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## Relationship Between Coronavirus Disease 2019 and Alzheimer's Disease

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### ABSTRACT

The Covid 19 pandemic is causing global morbidity and mortality, straining health care systems, and disrupting society, putting individuals with Alzheimer's disease and related dementias (ADRD) at risk of significant harm. In this review paper, we examine the current and expected impact of the pandemic on individuals with ADRD. Recent case studies show that Covid 19 can have a negative effect on patients with neurological disorders such as Alzheimer's Disease (AD). Our team has analyzed the extensive amount of papers that explore this connection and have summarized the ones most relevant. COVID 19 is known to produce neurological manifestations and is able to infect the Central Nervous System, potentially via the olfactory bulb. Patients with Alzheimer's often have accompanying complications that make them particularly vulnerable. It is important to also look at the

indirect social effects of the pandemic, such as limited social interaction and an increase in anxiety.

**KEYWORDS:** Covid 19, Neurology, Alzheimer's Disease, Related Dementia, SARS CoV 2, ACE 2, Olfactory Bulb, Accelerated Onset

## INTRODUCTION

The Coronavirus disease 2019 (Covid 19) pandemic has led to over 3 million deaths worldwide and has caused permanent damage in many more. Covid 19 has also exacerbated many underlying conditions, specifically ones that involve cardiopulmonary and neurological complications.

In this review paper, we will be discussing the connection between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) and Alzheimer's disease. A mutualistic relationship between AD and Covid 19 seems to exist. On the one hand, Covid 19 patients seem to be prone to developing AD. On the other hand, AD patients could be more susceptible to severe Covid 19 [37]. It is important to note that published literature also indicates a possibility of AD being a protective factor against severe Covid 19 symptoms. These researchers have studied AD patients who had adequate access to healthcare showed resilience to Covid 19 with shorter hospital stays[14].It's worth mentioning that the relationship between Covid 19 and dementia is unclear in literature at this time. During normal times, individuals with Alzheimer's disease and related dementias (ADRD) are among the most vulnerable persons in society, depending on family or professional caregivers for their day to day survival. This pandemic further exacerbates their vulnerability, due to both the morbidity and mortality from Covid 19 and the indirect effects of the pandemic on the social supports and the health care system on which they depend [32].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), as well as all members of the human coronaviruses (CoVs) family, is an opportunistic pathogen of the central nervous system (CNS) [37]. The neurological signs and symptoms associated with SARS-CoV-2 infection, such as confusion, headache, hypogeusia/ageusia, hyposmia/anosmia, dizziness, epilepsy, acute cerebrovascular disease [37, 38], are caused by the direct invasion of the virus into the CNS, and the subsequent interaction between SARS-CoV-2 spike protein

and the angiotensin-converting enzyme 2 (ACE2). Post-mortem studies revealed the presence of both SARS-CoV-2 antigen and RNA in the brain tissue of Covid 19 patients [37].

## **METHODS**

In this paper, we analyzed all published reports on Covid 19-associated Alzheimer's Disease (AD) in hopes of shedding light on potentially overlooked, yet significant, neurologic complications of the virus. Published literature was compiled using Pubmed, Google Scholar, and Scopus as search engines. We identified isolated case reports, case series, and cohort studies. Covid 19, Alzheimer's Disease, Sars Cov 2, and Neurology were used as keywords in the search. Studies lacking the focus on neurology were excluded in our search. The last search was done on the 18th of June 2021, however new information about the virus is being added to the literature on a daily basis.

## **NEUROLOGICAL MANIFESTATIONS OF COVID 19**

Extensive analysis of literature yields a solid link to the neurological manifestations of severe Covid 19 illness in addition to the more commonly experienced pulmonary manifestations in patients suffering from Covid 19. In a retrospective observational study that was done at 3 centers (Main District, West Branch, and Tumor Center) of Union Hospital of Huazhong University of Science and Technology (Wuhan, China), it was shown that 36.4% of patients with severe Covid 19 infections had neurological manifestations [19]. Of the 214 patients in this study (mean [SD] age, 52.7 [15.5] years; 87 men [40.7%]) with Covid 19, 126 patients (58.9%) had nonsevere infection and 88 patients (41.1%) had severe infection according to their respiratory status. Overall, 78 patients (36.4%) had neurologic manifestations [19]. Compared to patients that have suffered a nonsevere infection, patients that have suffered a severe infection were older, had more underlying disorders such as hypertension, and showed fewer typical symptoms of Covid 19, such as fever and cough [19]. Patients with more severe infection had neurologic manifestations, such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]) [19].

Given high rates of Covid 19 infection in the general population, coincidental occurrence of neurologic events is likely. However, currently there is convincing evidence that SARS-CoV-

2 can involve the nervous system, and its neurotropic potential is increasingly well established [20]. A case study from Japan in May of 2020, found an incident that describes the first case of a 24 year old male patient, who was brought in by the ambulance due to a convulsion accompanied by unconsciousness which was later diagnosed with aseptic encephalitis with SARS-CoV-2 RNA in cerebrospinal fluid [21].

