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RECENT RESEARCH ON THE ROLE OF VIRAL INFECTION AS A CAUSE AND SPEED UP THE PROGRESSION OF ALZHEIM'R'S DISEASE

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disease for which only symptomatic treatments are available, other than the recently FDA-approved aducanumab. This lack of effective treatment necessitates the study of alternative pathways that may contribute to disease development. Given the recent SARS-CoV-2 pandemic and the troubling neurological complications observed in some patients, the onset and/or progression of microbial viral infections may have an impact on Alzheimer's disease. It is desirable to (re)examine the feasibility of the theory. Here we review key evidence for this theory, with a particular focus on his two viruses: HSV-1 and SARS-CoV-2. Additionally, we discuss the possible involvement of extracellular vesicles (EVs). This review will contribute to a more rational approach to possible treatment strategies for Alzheimer's disease patients.

Key words: *AD, neurodegenerative disorder, aducanumab, viral infection, HSV-1 and SARS-CoV-2.*

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INTRODUCTION:

[1] It is the most common form of dementia, currently affecting more than 50 million people worldwide, and this number is expected to increase in the coming decades. There are two main types of AD, although the effects of the disease are similar. One is early-onset AD (EOAD), which usually begins before age 65, and the other is late-onset AD (LOAD), which occurs after age 65. Therefore, previous studies have mainly focused on evaluating therapies aimed at reducing pathological aggregates of Aβ or p-tau or attenuating neuroinflammation. Due to the lack of disease-modifying treatments and the increasing number of patients with Alzheimer's disease, there is an urgent need to investigate other hypotheses that may contribute to the development of Alzheimer's disease.

[2]In light of the coronavirus disease 19 (COVID-19) pandemic and associated neurological complications in some patients, one of the more controversial hypotheses, the viral infection hypothesis, has received increasing attention. The idea that viral infections can influence the development of Alzheimer's disease dates back to 1982. Proposed the idea that recurrent infections with human herpesvirus (HSV)-1 play a role in the development and/or progression of AD. According to the "direct infection theory," viruses invade the brain and either kill neurons or activate antiviral responses. In contrast to the direct hypothesis, the 'indirect infection hypothesis' proposes that the virus does not need to invade the brain to cause the pathology of Alzheimer's disease, and that its effects are mediated through virus-induced systemic inflammation.

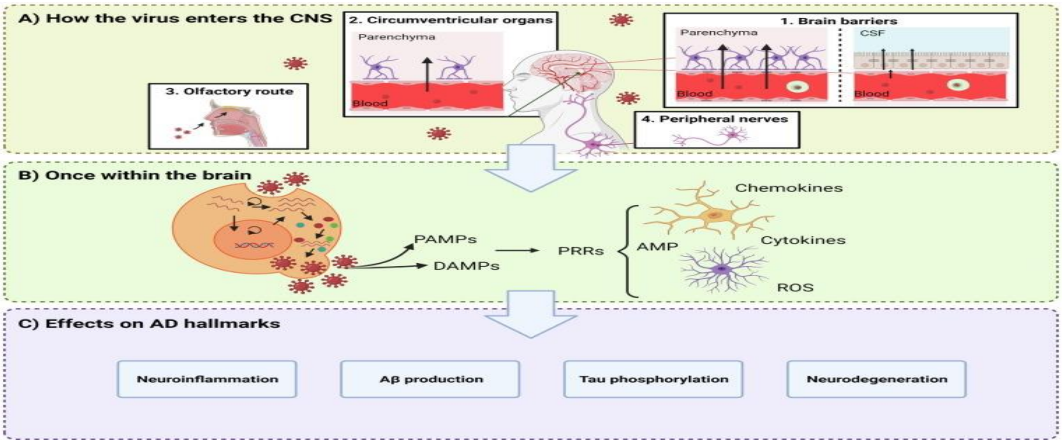
EVIDENCE FOR THE VIRAL INFECTION THEORY:

[3]Post-mortem theory : The first proof came from a post-mortem investigation that discovered HSV-1 - affected regions in the brains of patient with early stage AD coexisted with a plaque and p-tau tangles. Additionally , 5-6 years following intracerebral injection of human post – morterm AD brain tissue , Baker`s group demonstrated an induction of A plaque in marmosets . This finding led to the hypothesis that the post – morterm brains of AD patients must contain a transmissible component.

