Alzheimer's disease risk after COVID-19: a view from the perspective of the infectious hypothesis of neurodegeneration

Eugenia Olivera, Albany Sáez, Lila Carniglia, Carla Caruso, Mercedes Lasaga, Daniela Durand*

Abstract

In light of the rising evidence of the association between viral and bacterial infections and neurodegeneration, we aimed at revisiting the infectious hypothesis of Alzheimer's disease and analyzing the possible implications of COVID-19 neurological sequelae in long-term neurodegeneration. We wondered how SARS-CoV-2 could be related to the amyloid-β cascade and how it could lead to the pathological hallmarks of the disease. We also predict a paradigm change in clinical medicine, which now has a great opportunity to conduct prospective surveillance of cognitive sequelae and progression to dementia in people who suffered severe infections together with other risk factors for Alzheimer's disease.
Key Words: Alzheimer; amyloid beta; antimicrobial; cognitive decline; COVID-19; infectious hypothesis; long-term sequelae; neurodegeneration; neuroinflammation; neurological symptoms; neurotropism; SARS-CoV-2

From the Contents

Introduction

It is now vox populi that coronavirus disease 2019 (COVID-19) leaves real neurological sequelae, including loss of taste and smell, or even encephalitis, cerebrovascular disorders, or long-term cognitive deficits. This is an issue of major concern worldwide. How long can these signs persist? Is there an actual risk of long-term brain damage or a real increased risk of developing some kind of dementia over time? Among the multiple existing voices, information may not always be reliable or scientifically supported. In this context, revisiting the infectious hypothesis of Alzheimer's disease (AD) gains major relevance. Under this hypothesis, the root cause of AD is a pathogen that triggers an immune reaction involving amyloid-β (Aβ) as an antimicrobial agent. Thereafter, some kind of disequilibrium in Aβ turnover (probably related to the aging process) leads to its pathological accumulation and AD development. The present article aimed at reviewing the most recent literature supporting the infectious hypothesis of AD, and addressed the probable risk of developing Alzheimer-like dementia after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, based on evidence linking viral infections and amyloidosis.

Data Sources

The following terms and combinations of terms were searched in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scholar Google (https://scholar.google.com/) databases or in https://clinicaltrials.gov/: "COVID-19", "SARS-CoV-2", "infection", "neurological sequelae", "dementia", "Alzheimer", "amyloidosis", "Infectious Hypothesis of Alzheimer" "ACE2", "cognitive deterioration", "prospective", "retrospective", "excitotoxicity", "glutamate receptors". Additional disease-specific parameters were "herpes simplex type 1" OR "gingivitis" PLUS "neurological disorders" OR "Alzheimer". Pre-prints were excluded. Selected articles were also searched for references. All articles referring to psychiatric conditions (including AD) predisposing to COVID-19 infection were excluded. An additional filter for articles published in 2022 was included to focus on clinical studies with a wider observational window. Detractor positions to the Infectious Hypothesis of AD etiology were specifically searched for to cover the two currents. Date of the last search: May 31, 2022.

Infectious Hypothesis: Its Origins

Microbes are present in most elderly brains (Link, 2021). Spirochaete-induced syphilitic dementia formerly became popular through famous artists of the 18th century. Moreover, the occurrence of "resilient" brains showing widespread Aβ deposition and tangles in absence of signs of either dementia or neuroinflammation emphasizes the role of aberrant innate immunity in AD (Moir et al., 2018).

The infectious hypothesis proposes a pathogen as the root cause of sporadic AD and is based on increasing evidence of some viruses and bacteria frequently found in histopathological analysis of post-mortem brain from AD patients. The first approach to an infection as the possible etiology of AD was postulated by Dr. Oskar Fischer, contemporaneously with Alzheimer's first report in 1907 (Fischer, 1907). Since then, several scientists have investigated the link between pathogens and AD development. In the beginning, infectious hypothesis followers were ignored or ridiculed, especially because the proposition was seen as a replacement for the Amyloid Cascade Hypothesis. However, over the last decades, the hypothesis has gained relevance and adepts among neuroscientists, and valuable clues regarding how both theories can coexist have been found (Abbott, 2020). Since the 1990 decade, different laboratories have associated infection with the etiology of AD. Spirochetes and *C. pneumoniae* were found in blood, cerebrospinal fluid (CSF), and brain tissue from AD individuals (Miklossy, 1993; Balin et al., 1998). Systemic infection by *C. pneumoniae* was associated with a 5-fold increase in AD occurrence (Balin et al., 2008). An association study by Bu et al. (2015) including 128 AD patients and 135 healthy controls provides evidence of infectious burden, involving viruses and bacteria, which is associated with AD. Sepsis survivors were associated with new cognitive impairment and functional disability (Iwashyna et al., 2010). Moreover, HIV-associated neurological disorders cause AD-like symptomatology (Smail and Brew, 2018). These studies support the notion that AD might have an infectious etiology.

Although no consensus exists on how an infectious pathogen can explain the pathological features of AD, the most accepted view holds that proinflammatory cytokines produced by innate immunity during an infection (tumor necrosis factor-α, interleukin-1β, interferon-γ) promote an inflammatory process, consequently increasing Aβ synthesis and accumulation, as well as hyperphosphorylation and aggregation of tau (Seaks and Wilcock, 2020). Based on genome-wide association study analysis of polymorphisms in AD individuals, Porcellini et al. (2010) argue that the concomitant presence of several polymorphisms in genes related to susceptibility to brain viral infections in the same individual (NC-2 or herpes virus entrance-B, apolipoprotein E (APOE4), complement receptor CR1, among other genes) might represent a genetic signature of AD. On the same line, Readhead et al. (2018) found genes involved in virus response differentially expressed between healthy controls and preclinical AD individuals.

Although substantial evidence supports the infectious hypothesis as a possible origin of AD, like any paradigm-changing theory, it is still regarded with some skepticism. The main arguments emphasize the need for large longitudinal population data sets to corroborate the relevance and reproducibility of results. Further, John Hardy affirmed, concerning the article of Readhead et al. (2018): "My concern about this work is that I find it difficult to square with the occurrence of AD in all Down's syndrome and in all carriers of some APP and PSEN mutations [...] We have to suppose that Down's cases and the mutation cases either have a different disease mechanism or that for some reason, they are uniquely susceptible to these infections" (https://www.alzforum.org/news/research-news/aberrant-networks-alzheimers-tied-herpes-viruses). Despite these public declarations, we were unable to find any published articles arguing against the infectious hypothesis. Mawanda and Wallace (2013) provided some valuable criticisms of the findings in this field, but stated that "the amount of evidence suggestive of an association between AD and an infectious cause is too substantial to ignore". They mainly argued that no single infectious agent was shown to be causative of AD; that several studies used indirect methods for pathogen detection; or that, alternatively, AD neuropathology might increase the susceptibility of affected areas to infections. Anyway, the same pioneers of the infectious hypothesis are also cautious about referring to pathogens as a direct cause of AD, but instead as a prequel of the Amyloid Hypothesis. A schematic image of the main points of this hypothesis is shown in **Figure 1**.
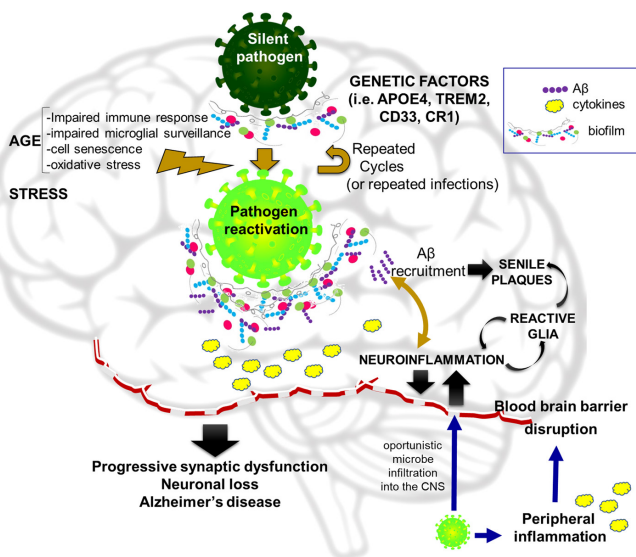

Figure 1 | **The infectious hypothesis of Alzheimer's disease etiology.**
Repeated cycles of viral reactivation into the CNS as well as repeated infections throughout a lifetime, combined with impaired immune response by aging, lead to neuroinflammation and Aβ accumulation as part of biofilm, with the consequent BBB disruption. On the other hand, it was proposed, even for SARS-CoV-2, that the incidence of pathogens in Alzheimer's disease brains increases as a consequence of opportunistic microbe infiltration after BBB disruption caused by systemic inflammation. Aβ: Amyloid-β; APOE4: apolipoprotein E 4 isoform; BBB: blood-brain barrier; CD33 or Siglec-3: sialic acid binding Ig-like lectin 3; CNS: central nervous system; CR1: complement receptor 1; TREM2: triggering receptor expressed on myeloid cells 2.

