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Review

Infectious agents and Alzheimer's disease

Thomas Piekut[1], Mikołaj Hurła[1], Natalia Banaszek[1], Paulina Szejn[1], Jolanta Dorszewska[1,*], Wojciech Kozubski[2], Michał Prendecki[1]

[1]Laboratory of Neurobiology, Department of Neurology, Poznan University of Medical Sciences, 60-355 Poznan, Poland
[2]Chair and Department of Neurology, Poznan University of Medical Sciences, 60-355 Poznan, Poland
*Correspondence: dorszewskaj@yahoo.com; jolanta.dorszewska@ump.edu.pl (Jolanta Dorszewska)
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Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide. Individuals affected by the disease gradually lose their capacity for abstract thinking, understanding, communication and memory. As populations age, declining cognitive abilities will represent an increasing global health concern. While AD was first described over a century ago, its pathogenesis remains to be fully elucidated. It is believed that cognitive decline in AD is caused by a progressive loss of neurons and synapses that lead to reduced neural plasticity. AD is a multifactorial disease affected by genetic and environmental factors. The molecular hallmarks of AD include formation of extracellular β amyloid (Aβ) aggregates, neurofibrillary tangles of hyperphosphorylated tau protein, excessive oxidative damage, an imbalance of biothiols, dysregulated methylation, and a disproportionate inflammatory response. Recent reports have shown that viruses (e.g., Herpes simplex type 1, 2, 6A/B; human cytomegalovirus, Epstein-Barr virus, hepatitis C virus, influenza virus, and severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), bacteria (e.g., *Treponema pallidum, Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcmitans*, *Eikenella corrodens*, *Treponema denticola*, and *Helicobacter pylori*), as well as eukaryotic unicellular parasites (e.g., *Toxoplasma gondii*) may factor into cognitive decline within the context of AD. Microorganisms may trigger pathological changes in the brain that resemble and/or induce accumulation of Aβ peptides and promote tau hyperphosphorylation. Further, the mere presence of infectious agents is suspected to induce both local and systemic inflammatory responses promoting cellular damage and neuronal loss.

Here we review the influence of infectious agents on the development of AD to inspire new research in dementia based on these pathogens.

Keywords: Alzheimer's disease; Dementia; Cognitive decline; Virus; Bacteria; Parasite; Infectious agents

1. Introduction

In recent years, the steady aging of populations in predominantly developed countries has surfaced as both a success of modern medicine and an impending challenge for health care systems. The latter is associated with an increasing number of disorders characteristic for old age, including various degrees of cognitive impairment and dementia [1]. Epidemiologic studies have shown that dementia occurs relatively often in the general population and that its incidence is age-dependent. The frequency of dementia climbs from 1–10% in adults over 65 years old to 20–25% in those over 80 years old [2], and may be seen in as many as 30–40% of nonagenarians [3]. It has been projected that by the year 2040, the number of people affected by dementia will exceed 80 million [4] and could possibly grow to a staggering 130 million halfway through the 21st century [1]. Dementia drastically reduces quality of life by causing progressive decline of cognitive and executive functions including memory, attention, orientation, language, praxis, and visuospatial functions, and may lead to changes in behavior such as negative affect or a reversal of the sleep-wake cycle. Advancing disease makes patients suffering from dementia highly dependent on their caregivers [5,6], a reality which has become particularly appreciable in the wake of the coronavirus disease 2019 (COVID-19) pandemic.

Neurodegenerative processes may be listed among the most common causes of cognitive impairment. Alzheimer's disease (AD) is the most common cause of dementia, accounting for nearly half of the cases reported worldwide. There are two major hallmarks of AD which play a crucial role in the pathophysiology of the disease: the extracellular accumulation of the amyloid-beta peptide (Aβ) and the largely intracellular aggregation of neurofibrillary tangles of hyperphosphorylated tau protein that leads to neuronal cytoskeletal degeneration [7]. These pathologies are also thought to lead to synaptic degeneration and death of certain populations of neurons [8] and may be accompanied by the deposition of vascular Aβ aggregates and inflammation [9]. While mutations in genes coding amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) have been associated with Aβ pathology, the causes of Aβ plaque formation in individuals presenting with sporadic AD remain to be identified and characterized [10]. Sporadic AD may develop in the context of mutations in as yet

unidentified genes, DNA oxidative damage, and dysregulated gene methylation [2]. Moreover, such changes could be facilitated by dietary insufficiencies leading to an imbalance of biothiols including homocysteine and glutathione that might compromise cellular repair mechanisms and allow for increased oxidative damage [11].

In light of the multifactorial nature of AD, latent infections should not be discounted among the external factors potentially playing a role in its pathogenesis. Recent reports have provided data suggesting that certain microorganisms such as viruses, bacteria and unicellular parasites may be associated with cognitive decline. Microbes may either induce formation of AD-like pathology in the brain or acting indirectly, over-stimulate the immune system leading to an excessive inflammatory response such that may fuel certain neurodegenerative changes [12]. Examining the role of infectious agents and the inflammatory response associated with them in the context of AD might facilitate earlier diagnosis and lead to the identification of novel targets for treatment [3,12].

2. Viruses and Alzheimer's disease

2.1 Severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the COVID-19 pandemic, may result in asymptomatic infection in about 15% of the individuals who contract it [13] and precipitate life-threatening disease in others. While acute respiratory symptoms typify the infection and have garnered a preponderance of the clinical and research attention directed at combatting the pandemic, neurological symptoms have been reported in approximately 30% of patients hospitalized for COVID-19 and may represent the initial manifestation of the disease [14,15]. Numerous neurological manifestations ranging from headache, anosmia, and dysgeusia to more serious conditions including corticospinal tract signs, Guillain-Barré syndrome, ischemic stroke, encephalopathy, and meningoencephalitis have been reported [14,16]. The potential impacts of SARS-CoV-2 on neurodegenerative diseases have also been considered. The most common of these, Alzheimer's disease (AD) is the leading cause of dementia and may be particularly vulnerable to the effects of SARS-CoV-2 by virtue of the fact that a dysregulated renin-angiotensin system (RAS) is implicated in both conditions.

SARS-CoV-2 infectivity is predicated upon the virus exploiting angiotensin-converting enzyme 2 (ACE2) to gain entry into host cells. While necessary, however, ACE2 is not sufficient for this process to occur in all cells [14,17]. The transmembrane serine protease 2 (TMPRSS2) must first prime the SARS-CoV-2 spike glycoprotein (S-protein) to allow for its association with the Ser19-Asp615 extracellular region on ACE2 [14]. Several lines of evidence point to this route of viral internalization having a particular bearing on AD. Firstly, ACE2 was found to be upregulated five-fold in tissue autopsied from AD patients versus controls [18]. Although this heightened expression can occur secondary to the treatment of AD with *ACE* inhibitors or angiotensin receptor blockers (ARBs) [14], ACE2 might serve a protective function given that decreased levels of the enzyme were found to associate with increased Aβ and phosphorylated tau pathology [19]. Secondly, genome-wide association studies recently pinpointed the gene encoding angiotensin-converting enzyme 1 (ACE1, ACE) as a risk factor for AD [20]. ACE1 promotes angiotensin II (ATII) activity at angiotensin type 1 receptors (AT1) thereby inducing vasoconstriction and promotes inflammation [14,21]. Opposing ACE1, ACE2 favors the conversion of ATII to AT1-7 the latter of which exerts vasodilatory effects, likely via MAS1 proto-oncogene (MAS1) [14,21]. Interestingly, the presence of the ACE1 deletion allele, which is associated with decreased ACE2 levels and occurs more commonly among AD sufferers, was found to correlate negatively with incidence of COVID-19 [22].

Other factors beyond the RAS also likely contribute to effects of SARS-CoV-2 on the CNS and AD risk. A recent interactome identified that the coronavirus S-protein binds the alpha-secretase a disintegrin and metalloproteinase-9 (ADAM-9), which is thought to exert a protective effect against AD [14,23], however, whether the said interaction has clinical bearing remains to be determined. Further, the *APOE* ε4-allele, a known risk factor for late-onset AD, was recently correlated with an increased risk of severe COVID-19 infection [24], however this relationship might be confounded by ACE2 expression level [25]. Astrocytic ApoE4 was recently found to promote cholesterol delivery to neurons, driving lipid raft formation and potentiating development of Aβ [26]. Interestingly, cholesterol was identified as required for SARS-CoV-2 S-protein-host membrane fusion and linked with the formation of syncytia in the lungs of patients with particularly severe COVID-19 [27]. Lastly, it is possible that amyloid fibrils might, as is the case with other viruses, entrap SARS-CoV-2 particles and thereby lead to polarization of microglia toward a pro-inflammatory phenotype, effectively providing fertile ground for neurodegenerative changes [28,29] (Table 1, Ref. [25,29–46]). In line with this idea, cerebrospinal fluid (CSF)-specific increases in interleukin -1β (IL-1β) and -12 (IL-12), hallmarks of the said phenotype, were identified in COVID-19 patients with neurological manifestations [15]. Furthermore, ischemic damage sustained by white matter following virally-induced cerebral hypoperfusion might explain some of the cognitive deficits experienced by COVID-19 sufferers and promotes Aβ accumulation [25]. Nonetheless, the hypothesis that SARS-CoV-2 may seed neurodegenerative changes still requires considerable research [30].

While evidence for an association between COVID-19 and AD pathogenesis exists, the capacity of SARS-CoV-2 to invade neurons remains contested. While mRNA expression might not correlate well with protein expression, both

Table 1. The influence of chosen pathogens on cognitive functions in context of Alzheimer's disease.

Pathogen	Influence on cognitive functions	Reference
SARS-CoV-2	Increased risk of cognitive impairment Potentially increased risk of AD	[25,29,30]
HSV-1	Increased risk of AD	[31]
HSV-2	Increased risk of cognitive impairment	[32]
VZV	Increased risk of AD	[33]
EBV	Potentially increased risk of AD	[34]
CMV	Increased risk of cognitive impairment	[35]
HHV-6	Increased risk of AD	[34]
HCV	Increased risk of cognitive impairment	[36]
H5N1	Increased risk of AD	[37]
CA/09 H1N1	Increased risk of AD	[38]
Borrelia burgdorferi	Increased risk of AD	[39,40]
Treponema pallidum	Increased risk of dementia	[41]
Chlamydia pneumoniae	Increased risk of AD	[42]
Bacteria causing periodontitis*	Increased risk of cognitive impairment	[43]
Propionibacterium acnes	Increased risk of AD	[44]
Helicobacter pylori	Increased risk of dementia	[45]
Toxoplasma gondii	Increased risk of AD	[46]

**Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcmitans*, *Eikenella corrodens* and *Treponema denticola*; HSV1, Herpes Simplex virus 1; HSV2, Herpes Simplex virus 2; HHV6, human betaherpesvirus 6; CMV, human cytomegalovirus; EBV, Epstein-Barr virus; H5N1, influenza virus strain H5N1; CA/09 H1N1, influenza virus strain H1N1.

ACE2 and TMPRSS2 are considered to be poorly expressed in the CNS [14]. However, their expression may increase in the brain via the circulatory system or the nasal cavity via the olfactory nerve, which may explain the loss of smell in the course of COVID-19 infection [15]. Moreover, it is suggesting that SARS-CoV-2 might use other host proteins as vehicles for entry. Neuropilin 1 (NRP1), while neither sufficient nor necessary, potentiated SARS-CoV-2 entry into human embryonic kidney (HEK-293T) cells [17]. Notably, the rich expression of NRP1 in pulmonary and olfactory tissues [17] accords with the known tropism of the virus. The serine exopeptidase dipeptidylpeptidase 4 (DPP4), also known as cluster of differentiation 26 (CD26), has also come under scrutiny as a potential target of SARS-CoV-2, which too might be implicated in AD. Associated most commonly with the breakdown of incretins, DPP4 was found to be the cellular portal of entry for the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) [47]. Bioinformatics analyses have revealed that while the S-protein of SARS-CoV-2 has a decreased affinity for DPP4 as compared with MERS-CoV, the former coronavirus is unique in being able to bind both ACE2 and DPP4 with appreciable strength [48]. Expressed predominantly in innate lymphoid cells, naïve CD4+ and CD8+ T cells, and plasmacytoid dendritic cells [49], DPP4 might not seem like an obvious factor linking COVID-19 and AD, however, several reports have identified that DPP4 inhibitors, commonly used in the treatment of type 2 diabetes mellitus, might also have utility in the treatment of neurodegenerative conditions [50,51]. This utility might stem from the effects of DPP4 inhibitors on glucose metabolism, but also likely derives out of their anti-inflammatory and anti-fibrotic actions, which would be expected to alleviate the course of COVID-19 [52].

Further, age-related impairment of the blood-brain barrier (BBB), combined with an inflammation-induced reduction of BBB integrity such that may be seen in the context of AD [53] might render the CNS more susceptible to SARS-CoV-2 neuroinvasion. At the same time, SARS-CoV-2 causes endothelial dysfunction and enhances vascular permeability which may compromise BBB function [25]. Although viral entry into the CNS has been stipulated to occur by both hematogenous spread and ascension along olfactory fibers via synaptic transmission [25], the predominating route is not known. While earlier autopsy studies aimed at confirming the presence of SARS-CoV-2 in neural tissue via qRT-PCR and immunohistochemistry yielded equivocal results [54], more recent work has identified viral proteins in cortical neurons [55] as well as cranial nerves and cells within the brainstem [56]. Moreover, experiments conducted on organoids comprised of forkhead box protein G1 (FOXG1), paired box protein Pax-6 (PAX6), and B-cell lymphoma/leukemia 11B (CTIP2)-expressing dorsal cortical neurons and mice overexpressing human ACE2 have provided *in vitro* and *in vivo* evidence, respectively, of the neuroinvasive capacity of SARS-CoV-2 [55]. Nonethe-

less, analyses on the former showed no correlation between virus-infected cells and expression of ACE2, TMPRSS2, or NRP1 [55]. Indeed, many of the neurological manifestations of SARS-CoV-2 infection might stem not from direct viral invasion but from autoimmune processes secondary to the body's generation of antibodies against viral particles [15]. That autopsy reports did not identify lymphocytosis in SARS-CoV-2-positive tissue contrasts with what would be expected for a neurotropic virus [55], and bolsters the above hypothesis, insofar as autoimmunity is associated with lymphopenia [57].