[4]Epidemiologicalstudies : Two of these studies showed an association between the detection of anti-HSV IgM and a higher risk for AD development. In the third study, the number of persons positive for anti-HSV IgM was too small to detect any possible association. However, Lovheim 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. The discrepancy between these epidemiological studies can be explained by the fact that the study of Lovheim et al. 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. 3 % of the untreated HSV-infected patients during the next ten years. 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.

THE MECHANISMS BEHIND THE VIRAL INFECTION THEORY:

[5]According to viral infection theory, AD pathology may ultimately result from a viral infection. Various theories are put out to account for this casual connection. Here, we present the accepted theories of direct and indirect causality (fig.1) as well as a recently hypothesise EV – related mechanism.



[6]According to the idea of viral infection, direct viral infection of the brain can cause Alzheimer's disease (AD). (a) First, the virus invades the brain. This can happen in different ways. Thus, - 86 crosses the blood-brain barrier (BBB, left) and blood-cerebrospinal fluid barrier, both in transcellular and paracellular migration (BCSFB, right). Via "Trojan Horse". This technique allows the virus to overcome these barriers by passing through periventricular organs that lack the BBB87. via the olfactory pathway by infection of sensory neurons in the epithelial membrane, 89 via peripheral nerves innervating peripheral organs. (b) Once the virus reaches the brain, it begins to multiply, resulting in the release of PAMPs and DAMPs. These are recognized by PRRs and lead to the release of inflammatory mediators (cytokines, chemokines, AMPs, reactive oxygen species, etc.). Ultimately, a whole repertoire of immune responses to the virus is generated, characterized by an inflammatory response and activation of microglial cells and astrocytes. This immune response is necessary to eliminate the virus. However, a chronic, sustained inflammatory response and multiple viral attacks over a lifetime can lead to hallmarks of Alzheimer's disease, such as neuroinflammation, Aβ deposition, tau phosphorylation, and neurodegeneration.

Abbreviation: CNS, central nervous system. CSF, cerebrospinal fluid. PAMP, pathogen-associated molecular pattern; DAMPs, damage-associated molecular patterns; PRR, pathogen recognition receptor; AMP, antimicrobial peptide; ROS, reactive oxygen species.Aβ, amyloid beta.

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

[7] Direct viral infection of the brain and its impact on the pathology of Alzheimer`s disease A method that may allow viruses to directly invade the brain. According to the idea of direct infection, the virus could directly enter and infect the brain, causing Alzheimer's disease. Currently, four different infection routes have been proposed: via the brain barrier, periventricular organs (CVO), olfactory bulb, and peripheral nerves. First, it is thought that some viruses can enter the brain by crossing or infecting the blood-brain barrier (BBB) or blood-cerebrospinal fluid barrier (BCSFB). The BBB protects the central nervous system and is composed of endothelial cells, astrocytes, and pericytes (CNS). The CVO of the brain is an area without adequate barriers and tight connections between capillary endothelial cells. Consequently, these CVOs facilitate virus entry from the bloodstream into the brain parenchyma. The epithelial membrane surrounding olfactory sensory neurons can be infected by viruses such as HHV. Via retrograde axonal transport, the virus enters the olfactory bulb and central nervous system. When these patterns bind to the corresponding pattern recognition receptors (PRRs), inflammatory mediators are generated [e. Ultimately, a whole repertoire of immune responses to the virus is generated, characterized by an inflammatory response and activation of microglial cells and astrocytes.

Direct viral effects on neuroinflammation.

[8]Neuroinflammation is primarily caused by the production of proinflammatory cytokines released by microglia and astrocytes. Once activated, microglia migrate to the site of infection and induce an innate immune response, resulting in the release of inflammatory cytokines and oxidative and nitrifying compounds. Microglia Chronic or Through repeated activation and the associated release of pro-inflammatory and neurotoxic mediators, direct or indirect neuronal death suppresses axonal transport and neurogenesis. In turn, activated microglia can also activate astrocytes, resulting in further neuronal damage through the release of proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin (IL)-1β.