Infections and Neurodegenerative Diseases

Sipilä et al. (2021) studied the risk of AD and other dementias across a wide range of hospital-treated bacterial and viral infections in two large cohorts (260,490 people in the primary cohort and 485,708 people in the replication cohort) with long follow-up periods. Hospitalization for any infectious disease was associated with increased dementia risk even after restricting the analysis to new dementia cases, the risk was higher in the cases of repeated episodes of hospital-treated infections. Among types of infections, central nervous system (CNS) and extra-CNS infections were both significant risk factors for dementia, whereas, among types of dementia, vascular dementia correlated

better with infections than AD did. Based on the absence of infection specificity, the authors suggested that "increased dementia risk is driven by general inflammation rather than specific microbes". Lövheim et al. (2018) also stated that the interaction between two different viral infections, but not a single virus, was associated with AD development.

Herpes simplex virus type 1 (HSV-1) can live within the host establishing a latent infection, thus evading the immune response. It can be then reactivated to a lytic state, triggered by stress or co-infections that weaken the immune system (Jamieson et al., 1991). HSV-1 can enter the CNS via axonal retrograde transport to infect the cell nucleus of sensory ganglia (Shimeld et al., 2001). Herpes simplex encephalitis can damage the limbic system, a region particularly affected by AD (Roos, 2014). A hazard ratio of 2.564 for the development of dementia in the HSV-infected cohort relative to the age-matched non-HSV cohort was found. It is known that carrying the APOE4 gene variant is a risk factor for AD. APOE and HSV-1 use the same binding site to enter the cell, the heparan sulfate proteoglycans. Linard et al. (2020) showed that APOE4 carriers with frequent HSV reactivation are at higher risk of AD and, among APOE4 non-carriers, no association was found between HSV-1 and AD. This may be consistent with murine studies in which APOE4 was associated with a higher HSV-1 load in mouse brains and an increased risk of cold sores compared to APOE3. Remarkably, a reduction of dementia development risk in patients affected by HSV infections was found upon treatment with antiherpetic medications. A Phase II trial is currently evaluating the efficacy of valacyclovir in slowing cognitive decline in 130 people with mild AD who tested positive for HSV-1 or -2 (ClinicalTrials.gov Identifier: NCT03282916). However, other groups did not detect HSV in elderly brains or an association with AD risk factors. By using complementary, very sensitive methods of pathogen sequence detection from three independent repositories, Allnutt et al. (2020) concluded that there are no significant differences in viral detection between AD and non-AD controls. A discrepancy is also observed when determining anti-HSV antibodies in a longitudinal population-based cohort of elderly subjects followed for 14 years (Letenneur et al., 2008). Controlled for age, gender, educational level, and APOE4 status, IgM-positive subjects showed a significantly higher risk of developing AD while no significantly increased risk was observed in IgG-positive subjects.

Periodontitis is a generalized infection of the supporting tissues of teeth and can be caused by the progressive accumulation of bacterial biofilm made of oral pathogens such as *P. gingivalis* and *A. actinomycetemcomitans* (Cheng et al., 2016). Every time a person infected with periodontitis brushes his/her teeth, bacteremia risk increases. Successive bacteremia events provoke the release of pro-inflammatory virulence factors that, over time, weaken the blood-brain barrier (BBB) and allow pathogens to enter the CNS (Olsen, 2021). *P. gingivalis* can modify the peripheral and intracerebral immune responses and therefore lead to the progression of neurodegenerative diseases such as AD. Ilievski et al. (2018) and Zeng et al. (2021) found that at least two bacterial enzymes (cathepsin B and gingipains) can interact with the amyloid precursor protein (APP) and neuronal tau, resulting in the formation of Aβ and neurofibrillary tangles. Virulence factors of *P. gingivalis* can contribute to AD and clinical studies are currently evaluating the beneficial effect of gingipain inhibitors in AD patients (Dominy et al., 2019). The chronic nature of low-level infections such as gingivitis and periodontitis could affect the capacity of defense by the microglial cells causing Aβ to accumulate into plaques (Olsen and Singhrao, 2020). A previous study has shown that patients with periodontal disease for at least 10 years have double the risk of developing AD (Chen et al., 2017).

Far from being an exhaustive review addressing bacterial or viral pathogens linked to neurodegenerative disorders, the reported evidence serves as a framework to introduce the possible association of SARS-CoV-2 with AD. Whether this implies a direct causal relationship or derives from a chronic inflammatory response to the pathogen remains to be determined, but inflammation is a very significant component of the disease etiology. Complement factors and clustering of activated microglia within plaques, as well as gliosis, are well documented in AD brains, whereas genes encoding inflammation-related proteins like clusterin and complement receptor CR1 are among AD risk factors identified by genome-wide association studies (Eikelenboom et al., 2012). A 17-year follow-up study by Tao et al. (2018) including longitudinal C-reactive protein measurements showed that APOE4 coupled with chronic systemic low-grade inflammation was associated with increased risk and accelerated onset of AD in a pattern dependent on the C-reactive protein level. The accumulative detrimental effect of low-grade chronic inflammation can be enhanced by the expression of high-risk AD variants of genes like APOE, TREM2, CR1, or CD33, which are involved in innate immunity (Bocharova et al., 2021).

Pathogens and Amyloidosis: the Mechanistic Link to the Etiology of Alzheimer's Disease?

The infectious hypothesis was quickly accompanied by the complementary Antimicrobial Protection Hypothesis conceived by Moir and Tanzi's group. These researchers highlight the physiological role of Aβ as "an ancient, highly conserved effector molecule of innate immunity with antimicrobial properties" (Moir et al., 2018). Within this conceptual framework, senile plaques should be seen as a manifestation of the disease, not the cause, becoming the "friendly fire" contributing to neurotoxicity. Thus, the antimicrobial protection hypothesis of AD does not necessarily invalidate the amyloid cascade

hypothesis. The seminal work demonstrating that Aβ is an antimicrobial peptide compared Aβ to LL37 (a powerful antimicrobial agent active against various bacteria and fungi) and showed that synthetic Aβ reduced the growth of pathogens like *E. faecalis*, *S. aureus*, and *C. albicans*, among others by up to 200-fold *in vitro* (Soscia et al., 2010). Aβ also had antiviral activity against HSV-1 (Bourgade et al., 2016) and influenza A (White et al., 2014). The presence of microbes serves as a surface for nucleation of amyloid aggregates, thereby allowing for amyloid deposition as a biofilm matrix (Fulop et al., 2018; **Figure 1**). Direct interaction between βAPP and HSV-1 was reported by Cheng et al. (2011) and acyclovir was able to block HSV1-induced Aβ and tau pathology (Wozniak et al., 2011). Aβ oligomers inhibited HSV-1 infection *in vitro* and protected mice from acute viral encephalitis induced by HSV-1 (Eimer et al., 2018). AD brain homogenates from Aβ-enriched regions showed elevated antimicrobial activity against *C. albicans* compared to non-AD samples (Soscia et al., 2010). In agreement with these results, elevated infection rates were reported as a side effect of a clinical trial using the Aβ-lowering drug tarenflurbil (Green et al., 2009). However, there are also counterarguments to this hypothesis, such as the study by Bocharova et al. (2021), which found that the 5×FAD genotype failed to protect mice against HSV-1 infection. They showed that young 5×FAD mice that survived infection cleared HSV-1 without triggering Aβ aggregation; whereas, in aged mice, HSV-1 replication was inhibited in Aβ-positive areas but no evidence of viral entrapment by Aβ was found. Instead, the protective effect may be attributable to chronic microglial activation.