SARS-CoV-2 might also affect AD patients indirectly by necessitating changes to treatment indicated for the disorder. While the ACE2 activator diminazene aceturate [58] and the ARB losartan [59] have been shown to reduce AD neuropathology and improve cognitive performance, the possibility of their potentiating a more severe SARS-CoV-2 infection theoretically exists. Nonetheless, an association between angiotensin converting enzyme inhibitors (ACEI)/ARB therapy and greater COVID-19 risk was identified neither in an AD-specific [60], nor general patient context [61]. Discontinuation of ACEI/ARB therapy due to COVID-19 might be especially contraindicated in women with AD, seeing how results in mice suggest that females are likelier to experience particularly debilitating effects of pathologic *ACE* variants [20]. Further, activity of the cholinesterase inhibitors donepezil and galantamine frequently used as part of AD therapy may increase when used concomitantly with chloroquine/hydroxychloroquine or the antivirals lopinavir-ritonavir, both of which have been used to treat COVID-19, largely as a result of the viral therapeutics' metabolism by cytochrome P450 (CYP) 3A4-isoform and inhibition of CYP2D6-isoform, necessitating heightened vigilance during the treatment of patients suffering from both diseases [62]. Moreover, quarantining and isolation are not conducive to cognitive exercise and so the COVID-19 pandemic may exacerbate existing neuropsychiatric facets of AD or precipitate their occurrence [28,63,64]. Unfortunately, some demographics may be disproportionately affected by the pandemic. A Michigan study identified that the risk for both COVID-19 and AD and related dementias is greater for Black adults [28]. Clinicians will need to integrate all of these factors if they are to provide optimal care for individuals affected by both AD and COVID-19.

2.2 Herpesviridae

The *Herpesviridae* family includes human herpesviruses 1 to 8 (HHV 1–8), which are common causes of many diseases ranging from the relatively innocuous cold sore (HHV-1) to debilitating Kaposi's sarcoma (HHV-8). HHV-1, HHV-2, HHV-4, HHV-5 and HHV-6A/B warrant closer consideration due to their potential contribution to the pathophysiology of AD.

Herpes Simplex Virus (HSV) is a member of the *Herpesviridae* family and one of the most widespread viruses in the human population. About 80% of older adults in the USA have at one point incurred HSV infection and have serum antibodies against the virus [65,66]. Herpes viruses are characterized by their large size, double-stranded DNA genome and ability to cause lifelong infections [67].

HSV neural infection occurs by two main routes. The first involves infecting epithelial cells of the oral and nasal mucosae, which can lead to sensory neuron ascension. Subsequent axonal transport leads to viral transmission into the central nervous system (CNS) [68–70]. The second path is that of hematogenous dissemination, where the virus crosses the BBB to enter the CNS [71–73].

HSV may result in an asymptomatic latent infection, where the virus lies dormant within neurons until the lytic cycle is triggered by an adverse reaction to a drug or immunodeficiency secondary to physiological aging or myriad pathophysiological processes [74,75]. Nonetheless, this dormant state might well be surreptitious, with viral particles seeding pathology prior to any clinical manifestation of disease. Multiple autopsy studies on AD patients have shown that HSV-1 DNA is often present in regions critical to the development of AD [76–81]. When present, HSV-1 localized predominantly to Aβ plaques, suggesting that it might influence fibril aggregation [82]. Three mechanisms of HSV-associated Aβ accumulation have been examined. Shipley *et al.* [83] posited that by interfering with β-amyloid precursor protein (APP) metabolism, HSV-1 led to elevated levels of Aβ40 and Aβ42 in human neuroblastoma and glioblastoma cells *in vitro*. Another hypothesis [84] suggests that HSV-1 glycoprotein B might seed Aβ aggregation, seeing how the two proteins share considerable homology at the amino acid level. Finally, HSV-1 might influence APP phosphorylation in a calcium-dependent manner[85]. HSV-1 binding to cell membranes was found to result in neuronal hyperexcitability such that dysregulated calcium flux and thereby increased phosphorylation of APP at Thr668. Further, the neurons affected by virally-mediated hyperexcitability were found to have higher levels of Aβ build of 42 amino acids (Aβ42). Interestingly, administration of the calcium channel blockers nifedipine and 2-aminoethoxydiphenyl borate abrogated the pathologic changes, as evidenced by their decreasing intra-neuronal Aβ [85,86]. More recently, the association between HSV and the formation of Aβ plaques was backed up by studies correlating elevated levels of HSV with the presence of the apolipoprotein E (*APOE*) E4 allele [74,87], a known risk factor for AD [88]. In addition, HSV-1 may cause tau hyperphosphorylation insofar as viral kinases may target host proteins [74,89–93]. Immunologic response to HSV may be yet another mechanism promoting neurodegeneration. In one study on 512 elderly persons there was a significant association between AD risk and the presence of anti-HSV-1 immunoglobulin M (IgM), but not anti-HSV-1 immunoglobulin G (IgG) antibodies [94].

Apart from HSV, other members of the *Herpesviridae* family may contribute to the pathogenesis of AD. HHV-3, also known as Varicella-zoster virus (VZV), is responsible for varicella in children and herpes zoster in adults [95]. This virus is capable of causing latent infection after crossing the BBB or by cross-axonal retrograde transport from skin vesicles [96]. In the latent state, VZV usually inhabits the cranial nerve ganglia, dorsal root ganglia and autonomic ganglia [97–104]. A recent study found that VZV infection is associated with an increased risk of dementia such that might be attenuated through the administration of antiviral therapy [105]. An increased risk for AD, irrespective of gender was also identified in a study on herpes zoster patients above 65 years of age [33] (Table 1). VZV might be involved in AD pathogenesis through its activity on insulin-degrading enzyme (IDE), a zinc metalloprotease associated with Aβ degradation [106]. IDE is known to be one of the key cellular receptors for VZV and the interaction between the viral glycoprotein E and the metalloprotease might be the mechanism underlying neuron to neuron transport of the virus [107,108]. Furthermore, IDE might suppress the purported antiviral properties of Aβ, which further implies that VZV is a risk factor of AD [109].

Epstein-Barr Virus (EBV) or HHV-4 affects as much as 95% of the global population, most of whom come into contact with it in the early stages of life. While EBV infection is usually oligo-symptomatic, in some patients the virus can cause severe disease, subsequent to which the virus may remain in B-lymphocytes [110]. Recent studies have shown that this process might be associated with development of AD. Carbone *et al*. (2014) found EBV DNA in the blood of 45% of the AD patients participating in the study and in 6% of AD patient brain samples. Interestingly, all EBV positive brain samples originated from carriers of the pathogenic *APOE* E4 allele [34].

HHV-5, also known as human cytomegalovirus (CMV) also frequently results in nothing but an innocuous latent infection [111,112]. Still, an association between CMV and AD has been made [113]. Depending on the demographic, the percentage of individuals that carry CMV blood antigens ranges from 20% up to 100% [114–116]. Some reports suggest that infection with CMV may be associated with cognitive impairment. According to Aiello *et al*. [114], a significant proportion of patients with increased levels of CMV blood markers experienced a substantial drop in cognitive performance after a 4-year period. Further, significant elevation of CMV markers was reported in a group of individuals over the span of 5 years, during which period they developed clinical AD [34] (Table 1). Importantly, plasma CMV IgG levels were found to correlate with increased density of neurofibrillary tangles (NFTs) [117].

Human betaherpesvirus 6A/B (HHV-6A/B) can enter the CNS via the olfactory tract leading to HSV-1 like latent infection [118]. Nonetheless, damage to glia and neurons post HHV-6 infection has been reported [119–124]. Multiple reports point to a large association between HHV-6 and AD. A study by Readhead *et al*. [125] on more than 1000 brain samples showed high levels of HHV-6 in the tissue of AD patients. Eimer *et al*. [126] demonstrated that increased Aβ accumulation may occur in patients infected by HHV-6A/B. Moreover, HHV-6 interference in autophagy may promote AD neuropathology [127,128]. Lastly, by infecting glia HHV-6 may result in a pro-inflammatory state characterized by increased levels of IL-6 and IL-8 [123,129] such that is thought to favor neurodegenerative processes.

2.3 Hepatitis C virus

Hepatitis C virus (HCV) is a small, single-stranded, enveloped virus that can cause chronic hepatitis and puts individuals at increased risk of developing hepatocellular carcinoma. Recent studies have shown that 2.8% of the global population may be infected with HCV which corresponds to more than 185 million cases worldwide [130]. An association between HCV infection and CNS manifestations was first discovered over 15 years ago, since which time our understanding of the neurotropic nature of the virus has grown considerably [131]. While HCV has been identified as a risk factor for AD, how the virus is involved in neurodegeneration remains to be elucidated. Still, two non-mutually-exclusive mechanisms have been suggested. HCV may cross the BBB and directly exert toxic effects on neuronal tissue or initiate CNS or systemic inflammation conducive to neurodegeneration [132]. Another possible link between HCV infection and AD is based on virally-induced overexpression of cholesterol 25-hydroxylase gene (*CH25H*) and consequent overproduction of 25-hydroxycholesterol (25OHC) [133,134]. Cholesterol containing lipid rafts are thought to potentiate viral entry into cells but likewise serve as hubs for pathologic cleavage of APP [135]. Interestingly, the type-I interferons (IFN) generated in response to HCV infection that drive overexpression of *CH25H* may prime 25OHC to block virus-cell membrane fusion [134,136,137]. In mice treated with the toll-like receptor 4 (TLR4) agonist, lipopolysaccharide (LPS), 25OHC synthesis was greatly augmented and accompanied by increased CNS production of the pro-inflammatory cytokine IL-1β [138]. This increase was particularly pronounced in transgenic mice bearing the *APOE* E4 variant, in whom 25OHC levels were higher than in other *APOE* variants [138]. High levels of IL-1β may induce neuroinflammation leading to degeneration of neuronal tissue and possible memory deficits [139,140].

2.4 Influenza viruses

The Influenza A virus is characterized by a single-stranded segmented genome and is a chief causative agent of the seasonal flu. The virus is known to undergo both antigenic drift and antigenic shift, the latter of which, particularly, has given rise to epidemics in-

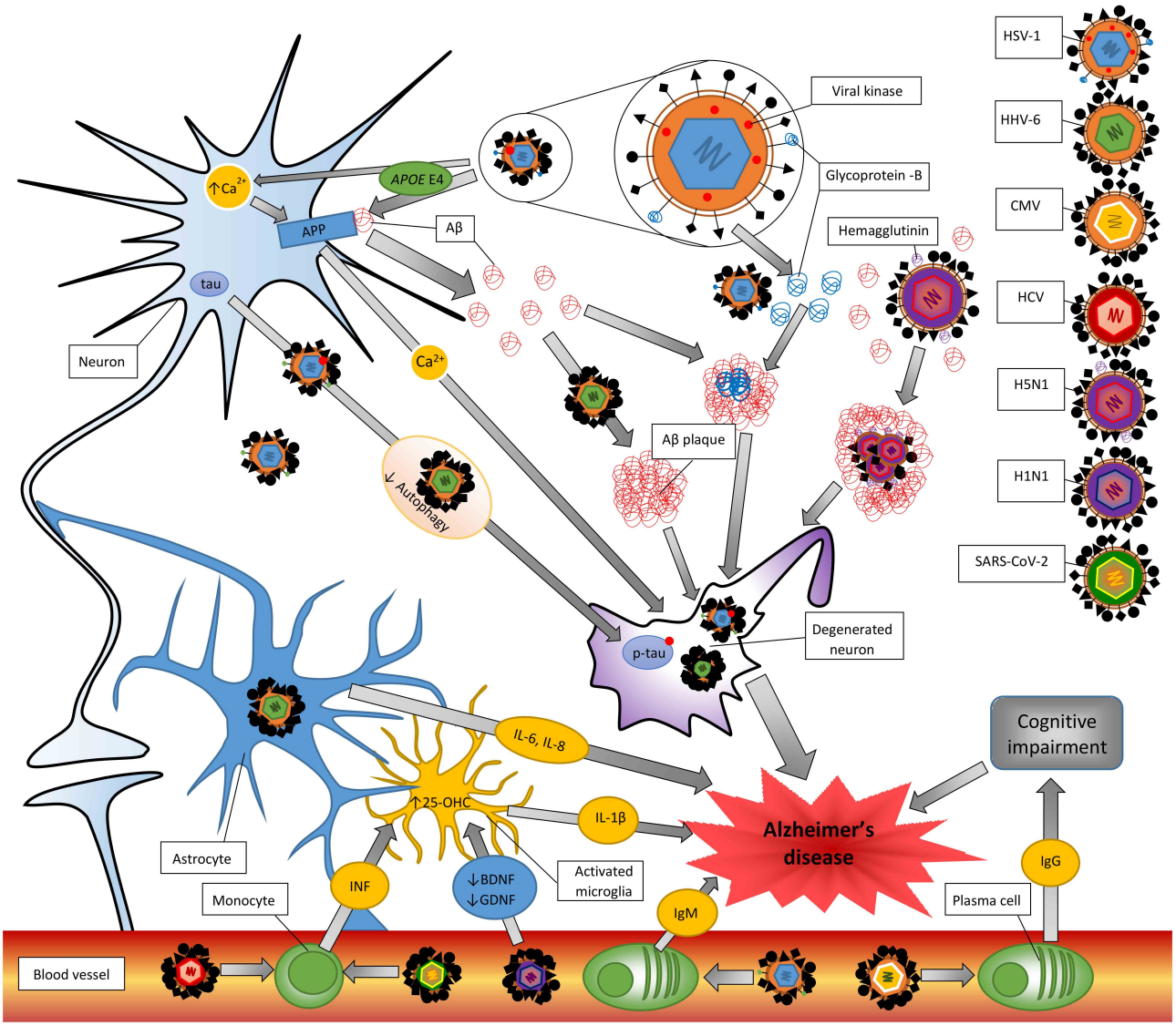

Fig. 1. The pathomechanism of virus-associated neurodegeneration. Herpes simplex virus 1 (HSV-1) resides in neurons and may induce aggregation of Aβ in Alzheimer's disease (AD) by various mechanisms, that may be facilitated by the presence of *APOE* E4 genotype. HSV-1 may affect turnover of amyloid precursor protein (APP) to produce more amyloid β (Aβ), subsequently, viral glycoprotein B might serve as a primal starter for Aβ aggregation. HSV-1 may also influence APP and tau protein phosphorylation mediated by calcium ions (Ca^{2+}).The process may be induced by viral kinases, that lead to neuronal degeneration. Furthermore, HSV-1 may activate plasma cells to produce immunoglobulins M (IgM), whose increased levels has been linked do AD pathology. Conversely, to HSV-1 human betaherpesvirus 6A/B (HHV-6A/B) has the ability to affect both astrocytes and neurons. HHV-6 infection may reduce autophagy and lead to increased Aβ accumulation and tau protein hyperphosphorylation. Moreover, glia under influence of HHV-6 secrete interleukin-6 (IL-6) and interleukin-8 (IL-8), whose excessive levels may promote neuroinflammation. Subsequently, cytomegalovirus infection has been associated with increase of immunoglobulins G (IgG) production, associated with future cognitive impairment. Similar systemic response may be induced by hepatitis C virus (HCV) infection, that stimulates production of interferon-1 (IFN), followed by overproduction of 25-hydroxycholesterol (25-OHC) and release of interleukin-1β by microglia, that lead to inflammatory response and neuronal loss.

