as neurodegeneration in the CNS. However, because the SARS-CoV-2 protein was only detected in a very small number of cells, no viral particle was found in the brains of these rhesus monkeys and no efficient replication seems to occur *in vitro* in cell lines associated with the CNS, the researchers suggest that SARS-CoV-2 cannot efficiently infect and replicate in the CNS and that the pathological lesions are caused by cytokines in the CNS or by systemic inflammation.[142] The fact that SARS-CoV-2 replication and infection is inefficient in the CNS can also provide an explanation about why controversial results are obtained regarding the detection of SARS-CoV-2 in post-mortem brains and CSF of deceased COVID-19 patients. Furthermore, it must be noted that, next to direct CNS invasion and systemic inflammation, neurological symptoms could also be caused by peripheral organ dysfunction, such as lung dysfunction, and cerebrovascular changes.[75]

The long-term effects of SARS-CoV-2 infections are difficult to predict because the virus has only recently emerged. However, studies are starting to give evidence that infected persons can have a potentially increased risk to develop AD later in life or that a SARS-CoV-2 infection might lead to disease acceleration in AD patients. For example, in the study of Helms *et al.*, 33 % of the COVID-19 patients who were discharged from hospital suffered from impairment of cognitive skills and motor dysfunction.[143] In agreement, Bliddal *et al.* reported that 13 % of the 129 supervised non-hospitalized participants with symptoms had memory deficits as a persistent symptom.[144]

Effects of SARS-CoV-2 infection on neuroinflammation. As mentioned above, intranasal inoculation of SARS-CoV-2 can induce neuroinflammation in rhesus monkeys.[142] This was suggested by the detection of inflammatory mediators and the infiltration of perivascular inflammatory cells in the hippocampus and *medulla oblongata*. The observed neuroinflammation can be induced by systemic inflammation and/or direct invasion of the virus into the brain. Yang *et al.* investigated post-mortem brains of COVID-19 patients and observed that genes involved in inflammation, for example interferons, and the complement pathway are upregulated in cells of the CP.[145] In addition, the epithelium of the CP signals toward the cortex. This communication is related to complement pathways signaling toward microglia and inflammatory pathways signaling toward glial cells and neurons. As a result, microglia and astrocytes are activated and contribute to neuroinflammation. Looking more closely to the subpopulations of the microglia and astrocytes in the post-mortem brains, Yang *et al.* observed that the gene expression profile of the COVID-19-associated microglia subpopulation overlaps with AD-associated microglia, whereas the COVID-19-associated astrocyte subpopulation is mainly characterized by an increased expression of glial fibrillary acidic protein (GFAP) and inflammatory factors such as IFITM3.[145] Besides, the strength of the induced inflammatory response could depend on the genetic background of the patient. Magusali *et al.* showed that single nucleotide polymorphisms in the OAS1 gene increase the risk of AD development and that related variants of this gene are also associated with the severity of COVID-19.[146] The *OAS1* gene is expressed in microglia and seems to be involved in limiting proinflammatory responses. Because the *OAS1* variants are expressed to a lower extent than their wild type counterpart, more inflammation could take place in patients carrying an *OAS1* variant,[146] which might make these SARS-CoV-2-infected patients more prone to develop AD.

Effects of SARS-CoV-2 infection on Aβ accumulation. Yang *et al.* reported increased *IFITM3* expression in astrocytes and neurons of SARS-CoV-2-infected persons, and IFITM3 was shown to increase $A\beta_{40}$ and $A\beta_{42}$ levels, suggesting that the latter also occurs upon SARS-CoV-2 infection.[65,145] Reduction of Aβ clearance can also occur as a result of systemic inflammation that disrupts the Aβ microglial clearance function.[147] In addition, clearance of $A\beta_{42}$ might potentially be reduced by the interaction between $A\beta_{42}$ and the S protein of SARS-CoV-2. The latter was demonstrated by Hur *et al.* using, among others, C57BL/6 mice. More precisely, when $A\beta_{42}$ was injected intravenously in combination with the extracellular domain of the S protein, a reduced clearance of $A\beta_{42}$ in the blood of these mice was observed.[148] Taken together, the increase in Aβ production together with the decreased clearance can ultimately lead to an increase in Aβ deposition. This is further supported by the detection of increased levels of $A\beta_{40}$ and $A\beta_{42}$ in neuronal EVs in COVID-19 patients with and without neurological symptoms.[149]