Neurological Manifestations of SARS-CoV-2

Despite literature reporting that the hazard ratio for SARS-CoV-2 infection is higher in people with AD and other neurodegenerative disorders, the goal of this review was to analyze evidence of the risk of developing AD after COVID-19 infection; therefore, our search was narrowed in this direction. At this point, we should stress that all evidence reported here was used to infer, under the infectious hypothesis view, whether there is a scientifically-supported potential risk of developing AD among SARS-CoV-2 infected subjects. However, any approach to this question should consider the undeniable effects of lockdown, isolation, and isolation-linked mood disorders on brain function, or even the social and economic impact of the pandemic on the global health of people.

In addition to respiratory and cardiac manifestations, one-third of patients with COVID-19 developed neurological symptoms like headache, disturbed consciousness, paresthesia, brain tissue edema, stroke, neuronal degeneration, or encephalitis (Lou et al., 2021). Even patients without observable neurological manifestations exhibited neurological microstructure changes at the 3-month follow-up (Qin et al., 2021). Pistarini et al. (2021) and Mazza et al. (2021) found a high prevalence of cognitive impairments, especially executive functions and motor coordination, in both COVID-19 and post-COVID-19 patients. Fleischer et al. (2021) carried out a prospective, cross-sectional study of 102 SARS-CoV-2 PCR-positive patients. Of these, 59.8% of patients had neurological involvement including general weakness and cognitive decline or delirium (24.5%), impaired taste or smell (9.8%), or severe events including cerebral ischemia (23.5%). In a longitudinal study (Atahualpa project by Del Brutto et al., 2021), cognitive evaluations in previously cognitively healthy individuals at 6 months after the SARS-CoV-2 outbreak yielded an odds ratio for developing cognitive decline of 18.1 times higher among SARS-CoV-2 seropositive individuals. Taquet et al. (2021) carried out a retrospective cohort study using the electronic health record network (with over 81 million patients analyzed) and estimated the incidence of 14 neurological and psychiatric outcomes in the 6 months after a confirmed diagnosis of COVID-19: intracranial hemorrhage; ischemic stroke; parkinsonism; Guillain-Barré syndrome; nerve, nerve root, and plexus disorders; myoneural junction and muscle disease; encephalitis; dementia; psychotic, mood, and anxiety disorders; substance use disorder; and insomnia. Among 236,379 patients diagnosed with COVID-19, the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33.62%, with 12.84% receiving their first such diagnosis, the incidences being higher among patients who had been admitted to an intensive care unit. The values were significantly higher for patients who had COVID than those who had influenza or other respiratory tract infections as control cohorts. By contrast, in another cohort (Mattioli et al., 2021), cognitive impairments detected 4 months after mild-moderate SARS-CoV-2 infection were not significantly different from non-COVID-19 cases and Kanberg et al. (2021) found a normalization of CNS injury blood biomarkers after 6 months of COVID diagnosis, regardless of previous disease severity or persisting neurological symptoms.

We next restricted the search to papers published only in 2022 to include longitudinal, prospective, or retrospective studies with a wider time window for observational changes. According to data from COVID patients symptomatic after 2 months from diagnosis, 85% still reported symptoms one year after onset, with some symptoms showing decreased prevalence over time (e.g., loss of taste/smell, brain fog/attention deficits), others a stable prevalence over time (e.g., dyspnea), and others increased prevalence over time (e.g., paresthesia) (Tran et al., 2022). This study reported a slightly decreased prevalence of memory problems one year after the onset (55.7% to 50.2%). A retrospective cohort study by Kim et al. (2022) of predictors for new-onset mental disorders among patients with mild to moderate COVID-19 showed that 22.3% of patients were newly diagnosed with mental disorders during hospitalization, with length of stay and self-reported depressive symptoms at the time of admission being among the main risk factors for

psychiatric diagnosis. Impaired Mini-Mental State Examination performances were highly prevalent in mild-to-moderate COVID-19 patients (26.3%), but, surprisingly, intensive care unit-admitted patients made fewer errors on the Mini-Mental State Examination than those not admitted, after adjusting for risk factors and age (Manera et al., 2022).

In addition, brain changes including glucose hypometabolism and neurotransmitter alterations detected by positron emission tomography in COVID patients have been reviewed by Fontana et al. (2020). A particular longitudinal study by Douaud et al. (2022) investigated brain changes in participants of UK Biobank who were imaged twice by magnetic resonance imaging, before and after COVID-19, a design that made it possible to discard any previous alteration which might lead to misinterpretation of disease effects. The authors identified a reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus (a limbic region that has a crucial, integrative role for episodic memory); changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex; and reduced global brain size in the SARS-CoV-2 cases compared to controls. These changes correlated with a greater cognitive decline between the two time points and did not overlap with those presented in non-COVID-19 pneumonia cases. **Table 1** summarizes data from these studies.

To sum up, the real long-term cognitive alterations in post-COVID patients, as well as the causal link with SARS-CoV-2 infection, are still elusive. However, considering the slow progression of AD since the first brain changes, cognitive performance should be followed up over a much longer period.

On the other hand, after the coronavirus pandemics in 2002 and 2012, one in five recovered individuals reported depressed mood, insomnia, anxiety, irritability, fatigue, and sleep disorders (de Erausquin et al., 2021). Then, is there a common mechanism for coronaviruses leading to neurological symptoms? Are these mood disorders natural after any overwhelming disease? Or do these similarities between diseases support the multiple pathogen cause of "infectious" AD?

SARS-CoV-2 Neurotropism *versus* Systemic Inflammation

Beta-coronaviruses including SARS-CoV-2 are thought to invade the CNS by binding their spike proteins to the angiotensin-converting enzyme 2 (ACE2) receptors on the olfactory epithelium. Compared to other CoVs, SARS-CoV-2 spike protein displays a 10–20-fold increased affinity toward ACE2 (Wrapp et al., 2020). The first evidence for neurotropism of the virus relied on the first neurological symptom described for COVID-19, anosmia. Interestingly, hyposmia has also been reported in early-stage AD (Meinhardt et al., 2021). Human CoV infection, along with other respiratory virus infections such as influenza, is shown to spread throughout the CNS, especially the temporal region and hippocampus associated with learning/cognitive changes (Dolatshahi et al., 2021). Besides ACE2 receptors, viral transmission is supposed to include trans-synaptic transfer across infected neurons, involving the olfactory nerve, as reviewed in (de Erausquin et al., 2021). The olfactory tract connects to brain regions closely related to cognition and memory. The presence of SARS-CoV-2 in the olfactory bulb leads to the activation of non-neuronal cells, such as mast cells, microglia, and astrocytes, and the release of pro-inflammatory cytokines (Ciaccio et al., 2021). The brain damage might also be a consequence of the loss of sensory input due to anosmia (Douaud et al., 2022). Furthermore, neurons and glia also express ACE2 and can internalize SARS-CoV-2. Neuronal infection is achieved in mice humanized at the ACE2 gene (Song et al., 2021). In turn, the occupation of ACE2 with the virus may lead to a decline in ACE2 activity, which acts as a neuroprotective factor (Dolatshahi et al., 2021).