Respiratory viruses, including influenza virus H5N1 may also play role in AD pathology. H5N1 virus express Aβ-like hemagglutinin, that promotes Aβ aggregation and enhances proration of neurons, that lead to cellular damage and apoptosis. Conversely, influenza virus H1N1 is not neurotropic and promote neurodegeneration via reduction of neurotrophic factors: BDNF and GDNF, followed by activation of microglia and neuroinflammation. Analogically, SARS-CoV-2 virus does not damage the neurons per se, but enhances inflammatory response that promotes neuronal death and thus cognitive impairment.

cluding the avian flu and the swine flu, caused by the serotypes of hemagglutinin-5-neuraminidase-1 (H5N1) and hemagglutinin-1-neuraminidase-1 (H1N1), respectively. Serotypes are named according to variants of the viral proteins hemagglutinin (H) and neuraminidase (N), which, broadly speaking, allow the virus to gain entry into host cells and facilitate lysis after intracellular replication is complete, respectively. Interestingly, H5N1 has been implicated in the phosphorylation and aggregation of alfa-synuclein (ASN), whose role in Parkinson's disease (PD) neurodegeneration has been well established [37]. While the said pathology plays a more obvious role in the pathogenesis of Lewy body dementia and PD, the structural similarity between Aβ and influenza hemagglutinin suggests that H5N1 may also be involved in the development of AD [141]. Specifically, similarities lies in the C-termini of the two proteins, where hemagglutinin harbors a domain responsible for cell membrane binding [142]. That accords with the hypothesis of membrane-poration derived neurotoxicity, in which influenza virus is thought to play a role [141,143,144].

Aβ42 is a well-characterized major component of Aβ plaques in AD, recently conjectured to possess antiviral properties. One study found that Aβ42 aggregated influenza virus, acted as chemotaxis for neutrophils, and strengthened neutrophil hydrogen peroxide release [145]. The said aggregating ability is thought to be conferred by a Aβ42 C-terminal loop comprised of residues from Met35 to Ala42, which is also mechanistically implicated in Aβ42 oligomerization [146,147].

Another influenza serotype that might also be related to a pathological neural changes is CA/09 H1N1. This virus does not actively cross the BBB and is thought to be non-neurotropic [38]. Nonetheless, in one study it was shown to lead to microglial overactivation that remained pronounced for three weeks post infection and was sustained to a lesser degree for as long as 90 days [38]. The infection was accompanied by down-regulation of brain-derived neurotrophic factor (*BDNF*) and glial cell-derived neurotrophic factor (*GDNF*), genes which encode neurotropic factors essential for maintaining neural plasticity. Furthermore, BDNF and GDNF are responsible for regulating microglial activation, and their decreased expression may lead to CNS inflammation, which coupled to reduced brain plasticity, increases the risk for AD dementia [38].

The neurodegenerative effects of viral infection have been summarized in Fig. 1.

3. Prokaryotic organisms and the pathogenesis of Alzheimer's disease

The first hypothesis linking prokaryotic microorganisms and AD was forwarded by Alzheimer and other scientists in the early 20th century [148]. Recent research trends point to a recrudescence in conjecturing about the role of prokaryotes in neurodegeneration. In addition to transmissible infections, natural florae of the oral cavity, lungs, gastrointestinal tract, and urinary tract may become dysregulated due to pharmaceuticals or physiological changes and cause disease. Importantly, inflammation secondary to bacterial infection must be considered in addition to the potential direct pathologic effects of microorganisms on the CNS.

3.1 Spirochetes

Among the bacteria capable of inducing excessive inflammation in the CNS are spirochetes [149,150]. Spirochetes are gram-negative, helical bacteria, with neurotropism for the trigeminal ganglion and nerve [151,152]. They are able to penetrate the host by utilizing three different mechanisms: hematogenous dissemination, ascension along nerve fibers of the *tractus olfactorius* and adjacent *fila olfactoria*, and via the lymphatics. Recently, spirochetal invasion of the olfactory tracts and bulbs of patients with early evidence of AD neurodegeneration was demonstrated [153]. Once in the CNS spirochetes may lead to latent infection [154,155]. The presence of spirochetes has been reported in the CSF, blood, and brain of AD patients, with neural invasion being 8-fold more frequent among those with AD as compared to controls [152,155,156]. Seeing how spirochetes may require amyloid like proteins in order to maintain their lifecycle in the CNS, bacterial amyloids could promote Aβ deposition in the brain [155,157].

The spirochetes that are most widely researched in the context of AD are *Borrelia burgdorferi* and *Treponema pallidum*. *B. burgdorferi* is the causative agent of Lyme disease (borreliosis), in the late phase of which bacterial infection may lead to cortical atrophy and microgliosis, which are considered to be precursors of dementia [155,158]. Currently, the number of borreliosis cases is steadily increasing in European countries and thus, a growing number of researchers are probing the possible association between spirochetal invasion of the brain and development of AD [158]. The presence of *B. burgorferi* in the cerebral cortex of the brains of AD patients was shown for the first time in studies by MacDonald and Miklossy and co-authors [39,159]. The chronic inflammation induced by *B. burgorferi* may result in abnormal phosphorylation of the protein tau, leading to microtubule dysfunction and NFT formation. In a group of patients suffering from both AD and neuroborreliosis, *B. burgorferi* antigens were detected in numerous structures including NFTs, Aβ, neurons, neuropil threads, senile plaques, and leptomeningeal and cortical vessels [151,155,159]. Further, intracytoplasmic granules, resembling those appearing during AD granulovacuolar neuronal degeneration, in addition to increased levels of APP, Aβ, and hyperphosphorylated tau proteins have been found in astrocytes in neuroborreliosis [40]. In *ex vivo* studies, exposure to *B. burgdorferi* triggered glial cell production of the cytokines IL-1β, IL-6, IL-8, cyclooxygenase-2 (COX-2), and the chemokine B lymphocyte chemoattractant (CXCL13) and excessive apoptosis of glia and neurons

[160]. The association between AD and *T. pallidum*, another spirochete, is less clear. *T. pallidum* is the cause of syphilis, one of the most common sexually transmitted diseases (STDs). Chronic infection with *T. pallidum* may lead to tertiary syphilis, which may be characterized by cardiovascular as well as neurological manifestations. The symptoms of neurosyphilis include memory deterioration, and so the disease should be part of the differential diagnosis for AD [161]. Chronic syphilis leads to progressive dementia, likely due to lipoprotein-induced sustained inflammation, local amyloidosis, and cortical atrophy [150,160–164]. Indeed, more studies will be needed in order to determine whether a connection between *T. pallidum* infection and AD exists.

3.2 Chlamydia

Chlamydia pneumoniae is a Gram-negative intracellular pathogen antibodies against which are detectable in as many as 80% of individuals between 60 to 70 years of age [165]. Presumably, chlamydia are able to penetrate to the CNS via the olfactory route, similarly to other, previously discussed microorganisms [166]. The presence of *C. pneumonia* in the CSF and brain of AD patients has been highlighted by many authors [167–172]. Balin *et al*. [168] identified *C. pneumonia* in 17 of 19 post-mortem frozen brain fragments from AD patients, as compared to a single positive PCR-test result in control brain samples. Similar results were obtained by Gérard *et al*. [170] who detected *C. pneumonia* in 20 of 25 AD postmortem brain samples and in only 3 of 27 from the control group. Importantly, infected cells co-localized nearby senile Aβ plaques and NFTs [170]. Pericytes, microglia, astrocytes and endothelial cells are also susceptible to infection by chlamydia [168,173]. Interestingly, reactive astrocytes in the context of chlamydial infection were found to localize to Aβ plaques [174]. There is an ongoing discussion about chlamydial antigens and their impact on extracellular lipids and proteins in the brain. These antigens may affect soluble oligomeric forms of amyloid including Aβ-derived diffusible ligands (ADDLs). Mature AD plaques usually do not contain these molecules. However, amyloid residues and chlamydia appear in the same cortical regions of the brain. As a result, further investigation is required to understand the connection between *C. pneumonia* and AD.

3.3 Bacteria of the oral cavity

Recent studies have pointed out that the oral cavity may be one of the most important reservoirs of bacteria capable of infecting the brain and promoting the onset of dementia. Periodontal disease may induce a systemic inflammatory response thereby effecting changes at distant sites. Amid the pathogens causing periodontitis, the potential involvement of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcmitans*, *Eikenella corrodens* and *Treponema denticola* in the pathogenesis of AD has been considered, but detailed commentary on each is beyond the scope of this review [175,176].

Periodontitis leads to the destruction of tissues surrounding the teeth and is a significant problem predominantly affecting the elderly [177,178]. In 2019, the NHANES III study showed that periodontitis was significantly associated with cognitive impairment [43]. The symptoms of periodontitis, including gingival bleeding, loss of periodontal attachment, and finally loss of teeth are caused by bacterial LPS which provokes the immune response to generate tumor necrosis factor α (TNF-α), IL-1, IL-1β and IL-6 [43]. These locally produced cytokines may enter the bloodstream and lead to chronic systemic inflammation. Thus, periodontal disease may be classified as a "low-grade systemic disease" and is characterized by increased levels of C-reactive protein (CRP) [177]. Studies have pointed to periodontitis as an AD risk factor by way of chronic oral infection amplifying inflammatory processes in the brain [153,179–182]. AD patients with periodontal disease expressed considerably increased levels of TNF-α and antibodies specific to periodontal bacteria [183,184]. During periodontitis, inflammatory signals are transferred from macrophages to microglia in the brain and as a result, patients may present with symptoms of neuroinflammation. This may contribute to the initiation and progression of AD as well as other forms of cognitive deterioration [185].

Propionibacterium acnes is another periodontal pathogen possibly associated with the risk of developing AD. These bacteria may enter the CNS and infect the brain via hematogenous spread [186]. In young individuals, the bacteria usually act as epidermal commensals, but are a common cause of acne vulgaris. Still, *P. acnes* has been identified in the frontal cortex of patients with AD [44]. While a connection between *P. acnes* infection and AD has not yet been firmly established, there are reports indicating that in some cases effective treatment against *P. acnes*, such as cephalosporine combined with estrogen and enalapril may lead to memory improvement and stabilization of clinical symptoms, as shown in two AD case reports [44,151].

3.4 Bacteria of the gastro-intestinal tract

Helicobacter pylori is a curved, Gram-negative bacterium that may lead to stomach ulcers and gastric cancers and is estimated to be present in more than 50% of the population worldwide. Apart from its effects on the gastrointestinal system, many studies have implicated *H. pylori* in other diseases, such as respiratory or neurodegenerative disorders [151,187]. Kontouras *et al*. [188] showed that among 27 AD patients, 100% presented with high levels of anti *H. pylori* IgG antibodies in the serum and CSF. A 20-year longitudinal study performed on 603 patients above 65 years of age showed that the presence of IgG antibodies against *H. pylori* was associated with a 1.46 fold increased