[9] During viral infection, proinflammatory mediators occur that increase the expression of β- and γ-secretase, the enzymes required for the cleavage of APP to Aβ. Regulation of β-secretase expression appears to occur through glycogen synthase kinase (GSK)-3β, whereas γ-secretase activity is regulated, inter alia, by interferon (IFN)-inducible transmembrane protein 3 (IFITM3). The latter transmembrane protein is produced during viral infection and is known to be part of the innate immune system , showed that pro-inflammatory cytokines induce the expression of Ifitm3 in neurons and astrocytes, and this is associated with increased levels of Aβ40 and Aβ42. Furthermore, their studies revealed that this occurs by binding to IFITM3 near the active site of γ-secretase, thereby upregulating the activity of this enzyme. As the pro-inflammatory state persists and Aβ continues to accumulate, altered microglial function and astrocyte dysfunction occur, leading to decreased expression of phagocytic receptors on microglial cells.

Direct viral effects on NFT.

[10] Reported that pro-inflammatory cytokines cause tau phosphorylation by increasing the activity of tau kinase. In AD patients, IDO activity and she QA levels appear to be increased . This may be due to a viral infection, since the IDO activity of immune cells

increases during inflammation. Finally, viruses can also cause neurodegeneration through increased expression of QA. This compound causes QA-induced excitotoxic properties by activating N-methyl-D-aspartate receptors, increasing cytosolic Ca2+ concentration, degrading ATP, and forming free radicals. Additionally, the pyrin domain-containing protein 3 (NLRP3) inflammasome is activated by the virus itself or by DAMPs released from infected cells as part of the antiviral response. This ultimately leads to pyroptosis, a lytic cell death pathway in which many proinflammatory cytokines and DAMPs, including IL-1β and IL-18, are released. Found that caspase-1 (CASP1) is more highly expressed in the brains of patients with Alzheimer`s disease and mild cognitive impairment, and that NLRP3 and CASP1 deficiency results in reduced We showed that memory impairment was improved and Aβ clearance was increased. Overall, knowing that the virus can cause all the hallmarks of AD, a sustained response, viral reactivation, or viral reinfection, the damage accumulates and ultimately leads to the development of AD.

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

[11]Recently, we conducted a detailed study on the role of peripheral inflammation in the progression of Alzheimer`s disease. With infection following the neural pathway, the thoracic and abdominal cavities generate inflammatory signals that stimulate the vagus afferent nerve. Furthermore, immune cells and inflammatory mediators can invade the brain parenchyma through active transport and disruption of the brain's protective barrier as a result of systemic inflammation. Activation of signaling pathways within vascular cells can also cause the formation of prostaglandins, which can lead to the transmission of inflammation. Furthermore, systemic inflammation can damage the brain's protective barrier, allowing inflammatory mediators and immune cells to reach the brain parenchyma via active transport. Activation of vascular cell signaling can also cause the production of prostaglandins, which can spread inflammation. Preclinical research on how peripheral viral infection affects Alzheimer's disease symptoms. A growing body of evidence from preclinical and clinical studies shows an association between the effects of systemic inflammation and the development of neurodegenerative diseases. Preclinical studies investigating the role of systemic inflammation in AD have primarily used the immunostimulatory molecule lipopolysaccharide (LPS) to induce systemic inflammation. Our group has recently We showed that injection of LPS in a mouse model of APP can reduce mild peripheral inflammation. NL-G-F mice have peripheral immune cell infiltration into the brain, loss of BBB integrity, sustained microglial activation, neuronal dysfunction, and higher Aβ compared to PBS-treated his APP NL-G-F mice. However, since the systemic inflammation induced by peripheral injection of LPS indicates a bacterial peripheral infection, polyriboinosinic acid-polyribocytidylic acid (polyI:C) may be a good ligand to mimic viral systemic inflammation. To mimic viral systemic inflammation, polyriboinosinic acid-polyribocytidylic acid (Poly I: C) may be an excellent ligand. Similar results were obtained with prenatal injection of poly I: C into WT mice, resulting in increased his APP levels, tau phosphorylation, and memory deficits later in life. A clinical study on the indirect effects of peripheral viral infection on AD traits. In addition to preclinical studies, clinical studies have also highlighted the association between peripheral inflammation and the development of Alzheimer's disease. Additionally, Alzheimer's disease patients and people with mild cognitive impairment are characterized by increased levels of pro-inflammatory substances.