In addition to ACE2, SARS-CoV-2 can enter the brain via other molecular mediators like neuropilin-1, transmembrane serine protease, CD-147, cathepsin L, and two pore segment channel-2. In contrast to ACE2, CD147 is greatly expressed in the brain (Qiao et al., 2020). Neuropilin-1 is not only expressed in the respiratory epithelium but also the olfactory epithelium, and is highly expressed in endothelial cells, excitatory neurons, and nasal cavity epithelial cells (Iadecola et al., 2020), which may mediate virus entry into the CNS. In COVID-19 postmortem brains, expression of ACE2 was highest in oligodendrocytes, while transmembrane serine protease 2 and transmembrane serine protease 4 were highest in neurons, cathepsin L was highest in microglia, and two pore segment channel-2 was highest in astrocytes (Matschke et al., 2020).

However, direct evidence of SARS-CoV-2 neurotropism is more elusive. Viral components have been detected in brains or CSF (Hosseini et al., 2020; Huang et al., 2020; Khodamoradi et al., 2020; Matschke et al., 2020; Moriguchi et al., 2020; Xiang et al., 2021). Paniz-Mondolfi et al. (2020) reported the postmortem presence of the virus in neural and capillary endothelial cells in the frontal lobe tissue of a COVID-19 patient, with clinical correlates of worsening neurologic symptoms. In contrast, neither viral RNA nor particles were found in brain tissue by other researchers (Helms et al., 2020; Edén et al., 2021; Pilotto et al., 2021). Gagliardi et al. (2021) detected viral RNA in the frontal cortex only by using a very sensitive method (droplet digital PCR), suggesting that SARS-CoV-2 does not actively infect and replicate in the brain. However, since evidence of SARS-CoV-2 occurrence in the brain is not conclusive, most researchers are biased toward thinking of neurological symptoms during the "long COVID" as a consequence of the infection-

Table 1 | Summary of research studies investigating neurologic involvement in COVID-19

Type of study	Population/Cohort	n	Follow-up	Main results	Adjustments	Reference
Prospective	COVID patients without neurological manifestations	51 mild/severe COVID *versus* 31 controls	3 mon	Decreased cortical thickness and cerebral blood flow in severe COVID patients versus mild disease. Correlation with inflammatory markers.	Age	Qin et al., 2021
Prospective	COVID survivors from IRCCS San Raffaele Hospital; Milan	226	1 and 3 mon	Depressive symptomatology, poor performance in at least one cognitive domain. Correlation with immune-inflammation index	Age, sex, hospitalization were factors included in the statistical analysis	Mazza et al., 2021
Cross-sectional, exploratory	Patients admitted to rehabilitation in San Raffaele Hospital	40 (20 subacute phase COVID, 20 post-COVID)		Neuropsychological deficits, cognitive impairment	Age and education	Pistarini et al., 2021
Prospective	Healthcare workers with mild COVID in Brescia	120 COVID *versus* 30 controls	4 mon	No significant differences in neuropsychological or cognitive tests	Age and education	Mattioli et al., 2021
Retrospective	TriNetX electronic health records network	Over 81 million patients: COVID group (236,379), Influenza group, any respiratory tract infection group	6 mon	Neurological and psychiatric morbidity in the 6 months after COVID	Age, sex, ethnicity, and several morbidities were set and matched for	Taquet et al., 2021
Prospective	Adult COVID patients enrolled in the ComPaRe long COVID cohort, France	968	12 mon	Persisting symptoms 1 year after onset	Age, gender, hospitalization	Tran et al., 2022
Retrospective	NMC Seoul	130		22.3% prevalence of new-onset mental disorders among patients with mild-moderate COVID	CCI score core ≥ 1, hospital length of stay, and self-reported depressive symptoms. (Age was significantly different between groups)	Kim et al., 2022
Retrospective	Instituti Clinici Scientifici Maugeri, Italy	152		Higher prevalence of impaired performance in cognitive tests in mild-moderate COVID patients, but fewer errors on the MMSE in ICU-admitted patients	Age as covariate. Previous neurological conditions.	Manera et al., 2022
Prospective, longitudinal	UK Biobank	785 (401 cases who tested positive for SARS-CoV-2 between the two MRI scans and 384 controls)	141 d average	Reduced grey matter and global brain size, tissue damage, and impaired cognition in COVID cases.	Age, hospitalization	Douaud et al., 2022
Prospective, longitudinal	University Hospital of Essen	102 COVID patients classified for disease severity and neurological involvement (unspecific, mild, severe)		24.5% incidence of general weakness or cognitive decline. 12% prevalence of cerebral ischemia and BBB disruption. CSF negative for SARS-CoV-2 but elevated IL levels and gliosis.	Average age did not significantly differ between patients with no, unspecific, mild, or severe neuroinvolvement	Fleischer et al., 2021
Retrospective	COVID patients who died between March-April 2020 in Hamburg	43		Ischemic lesions in 14% patients, high prevalence of gliosis and T cell infiltration. 53% brains positive for SARS-COV-2 but not associated to the severity of neuropathological changes	No	Matschke et al., 2020
Retrospective	COVID Biobank Columbia University	Brains from 10 COVID patients and age- and sex-matched controls		Activation of inflammatory pathways and oxidative stress, increased AMPK, GSK3β, and hyperphosphorylated tau	Grouped by age (< 58/> 66 years)	Reiken et al., 2022
Prospective	LIINC observational cohort study	24 COVID cases (16 with and 8 without neurological symptoms) and 12 pre-pandemic control samples	1 and 3 mon	Increased IL-4, Aβ, NfL, and tau in COVID patients. IL-6 and NfL correlated with age only in COVID patients with neuroinvolvement	Not significant differences in age between groups	Sun et al., 2021
Prospective, longitudinal	Atahualpa Project	93 individuals with normal baseline MRI pre-pandemic, at least one pre-pandemic cognitive evaluation, and no previous neurological or psychiatric manifestations. 52 COVID group, 41 controls	Not specified	The odds for developing cognitive decline were 18.1 times higher among SARS-CoV-2 seropositive individuals	Age, gender, body mass, blood pressure, sleep quality	Del Brutto et al., 2021
Cross-sectional, exploratory, prospective	University College London Hospital	21 COVID cases with neurological symptoms, 23 controls	Not specified	Reduced CSF sAPPα, sAPPβ, Aβ$_{40}$, Aβ$_{42}$, and GFAP, but increased NfL and proinflammatory CK in COVID cases.	Not specified. Age was significantly different between groups (average age higher in controls)	Ziff et al., 2022
Prospective	Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg	100 COVID cases (24 mild, 28 moderate, 48 severe) without pre-existing neurological diseases and healthy age-matched controls	6 mon	Increased blood levels of NfL and GFAP in acute severe COVID, but normalized levels after 6 months, despite persisting neurological symptoms	Age as covariate	Kanberg et al., 2021

Aβ: Amyloid beta peptide; AMPK: AMP-activated protein kinase; BBB: blood-brain barrier; CK: cytokines; CSF: cerebrospinal fluid; GFAP: glial fibrillary acidic protein; GSK3β: glycogen synthase kinase-3 beta; ICU: intensive care unit; IL: interleukin; MMSE: mini-mental state examination; MRI: magnetic resonance imaging; NfL: neurofilament light chain; sAPPα/β: secreted amyloid precursor protein alpha/beta.

triggered inflammatory response. Under this view, it is not surprising that treatment with anti-inflammatory drugs in hospitalized COVID patients prevented "long COVID" emergence. Thus, the question is whether SARS-CoV-2 induces a primary or secondary encephalopathy linked to several major COVID-linked events: inflammation, hypoxia by respiratory failure, hypoperfusion, assisted ventilation, autoimmunity, and BBB disruption (Ali Awan et al., 2021; de Erausquin et al., 2021). Altered BBB could allow the infiltration of immune cells, which may contribute to cognitive decline (Ciaccio et al., 2021). Activation of microglia, variable degrees of astrogliosis, and infiltration with CD8-positive T cells are the main findings reported in a comprehensive neuropathological study of patients who died from COVID-19 (Matschke et al., 2020). As stated by Fleischer et al. (2021), among COVID patients with cerebral ischemia, 50% had BBB disruption and increased interleukin levels in CSF, but all CSF tested negative for SARS-CoV-2 RNA. Antibodies against neuronal and glial epitopes were detected in 35% of the patients tested. The authors interpreted these results as neurological compromise driven by inflammation due to BBB disruption and cytokine release, rather than direct viral invasion. The increased risk of cerebrovascular accident is a manifestation of SARS-CoV-2-provoked cytokine storm and coagulation abnormalities (Wu et al., 2020). In particular, hypoxia/ischemia contributes to the degradation of BBB through the activation of matrix metalloproteinases, which break down the basal lamina and tight junctions of the endothelium (Yang and Rosenberg, 2011). In COVID-19 cases, dysfunction of endothelial cells added to inflammation may lead to abnormalities in

coagulation and thrombo-inflammatory processes, promoting vasculopathy (Barbosa et al., 2021). Indeed, endothelial cells express ACE2 and high levels of neuropilin-1, which makes them susceptible to infection by SARS-CoV-2 (Wenzel et al., 2021). Besides systemic effects, SARS-CoV-2 infection can induce microvascular alterations, like the formation of string vessels likely derived from endothelial cell death after SARS-CoV-2-induced survival factor degradation (Wenzel et al., 2021). These facts warn us about a possible association of COVID-19 with vascular dementia, which, in turn, shares pathognomonic signs with AD.