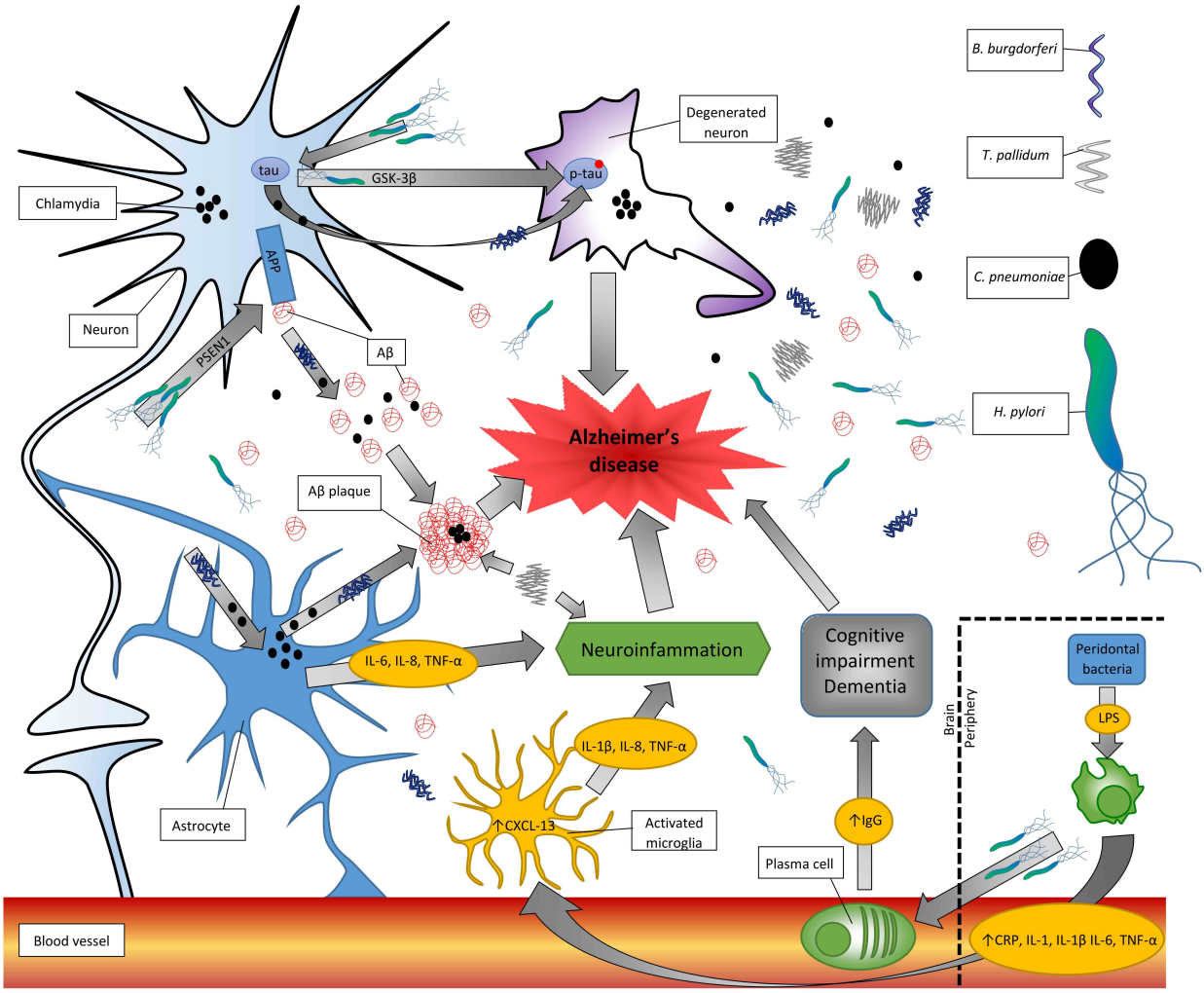

Fig. 2. The pathomechanism of bacteria-associated neurodegeneration. The infection of the central nervous system by *Borrelia burgdorferi* activates microglia to produce proinflammatory cytokines—e.g., interleukin-1β (IL-1β), -8 (IL-8) and tumor necrosis factor α (TNF-α). Similarly, the bacteria activates astrocytes to release IL-6, IL-8 and TNFα. *B. burgdorferi* antigens may also act as seeders of amyloid β (Aβ) aggregation and promote hyperphosphorylation of tau protein (p-tau). *Treponema pallidum*, similarly may facilitate Aβ plaque formation, activate neuroinfalmmatory response, and thus increase risk of Alzheimer's disease (AD).
Likewise, the infection with *Helicobacter pylori* and periodontal bacteria via lipopolysaccharide (LPS) may induce production of inflammation-associated markers, e.g., c-reactive protein (CRP), interleukins: -1, -1β, -6 (IL-1, IL-1β, IL-6) and tumor necrosis factor α (TNF-α) that facilitate activation of microglia, by increasing expression of chemokine (C-X-C motif) ligand 13 (CXCL-13) and thus induces neuroinflammatory response. Moreover, *H. pylori* promotes Aβ release by activating presenilin 1 (PSEN1), as well as formation of p-tau, mediated by glycogen synthase kinase 3 beta (GSK-3β). Subsequently, the high concentration of anti-*H. pylori* immunoglobulin G (IgG) has been associated with cognitive impairment and developing dementia.
Conversely, the intracellular *Chlamydia pneumoniae*, may enter both neurons and astrocytes. In neurons *C. pneumoniae* induce formation of p-tau and neuronal degeneration, while in astrocytes the bacteria induces hyperactivity that enhances Aβ aggregation. The latter may be also facilitated by bacterial lipids. The above processes collectively have been associated with increased risk of cognitive decline and AD.

risk of developing dementia, as compared with the control group [45] (Table 1). Further, *in vitro* studies performed using mouse neuroblastoma N2a cells transfected with the human *APP* gene demonstrated that cells infected with *H. pylori* produced increased presenilin 2 (PS2) and Aβ42. Moreover, *H. pylori* infection of N2a cells led to activation of glycogen synthase kinase-3β and subsequently increased hyperphosphorylation of tau protein [189,190]. Similar results have been observed *in vivo*. After intraperitoneal injection with *H. pylori*, rats developed marked memory deficits and had higher cortical and hippocampal levels of PS2 and Aβ42. While the mechanism by which *H. pylori*

infection impacts AD is still unknown, molecular mimicry and its capacity to impart a chronic low-grade inflammatory state should be considered [191,192]. Fig. 2. depicts the proposed mechanisms underlying bacteria-induced neurodegeneration.

4. Protozoa and Alzheimer's disease

The eukaryotic protozoa, among which numerous human parasites may be identified, might also influence the start and course of neurodegeneration. Only *Toxoplasma gondii*, whose effects on cognitive functioning have been relatively well characterized will be considered here. *T. gondii* is an intracellular pathogen with multiple intermediate hosts, but mainly parasitizes warm-blooded animals. *T. gondii* infection affects approximately 30% of the global population with its prevalence varying depending on sanitary conditions, educational and cultural background, and profession [193]. *T. gondii* spreads via oocysts, thick-walled spores resistant to environmental conditions. In humans, consumption of oocyst contaminated water or food and placental transmission are the main routes whereby infestation with the parasite occurs [194]. In immunocompetent patients, the initial phase of infection is oligosymptomatic. Nevertheless, at this stage *T. gondii* spreads through the organism as a tachyzoite, a rapidly-proliferating form recognized by the host immune system [195,196]. Monocytes and dendritic cells recruited during this initial immune response undergo activating changes including actin cytoskeleton remodeling, signaling downstream of the gamma-aminobutyric acid (GABA) receptor, and upregulation of the chemokine receptor CCR7 [197–199]. During the persistent phase, the protozoan transforms into a slow-growing bradyzoite and encysts. This form strives to avoid the immune response and resides in various human tissues, primarily in the CNS and muscles leading to chronic and latent infection [200]. The exact mechanism through which the parasite crosses the BBB is still unknown, however, there are several hypotheses for how *T. gondii* might invade the CNS. In a trojan horse-like mechanism, infected monocytes display increased mobility and transfer *T. gondii* across the BBB into the CNS [201–203]. In transendothelial migration, infected cells express cluster of differentiation molecule 11B (CD11b)/intercellular adhesion molecule 1 (ICAM1) integrins, which facilitates parasite adhesion and migration across endothelial cells [199,203,204]. Finally, in paracellular migration protozoa gain access into the CNS via actin-myosin motors, exhibiting a movement called "gliding motility". This allows the parasites to elide host immune barriers and penetrate across tight junctions as well as polarized cell monolayers. Increased expression of *T. gondii* adhesive microneme protein 2 (MIC2) and excessive interaction with the ICAM-1 is thought to allow passage across highly selective biological barriers including the BBB [205,206].

How long-term infection influences neurological functions is still largely unknown [207,208]. Recent studies have shown that persistent exposure to *T. gondii* might increase the risk of developing neurodegenerative disorders such as AD and PD, as well as schizophrenia, migraine and bipolar disorder type I [209–212]. Importantly, a significant association between the presence of antibodies against *T. gondii* in elder patients and impaired cognitive abilities has been identified [32]. Studies based on animal models have shown that chronic toxoplasmosis may also cause behavioral alterations such as neophobia, affect learning, and disrupt memory [213]. Mice with toxoplasmosis were shown to have reduced nerve fiber density and loss of synapses in infected brain zones, and especially in somatosensory areas [214]. *In vitro* studies have reported that *T. gondii* can infect and form cysts in astrocytes and neurons, but only the former are capable of eliminating the intracellular form of the protozoan [215–218]. Additionally, several simulations have revealed that toxoplasmosis might cause tau hyperphosphorylation and Aβ plaque deposition in the hippocampus and prefrontal cortex [219]. Nonetheless, other models found no correlation between neuroinflammation induced by T. *gondii* and AD or any other neurological disorder, including dementia [220].

One of the mechanisms responsible for the appearance of AD-like symptoms in toxoplasmosis may be altered glutamine, dopamine or GABA neurotransmission [219,221]. Specifically, *T. gondii* infection might impact the glutamatergic *N*-methyl-*D*-aspartate (NMDA) receptor (NMDAR), which mediates neurotransmission at excitatory synapses and participates in synaptic plasticity [222]. Studies performed in wild type mice have shown that toxoplasmosis may induce increased expression of NMDARs in the cortex and hippocampus, as well as production of hyperphosphorylated tau and Aβ plaques in the brain [219]. The degeneration of synaptic connections and the ensuing behavioral changes that have been observed in mice with chronic toxoplasmosis might arise from the presence of NMDAR autoantibodies, which impede internalization of the channels [223]. In addition, wild-type mice infested with *T. gondii* were shown to exhibit behavioral modifications, such as anxiety disorder, and also suffered from neuronal apoptosis in the olfactory bulb which led to changes in olfactory sensitivity. Interestingly, the olfactory impairment was significantly marked only in male mice [219].

The next neurotransmitter presumably related to AD-like symptoms in toxoplasmosis is GABA, the main inhibitory neurotransmitter in the CNS [224]. The cognitive deterioration that occurs in some cases of the disease may be related to *T. gondii*-induced disruption of GABA turnover [225]. It is known that changes to the GABAergic system including reduced expression of the GABA receptor α1 and γ1 subunits in the temporal cortices may be seen in AD [226]. Furthermore, GABA signaling is involved in cellular migration and metastasis. This pathway

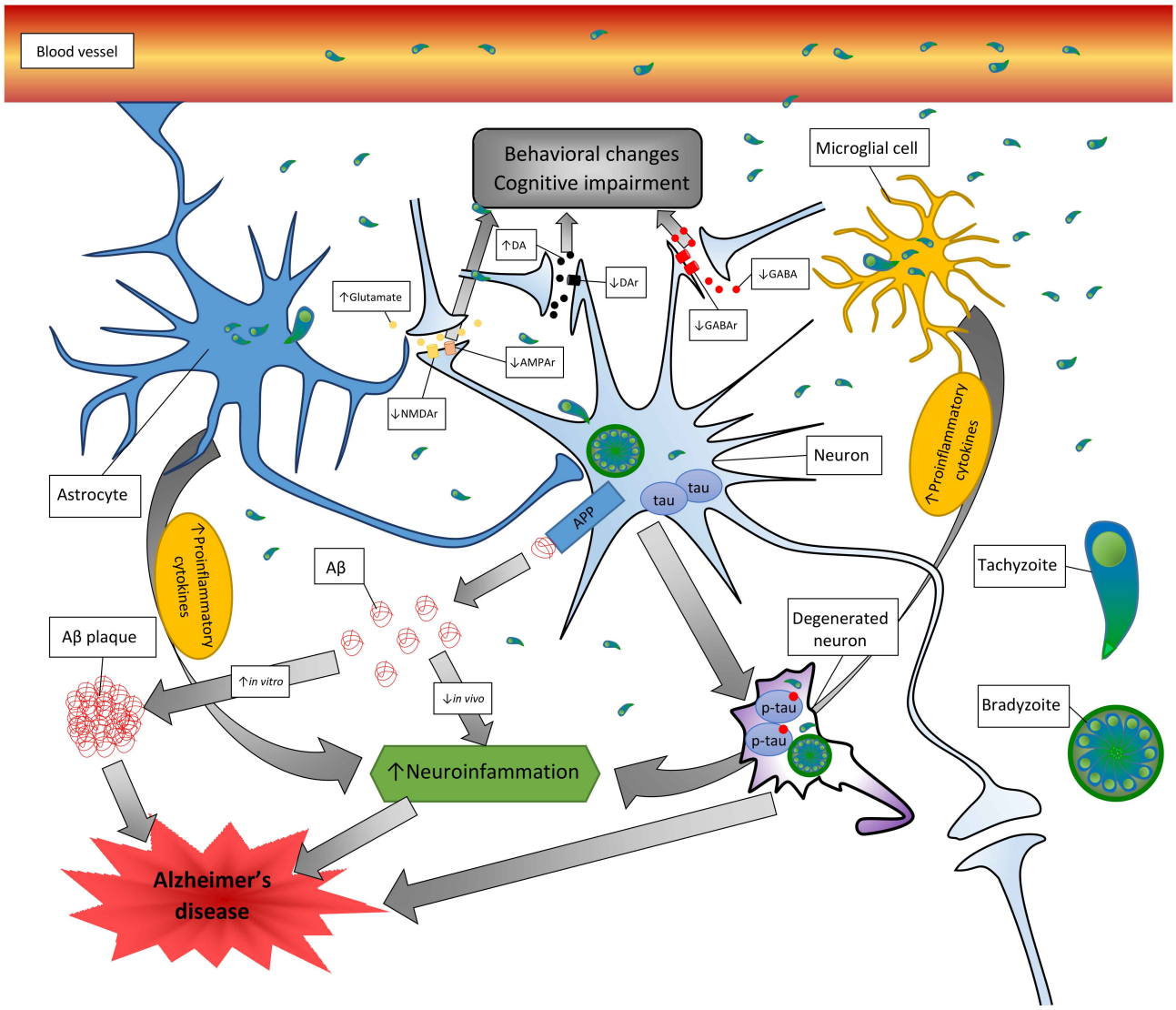

Fig. 3. The possible effects of *Toxoplasma gondii* infection on brain cells. AMPAr, AMPA receptor; DA, dopamine; DAr, DA receptor; GABA, gamma-butyric acid; GABAr, GABA receptor; NMDAr, NMDA receptor; Aβ, amyloid β; tau, tau protein; p-tau, hyperphosphorylated tau protein.

T. gondii may infect neurons and other brain cells, including astrocytes and microglia. Infected glia produce proinflammatory cytokines that activate nuroinflammatory response. The neuronal infection leads to overproduction of Aβ (*in vitro*) and p-tau (*in vitro* & *in vivo*), as well as causes disruption in neurotransmitter systems: dopaminergic, GABAergic and glutamatergic, that may induce behavioral changes, cognitive decline and neurodegeneration. These processes may increase risk of developing Alzheimer's disease in susceptible individuals.

is thought to be exploited by *T. gondii*, in that parasite-triggered GABAergic signaling provokes increased migration of infected dendritic cells [197]. A similar mechanism is observed in the CNS, where activated microglial cells signaling with GABA facilitate the spread of *T. gondii* in brain tissue [227]. Additionally, there are studies indicating that nonproliferating *T. gondii* might produce GABA themselves, however, the secretion of the neurotransmitter is a non-active process, presumably generated by dead bradyzoites. This may lead to alteration in GABAergic transmission and cause neurobehavioral changes [225,228]. Moreover, decreased GABAergic signaling might also arise from NMDAR dysfunction, seeing how those channels are co-expressed in GABAergic interneurons [229].