VIRUSES INVOLVED IN AD PATHOLOGY :

[12] **HSV-1 : HSV-1 :** HSV-1 is a neurotropic virus and based on serological tests ~ 80 % of the human population is infected with this virus. Typically, an infection begins in the mucosal epithelium and spreads via the peripheral nervous system. More specifically, dynein motor proteins help the virus move from a neuronal axon's terminal end to the centrosome. HSV-1 enters the centrosome and inserts its viral DNA into the neurons' nuclei through nuclear pores. Surprisingly, the kinesin motor proteins of epithelial cells that are integrated into the viral particle and transported by the virus aid in this process. When the viral DNA enters the nucleus, it integrates with the genome and compels the infected cells to produce additional viral copies. In the sensory neurons of the trigeminal ganglia (TG), HSV-1 remains dormant and has the potential to reactivate. It has been demonstrated that HSV-1 may enter the CNS, cause encephalitis, and that HSV-1 DNA is found in post-mortem brains, hence it is hypothesised that HSV-1 can also become latent in the brain.6 Lewandowski et al., among others, provided evidence of this by demonstrating how latency was created in the cotton rat and mouse brain and TG following initial labial HSV-1 infection. 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.

[13]AMYLOID-BET :

Amyloid precursor protein, a larger type 1 membrane glycoprotein, is cleaved by proteases to generate A-aggregates (APPs). APP is involved in signal transduction, intracellular trafficking, neuronal development, and homeostasis. When APP is degraded by the enzymes -secretase and -secretase, a peptide with 37–49 amino acid residues is formed. These plaques also lead to the production of 4-hydroxynonenal, a toxic aldehyde involved in lipid peroxidation and disruption of cellular homeostasis . Aβ aggregation also causes DNA damage and the initiation of an inflammatory response, leading to loss of neuronal synapses and ultimately neuronal death. Interestingly, Aβ acts as an antimicrobial peptide (AMP) and has been shown to be effective against viruses, bacteria, and fungi. Aβ has been shown to function similarly to the cathelicidin AMP LL-37. Aβ was found to be effective against the bacterium Streptococcus pneumoniae and the fungus Candida albicans, the causative agents of bacterial meningitis and neurocandidiasis, respectively. In fact, Aβ has been shown to be as effective as the antiviral drug acyclovir 103 in inhibiting HSV-1 neuropathology.

PATHOGENS AND AD

Viral pathogens in neurodegeneration and AD
Bacterial Pathogens and AD
Otherpathogens and AD

PATHOGEN-BASED BIOMARKERS:

[14]Given the research associating different viruses with AD and age-related cognitive decline, it may make sense to utilise biomarkers based on pathogen exposure to gauge an aged person's risk for acquiring AD. Antimicrobial therapy intervention in situations of active infection may be a useful strategy for lowering the risk of AD, especially in patients who are elderly.Below, we go over a few pathogen-based biomarkers that have been connected to Alzheimer's disease and cognitive decline (Table 1).

	Biomarker	source	Description
Antimicrobial peptides			
	α-Defensin 1	Blood	Increase in blood of AD patient.
	α-Defensin 2	Blood	Increase in blood of AD patients.
	Lactoferrin	saliva	Decrease with AD and aMCI
	Lipocalin-1	Tears	Decrease in AD.
	Dermcidin	Tears	Increased in AD.
	Lysozyme-C	Tears	Decreased in AD
	Lacritin	Tears	Decreased in AD
Antibiotics	IgG against Epstein-Barr virus	Blood	Correlates with development of a aMCI.
	IgG and IgA against C. pneumonia	Blood	Detectable patients with vascular dementia.
	IgG against HSV-2	Blood	Correlates with cognitive decline.
	IgM against CMV	Blood	Correlates with cognitive decline
	IgG against T. gondii	Blood	Correlative with cognitive decline
	IgM against HSV-1	Blood	Associated with Increase risk of AD.
	IgG against H. pylori	Blood	Associated with lower MMSE scores
Other			
	Fungal Proteins and DNA	CSF, Blood	Detectable in AD patients.
	Gut Microbiome composition	Fecal matter	Correlates to gut dysbiosis and cognitive decline
	Porphyromonasgingivalis	CSF	Identified in 96% of postmortem brain tissue samples of AD patients.