Evidence of Alzheimer's Disease-Like Neuropathology after COVID-19

There is literature indicating that human CoVs can remain dormant in neurons (Arbour et al., 1999) and that COVID-19 associates with generalized gene expression regulation in the brain, which may contribute to its long-standing effects (Yang et al., 2021). Extensive inflammation and degeneration have been shown in COVID-19 brains, including those of people without neurological symptoms, and an overlap was found between marker genes of AD and genes that are upregulated in COVID-19 infection (Yang et al., 2021). Inflammatory biomarkers including interleukin-6, interleukin-1, TNF, complement proteins, and galectin-3 have been proposed as common prognostic biomarkers between SARS-CoV-2 infection and AD, as reviewed in (Ciaccio et al., 2021) and (Rahman et al., 2021). The activation of the NLRP3 inflammasome, triggered during SARS-CoV-2 infection, could lead to downstream tau aggregation and neurodegeneration (Reiken et al., 2022).

Besides viral neurotropism and inflammation resulting from a cytokine storm, infection with SARS-CoV-2 may also initiate protein aggregation via heparin-binding sites and/or spike-derived peptides, leading to amyloid fibrils just like those in AD (Tavassoly et al., 2020). Elevated levels of Aβ, neurofilament light chain, neurogranin, glial fibrillary acidic protein, and tau were reported in CSF from patients 1–3 months after recovery from COVID-19 (Ciaccio et al., 2021; Sun et al., 2021), showing correlation with neurological symptoms. These markers were also increased in the extracellular vesicles of neural origin of individuals recovering from COVID-19 (with or without self-perceived neurological symptoms) and coincide with extracellular vesicles of neural origin content found in AD (Sun et al., 2021).

Several authors have reported shared gene signatures between AD and COVID-19. Reiken et al. (2022) showed that SARS-CoV-2 infection activates inflammatory signaling and oxidative stress pathways and increases AMPK and GSK3β phosphorylation, resulting in hyperphosphorylation of tau, but normal APP processing in COVID-19 patients' cortex and cerebellum. There was reduced calbindin expression rendering both tissues vulnerable to Ca^{2+}-mediated pathology. Interestingly, brains from both young and aged patients demonstrated increased tau phosphorylation in the cerebellum, which is not typical of AD (Reiken et al., 2022). Remarkably, Ramani et al. (2020) showed that SARS-CoV-2 enters 3D human brain organoids within 2 days of exposure, mainly targeting neurons, which displayed tau mislocalization, hyperphosphorylation, and apparent cell death. However, in agreement with the suggestion of Gagliardi et al. (2021) mentioned above, SARS-CoV-2 does not appear to efficiently replicate within the brain organoids.

The Triggering Receptor Expressed on Myeloid cells 2 gene (TREM2) is expressed in microglia and stimulates phagocytosis while suppressing cytokine production and inflammation (Rohn, 2013). Gene variants of TREM2 have been linked to AD risk. However, the knockout of TREM2 inhibits neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy (Leyns et al., 2017), suggesting the dual roles of TREM2. Interestingly, Wu et al. (2021) found that TREM2 was induced in T cells in the blood and lungs of patients with COVID-19. TREM2 binds to SARS-CoV-2 membrane protein through its immunoglobulin domain, promoting the T helper cell response. These results also support the association between infectious processes and AD risk genes.

COVID-19 and Amyloid-β

The exploratory prospective study of Ziff et al. (2022) found that patients with neurological syndromes within 40 days of symptomatic COVID infection had significantly reduced CSF soluble amyloid precursor protein (sAPP)-α and sAPPβ, as well as $Aβ_{40}$, $Aβ_{42}$, and $Aβ_{42}/Aβ_{40}$ ratio compared to controls, indicative of AD risk. Patients with COVID-19 neurological syndromes showed significantly increased neurofilament light chain and proinflammatory cytokines and this negatively correlated with sAPPα and sAPPβ CSF levels. Conversely, glial fibrillary acidic protein was significantly reduced in CSF from COVID-19 patients with neurological symptoms, and this positively correlated with sAPPα and sAPPβ CSF levels. All CSF samples were SARS-CoV-2 PCR-negative. Lower sAPPα and glial fibrillary acidic protein might indicate astrocyte dysfunction and impaired neuroprotection since astroglial sAPPα is protective against neurotoxicity of Aβ (Durand et al., 2017).

Inflammatory cytokines induce the expression of the interferon-induced transmembrane protein 3 (IFITM3) in neurons and astrocytes, which upregulates γ-secretase activity, thereby increasing the production of Aβ (Hur et al., 2020). But IFITM3 is also a viral particle sequestration protein and SARS-CoV-2 significantly upregulates *IFITM3* (Sardar et al., 2020). Comparative transcriptomic studies showed that FYN kinase and IFITM3 biological networks were significantly enriched in several COVID-19 datasets containing SARS-CoV-2 upregulated genes (Vavougios et al., 2021a), priming

APP for gamma processing and Aβ generation. After having found pathways and gene signatures shared between AD and COVID infection, Vavougios et al. (2021b) outlined that "IFITM3, exosomal hyperphosphorylated tau, and Aβ-nucleic acid complex may constitute a feed-forward signal expanding from a primary site of neuroinfection via afferent projections; the signal itself would propagate AD pathology even in the absence of infection". Indeed, Camacho et al. (2021) performed a meta-analysis of the genes regulated in response to SARS-CoV-2 S protein binding to brain microvascular endothelial cells, which helped predict a decrease in APP expression in the early stages of COVID infection and an increase in APP expression in later stages of infection involving inflammatory damage.

On the other hand, Hsu et al. (2021) demonstrated that $Aβ_{42}$, but not $Aβ_{40}$, binds to various viral proteins with a preferentially high affinity for the S1 subunit of SARS-CoV-2 spike protein and the viral receptor ACE2, and strengthens the binding of SARS-CoV-2 S1 protein to ACE2, thereby enhancing viral entry. This result clearly objects the antimicrobial property of Aβ. **Figure 2** summarizes all these recent findings.
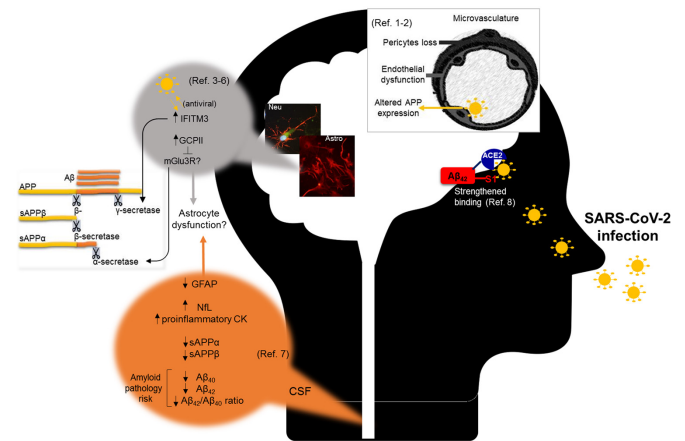

Figure 2 | Different pathways and cell types reported involved in the association between SARS-CoV-2 and amyloid pathology.
Cited references (Ref.) are as follows: (1) Rizk, 2021; (2) Camacho et al., 2021; (3) Sardar et al., 2020; (4) Reiken et al., 2022; (5) Hur et al., 2020; (6) Durand et al., 2017; (7) Ziff et al., 2022; (8) Hsu et al., 2021. ACE2: Angiotensin converting enzyme 2; APP: amyloid precursor protein; CK: cytokines; CSF: cerebrospinal fluid; GCPII: glutamate carboxypeptidase II; GFAP: glial fibrillary acidic protein; IFITM3: interferon-induced transmembrane protein 3; mGlu3R: metabotropic glutamate receptor 3; NfL: neurofilament light chain; sAPPα: secreted amyloid precursor protein alpha; sAPPβ: secreted amyloid precursor protein beta.