Dopamine is responsible for controlling a wide range of neurological functions including motor skills and pathways governing motivation and as such, a dysfunctional dopaminergic system might trigger some of the neuropsychiatric manifestations of AD [230]. Correlations exist between AD and a dysregulated dopaminergic system particularly in the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the locus coeruleus (LC). Murine

models of AD have evidenced significant changes in memory processes and cognitive abilities caused by dopaminergic neuron impairment in the VTA [231]. *T. gondii* exerts an effect on the dopaminergic system by leading to decreased expression of the dopamine transporter (DAT) and the vesicular monoamine transporter 2 (VMAT2). In addition, two genes in the *T. gondii* genome, aromatic amino acid hydroxylase 1 and 2 (*AAH1* and *AAH2*) encode enzymes which may be involved in production of l-3,4- dihydroxyphenylalanine (L-DOPA) [232]. These mechanisms may induce increased dopamine concentration in synapses. Indeed, underexpression of the genes dopamine receptor D1, -D2 and D4 (*DRD1*, *DRD2* and *DRD4*, respectively) and G protein-Coupled Receptor Kinase 6 (*GRK6*) causing decreased dopamine receptor availability led to elevated dopamine levels in mice with toxoplasmosis [221]. Abnormal dopamine levels can disrupt motor and executive functions and lead to the development of symptoms characteristic of neurodegenerative disease. Moreover, it has been demonstrated that hyperactivity of dopaminergic neurotransmission pathways impacts prefrontal cortex functions and may lead to cognitive impairment [233].

While *T. gondii* infection may be associated with cognitive decline through its ability to dysregulate neurotransmission, it has not been found to promote aggregation of pathological proteins. Two independent teams of researchers working on AD-mice models infected with *Toxoplasma* strain Type II evidenced that chronic toxoplasmosis may actually reduce Aβ plaque burden and act as a potential protective factor for cognitive decline [162,234]. This phenomenon might be explained by two mechanisms. The protective activity of *T. gondii* infection might be provided by the up-regulation of anti-inflammatory cytokines including transforming growth factor β (TGF-β) and IL-10. The second hypothesis suggests that the recruitment of highly phagocytic monocytes in response to infection decreases deposition of Aβ plaque. Notably, both studies assessed that the reduction of Aβ burden secondary to infection with *T. gondii* was greater than 60% [162,234]. Unfortunately, immunohistochemical analysis of the association between *T. gondii* infection and tau protein phosphorylation revealed that the formation of NFTs was significantly increased in infected mice brains, especially in the cortex and hippocampus, regions vital for memory and cognitive function [219]. The cognitive effects of *T. gondii* infection have been summarized in Fig. 3.

In summary, *T. gondii* infection may constitute a potential risk factor for AD (Table 1), however, the mechanisms whereby it might seed neurodegenerative changes in the brain are still unclear and require further research.

5. Conclusions

AD is the most common cause of progressive, irreversible dementia in older adults and constitutes a vital socioeconomic issue in developed countries with aging populations. While it is known that AD is a multifactorial disease, affected by both genetic and environmental factors, its pathogenesis is not fully understood. Moreover, existing pharmacotherapy for AD is limited and provides only moderate relief for patients in the early stages of the disease. Despite years of research focused on molecular mechanisms of neurodegeneration, there is still no treatment that addresses the cause of AD.

Recently, increasing attention has been placed on the microorganismal hypothesis of AD development. Studies have demonstrated that microorganisms frequently co-localize with pathological changes in the CNS, suggesting that viral, bacterial and parasitic infections may contribute to neurodegeneration. Multiple reports have shown that infectious agents may facilitate the Aβ cascade, either by producing amyloid-like molecules that seed formation of Aβ plaques, or by enhancing the production of endogenous Aβ. Further, it has been shown that brain infection may promote hyperphosphorylation of tau protein thereby leading to neuronal degeneration and loss of synapses. Moreover, both local and systemic infection may over-stimulate the immune system, inducing microglial and astrocytic activation and the release of pro-inflammatory cytokines. This process has been repeatedly linked with excessive oxidative stress, which has surfaced as a major factor in the pathogenesis of AD and other neurodegenerative conditions in recent years. While this review has pointed to important associations between infectious agents and AD, further controlled research is needed if the microorganismal hypothesis is incite funding for novel therapeutics.

Abbreviations

25OHC, 25-hydroxycholesterol; *AAH1/2*, aromatic amino acid hydroxylase 1/2 coding genes; *ACE*, angiotensin-converting enzyme 1 coding gene; ACE1/2, angiotensin-converting enzyme 1/2; ACEI, angiotensin converting enzyme inhibitors; AD, Alzheimer's disease; ADAM-9, alpha-secretase a disintegrin and metalloproteinase-9; ADDLs, Aβ-derived diffusible ligands; *APOE*, apolipoprotein E coding gene; *APP*, amyloid precursor protein coding gene; APP, β-amyloid precursor protein; ARBs, angiotensin receptor blockers; ASN, alfa-synuclein; AT1-7, angiotensin type 1-7 receptors; ATII, angiotensin II; Aβ, β amyloid; Aβ40/42, Aβ build of 40/42 amino acids; BBB, blood-brain barrier; *BDNF*, brain-derived neurotrophic factor coding gene; CD11b, cluster of differentiation molecule 11B; *CH25H*, cholesterol 25-hydroxylase gene; CMV, human cytomegalovirus; CNS, central nervous system; COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; CSF, cerebrospinal fluid; CTIP2, B-cell lymphoma/leukemia 11B; CXCL13, chemokine B lymphocyte chemoattractant; CYP, cytochrome P450; DAT, dopamine transporter; DPP4, serine exopeptidase dipeptidylpeptidase 4; *DRD1/2/4*, dopamine receptor D1/D2/D4 coding genes; EBV,

Epstein-Barr Virus; FOXG1, forkhead box protein G1; GABA(R), gamma-aminobutyric acid (receptor); *GDNF*, glial cell-derived neurotrophic factor coding gene; *GRK6*, G protein-coupled receptor kinase 6 coding gene; H1N1, hemagglutinin-1-neuraminidase-1; H5N1, hemagglutinin-5-neuraminidase-1; HCV, Hepatitis C virus; HEK-293T, human embryonic kidney cells; HHV 1–8, human herpesviruses 1–8; HSV, Herpes Simplex Virus; ICAM1, intercellular adhesion molecule 1; IDE, insulin-degrading enzyme; IgG, immunoglobulin G; IgM, immunoglobulin M; Interleukin-1β/6/8, IL-1β/6/8; LC, locus coeruleus; L-DOPA, l-3,4-dihydroxyphenylalanine; LPS, lipopolysaccharide; MAS1, MAS1 proto-oncogene; MERS-CoV, Middle Eastern respiratory syndrome coronavirus; NAc, nucleus accumbens; NFTs, neurofibrillary tangles; NMDA(R), *N*-methyl-*D*-aspartate (receptor); NRP1, Neuropilin 1; PAX6, paired box protein Pax-6; PD, Parkinson's disease; PS2, presenilin 2; *PSEN1/2*, presenilin 1/2 coding genes; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-protein, SARS-CoV-2 spike glycoprotein; STDs, sexually transmitted diseases; TGF-β, transforming growth factor β; TLR4, toll-like receptor 4; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor α; VMAT2, vesicular monoamine transporter 2; VTA, ventral tegmental area; VZV, Varicella-zoster virus.

Author contributions

TP—preparing the part concerning putative contribution of SARS-CoV-2 in a pathogenesis of Alzheimer's disease; whole manuscript language correction; MH—preparing the part concerning possible role of viral agents (except SARS-CoV-2) in the pathogenesis of Alzheimer's disease; NB—preparing the part concerning putative contribution of bacterial agents in the pathogenesis of Alzheimer's disease; PS—preparing the part concerning possible association of Toxoplasma gondii in the pathogenesis of Alzheimer's disease; JD—formulating of the article frames, substantive consulting, correction of the manuscript; WK—substantive consulting, correction of the manuscript; MP—preparing the abstract, introduction and conclusion sections, preparing all the figures, work management, substantive correction and formatting of the article.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. JD is serving as Guest Editor of this special issue and one of the Editorial Board members of this journal. We declare that JD had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to RF.

References

[1] Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World alzheimer report 2015. The global impact of dementia: an analysis of prevalence, incidence, cost and trends updates. Alzheimer's Disease International. 2015; 2015: 1–87.

[2] Dorszewska J, Prendecki M, Oczkowska A, Dezor M, Kozubski W. Molecular basis of familial and sporadic Alzheimer's disease. Current Alzheimer Research. 2016; 13: 952–963.

[3] Prendecki M, Kowalska M. Toton E Kozubski W. Genetic editing and pharmacogenetics in current and future therapy of neurocognitive disorders. Current Alzheimer Research. 2020; 17: 238–258.

[4] Holle R, Grässel E, Ruckdäschel S, Wunder S, Mehlig H, Marx P, *et al*. Dementia care initiative in primary practice: study protocol of a cluster randomized trial on dementia management in a general practice setting. BMC Health Services Research. 2009; 9: 91.

[5] Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, *et al*. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimer's & Dementia. 2016; 12: 292–323.

[6] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World alzheimer report 2016. Improving healthcare for people living with dementia. Coverage, quality and costs now and in the future. Alzheimer's Disease International. 2016; 1–140.

[7] Lee VM, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. Annual Review of Neuroscience. 2001; 24: 1121–1159.

[8] Braak H, Braak E. Neuropathological staging of Alzheimerrelated changes. Acta Neuropathologica. 1991; 82: 239–259.

[9] Goedert M, Spillantini MG. A century of Alzheimer's disease. Science. 2006; 314: 777–781.

[10] Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. Journal of Clinical Investigation. 2005; 115: 1449–1457.

[11] Prendecki M, Florczak-Wyspianska J, Kowalska M, Ilkowski J, Grzelak T, Bialas K, *et al*. Biothiols and oxidative stress markers and polymorphisms of TOMM40 and APOC1 genes in Alzheimer's disease patients. Oncotarget. 2018; 9: 35207–35225.

[12] Li F, Hearn M, Bennett LE. The role of microbial infection in the pathogenesis of Alzheimer's disease and the opportunity for protection by anti-microbial peptides. Critical Reviews in Microbiology. 2021; 47: 240–253.

[13] He J, Guo Y, Mao R, Zhang J. Proportion of asymptomatic coronavirus disease 2019: a systematic review and meta-analysis. Journal of Medical Virology. 2020; 93: 820–830.

[14] Haghighi MM, Kakhki EG, Sato C, Ghani M, Rogaeva E. The intersection between COVID-19, the gene family of ACE2

and Alzheimer's disease. Neuroscience Insights. 2020; 15: 263310552097574.
[15] Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, *et al*. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, Behavior, and Immunity. 2020; 87: 18–22.
[16] Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, *et al*. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020; 143: 3104–3120.
[17] Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, *et al*. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020; 370: 856–860.
[18] Ding Q, Shults N, Harris B, Suzuki Y. Angiotensin-converting enzyme 2 (ACE2) is upregulated in Alzheimer's disease brain. BioRxiv. 2020. (in press)
[19] Kehoe PG, Wong S, Al Mulhim N, Palmer LE, Miners JS. Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-β and tau pathology. Alzheimer's Research & Therapy. 2016; 8: 50.
[20] Cuddy LK, Prokopenko D, Cunningham EP, Brimberry R, Song P, Kirchner R, *et al*. Aβ-accelerated neurodegeneration caused by Alzheimer's-associatedACEvariant R1279Q is rescued by angiotensin system inhibition in mice. Science Translational Medicine. 2020; 12: eaaz2541.
[21] Quitterer U, AbdAlla S. Improvements of symptoms of Alzheimer‘s disease by inhibition of the angiotensin system. Pharmacological Research. 2020; 154: 104230.
[22] Delanghe JR, Speeckaert MM, De Buyzere ML. COVID-19 infections are also affected by human ACE1 D/I polymorphism. Clinical Chemistry and Laboratory Medicine. 2020; 58: 1125–1126.
[23] Gordon D, Jang G, Bouhaddou M, Xu J, Obernier K, White K, *et al*. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020; 583: 459–468.
[24] Kuo C, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, *et al*. APOE e4 genotype predicts severe COVID-19 in the UK biobank community cohort. Journals of Gerontology. 2020; 75: 2231–2232.
[25] Miners S, Kehoe PG, Love S. Cognitive impact of COVID-19: looking beyond the short term. Alzheimer's Research & Therapy. 2020; 12: 170.
[26] Lee S, Jeong W, Cho S, Lee H, Jang Y, Lin Y, *et al*. ApoE4–carrying human astrocytes oversupply cholesterol into neurons and promote Aβ generation. Research Square. 2020. (in press)
[27] Sanders D, Jumper C, Ackerman P, Bracha D, Donlic A, Kim H, *et al*. SARS-CoV-2 requires cholesterol for viral entry and pathological syncytia formation. eLife. 2021; 10: e65962.
[28] Daugherty AM, Chopra T, Korzeniewski SJ, Levy P. COVID-19 as a risk factor for Alzheimer's disease and related dementia: a perspective from Detroit, MI. Psychiatry Research. 2020; 294: 113557.
[29] Naughton SX, Raval U, Pasinetti GM. Potential novel role of COVID-19 in Alzheimer's disease and preventative mitigation strategies. Journal of Alzheimer's Disease. 2020; 76: 21–25.
[30] Abate G, Memo M, Uberti D. Impact of COVID-19 on Alzheimer's disease risk: viewpoint for research action. Healthcare. 2020; 8: 286.
[31] Harris SA, Harris EA. Molecular mechanisms for herpes simplex virus type 1 pathogenesis in Alzheimer's disease. Frontiers in Aging Neuroscience. 2018; 10: 48.
[32] Nimgaonkar VL, Yolken RH, Wang T, Chang CH, McClain L, McDade E, *et al*. Temporal cognitive decline associated with exposure to infectious agents in a population-based, aging cohort. Alzheimer Disease and Associated Disorders. 2016; 30: 216–222.
[33] Ukraintseva S, Akushevich I, Yashkin A, Krachenko JV, Arbeev K, Kulminsky A, *et al*. On the role of infection in Alzheimer's disease (AD): herpes viruses are associated with significant increase in AD risk in a large population—representative sample of elderly individuals. Alzheimer's & Dementia. 2017; 13: 1423–1424.
[34] Carbone I, Lazzarotto T, Ianni M, Porcellini E, Forti P, Masliah E, *et al*. Herpes virus in Alzheimer's disease: relation to progression of the disease. Neurobiology of Aging. 2014; 35: 122–129.
[35] Stebbins RC, Noppert GA, Yang YC, Dowd JB, Simanek A, Aiello AE. Immune response to cytomegalovirus and cognition in the health and retirement study. American Journal of Epidemiology. 2021; 190: 786–797.
[36] Amirsardari Z, Rahmani F, Rezaei N. Cognitive impairments in HCV infection: from pathogenesis to neuroimaging. Journal of Clinical and Experimental Neuropsychology. 2019; 41: 987–1000.
[37] Jang H, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, *et al*. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. Proceedings of the National Academy of Sciences. 2009; 106: 14063–14068.
[38] Sadasivan S, Zanin M, O'Brien K, Schultz-Cherry S, Smeyne RJ. Induction of microglia activation after infection with the non-neurotropic A/CA/04/2009 H1N1 influenza virus. PLoS ONE. 2015; 10: e0124047.
[39] Miklossy J, Khalili K, Gern L, Ericson RL, Darekar P, Bolle L, *et al*. Borrelia burgdorferi persists in the brain in chronic Lyme neuroborreliosis and may be associated with Alzheimer disease. Journal of Alzheimer's Disease. 2004; 6: 639–649.
[40] Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, *et al*. Beta-amyloid deposition and Alzheimer's type changes induced by Borrelia spirochetes. Neurobiology of Aging. 2006; 27: 228–236.
[41] Gonzalez H, Koralnik IJ, Marra CM. Neurosyphilis. Seminars in Neurology. 2019; 39: 448–455.
[42] Al-Atrache Z, Lopez DB, Hingley ST, Appelt DM. Astrocytes infected with Chlamydia pneumoniae demonstrate altered expression and activity of secretases involved in the generation of β-amyloid found in Alzheimer disease. BMC Neuroscience. 2019; 20: 6.
[43] Stewart R, Sabbah W, Tsakos G, D'Aiuto F, Watt RG. Oral health and cognitive function in the third National Health and Nutrition Examination Survey (NHANES III). Psychosomatic Medicine. 2008; 70: 936–941.
[44] Kornhuber HH. Propionibacterium acnes in the cortex of patients with Alzheimer's disease. European Archives of Psychiatry and Clinical Neuroscience. 1996; 246: 108–109.
[45] Roubaud Baudron C, Letenneur L, Langlais A, Buissonniere A, Megraud F, Dartigues JF, *et al*. Does helicobacter pylori infection increase incidence of dementia? The Personnes Agées QUID study. Journal of the American Geriatrics Society. 2013; 61: 74–78.
[46] Nayeri Chegeni T, Sarvi S, Moosazadeh M, Sharif M, Aghayan SA, Amouei A, *et al*. Is toxoplasma gondii a potential risk factor for Alzheimer's disease? A systematic review and meta-analysis. Microbial Pathogenesis. 2019; 137: 103751.
[47] Boutoleau-Bretonnière C, Pouclet-Courtemanche H, Gillet A, Bernard A, Deruet AL, Gouraud I, *et al*. The effects of confinement on neuropsychiatric symptoms in alzheimer's disease during the COVID-19 crisis. Journal of Alzheimer's Disease. 2020; 76: 41–47.
[48] Li Y, Zhang Z, Yang L, Lian X, Xie Y, Li S, *et al*. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. IScience. 2020; 23: 101160.
[49] Radzikowska U, Ding M, Tan G, Zhakparov D, Peng Y,