[15]There are many infections that have been linked to the development of AD and the beginning of cognitive impairment. Additionally, it was discovered that -Defensins 1 and 2 were raised in AD patients` blood, suggesting that they could serve as a reliable biomarker for determining AD status Lactoferrin is another anti-microbial protein that might work well as a biomarker for AD. When compared to controls, saliva samples from patients with amnesiac mild cognitive impairment (aMCI) and AD exhibited lower

levels of lactoferrin, and a significant negative link was discovered between lactoferrin and aMCI and AD patients. Many antimicrobial proteins that function as a component of the innate immune system are found in tears. Tear proteins may be useful biomarkers because studies have demonstrated that they are differently expressed in AD patients. Tear samples from AD patients have been used to describe changes in the expression of the antimicrobial proteins lipocalin-1, dermcidin, lysozyme-C, and lacritin in particular. Antibiotics as Biomarkers for A Blood tests can easily identify antibodies against microorganisms linked to AD, which may be a reliable technique to determine AD risk in elderly people. Studies have linked the development of cognitive impairment with antibodies to different infections. For instance, it has been demonstrated that the development of aMCI correlates with higher levels of IgG against the Epstein-Barr virus (EBV). Patients with vascular dementia have been found to have pneumoniae IgG antibodies against HSV-2, CMV, and TOX have also been linked to cognitive deterioration in those over 65 and may also be useful as reasonable biomarkers. Although the study by 19 found no link between HSV-1 antibodies and cognitive impairment, other studies have shown that HSV-1 antibodies may serve as possible biomarkers for AD . It was discovered that among AD patients, the presence of IgG antibodies against H. . AD has also been linked with increased T. gondii IgG antibodies. These antibodies can serve as potential AD biomarkers, given the high prevalence of T. gondii infection globally .

[16]Other potential biomarkers:

Other pathogens such as fungi may also serve as potential biomarkers in AD. Fungal proteins and DNA have been detected in the CSF of an AD patient. Additionally, fungal polysaccharides, proteins, and DNA have been detected in blood samples of AD patients . The association between the gut microbiome and various neurological diseases has become an area of increasing interest in recent years and may be another option to consider for monitoring the progression of Alzheimer's disease. Given the increased relative abundance of Verrucomicrobia and Proteobacteria bacteria in Alzheimer's disease, variations in the composition of the gut microbiome detected in stool samples may also be a potential preclinical biomarker for Alzheimer's disease. There is a possibility that it will be. Products of the gut microbiota, such as microbial amyloid and the neurotoxin BMAA, play a role in neurodegeneration and could potentially also serve as AD biomarkers 33,46.

CONCLUSION AND DISCUSSION:

Concluding remarks and future treatment perspectives:

[17] Alzheimer's disease tends to be the third leading cause of death after heart disease and cancer, and its prevalence is increasing alarmingly around the world. Despite efforts to elucidate the pathogenesis, there are currently no treatments or therapies that reverse or halt disease progression, except for aducanumab, which was recently approved by the FDA. Its therapeutic efficacy is still controversial. As increasing evidence points to the potential role of viruses in the onset and progression of Alzheimer's disease, antiviral therapy may represent a new therapeutic approach to halt or alter the progression of Alzheimer's disease. To date, clinical evaluation of antiviral therapy as a therapeutic strategy for Alzheimer's disease is limited. However, preclinical studies are promising and suggest that antiviral drugs should be considered as potential treatments. Antiviral drugs tested to date have been selected based on their ability to inhibit HSV-1 replication and include bioflavonoids such as acyclovir, penciclovir, Bay 57-1293, fucoidan, and gingettin, among others· These drugs have been primarily evaluated in HSV. Furthermore, combining acyclovir treatment with dexamethasone ameliorates Aβ-induced cognitive impairment in mice injected with Aβ oligomers[164-166]. This was explained by possible neuroinflammation, synaptic damage, tau phosphorylation, and decreased activation of microglia and astrocytes. No improvement in cognitive function was observed when acyclovir or dexamethasone was used alone. Furthermore, special attention should be paid to the clinical evaluation of dexamethasone, as adverse effects are observed when dexamethasone is administered long-term to AD mice. Next, use of ginggetin in APP/PS1 transgenic mice reduced Aβ plaques. To our knowledge, to date he has only published the results of one clinical trial (Phase II). This study investigated the effects of an antiviral drug, namely valacyclovir, in HSV-1-positive AD patients and showed that this treatment improved the mean Mini-Mental State Examination (MMSE) score (Table 2). Clinical trial II (Table 2) on the administration of valacyclovir to AD patients was recently initiated (NCT03282916, NCT04710030). The results of these studies, together with further preclinical studies, may provide further insight and open new windows into the importance of viruses, particularly HSV-1, HSV-2, and SARS-CoV-2, in the pathology of 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

[18]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.