Proposed Targets for Neurorepair Might Be Altered by SARS-CoV-2

COVID-19 can cause autoimmune reactions and glutamate excitotoxicity (Dolatshahi et al., 2021). Systemic inflammation leads to decreased production of monoamines and trophic factors and activation of microglia, resulting in increased glutamate and N-methyl-D-aspartate levels, leading to excitotoxicity (Boldrini et al., 2021). Dysfunctional astrocytes may add to increased excitotoxicity by impaired glutamate clearance activity. Wang et al. (2021b) showed that pericytes, when integrated into a cortical organoid, are susceptible to infection with SARS-CoV-2 and mediate virus spreading to astrocytes, which exhibit an inflammatory type I response and cell death. In line with a limited capacity of astrocytes to clear excitotoxic glutamate, it has been suggested by Reiken et al. (2022) that subtype 3 metabotropic glutamate receptor (mGlu3R) may be underactivated in astrocytes from COVID brains. The authors reported elevated expression of glutamate carboxypeptidase 2 in COVID-19 brains, which may contribute to increased PKA signaling by inhibiting mGlu3R. Since mGlu3R has been broadly reported to induce astroglial glutamate transporters and reduce excitotoxicity, a failure in mGlu3R activity could contribute to increased excitotoxicity in COVID brains.

Although highly homologous in their sequences, mGlu3 and mGlu2 receptors exhibit relevant functional differences, at least regarding AD involvement. While mGlu3R is neuroprotective against Aβ, mGlu2R was shown to potentiate Aβ neurotoxicity *in vitro* (Caraci et al., 2011). Interestingly, it has been recently demonstrated that mGlu2R is an internalization factor for SARS-CoV-2 since it directly interacts with SARS-CoV-2 spike protein, and knockdown of mGlu2R decreases internalization of SARS-CoV-2 but not cell binding. Further, knocking out mGlu2R in mice abolishes SARS-CoV-2 infection in the nasal turbinates and significantly reduces viral infection in the lungs (Wang et al., 2021a).

Conclusions

Evidence for pathogens leading to AD adds to the presumption of long-term neuropsychiatric sequelae of COVID-19. Carefully tracking the neurological

impact of COVID-19 emerges as a major scientific challenge. Reported results regarding the cognitive decline in a significant portion of COVID-19 patients, Aβ and tau pathways altered by SARS-CoV-2, neurotoxic glial profile in response to the virus, and brain changes in discrete regions related to learning/memory, made us aware of a possible etiological link between this viral infection and AD. Although undesirable, the COVID pandemic will indeed allow scientists to explore the infectious hypothesis prospectively in a wide population. We will also be able to test preventive interventional strategies aimed at promoting synaptic plasticity that may overcome COVID-induced brain damage within an appropriate time window to delay late-onset AD. Up to May 2022, a search for "SARS CoV 2 infection AND cognitive" terms on the clinicaltrials.gov site yielded 90 clinical trials, whereas the terms "SARS CoV 2 infection cognitive long term" yielded 11 results, with none planning for long follow-up periods. This invites us to subscribe to the concern of Itzhaki et al. (2016) about neglected clinical prospective studies on pathogen-driven neurodegeneration.

References

Abbott A (2020) Are infections seeding some cases of Alzheimer's disease? Nature 587:22-25.

Ali Awan H, Najmuddin Diwan M, Aamir A, Ali M, Di Giannantonio M, Ullah I, Shoib S, De Berardis D (2021) SARS-CoV-2 and the brain: what do we know about the causality of 'cognitive COVID? J Clin Med 10:3441.

Allnutt MA, Johnson K, Bennett DA, Connor SM, Troncoso JC, Pletnikova O, Albert MS, Resnick SM, Scholz SW, De Jager PL (2020) Human herpesvirus 6 detection in Alzheimer's disease cases and controls across multiple cohorts. Neuron 105:1027-1035.

Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ (1999) Acute and persistent infection of human neural cell lines by human coronavirus OC43. J Virol 73:3338-3350.

Balin BJ, Gérard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol 187:23-42.

Balin BJ, Little CS, Hammond CJ, Appelt DM, Whittum-Hudson JA, Gérard HC, Hudson AP (2008) Chlamydophila pneumoniae and the etiology of late-onset Alzheimer's disease. J Alzheimers Dis 13:371-380.

Barbosa LC, Goncalves TL, de Araujo LP, de Oliveira Rosario LV, Ferrer VP (2021) Endothelial cells and SARS-CoV-2: an intimate relationship. Vascul Pharmacol 137:106829.

Bocharova O, Pandit NP, Molesworth K, Fisher A, Mychko O, Makarava N, Baskakov IV (2021) Alzheimer's disease-associated β-amyloid does not protect against herpes simplex virus 1 infection in the mouse brain. J Biol Chem 297:100845.

Boldrini M, Canoll PD, Klein RS (2021) How COVID-19 affects the brain. JAMA Psychiatry 78:682-683.

Bourgade K, Le Page A, Bocti C, Witkowski JM, Dupuis G, Frost EH, Fülöp Jr T (2016) Protective effect of amyloid-β peptides against herpes simplex virus-1 infection in a neuronal cell culture model. J Alzheimers Dis 50:1227-1241.

Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, Liang CR, Wang QH, Wang X, Cao HY (2015) A study on the association between infectious burden and Alzheimer's disease. Eur J Neurol 22:1519-1525.

Camacho RC, Alabed S, Zhou H, Chang SL (2021) Network meta-analysis on the changes of amyloid precursor protein expression following SARS-CoV-2 infection. J Neuroimmune Pharmacol 16:756-769.

Caraci F, Molinaro G, Battaglia G, Giuffrida ML, Riozzi B, Traficante A, Bruno V, Cannella M, Merlo S, Wang X (2011) Targeting group II metabotropic glutamate (mGlu) receptors for the treatment of psychosis associated with Alzheimer's disease: selective activation of mGlu2 receptors amplifies β-amyloid toxicity in cultured neurons, whereas dual activation of mGlu2 and mGlu3 receptors is neuroprotective. Mol Pharmacol 79:618-626.

Ciaccio M, Lo Sasso B, Scazzone C, Gambino CM, Ciaccio AM, Bivona G, Piccoli T, Giglio RV, Agnello L (2021) COVID-19 and Alzheimer's disease. Brain Sci 11:305.

Chen CK, Wu YT, Chang YC (2017) Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther 9:1-7.

Cheng SB, Ferland P, Webster P, Bearer EL (2011) Herpes simplex virus dances with amyloid precursor protein while exiting the cell. PLoS One 6:e17966.

Cheng WC, van Asten SD, Burns LA, Evans HG, Walter GJ, Hashim A, Hughes FJ, Taams LS (2016) Periodontitis-associated pathogens P. gingivalis and A. actinomycetemcomitans activate human CD14+ monocytes leading to enhanced Th17/IL-17 responses. Eur J Immunol 46:2211-2221.

de Erausquin GA, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadri S (2021) The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. Alzheimers Dement 17:1056-1065.