Wawrzyniak P, *et al*. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. Allergy. 2020; 75: 2829–2845.
[50] D'Amico M, Di Filippo C, Marfella R, Abbatecola AM, Ferraraccio F, Rossi F, *et al*. Long-term inhibition of dipeptidyl peptidase-4 in Alzheimer's prone mice. Experimental Gerontology. 2010; 45: 202–207.
[51] Angelopoulou E, Piperi C. DPP-4 inhibitors: a promising therapeutic approach against Alzheimer's disease. Annals of Translational Medicine. 2018; 6: 255.
[52] Strollo R, Pozzilli P. DPP4 inhibition: preventing SARS-CoV-2 infection and/or progression of COVID-19? Diabetes/Metabolism Research and Reviews. 2020; 36: e3330.
[53] Erdő F, Denes L, de Lange E. Age-associated physiological and pathological changes at the blood-brain barrier: a review. Journal of Cerebral Blood Flow and Metabolism. 2016; 37: 4–24.
[54] Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, *et al*. Neuropathological features of COVID-19. New England Journal of Medicine. 2020; 383: 989–992.
[55] Song E, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, *et al*. Neuroinvasion of SARS-CoV-2 in human and mouse brain. Journal of Experimental Medicine. 2021; 218: e20202135.
[56] Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, *et al*. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurology. 2020; 19: 919–929.
[57] Merayo-Chalico J, Rajme-López S, Barrera-Vargas A, Alcocer-Varela J, Díaz-Zamudio M, Gómez-Martín D. Lymphopenia and autoimmunity: a double-edged sword. Human Immunology. 2016; 77: 921–929.
[58] Duan R, Xue X, Zhang Q, Wang S, Gong P, E Y, *et al*. ACE2 activator diminazene aceturate ameliorates Alzheimer's disease-like neuropathology and rescues cognitive impairment in SAMP8 mice. Aging. 2020; 12: 14819–14829.
[59] Royea J, Hamel E. Brain angiotensin II and angiotensin IV receptors as potential Alzheimer's disease therapeutic targets. GeroScience. 2020; 42: 1237–1256.
[60] Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, *et al*. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. Journal of the American Medical Association. 2020; 324: 168–177.
[61] Wong MCS, Wong S, Huang J, Yan B. Relating angiotensin—converting enzyme inhibitors or angiotensin receptor blockers with incidence or mortality of COVID-19. ESC Heart Failure. 2020; 7: 3119–3123.
[62] Balli N, Kara E, Demirkan K. The another side of COVID-19 in Alzheimer's disease patients: drug-drug interactions. International Journal of Clinical Practice. 2020; 74: e13596.
[63] Boutoleau-Bretonnière C, Pouclet-Courtemanche H, Gillet A, Bernard A, Deruet AL, Gouraud I, et al. The effects of confinement on neuropsychiatric symptoms in alzheimer's disease during the COVID-19 crisis. Journal of Alzheimer's Disease. 2020; 76: 41–47.
[64] Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and mitigating the impact of the COVID-19 pandemic on Alzheimer's disease and related dementias. American Journal of Geriatric Psychiatry. 2020; 28: 712–721.
[65] Ball MJ. Limbic predilection in alzheimer dementia: is reactivated herpesvirus involved? Canadian Journal of Neurological Sciences. 1982; 9: 303–306.
[66] Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, *et al*. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. Journal of the American Medical Association. 2006; 296: 964–973.
[67] Bradshaw MJ, Venkatesan A. Herpes simplex vrus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics. 2016; 13: 493–508.
[68] Dobson CB, Wozniak MA, Itzhaki RF. Do infectious agents play a role in dementia? Trends in Microbiology. 2003; 11: 312–317.
[69] Kastrukoff L, Hamada T, Schumacher U, Long C, Doherty PC, Koprowski H. Central nervous system infection and immune response in mice inoculated into the lip with herpes simplex virus type 1. Journal of Neuroimmunology. 1982; 2: 295–305.
[70] Lewandowski G, Zimmerman MN, Denk LL, Porter DD, Prince GA. Herpes simplex type 1 infects and establishes latency in the brain and trigeminal ganglia during primary infection of the lip in cotton rats and mice. Archives of Virology. 2002; 147: 167–179.
[71] Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F. Involvement of apolipoprotein E in the hematogenous route of herpes simplex virus type 1 to the central nervous system. Journal of Virology. 2002; 76: 12394–12398.
[72] Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F. ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. NeuroReport. 2003; 14: 1825–1827.
[73] Burgos JS, Ramirez C, Sastre I, Alfaro JM, Valdivieso F. Herpes simplex virus type 1 infection via the bloodstream with apolipoprotein E dependence in the gonads is influenced by gender. Journal of Virology. 2005; 79: 1605–1612.
[74] Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus. Frontiers in Aging Neuroscience. 2014; 6: 202.
[75] Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, *et al*. Microbes and Alzheimer's disease. Journal of Alzheimer's Disease. 2016; 51: 979–984.
[76] Ando Y, Kitayama H, Kawaguchi Y, Koyanagi Y. Primary target cells of herpes simplex virus type 1 in the hippocampus. Microbes and Infection. 2008; 10: 1514–1523.
[77] Beffert U, Bertrand P, Champagne D, Gauthier S, Poirier J. HSV-1 in brain and risk of Alzheimer's disease. Lancet. 1998; 351: 1330–1331.
[78] Caparros-Lefebvre D, Girard-Buttaz I, Reboul S, Lebert F, Cabaret M, Verier A, *et al*. Cognitive and psychiatric impairment in herpes simplex virus encephalitis suggest involvement of the amygdalo-frontal pathways. Journal of Neurology. 1996; 243: 248–256.
[79] Damasio AR, Van Hoesen GW. The limbic system and the localisation of herpes simplex encephalitis. Journal of Neurology, Neurosurgery & Psychiatry. 1985; 48: 297–301.
[80] Taylor SW, Lee DH, Jackson AC. Herpes simplex encephalitis presenting with exclusively frontal lobe involvement. Journal of Neurovirology. 2007; 13: 477–481.
[81] Wu H, Huang C, Chen S, Liang Y, Tsai J, Hsieh C, *et al*. Herpes simplex virus type 1 inoculation enhances hippocampal excitability and seizure susceptibility in mice. European Journal of Neuroscience. 2003; 18: 3294–3304.
[82] Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. Journal of Pathology. 2009; 217: 131–138.
[83] Shipley SJ, Parkin ET, Itzhaki RF, Dobson CB. Herpes simplex virus interferes with amyloid precursor protein processing. BMC Microbiology. 2005; 5: 48.
[84] Cribbs DH, Azizeh BY, Cotman CW, LaFerla FM. Fibril formation and neurotoxicity by a herpes simplex virus glycoprotein B fragment with homology to the Alzheimer's Aβ peptide. Biochemistry. 2000; 39: 5988–5994.
[85] Pierrot N, Santos SF, Feyt C, Morel M, Brion J, Octave J. Calcium-mediated transient phosphorylation of tau and amyloid precursor protein followed by intraneuronal amyloid-β accu-

mulation. Journal of Biological Chemistry. 2006; 281: 39907–39914.
[86] Piacentini R, Civitelli L, Ripoli C, Marcocci ME, De Chiara G, Garaci E, *et al*. HSV-1 promotes Ca^{2+}–mediated APP phosphorylation and aβ accumulation in rat cortical neurons. Neurobiology of Aging. 2011; 32: 2323.e13–2323.e26.
[87] Jayasuriya AN, Itzhaki RF, Wozniak MA, Patel R, Smit EJ, Noone R, *et al*. Apolipoprotein E-4 and recurrent genital herpes in individuals co-infected with herpes simplex virus type 2 and HIV. Sexually Transmitted Infections. 2008; 84: 516–517.
[88] Prendecki M, Florczak-Wyspianska J, Kowalska M, Ilkowski J, Grzelak T, Bialas K, *et al*. *APOE* genetic variants and apoE, miR-107 and miR-650 levels in Alzheimer's disease. Folia Neuropathologica. 2019; 57: 106–116.
[89] Ball MJ, Lukiw WJ, Kammerman EM, Hill JM. Intracerebral propagation of Alzheimer's disease: strengthening evidence of a herpes simplex virus etiology. Alzheimer's & Dementia. 2013; 9: 169–175.
[90] Liu L, Drouet V, Wu JW, Witter MP, Small SA, Clelland C, *et al*. Trans-synaptic spread of tau pathology *in vivo*. PLoS ONE. 2012; 7: e31302.
[91] Piacentini R, De Chiara G, Li Puma DD, Ripoli C, Marcocci ME, Garaci E, *et al*. HSV-1 and Alzheimer's disease: more than a hypothesis. Frontiers in Pharmacology. 2014; 5: 97.
[92] Pooler AM, Polydoro M, Wegmann S, Nicholls SB, Spires-Jones TL, Hyman BT. Propagation of tau pathology in Alzheimer's disease: identification of novel therapeutic targets. Alzheimer's Research & Therapy. 2013; 5: 49.
[93] Wozniak MA, Frost AL, Itzhaki RF. Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. Journal of Alzheimer's Disease. 2009; 16: 341–350.
[94] 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: e3637.
[95] Gilden D, Nagel MA, Cohrs RJ. Varicella-zoster. Handbook of Clinical Neurology. 2014; 123: 265–283.
[96] Mahalingam R, Wellish M, Wolf W, Dueland AN, Cohrs R, Vafai A, *et al*. Latent varicella-zoster viral DNA in human trigeminal and thoracic ganglia. New England Journal of Medicine. 1990; 323: 627–631.
[97] Clarke P, Beer T, Cohrs RJ, Gilden DH. Configuration of latent varicella-zoster virus DNA. Journal of Virology. 1995; 69: 8151–8154.
[98] Cohrs R, Mahalingam R, Dueland AN, Wolf W, Wellish M, Gilden DH. Restricted transcription of varicella-zoster virus in latently infected human trigeminal and thoracic ganglia. Journal of Infectious Diseases. 1992; 166: S24–S29.
[99] Gilden DH, Gesser R, Smith J, Wellish M, Laguardia JJ, Cohrs RJ, *et al*. Presence of VZV and HSV-1 DNA in human nodose and celiac ganglia. Virus Genes. 2001; 23: 145–147.
[100] Kam AC, Dan NG, Maclean J, Higgins D. Zoster related multiple cranial nerve palsies: an unusual complication following percutaneous balloon compression for trigeminal neuralgia. Journal of Clinical Neuroscience. 1999; 6: 261–264.
[101] Kushawaha A, Mobarakai N, Tolia J. A 46-year-old female presenting with worsening headache, nuchal rigidity and a skin rash in varicella zoster virus meningitis: a case report. Cases Journal. 2009; 2: 6299.
[102] Mahalingam R, Wellish M, Soike K, White T, Kleinschmidt-DeMasters BK, Gilden DH. Simian varicella virus infects ganglia before rash in experimentally infected monkeys. Virology. 2001; 279: 339–342.
[103] Terasaki S, Kameyama T, Yamamoto S. A case of zoster in the 2nd and 3rd branches of the trigeminal nerve associated with simultaneous herpes labialis infection—a case report. Kurume Medical Journal. 1997; 44: 61–66.
[104] Theil D, Horn AK, Derfuss T, Strupp M, Arbusow V, Brandt T. Prevalence and distribution of HSV-1, VZV, and HHV-6 in human cranial nerve nuclei III, IV, VI, VII, and XII. Journal of Medical Virology. 2004; 74: 102–106.
[105] Chen V, Wu CH, Huang CH, Yang SI, Kuo KY, Liang YH, *et al*. Herpes zoster and dementia: a nationwide population-based cohort study. The Journal of Clinical Psychiatry. 2018; 79: 16m11312.
[106] Bernstein H, Ansorge S, Riederer P, Reiser M, Frölich L, Bogerts B. Insulin-degrading enzyme in the Alzheimer's disease brain: prominent localization in neurons and senile plaques. Neuroscience Letters. 1999; 263: 161–164.
[107] Li Q, Ali MA, Cohen JI. Insulin degrading enzyme is a cellular receptor mediating varicella-zoster virus infection and cell-to-cell spread. Cell. 2006; 127: 305–316.
[108] Li Q, Ali MA, Wang K, Sayre D, Hamel FG, Fisher ER, *et al*. Insulin degrading enzyme induces a con-formational change in Varicella-Zoster Virus gE, and enhances virus infectivity and stability. PLoS ONE. 2010; 5: e11327.
[109] Bernstein H, Keilhoff G, Dobrowolny H, Steiner J. Binding varicella zoster virus: an underestimated facet of insulin-degrading enzyme´s implication for Alzheimer´s disease pathology? European Archives of Psychiatry and Clinical Neuroscience. 2020; 270: 495–496.
[110] Kutok JL, Wang F. Spectrum of Epstein-Barr virus-associated diseases. Annual Review of Pathology. 2006; 1: 375–404.
[111] Pawelec G, Derhovanessian E, Larbi A, Strindhall J, Wikby A. Cytomegalovirus and human immunosenescence. Reviews in Medical Virology. 2009; 19: 47–56.
[112] Tsutsui Y, Kosugi I, Kawasaki H, Arai Y, Han G, Li L, *et al*. Roles of neural stem progenitor cells in cytomegalovirus infection of the brain in mouse models. Pathology International. 2008; 58: 257–267.
[113] Lee KH, Kwon DE, Do Han K, La Y, Han SH. Association between cytomegalovirus end-organ diseases and moderate-to-severe dementia: a population-based cohort study. BMC Neurology. 2020; 20: 216.
[114] Aiello AE, Haan MN, Blythe L, Moore K, Gonzalez JM, Jagust W. The Influence of latent viral infection on rate of cognitive decline over 4 years. Journal of the American Geriatrics Society. 2006; 54: 1046–1054.
[115] Varga M, Görög D, Kári D, Környei E, Kis É, Túryné HJ, *et al*. Cytomegalovirus seroprevalence among solid organ donors in Hungary: correlations with age, gender, and blood group. Transplantation Proceedings. 2011; 43: 1233–1235.
[116] Wang GC, Kao WHL, Murakami P, Xue Q, Chiou RB, Detrick B, *et al*. Cytomegalovirus infection and the risk of mortality and frailty in older women: a prospective observational cohort study. American Journal of Epidemiology. 2010; 171: 1144–1152.
[117] Lurain NS, Hanson BA, Martinson J, Leurgans SE, Landay AL, Bennett DA, *et al*. Virological and immunological characteristics of human cytomegalovirus infection associated with Alzheimer disease. Journal of Infectious Diseases. 2013; 208: 564–572.
[118] Harberts E, Yao K, Wohler JE, Maric D, Ohayon J, Henkin R, *et al*. Human herpesvirus-6 entry into the central nervous system through the olfactory pathway. Proceedings of the National Academy of Sciences. 2011; 108: 13734–13739.
[119] Dietrich J, Blumberg BM, Roshal M, Baker JV, Hurley SD, Mayer-Pröschel M, *et al*. Infection with an endemic human herpesvirus disrupts critical glial precursor cell properties. Journal of Neuroscience. 2004; 24: 4875–4883.
[120] Donati D, Martinelli E, Cassiani-Ingoni R, Ahlqvist J, Hou J, Major EO, *et al*. Variant-specific tropism of human herpesvirus 6 in human astrocytes. Journal of Virology. 2005; 79: 9439–9448.