Effects of SARS-CoV-2 infection on Tau phosphorylation. Upon injection of mouse hepatitis virus (MHV), a model for human coronaviruses, Tau pathology is increased in transgenic AD mice.[150] In addition, Tau hyperphosphorylation is observed in 3D human brain organoids upon SARS-CoV-2 infection.[151] Next, elevated phosphorylated Tau levels are detected in neuronal

derived EVs in COVID-19 patients with and without neurological symptoms.[149] This induction of Tau phosphorylation could be caused by the proinflammatory stimulation of kinases that phosphorylate Tau.[63,152] In addition to this mechanism, the literature also suggests that respiratory dysfunction and hypoxia can promote Tau phosphorylation. This latter mechanism was demonstrated by Wen *et al.* who showed that cerebral ischemia, a condition in which there is a limited oxygen supply in the brain, induces hyperphosphorylation of Tau.[153] It is also possible that not only Tau phosphorylation but also total Tau production is increased in SARS-CoV-2 infection, because an increase in total Tau was observed in the CSF of COVID-19 patients with neurological symptoms.[154]

Effects of SARS-CoV-2 infection on neurodegeneration. Finally, neuroinflammation, Aβ accumulation and Tau phosphorylation can contribute to neurodegeneration, a process that probably also takes place in COVID-19 patients. The presence of neurodegeneration is supported by the presence of elevated levels of the neurofilament light (NFL) polypeptide in CSF, plasma and neuronal EVs of COVID-19 patients compared with controls and the observation of neurodegeneration when rhesus monkeys were intranasally inoculated with SARS-CoV-2.[142,149,154,155] The process of neurodegeneration could also be supported by NLRP3 activation induced by the coronavirus itself and associated pyroptosis.[156]

The combination of the above-described AD hallmarks together with synaptic loss and decreased expression of neurotransmission-associated genes in excitatory neurons, which also has been reported in COVID-19 patients, could lead to persistent clinical AD symptoms.[145] To complete the story between COVID-19 and AD, AD patients could also be more susceptible to develop severe COVID-19 symptoms. An indication for this statement is that in demented patients the COVID-19 mortality rate and vulnerability appear to be higher.[157–160] However, this higher vulnerability can also be explained by lower hygiene standards. Hsu *et al.* showed that $A\beta_{42}$ binds to the S1 protein of SARS-CoV-2 and with the human ACE2 receptor that was conjugated with Fc (hACE2-Fc). Moreover, when immobilized S1 was first incubated with $A\beta_{42}$ and then with hACE2-Fc, the strength of the binding of S1 to hACE2 is increased. Finally, to look close to the effect of the interaction of $A\beta_{42}$ and SARS-CoV-2, Vero cells were infected with $A\beta_{42}$ and a SARS-CoV-2 pseudoviruses. This test revealed that $A\beta_{42}$ increases the infectivity of SARS-CoV-2 pseudovirus and inflammation state of the Vero cells.[148]

Concluding remarks and future treatment perspectives

AD is on its way to becoming the third leading cause of death, just behind heart disease and cancer, with an alarming increase in prevalence worldwide. Despite efforts to unravel the etiopathogenesis, there is currently no cure or treatment available to reverse or stop the disease progression, except for the recently FDA-approved aducanumab, the therapeutic effect of which is still contested. As increasing evidence underscores the potential role of viruses in the development and progression of AD, antiviral therapies could become a new therapeutic approach to stop or alter the development of the disease. Until today, the clinical evaluation of antiviral therapies as treatment strategies for AD has been limited. However, preclinical studies are promising and suggest that antiviral drugs should be considered as potential therapeutics.[161] Antiviral drugs that have been tested so far are chosen for their ability to inhibit HSV-1 replication and include, among others, acyclovir, penciclovir, Bay 57–1293, fucoidans and bioflavonoids such as Ginkgetin.[123,162–167] These drugs are mostly evaluated in HSV-1-infected Vero cells and are associated with reduced Aβ deposition and Tau phosphorylation.[164–166] In addition, when acyclovir treatment is combined with dexamethasone, Aβ-induced cognitive impairment is improved in Aβ oligomer injected mice. This was declared by a potential decrease in neuroinflammation, synaptic damage, Tau phosphorylation and microglia and astrocyte activation. Cognitive improvement was not observed when acyclovir or dexamethasone was used alone.[162] In addition, special attention must be given to the clinical evaluation of dexamethasone

TABLE 2

Clinical studies on the effect of HSV antiviral treatment in Alzheimer's disease.