Dolatshahi M, Sabahi M, Aarabi MH (2021) Pathophysiological clues to how the emergent SARS-CoV-2 can potentially increase the susceptibility to neurodegeneration. Mol Neurobiol 58:2379-2394.

Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Mydel P, Hellvard A, Adamowicz K, Hasturk H, et al. (2019) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 5:eaau3333.

Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JL, Griffanti L, Duff E (2022) SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604:697-707.

Durand D, Carniglia L, Turati J, Ramírez D, Saba J, Caruso C, Lasaga M (2017) Amyloid-beta neurotoxicity and clearance are both regulated by glial group II metabotropic glutamate receptors. Neuropharmacology 123:274-286.

Edén A, Kanberg N, Gostner J, Fuchs D, Hagberg L, Andersson LM, Lindh M, Price RW, Zetterberg H, Gisslén M (2021) CSF biomarkers in patients with COVID-19 and neurologic symptoms: a case series. Neurology 96:e294-300.

Eikelenboom P, Hoozemans JJM, Veerhuis R, van Exel E, Rozemuller AJM, van Gool WA (2012) Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimers Res Ther 4:15.

Eimer WA, Kumar DKV, Shanmugam NKN, Rodriguez AS, Mitchell T, Washicosky KJ, György B, Breakefield XO, Tanzi RE, Moir RD (2018) Alzheimer's disease-associated β-amyloid is rapidly seeded by herpesviridae to protect against brain infection. Neuron 99:56-63.

Fischer O (1907) Miliare Nekrosen mit drusigen Wucherungen der Neuro-fibrillen, eine regelmässige Veränderung der Hirnrinde bei. Monatsschr Psychiatr Neurol 22:361.

Fleischer M, Köhrmann M, Dolff S, Szepanowski F, Schmidt K, Herbstreit F, Güngör C, Stolte B, Steiner KM, Stadtler C (2021) Observational cohort study of neurological involvement among patients with SARS-CoV-2 infection. Ther Adv Neurol Disord 14:1756286421993701.

Fontana IC, Bongarzone S, Gee A, Souza DO, Zimmer ER (2020) PET imaging as a tool for assessing COVID-19 brain changes. Trends Neurosci 43:935-938.

Fulop T, Witkowski JM, Bourgade K, Khalil A, Zerif E, Larbi A, Hirokawa K, Pawelec G, Bocti C, Lacombe G (2018) Can an infection hypothesis explain the beta amyloid hypothesis of Alzheimer's disease? Front Aging Neurosci 10:224.

Gagliardi S, Poloni ET, Pandini C, Garofalo M, Dragoni F, Medici V, Davin A, Visonà SD, Moretti M, Sproviero D (2021) Detection of SARS-CoV-2 genome and whole transcriptome sequencing in frontal cortex of COVID-19 patients. Brain Behav Immun 97:13-21.

Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH, Group TPS (2009) Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA 302:2557-2564.

Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M (2020) Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 382:2268-2270.

Hosseini AA, Shetty AK, Sprigg N, Auer DP, Constantinescu CS (2020) Delirium as a presenting feature in COVID-19: neuroinvasive infection or autoimmune encephalopathy? Brain Behav Immun 88:68.

Hsu JTA, Tien CF, Yu GY, Shen S, Lee YH, Hsu PC, Wang Y, Chao PK, Tsay HJ, Shie FS (2021) The effects of Aβ1-42 binding to the SARS-CoV-2 spike protein S1 subunit and angiotensin-converting enzyme 2. Int J Mol Sci 22:8226.

Huang YH, Jiang D, Huang JT (2020) SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. Brain Behav Immun 87:149.

Hur JY, Frost GR, Wu X, Crump C, Pan SJ, Wong E, Barros M, Li T, Nie P, Zhai Y (2020) The innate immunity protein IFITM3 modulates γ-secretase in Alzheimer's disease. Nature 586:735-740.

Iadecola C, Anrather J, Kamel H (2020) Effects of COVID-19 on the nervous system. Cell 183:16-27.

Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, Le K, Aljewari HW, O'Brien-Simpson NM, Reynolds EC, Watanabe K (2018) Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One 13:e0204941.

Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C, Clerici M, Cosby SL (2016) Microbes and Alzheimer's disease. J Alzheimers Dis 51:979-984.

Iwashyna TJ, Ely EW, Smith DM, Langa KM (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 304:1787-1794.

Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF (1991) Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. J Med Virol 33:224-227.

Kanberg N, Simrén J, Edén A, Andersson LM, Nilsson S, Ashton NJ, Sundvall PD, Nellgård B, Blennow K, Zetterberg H (2021) Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. EBioMedicine 70:103512.

Khodamoradi Z, Hosseini S, Gholampoor Saadi M, Mehrabi Z, Sasani M, Yaghoubi S (2020) COVID-19 meningitis without pulmonary involvement with positive cerebrospinal fluid PCR. Eur J Neurol 27:2668-2669.

Kim J, Seo YE, Sung HK, Park HY, Han MH, Lee SH (2022) Predictors of the development of mental disorders in hospitalized COVID-19 patients without previous psychiatric history: a single-center retrospective study in South Korea. Int J Env Res Public Health 19:1092.

Letenneur L, Pérès K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, Orgogozo JM, Gauthier S, Dartigues JF (2008) Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One 3:e3637.

Leyns CE, Ulrich JD, Finn MB, Stewart FR, Koscal LJ, Remolina Serrano J, Robinson GO, Anderson E, Colonna M, Holtzman DM (2017) TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. Proc Natl Acad Sci U S A 114:11524-11529.

Linard M, Letenneur L, Garrigue I, Doize A, Dartigues JF, Helmer C (2020) Interaction between APOE4 and herpes simplex virus type 1 in Alzheimer's disease. Alzheimers Dement 16:200-208.

Link CD (2021) Is there a brain microbiome? Neurosci Insights 16:26331055211018709.

Lou JJ, Movassaghi M, Gordy D, Olson MG, Zhang T, Khurana MS, Chen Z, Perez-Rosendahl M, Thammachantha S, Singer EJ (2021) Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. Free Neuropathol 2:2.

Lövheim H, Olsson J, Weidung B, Johansson A, Eriksson S, Hallmans G, Elgh F (2018) Interaction between cytomegalovirus and herpes simplex virus type 1 associated with the risk of Alzheimer's disease development. J Alzheimers Dis 61:939-945.

Manera MR, Fiabane E, Pain D, Aiello EN, Radici A, Ottonello M, Padovani M, Wilson BA, Fish J, Pistarini C (2022) Clinical features and cognitive sequelae in COVID-19: a retrospective study on N=152 patients. Neurol Sci 43:45-50.

Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M (2020) Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 19:919-929.

Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G (2021) Neurological and cognitive sequelae of Covid-19: a four month follow-up. J Neurol 268:4422-4428.

Mawanda F, Wallace R (2013) Can infections cause Alzheimer's disease? Epidemiol Rev 35:161-180.

Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, Ciceri F, Rovere-Querini P, Benedetti F, group C-BOCS (2021) Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun 94:138-147.

Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, Laue M, Schneider J, Brünink S, Greuel S (2021) Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci 24:168-175.

Miklossy J (1993) Alzheimer disease--a spirochetosis? Neuroreport 4:841-848.

Moir RD, Lathe R, Tanzi RE (2018) The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement 14:1602-1614.

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 94:55-58.

Olsen I, Singhrao SK (2020) Porphyromonas gingivalis infection may contribute to systemic and intracerebral amyloid-beta: implications for Alzheimer's disease onset. Expert Rev Anti Infect Ther 18:1063-1066.

Olsen I (2021) Can Porphyromonas gingivalis contribute to Alzheimer's disease already at the stage of gingivitis? J Alzheimers Dis Rep 5:237-241.

Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, Sordillo EM, Fowkes M (2020) Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 92:699-702.

Pilotto A, Masciocchi S, Volonghi I, Crabbio M, Magni E, De Giuli V, Caprioli F, Rifino N, Sessa M, Gennuso M (2021) Clinical presentation and outcomes of severe acute respiratory syndrome coronavirus 2–related encephalitis: the ENCOVID multicenter study. J Infect Dis 223:28-37.