[121] Lokensgard JR, Cheeran MC, Hu S, Gekker G, Peterson PK. Glial cell responses to herpesvirus infections: role in defense and immunopathogenesis. Journal of Infectious Diseases. 2002; 186: S171–S179.
[122] Prusty BK, Gulve N, Govind S, Krueger GRF, Feichtinger J, Larcombe L, *et al*. Active HHV-6 Infection of cerebellar purkinje cells in mood disorders. Frontiers in Microbiology. 2018; 9: 1955.
[123] Reynaud JM, Horvat B. Human herpesvirus 6 and neuroinflammation. ISRN Virology. 2013; 2013: 834890.
[124] Zerboni L, Che X, Reichelt M, Qiao Y, Gu H, Arvin A. Herpes simplex virus 1 tropism for human sensory ganglion neurons in the severe combined immunodeficiency mouse model of neuropathogenesis. Journal of Virology. 2013; 87: 2791–2802.
[125] Readhead B, Haure-Mirande J, Funk CC, Richards MA, Shannon P, Haroutunian V, *et al*. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron. 2018; 99: 64–82.
[126] Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, *et al*. Alzheimer's disease-associated beta-amyloid is rapidly seeded by *herpesviridae* to protect against brain infection. Neuron. 2018; 99: 56–63.e53.
[127] Romeo MA, Gilardini Montani MS, Gaeta A, D'Orazi G, Faggioni A, Cirone M. HHV-6a infection dysregulates autophagy/UPR interplay increasing beta amyloid production and tau phosphorylation in astrocytoma cells as well as in primary neurons, possible molecular mechanisms linking viral infection to Alzheimer's disease. Biochimica et Biophysica Acta. 2020; 1866: 165647.
[128] Uddin MS, Stachowiak A, Mamun AA, Tzvetkov NT, Takeda S, Atanasov AG, *et al*. Autophagy and Alzheimer's disease: from molecular mechanisms to therapeutic implications. Frontiers in Aging Neuroscience. 2018; 10: 4.
[129] Meeuwsen S, Persoon-Deen C, Bsibsi M, Bajramovic JJ, Ravid R, De Bolle L, *et al*. Modulation of the cytokine network in human adult astrocytes by human herpesvirus-6a. Journal of Neuroimmunology. 2005; 164: 37–47.
[130] Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013; 57: 1333–1342.
[131] Senzolo M, Schiff S, D'Aloiso CM, Crivellin C, Cholongitas E, Burra P, *et al*. Neuropsychological alterations in hepatitis C infection: the role of inflammation. World Journal of Gastroenterology. 2011; 17: 3369–3374.
[132] Chiu WC, Tsan YT, Tsai SL, Chang CJ, Wang JD, Chen PC. Hepatitis C viral infection and the risk of dementia. European Journal of Neurology. 2014; 21: 1068-e59.
[133] Blanc M, Hsieh W, Robertson K, Kropp K, Forster T, Shui G, *et al*. The transcription factor STAT-1 couples macrophage synthesis of 25-hydroxycholesterol to the interferon antiviral response. Immunity. 2013; 38: 106–118.
[134] Liu S, Aliyari R, Chikere K, Li G, Marsden MD, Smith JK, *et al*. Interferon-inducible cholesterol-25-hydroxylase broadly inhibits viral entry by production of 25-hydroxycholesterol. Immunity. 2013; 38: 92–105.
[135] Papassotiropoulos A, Lambert J, Wavrant-De Vrièze F, Wollmer MA, von der Kammer H, Streffer JR, *et al*. Cholesterol 25-hydroxylase on chromosome 10q is a susceptibility gene for sporadic Alzheimer's disease. Neuro-Degenerative Diseases. 2005; 2: 233–241.
[136] Liu S, Sanchez DJ, Cheng G. New developments in the induction and antiviral effectors of type I interferon. Current Opinion in Immunology. 2011; 23: 57–64.
[137] Park K, Scott AL. Cholesterol 25-hydroxylase production by dendritic cells and macrophages is regulated by type I interferons. Journal of Leukocyte Biology. 2010; 88: 1081–1087.
[138] Wong MY, Lewis M, Doherty JJ, Shi Y, Cashikar AG, Amelianchik A, *et al*. 25-Hydroxycholesterol amplifies microglial IL-1β production in an apoE isoform-dependent manner. Journal of Neuroinflammation. 2020; 17: 192.
[139] Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, *et al*. A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology. 2007; 32: 1106–1115.
[140] Liu X, Quan N. Microglia and CNS interleukin-1: beyond immunological concepts. Frontiers in Neurology. 2018; 9: 8.
[141] Crescenzi O, Tomaselli S, Guerrini R, Salvadori S, D'Ursi AM, Temussi PA, *et al*. Solution structure of the Alzheimer amyloid β-peptide (1–42) in an apolar microenvironment. European Journal of Biochemistry. 2002; 269: 5642–5648.
[142] Javadpour MM, Eilers M, Groesbeek M, Smith SO. Helix packing in polytopic membrane proteins: role of glycine in transmembrane helix association. Biophysical Journal. 1999; 77: 1609–1618.
[143] Kirkitadze MD, Condron MM, Teplow DB. Identification and characterization of key kinetic intermediates in amyloid β-protein fibrillogenesis. Journal of Molecular Biology. 2001; 312: 1103– 1119.
[144] Lin H, Bhatia R, Lal R. Amyloid beta protein forms ion channels: implications for Alzheimer's disease pathophysiology. FASEB Journal. 2001; 15: 2433–2444.
[145] White MR, Kandel R, Hsieh IN, De Luna X, Hartshorn KL. Critical role of C-terminal residues of the Alzheimer's associated β-amyloid protein in mediating antiviral activity and modulating viral and bacterial interactions with neutrophils. PLoS ONE. 2018; 13: e0194001.
[146] Ahmed M, Davis J, Aucoin D, Sato T, Ahuja S, Aimoto S, *et al*. Structural conversion of neurotoxic amyloid-beta (1–42) oligomers to fibrils. Nature Structural & Molecular Biology. 2010; 17: 561–567.
[147] Wagoner VA, Cheon M, Chang I, Hall CK. Impact of sequence on the molecular assembly of short amyloid peptides. Proteins. 2014; 82: 1469–1483.
[148] Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin. 1907; 18: 177–179. (In German)
[149] Bibi F, Yasir M, Sohrab SS, Azhar EI, Al-Qahtani MH, Abuzenadah AM, *et al*. Link between chronic bacterial inflammation and Alzheimer disease. CNS & Neurological Disorders Drug Targets. 2014; 13: 1140–1147.
[150] Ramesh G, Alvarez AL, Roberts ED, Dennis VA, Lasater BL, Alvarez X, *et al*. Pathogenesis of Lyme neuroborreliosis: borrelia burgdorferi lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes. European Journal of Immunology. 2003; 33: 2539–2550.
[151] Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Reviews in Molecular Medicine. 2011; 13: e30.
[152] Miklossy J. Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. Frontiers in Aging Neuroscience. 2015; 7: 46.
[153] Olsen I, Singhrao SK. Can oral infection be a risk factor for Alzheimer's disease? Journal of Oral Microbiology. 2015; 7: 29143.
[154] Christen-Zaech S, Kraftsik R, Pillevuit O, Kiraly M, Martins R, Khalili K, *et al*. Early olfactory involvement in Alzheimer's disease. Canadian Journal of Neurological Sciences. 2003; 30: 20–25.
[155] Miklossy J. Alzheimer's disease—a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. Journal