Approach	Stage	Refs
130 HSV-1 or −2-positive AD patients are treated with valacyclovir (n = 65) or placebo (n = 65) in a randomized double blind 78-week Phase II proof of concept trial. Patients receive an oral dose of 4 g daily by the uptake of 8 caplets of 500 mg per day.	The study is currently recruiting participants	NCT03282916 Phase II
50 patients that are characterized with the presence of AD biomarkers, show mild cognitive impairment (eMCI and lMCI) and who test positive for serum antibodies to HSV-1 or HSV-2 are treated with valacyclovir (n = 25) or placebo (25) in a randomized, double-blind, 52-week Phase II proof of concept trial. Patients receive an oral dose of 4 g daily by the uptake of 8 caplets of 500 mg per day.	The study is currently recruiting participants	NCT04710030 Phase II
36 anti-HSV IgG positive AD patients that also carry the APOε4 allele treated during a period of 4 weeks with valaciclovir in an open pilot trail. This drug was given orally-three times daily in doses of 500 mg during the first week and 1000 mg during the remaining weeks.	Feasible, tolerable and safe The mean MMSE score ↑ CSF sTREM2 level ↑ No significant effect on the CSF levels of total Tau and NFL	NCT02997982 Phase II[133]

This table summarizes the approach, outcome and clinical phase of clinical studies assessing the effect of HSV antiviral treatment on AD patients. Abbreviations: AD, Alzheimer's disease; n, number; HSV, herpes simplex virus; Ig, immunoglobulin; NFL, neurofilament light; CSF, cerebrospinal fluid; MMSE, mini-mental state examination; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

because opposite effects are observed when dexamethasone was administered for a long time to AD mice.[168] Next, when *APP/PS1* transgenic mice were treated with Ginkgetin, Aβ plaques were reduced and inflammation was decreased.[167] To our knowledge, the result of only one clinical trial (Phase II) has been published so far. This study investigated the effect of an antiviral drug, namely valacyclovir, in HSV-1-positive AD patients and shows that this treatment improved the mean mini-mental state examination (MMSE) score (Table 2).[133] In addition, two other Phase II clinical trials (Table 2) that administer valacyclovir to AD patients have recently been initiated (NCT03282916, NCT04710030). The outcome of these trials, together with additional preclinical studies, will give us further insight into the importance of viruses, especially HSV-1, HSV-2 and SARS-CoV-2, in the pathology of AD and possibly open a new window in the search for effective AD therapies.

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Glossary

ACE2: Angiotensin-converting enzyme 2
AD: Alzheimer's disease
AMP: Antimicrobial peptide
APOε: Apolipoprotein E
APP: Amyloid protein precursor
Ab: Amyloid beta
BACE1: Beta-secretase 1
BBB: Blood–brain barrier
BCSFB: Blood–cerebrospinal fluid barrier
CNS: Central nervous system
COVID-19: Coronavirus disease 19
CP: Choroid plexus
CSF: Cerebrospinal fluid
CVOs: Circumventricular organs
DAMPs: Damage-associated molecular patterns
DEG: Differentially expressed genes
Dpi: Days post infection
EOAD: Early-onset AD
EVs: Extracellular vesicles
GFAP: Glial fibrillary acidic protein
GSK: Glycogen synthase kinase
GWAS: Genome-wide association studies
hACE2: Human ACE2 receptor conjugated with Fc
HHV: Human herpes virus
HIV: Human immunodeficiency virus
HSV: Human herpesvirus
IDO: Indoleamine-2,3-oxygenase
IFITM3: Interferon-induced transmembrane protein 3
Ig: Immunoglobulin
IL: Interleukin
LOAD: Late-onset AD
LPS: Lipopolysaccharides
MHV: Mouse hepatitis virus
MMSE: Mini-Mental State Examination
NFL: Neurofilament light
NFT: Neurofibrillary tangles
NLRP3: Pyrin-domain-containing protein 3
PAMPs: Pathogen-associated molecular patterns
PFU: Plaque-forming unit
PICALM: Phosphatidylinositol-binding clathrin assembly protein
PolyI:C: Polyriboinosinic-polyribocytidilic acid
PRR: Pattern recognition receptor
PSEN1: Presenilin-1
PSEN2: Presenilin-2
p-Tau: Hyperphosphorylated Tau
QA: Quinolinic acid
S: Spike
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
sTREM2: Soluble triggering receptor expressed on myeloid cells 2
TG: Trigeminal ganglia
TLR: Toll-like receptor
TNF: Tumor necrosis factor
TS: Thermal stress
VSV-G: Vesicular stomatitis virus glycoprotein
VZV: Varicella zoster virus