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The authors have no conflict of interest to declare**.**

REFERENCES:

1. T. Fulop, Witkowski JM, Bourgade K, et al.(2018). "Can an infection hypothesis explain the beta amyloid hypothesis of Alzheimer's disease?", *Front Aging Neurosci.* 10:224.
2. Shi.M , Li .C, Tian X, et al.(2021), "Can control infections slow down the progression of Alzheimer's Disease?" Talking about the role of infections in Alzheimer's Disease, *Front Aging Neurosci* 13 : 434.
3. Patterson C, World Alzheimer Report 2018. Alzheimer's Disease International; 2018. doi:APO-260056.
4. Burns A, Iliffe S , (2009), Alzheimer's disease, BMJ 338
5. DeTure MA, Dickson D.W , (2019) "The neuropathological diagnosis of Alzheimer's disease", *Mol Neurodegener* 14 : 32.
6. Breitner JCS, Haneuse SJPA, Walker R , Dublin S, (2009) et al., "Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort", *Neurology* 72 : 1899–1905.
7. Orgogozo JM, Gilman S, (2003) et al., "Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization", *Neurology* 61 : 46–54.
8. Gannicliffe, R.N.P. Sutton, R.F. Itzhaki, Viruses, brain and immunosuppression, Psychol Med 16 (1986) 247–249.
9. N.S. Tzeng, C.H. Chung, F.H. Lin, C.P. Chiang, C.B. Yeh, S.Y. Huang, 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 15 (2018) 417–429.
10. K. Lopatko Lindman, E.S. Hemmingsson, B. Weidung, J. Brännström, M. Josefsson, J. Olsson, et al., Herpesvirus infections, antiviral treatment, and the risk of dementia-a registry-based cohort study in Sweden, Alzheimer's Dement (New York, N Y) 7 (2021) e12119.
11. H. Lövheim, J. Gilthorpe, A. Johansson, S. Eriksson, G. Hallmans, F. Elgh, Herpes simplex infection and the risk of Alzheimer's disease: A nested casecontrol study, Alzheimer's Dement 11 (2015) 587–592.
12. H. Lövheim, J. Gilthorpe, R. Adolfsson, L.G. Nilsson, F. Elgh, Reactivated herpes simplex infection increases the risk of Alzheimer's disease, Alzheimer's Dement 11 (2015) 593–599.
13. L. Letenneur, K. Pérès, H. Fleury, I. Garrigue, P. Barberger-Gateau, C. Helmer, et al., Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's Disease: a population-based cohort study, PLoS One 3 (2008) e3637.
14. Toscano EC de B, Sousa LF da C, Lima GK, Mesquita LA, Vilela MC, Rodrigues DH, et al. Neuroinflammation is associated with reduced SOCS2 and SOCS3 expression during intracranial HSV-1 infection. Neurosci Lett. 2020;736:135295. doi:10.1016/j.neulet.2020.135295.
15. M.A. Wozniak, R.F. Itzhaki, S.J. Shipley, C.B. Dobson, Herpes simplex virus infection causes cellular b-amyloid accumulation and secretase upregulation, Neurosci Lett 429 (2007) 95–100.
16. S. Santana, M.J. Bullido, M. Recuero, F. Valdivieso, J. Aldudo, Herpes simplex virus type I induces an incomplete autophagic response in human neuroblastoma cells, J Alzheimers Dis 30 (2012) 815–831. Reviews KEYNOTE REVIEW Drug Discovery Today d Volume 27, Number 11 d November 2022 KEYNOTE G. Alvarez, J. Aldudo, M. Alonso, S. Santana, F. Valdivieso, Herpes simplex virus type 1 induces nuclear accumulation of hyperphosphorylated tau in neuronal cells, J Neurosci Res 90 (2012) 1020–1029, https://doi.org/10.1002/ jnr.23003.
17. M.T. Heneka, M.J. Carson, J. El Khoury, G.E. Landreth, F. Brosseron, D.L. Feinstein, et al., Neuroinflammation in Alzheimer's disease, Lancet Neurol 14 (2015) 388–405.
18. K.A. Walker, B.N. Ficek, R. Westbrook, Understanding the role of systemic inflammation in Alzheimer's disease, ACS Chem Neurosci 10 (2019) 3340– 3342.
19. J. Xie, N. Gorlé, C. Vandendriessche, G. Van Imschoot, E. Van Wonterghem, C. Van Cauwenberghe, et al., Low-grade peripheral inflammation affects brain pathology in the App(NL-G-F)mouse model of Alzheimer's disease, Acta Neuropathol Commun 9 (2021) 163.