of Neuroinflammation. 2011; 8: 90.
[156] Miklossy J. Alzheimer's disease—a spirochetosis? Neuroreport. 1993; 4: 841–848.
[157] Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease (AD). Frontiers in Aging Neuroscience. 2015; 7: 9.
[158] Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012; 379: 461–473.
[159] MacDonald AB. Alzheimer's neuroborreliosis with transsynaptic spread of infection and neurofibrillary tangles derived from intraneuronal spirochetes. Medical Hypotheses. 2007; 68: 822–825.
[160] Ramesh G, Borda JT, Dufour J, Kaushal D, Ramamoorthy R, Lackner AA, *et al*. Interaction of the Lyme disease spirochete *Borrelia burgdorferi* with brain parenchyma elicits inflammatory mediators from glial cells as well as glial and neuronal apoptosis. American Journal of Pathology. 2008; 173: 1415–1427.
[161] Turner RS, Stubbs T, Davies DA, Albensi BC. Potential new approaches for diagnosis of Alzheimer's disease and related dementias. Frontiers in Neurology. 2020; 11: 496.
[162] Möhle L, Israel N, Paarmann K, Krohn M, Pietkiewicz S, Müller A, *et al*. Chronic *Toxoplasma gondii* infection enhances β-amyloid phagocytosis and clearance by recruited monocytes. Acta Neuropathologica Communications. 2016; 4: 25.
[163] Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in Alzheimer's disease. Scientific Reports. 2015; 5: 15015.
[164] Radolf JD, Goldberg MS, Bourell K, Baker SI, Jones JD, Norgard MV. Characterization of outer membranes isolated from Borrelia burgdorferi, the Lyme disease spirochete. Infection and Immunity. 1995; 63: 2154–2163.
[165] Contini C, Seraceni S, Cultrera R, Castellazzi M, Granieri E, Fainardi E. *Chlamydophila pneumoniae* infection and its role in neurological disorders. Interdisciplinary Perspectives on Infectious Diseases. 2010; 2010: 273573.
[166] Itzhaki RF, Wozniak MA, Appelt DM, Balin BJ. Infiltration of the brain by pathogens causes Alzheimer's disease. Neurobiology of Aging. 2004; 25: 619–627.
[167] Appelt DM, Roupas MR, Way DS, Bell MG, Albert EV, Hammond CJ, *et al*. Inhibition of apoptosis in neuronal cells infected with *Chlamydophila (Chlamydia) pneumoniae*. BMC Neuroscience. 2008; 9: 13.
[168] Balin BJ, Gérard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, *et al*. Identification and localization of *Chlamydia pneumoniae* in the Alzheimer's brain. Medical Microbiology and Immunology. 1998; 187: 23–42.
[169] Dreses-Werringloer U, Bhuiyan M, Zhao Y, Gérard HC, Whittum-Hudson JA, Hudson AP. Initial characterization of *Chlamydophila (Chlamydia) pneumoniae* cultured from the late-onset Alzheimer brain. International Journal of Medical Microbiology. 2009; 299: 187–201.
[170] Gérard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, *et al*. *Chlamydophila (Chlamydia) pneumoniae* in the Alzheimer's brain. FEMS Immunology and Medical Microbiology. 2006; 48: 355–366.
[171] Paradowski B, Jaremko M, Dobosz T, Leszek J, Noga L. Evaluation of CSF-Chlamydia pneumoniae, CSF-tau, and CSF-Abeta42 in Alzheimer's disease and vascular dementia. Journal of Neurology. 2007; 254: 154–159.
[172] Shima K, Kuhlenbäumer G, Rupp J. *Chlamydia pneumoniae* infection and Alzheimer's disease: a connection to remember? Medical Microbiology and Immunology. 2010; 199: 283–289.
[173] Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of *Chlamydia pneumoniae* in the Alzheimer's disease brain. BMC Neuroscience. 2010; 11: 121.
[174] Little CS, Hammond CJ, MacIntyre A, Balin BJ, Appelt DM. *Chlamydia pneumoniae* induces Alzheimer-like amyloid plaques in brains of BALB/c mice. Neurobiology of Aging. 2004; 25: 419–429.
[175] Fenno JC. *Treponema denticola* interactions with host proteins. Journal of Oral Microbiology. 2012; 4: 9929.
[176] Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanska L, de Leon MJ. Inflammation and Alzheimer's disease: possible role of periodontal diseases. Alzheimer's & Dementia. 2008; 4: 242–250.
[177] Gurav AN. Alzheimer's disease and periodontitis—an elusive link. Revista Da Associacao Medica Brasileira. 2014; 60: 173–180.
[178] Hatipoglu MG, Kabay SC, Güven G. The clinical evaluation of the oral status in Alzheimer-type dementia patients. Gerodontology. 2011; 28: 302–306.
[179] Abbayya K, Puthanakar NY, Naduwinmani S, Chidambar YS. Association between periodontitis and Alzheimer's disease. North American Journal of Medical Sciences. 2015; 7: 241–246.
[180] Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, *et al*. Periodontitis and cognitive decline in Alzheimer's disease. PLoS ONE. 2016; 11: e0151081.
[181] Polepalle T, Moogala S, Boggarapu S, Pesala DS, Palagi FB. Acute phase proteins and their role in periodontitis: a review. Journal of Clinical and Diagnostic Research. 2015; 9: ZE01–ZE05.
[182] Sochocka M, Sobczyński M, Sender-Janeczek A, Zwolińska K, Błachowicz O, Tomczyk T, *et al*. Association between periodontal health status and cognitive abilities. The role of cytokine profile and systemic inflammation. Current Alzheimer Research. 2017; 14: 978–990.
[183] Farhad SZ, Amini S, Khalilian A, Barekatain M, Mafi M, Barekatain M, *et al*. The effect of chronic periodontitis on serum levels of tumor necrosis factor-alpha in Alzheimer disease. Dental Research Journal. 2014; 11: 549–552.
[184] Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, *et al*. TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. Journal of Neuroimmunology. 2009; 216: 92–97.
[185] Wu Z, Nakanishi H. Connection between periodontitis and Alzheimer's disease: possible roles of microglia and leptomeningeal cells. Journal of Pharmacological Sciences. 2014; 126: 8–13.
[186] Preza D, Olsen I, Aas JA, Willumsen T, Grinde B, Paster BJ. Bacterial profiles of root caries in elderly patients. Journal of Clinical Microbiology. 2008; 46: 2015–2021.
[187] Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984; 1: 1311–1315.
[188] Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, *et al*. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. International Journal of Neuroscience. 2009; 119: 765–777.
[189] Wang X, Zeng J, Feng J, Tian Y, Liu Y, Qiu M, *et al*. *Helicobacter pylori* filtrate impairs spatial learning and memory in rats and increases β-amyloid by enhancing expression of presenilin-2. Frontiers in Aging Neuroscience. 2014; 6: 66.
[190] Wang X, Zeng J, Yang Y, Xiong Y, Zhang Z, Qiu M, *et al*. *Helicobacter pylori* filtrate induces Alzheimer-like tau hyperphosphorylation by activating glycogen synthase kinase-3β. Journal of Alzheimer's Disease. 2015; 43: 153–165.
[191] Franceschi F, Gasbarrini A, Polyzos SA, Kountouras J. Extragastric diseases and *Helicobacter pylori*. Helicobacter. 2015; 20: 40–46.
[192] Mawanda F, Wallace R. Can infections cause Alzheimer's dis-

ease? Epidemiologic Reviews. 2013; 35: 161–180.
[193] El Saftawy EA, Amin NM, Sabry RM, El-Anwar N, Shash RY, Elsebaie EH, *et al*. Can *Toxoplasma gondii* pave the road for dementia? Journal of Parasitology Research. 2020; 2020: 8859857.
[194] Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. International Journal for Parasitology. 2009; 39: 1385–1394.
[195] Bessières MH, Le Breton S, Séguéla JP. Analysis by immunoblotting of *Toxoplasma gondii* exo-antigens and comparison with somatic antigens. Parasitology Research. 1992; 78: 222–228.
[196] Partanen P, Turunen HJ, Paasivuo RT, Leinikki PO. Immunoblot analysis of *Toxoplasma gondii* antigens by human immunoglobulins G, M, and A antibodies at different stages of infection. Journal of Clinical Microbiology. 1984; 20: 133–135.
[197] Fuks JM, Arrighi RBG, Weidner JM, Kumar Mendu S, Jin Z, Wallin RPA, *et al*. GABAergic signaling is linked to a hypermigratory phenotype in dendritic cells infected by *Toxoplasma gondii*. PLoS Pathogens. 2012; 8: e1003051.
[198] Weidner JM, Kanatani S, Hernández-Castañeda MA, Fuks JM, Rethi B, Wallin RPA, *et al*. Rapid cytoskeleton remodelling in dendritic cells following invasion by *Toxoplasma gondii* coincides with the onset of a hypermigratory phenotype. Cellular Microbiology. 2013; 15: 1735–1752.
[199] Wohlfert EA, Blader IJ, Wilson EH. Brains and brawn: *Toxoplasma* infections of the central nervous system and skeletal muscle. Trends in Parasitology. 2017; 33: 519–531.
[200] Kim S, Boothroyd JC. Stage-specific expression of surface antigens by *Toxoplasma gondii* as a mechanism to facilitate parasite persistence. Journal of Immunology. 2005; 174: 8038–8048.
[201] Lachenmaier SM, Deli MA, Meissner M, Liesenfeld O. Intracellular transport of *Toxoplasma gondii* through the blood-brain barrier. Journal of Neuroimmunology. 2011; 232: 119–130.
[202] Lambert H, Hitziger N, Dellacasa I, Svensson M, Barragan A. Induction of dendritic cell migration upon *Toxoplasma gondii* infection potentiates parasite dissemination. Cellular Microbiology. 2006; 8: 1611–1623.
[203] Ueno N, Harker KS, Clarke EV, McWhorter FY, Liu WF, Tenner AJ, *et al*. Real-time imaging of *Toxoplasma*-infected human monocytes under fluidic shear stress reveals rapid translocation of intracellular parasites across endothelial barriers. Cellular Microbiology. 2014; 16: 580–595.
[204] Courret N, Darche S, Sonigo P, Milon G, Buzoni-Gâtel D, Tardieux I. CD11c- and CD11b-expressing mouse leukocytes transport single *Toxoplasma gondii* tachyzoites to the brain. Blood. 2006; 107: 309–316.
[205] Barragan A, Brossier F, Sibley LD. Transepithelial migration of *Toxoplasma gondii* involves an interaction of intercellular adhesion molecule 1 (ICAM-1) with the parasite adhesin MIC2. Cellular Microbiology. 2005; 7: 561–568.
[206] Harker KS, Jivan E, McWhorter FY, Liu WF, Lodoen MB. Shear forces enhance *Toxoplasma gondii* tachyzoite motility on vascular endothelium. mBio. 2014; 5: e01111–e01113.
[207] Ayyildiz H, Kalayci M, Karabulut N, Karaboga F. S100B and latent toxoplasmosis in Alzheimer's disease. International Journal of Medical Biochemistry. 2019; 2: 113–117.
[208] Flegr J, Horacek J. Negative effects of latent toxoplasmosis on mental health. Frontiers in Psychiatry. 2020; 10: 1012.
[209] Cetinkaya Z, Yazar S, Gecici O, Namli MN. Anti-*Toxoplasma gondii* antibodies in patients with schizophrenia—preliminary findings in a Turkish sample. Schizophrenia Bulletin. 2007; 33: 789–791.
[210] Koseoglu E, Yazar S, Koc I. Is *Toxoplasma gondii* a causal agent in migraine? American Journal of the Medical Sciences. 2009; 338: 120–122.
[211] Miman O, Kusbeci OY, Aktepe OC, Cetinkaya Z. The probable relation between *Toxoplasma gondii* and Parkinson's disease. Neuroscience Letters. 2010; 475: 129–131.
[212] Pearce BD, Kruszon-Moran D, Jones JL. The relationship between *Toxoplasma gondii* infection and mood disorders in the third National Health and Nutrition Survey. Biological Psychiatry. 2012; 72: 290–295.
[213] Kaushik M, Lamberton PHL, Webster JP. The role of parasites and pathogens in influencing generalised anxiety and predation-related fear in the mammalian central nervous system. Hormones and Behavior. 2012; 62: 191–201.
[214] Parlog A, Harsan L, Zagrebelsky M, Weller M, von Elverfeldt D, Mawrin C, *et al*. Chronic murine toxoplasmosis is defined by subtle changes in neuronal connectivity. Disease Models & Mechanisms. 2014; 7: 459–469.
[215] Fischer HG, Nitzgen B, Reichmann G, Gross U, Hadding U. Host cells of *Toxoplasma gondii* encystation in infected primary culture from mouse brain. Parasitology Research. 1997; 83: 637–641.
[216] Halonen SK, Lyman WD, Chiu FC. Growth and development of *Toxoplasma gondii* in human neurons and astrocytes. Journal of Neuropathology and Experimental Neurology. 1996; 55: 1150–1156.
[217] Peterson PK, Gekker G, Hu S, Chao CC. Human astrocytes inhibit intracellular multiplication of *Toxoplasma gondii* by a nitric oxide-mediated mechanism. Journal of Infectious Diseases. 1995; 171: 516–518.
[218] Schlüter D, Deckert M, Hof H, Frei K. *Toxoplasma gondii* infection of neurons induces neuronal cytokine and chemokine production, but gamma interferon- and tumor necrosis factor-stimulated neurons fail to inhibit the invasion and growth of *T. gondii*. Infection and Immunity. 2001; 69: 7889–7893.
[219] Torres L, Robinson S, Kim D, Yan A, Cleland TA, Bynoe MS. *Toxoplasma gondii* alters NMDAR signaling and induces signs of Alzheimer's disease in wild-type, C57BL/6 mice. Journal of Neuroinflammation. 2018; 15: 57.
[220] Alvarado-Esquivel C, Rico-Almochantaf YDR, Hernández-Tinoco J, Quiñones-Canales G, Sánchez-Anguiano LF, Torres-González J, *et al*. *Toxoplasma gondii* exposure and neurological disorders: an age- and gender-matched case-control pilot study. European Journal of Microbiology and Immunology. 2017; 7: 303–309.
[221] Wang T, Sun X, Qin W, Zhang X, Wu L, Li Y, *et al*. From inflammatory reactions to neurotransmitter changes: Implications for understanding the neurobehavioral changes in mice chronically infected with *Toxoplasma gondii*. Behavioural Brain Research. 2019; 359: 737–748.
[222] Johnston D, Williams S, Jaffe D, Gray R. NMDA-receptor-independent long-term potentiation. Annual Review of Physiology. 1992; 54: 489–505.
[223] Lang D, Schott BH, van Ham M, Morton L, Kulikovskaja L, Herrera-Molina R, *et al*. Chronic *Toxoplasma* infection is associated with distinct alterations in the synaptic protein composition. Journal of Neuroinflammation. 2018; 15: 216.
[224] Nava-Mesa MO, Jiménez-Díaz L, Yajeya J, Navarro-Lopez JD. GABAergic neurotransmission and new strategies of neuromodulation to compensate synaptic dysfunction in early stages of Alzheimer's disease. Frontiers in Cellular Neuroscience. 2014; 8: 167.
[225] Brooks JM, Carrillo GL, Su J, Lindsay DS, Fox MA, Blader IJ. *Toxoplasma gondii* infections alter GABAergic synapses and signaling in the central nervous system. mBio. 2015; 6: e01428–15.
[226] Limon A, Reyes-Ruiz JM, Miledi R. Loss of functional GABAA receptors in the Alzheimer diseased brain. Proceedings

of the National Academy of Sciences. 2012; 109: 10071–10076.
[227] Bhandage AK, Kanatani S, Barragan A. *Toxoplasma*-induced hypermigration of primary cortical microglia implicates GABAergic signaling. Frontiers in Cellular and Infection Microbiology. 2019; 9: 73.
[228] MacRae JI, Sheiner L, Nahid A, Tonkin C, Striepen B, McConville MJ. Mitochondrial metabolism of glucose and glutamine is required for intracellular growth of *Toxoplasma gondii*. Cell Host & Microbe. 2012; 12: 682–692.
[229] Lucchese G. From toxoplasmosis to schizophrenia via NMDA dysfunction: peptide overlap between *Toxoplasma gondii* and N-Methyl-d-Aspartate receptors as a potential mechanistic link. Frontiers in Psychiatry. 2017; 8: 37.
[230] Beaulieu J, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacological Reviews. 2011; 63: 182–217.
[231] Nobili A, Latagliata EC, Viscomi MT, Cavallucci V, Cutuli D, Giacovazzo G, *et al*. Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. Nature Communications. 2017; 8: 14727.
[232] McFarland R, Wang ZT, Jouroukhin Y, Li Y, Mychko O, Coppens I, *et al*. *AAH2* gene is not required for dopamine-dependent neurochemical and behavioral abnormalities produced by *Toxoplasma* infection in mouse. Behavioural Brain Research. 2018; 347: 193–200.
[233] Stibbs HH. Changes in brain concentrations of catecholamines and indoleamines in *Toxoplasma gondii* infected mice. Annals of Tropical Medicine and Parasitology. 1985; 79: 153–157.
[234] Jung B, Pyo K, Shin KY, Hwang YS, Lim H, Lee SJ, *et al*. *Toxoplasma gondii* infection in the brain inhibits neuronal degeneration and learning and memory impairments in a murine model of Alzheimer's disease. PLoS ONE. 2012; 7: e33312.