Pistarini C, Fiabane E, Houdayer E, Vassallo C, Manera MR, Alemanno F (2021) Cognitive and emotional disturbances due to COVID-19: an exploratory study in the rehabilitation setting. Front Neurol 12:643646.

Porcellini E, Carbone I, Ianni M, Licastro F (2010) Alzheimer's disease gene signature says: beware of brain viral infections. Immun Ageing 7:1-5.

Qiao J, Li W, Bao J, Peng Q, Wen D, Wang J, Sun B (2020) The expression of SARS-CoV-2 receptor ACE2 and CD147, and protease TMPRSS2 in human and mouse brain cells and mouse brain tissues. Biochem Biophys Res Commun 533:867-871.

Qin Y, Wu J, Chen T, Li J, Zhang G, Wu D, Zhou Y, Zheng N, Cai A, Ning Q (2021) Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. J Clin Invest 131:e147329.

Rahman MA, Islam K, Rahman S, Alamin M (2021) Neurobiochemical cross-talk between COVID-19 and Alzheimer's disease. Mol Neurobiol 58:1017-1023.

Ramani A, Müller L, Ostermann PN, Gabriel E, Abida-Islam P, Müller-Schiffmann A, Mariappan A, Goureau O, Gruell H, Walker A (2020) SARS-CoV-2 targets neurons of 3D human brain organoids. EMBO J 39:e106230.

Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, Haroutunian V, Sano M, Liang WS, Beckmann ND, Price ND (2018) Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 99:64-82.

Reiken S, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR (2022) Alzheimer's-like signaling in brains of COVID-19 patients. Alzheimers Dement 18:955-965.

Rizk MZ (2021) Alzheimer's disease susceptibility to Sars-CoV-2 and impact of viral infection on AD patients. Emed Res 3:100024.

Rohn TT (2013) The triggering receptor expressed on myeloid cells 2:"TREM-ming" the inflammatory component associated with Alzheimer's disease. Oxid Med Cell Longev 2013:860959.

Roos KL (2014) Encephalitis. Handb Clin Neurol 121:1377-1381.

Sardar R, Satish D, Birla S, Gupta D (2020) Integrative analyses of SARS-CoV-2 genomes from different geographical locations reveal unique features potentially consequential to host-virus interaction, pathogenesis and clues for novel therapies. Heliyon 6:e04658.

Seaks CE, Wilcock DM (2020) Infectious hypothesis of Alzheimer disease. PLoS Pathog 16:e1008596.

Shimeld C, Efstathiou S, Hill T (2001) Tracking the spread of a lacZ-tagged herpes simplex virus type 1 between the eye and the nervous system of the mouse: comparison of primary and recurrent infection. J Virol 75:5252-5262.

Sipilä PN, Heikkilä N, Lindbohm JV, Hakulinen C, Vahtera J, Elovainio M, Suominen S, Väänänen A, Koskinen A, Nyberg ST (2021) Hospital-treated infectious diseases and the risk of dementia: a large, multicohort, observational study with a replication cohort. Lancet Infect Dis 21:1557-1567.

Smail RC, Brew BJ (2018) HIV-associated neurocognitive disorder. Handb Clin Neurol 152:75-97.

Song E, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, Lu P, Weizman OE, Liu F, Dai Y (2021) Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med 218:e20202135.

Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD (2010) The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide. PLoS One 5:e9505.

Sun B, Tang N, Peluso MJ, Iyer NS, Torres L, Donatelli JL, Munter SE, Nixon CC, Rutishauser RL, Rodriguez-Barraquer I (2021) Characterization and biomarker analyses of post-COVID-19 complications and neurological manifestations. Cells 10:386.

Tao Q, Ang TFA, DeCarli C, Auerbach SH, Devine S, Stein TD, Zhang X, Massaro J, Au R, Qiu WQ (2018) Association of chronic low-grade inflammation with risk of Alzheimer disease in ApoE4 carriers. JAMA Netw Open 1:e183597.

Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ (2021) 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 8:416-427.

Tavassoly O, Safavi F, Tavassoly I (2020) Seeding brain protein aggregation by SARS-CoV-2 as a possible long-term complication of COVID-19 infection. ACS Chem Neurosci 11:3704-3706.

Tran VT, Porcher R, Pane I, Ravaud P (2022) Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun 13:1812.

Vavougios GD, Breza M, Mavridis T, Krogfelt KA (2021a) FYN, SARS-CoV-2, and IFITM3 in the neurobiology of Alzheimer's disease. Brain Disorders 3:100022.

Vavougios GD, Nday C, Pelidou SH, Gourgoulianis KI, Stamoulis G, Doskas T, Zarogiannis SG (2021b) Outside-in induction of the IFITM3 trafficking system by infections, including SARS-CoV-2, in the pathobiology of Alzheimer's Disease. Brain Behav Immun Health 14:100243.

Wang J, Yang G, Wang X, Wen Z, Shuai L, Luo J, Wang C, Sun Z, Liu R, Ge J (2021a) SARS-CoV-2 uses metabotropic glutamate receptor subtype 2 as an internalization factor to infect cells. Cell Discov 7:119.

Wang L, Sievert D, Clark AE, Lee S, Federman H, Gastfriend BD, Shusta EV, Palecek SP, Carlin AF, Gleeson JG (2021b) A human three-dimensional neural-perivascular 'assembloid' promotes astrocytic development and enables modeling of SARS-CoV-2 neuropathology. Nat Med 27:1600-1606.

Wenzel J, Lampe J, Müller-Fielitz H, Schuster R, Zille M, Müller K, Krohn M, Körbelin J, Zhang L, Özorhan Ü (2021) The SARS-CoV-2 main protease Mpro causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. Nat Neurosci 24:1522-1533.

White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, Hartshorn KL (2014) Alzheimer's associated β-amyloid protein inhibits influenza A virus and modulates viral interactions with phagocytes. PLoS One 9:e101364.

Wozniak MA, Frost AL, Preston CM, Itzhaki RF (2011) Antivirals reduce the formation of key Alzheimer's disease molecules in cell cultures acutely infected with herpes simplex virus type 1. PLoS One 6:e25152.

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260-1263.

Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, Liu C, Yang C (2020) Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 87:18-22.

Wu Y, Wang M, Yin H, Ming S, Li X, Jiang G, Liu Y, Wang P, Zhou G, Liu L (2021) TREM-2 is a sensor and activator of T cell response in SARS-CoV-2 infection. Sci Adv 7:eabi6802.

Xiang P, Xu X, Lu X, Gao L, Wang H, Li Z, Xiong H, Li R, Xiong Y, Pu L (2021) Case report: identification of SARS-CoV-2 in cerebrospinal fluid by ultrahigh-depth sequencing in a patient with coronavirus disease 2019 and neurological dysfunction. Front Med 8:629828.

Yang AC, Kern F, Losada PM, Agam MR, Maat CA, Schmartz GP, Fehlmann T, Stein JA, Schaum N, Lee DP, Calcuttawala K, Vest RT, Berdnik D, Lu N, Hahn O, Gate D, McNerney MW, Channappa D, Cobos I, Ludwig N, et al. (2021) Dysregulation of brain and choroid plexus cell types in severe COVID-19. Nature 595:565-571.

Yang Y, Rosenberg GA (2011) Blood–brain barrier breakdown in acute and chronic cerebrovascular disease. Stroke 42:3323-3328.

Zeng F, Liu Y, Huang W, Qing H, Kadowaki T, Kashiwazaki H, Ni J, Wu Z (2021) Receptor for advanced glycation end products up-regulation in cerebral endothelial cells mediates cerebrovascular-related amyloid β accumulation after Porphyromonas gingivalis infection. J Neurochem 158:724-736.

Ziff OJ, Ashton NJ, Mehta PR, Brown R, Athauda D, Heaney J, Heslegrave AJ, Benedet AL, Blennow K, Checkley AM (2022) Amyloid processing in COVID-19-associated neurological syndromes. J Neurochem 161:146-157.