Published literature suggests that there may be a direct link between SARS-CoV-2 and central nervous system invasion. Altered sense of smell and/or taste in uncomplicated early-stage Covid 19 patients is suggestive of a movement of the virus to the brain via the olfactory bulb, which enables the virus to reach and affect the brain [20]. SARS-CoV-2 has been shown to use the ACE2 receptor for cell entry. This receptor has also been detected over glial cells and neurons, which make it a potential target for Covid 19. Moreover, SARS-CoV-2 spike protein could interact with ACE2 expressed in the capillary endothelium; the virus may also damage the blood-brain barrier and enter the CNS by attacking the vascular system [22-23].

Furthermore, published literature has elaborated the possibility of indirect mechanisms of injury of SARS-CoV-2 and the nervous system. SARS-CoV-2 binds to ACE2 receptors with a higher affinity compared with SARS-CoV [24]. ACE2 is known to be a cardio cerebral vascular protection factor, which plays a major role in regulating blood pressure and anti atherosclerosis mechanisms. When bound to ACE2 receptors, SARS-CoV-2 viruses may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage and ischemic stroke [20]. In addition, when the virus replicates and proliferates in pneumocytes, it causes diffuse alveolar and interstitial inflammatory exudate, as well as the formation of membranes in the most severe forms. This, in turn, leads to alveolar gas exchange disorders causing hypoxia in the CNS, increasing the anaerobic metabolism in brain cells, inducing cellular and interstitial edema, obstructing cerebral flow blood, as well as ischemia and vasodilation in the cerebral circulation [20]. The immune response can also play a role in the indirect mechanism of injury of SARS-CoV-2 and the nervous system. Some patients with Covid 19 have died from hyperinflammatory syndrome (cytokine storm) and multiorgan failure. Coronaviruses also have the ability to infect macrophages and glial cells. Experimental models have shown that glial cells are capable of secreting proinflammatory factors, such as interleukin-6, interleukin-12, interleukin-15, and tumor necrosis factor alpha, after coronavirus infection [25-26].

Ultimately, we find that there is a solidated link between severe Covid 19 cases and neurological manifestations that can be caused by direct and indirect effects of SARS-COV-2 which may play a vital role in patients with Alzheimer's Disease.

## **PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE**

Alzheimer's disease (AD) can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles as a result of amyloid-beta peptide's ( $A\beta$ ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures[1]. It is important to note that Alzheimer's disease is the most common form of dementia in old age[2].

The commonest presentation of AD is of an elderly individual with insidious, progressive problems centered on episodic memory. At this stage, the patient may fulfil criteria for amnesic mild cognitive impairment(MCI) [3]. Some of the earliest symptoms manifest years before receiving a clinical diagnosis of dementia, including changes in mood, anxiety, and sleep. Heightened anxiety, depressive symptoms, apathy, and withdrawal are highly prevalent in preclinical or early stages of AD [4].

At present, only two classes of pharmacologic therapy are available for patients with AD. The cholinesterase inhibitors donepezil, rivastigmine, and galantamine are recommended therapy for patients with mild, moderate, or severe AD dementia as well as Parkinson's disease dementia. Memantine, which has activity as both a non-competitive N-methyl-D-aspartate receptor antagonist and a dopamine agonist, is approved for use in patients with moderate-to-severe AD (mini-mental state examination [MMSE] <15) who show difficulty with attention and alertness[5].

There are many risk factors for AD. Early reviews identified over 20 risk factors associated with Alzheimer's disease (AD) including age, familial inheritance, exposure to aluminium, traumatic brain injury (TBI), and associated co-morbidities such as vascular disease and infection[6]. It is interesting to note that early genetic linkage studies of numerous large pedigrees with early-onset AD (onset age: 30–50 years) led to the discovery of autosomal dominant mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes[7].

Interestingly, US National Institutes of Health highlighted diabetes mellitus, smoking, depression, mental inactivity, physical inactivity and poor diet as being associated with increased risk of cognitive decline, AD, or both[8]. It is important to note that AD has associations and implications with certain viruses. For example, AD intensifies through infectious agents like HIV[9]. In addition, emerging evidence supports the hypothesis of the role of neurotropic viruses from the herpesviridae family, especially Human herpesvirus 1 (HHV-1), Cytomegalovirus (CMV), and Human herpesvirus 2 (HHV-2), in AD neuropathology [10].

## **RELATIONSHIP BETWEEN AD AND COVID 19**

As already established, there are certain viruses that are associated with AD. It should come as no surprise that with the newly emerging literature about Covid 19, it is apparent that there may be a connection between Covid 19 and AD. With Covid 19, inflammatory mediators have been implicated in CNS manifestations, and immunological processes in peripheral nervous system (PNS) abnormalities, and plasma level of inflammatory cytokines had been reported to be associated with the status of AD progression and inversely related with immune response [11].

A growing body of evidence suggested a role for neuroinflammation. Systemic inflammation induces the activation of microglia and astrocytes, which in turn secrete pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ . Such biomarkers could be involved in the synaptic dysfunction, inducing neurodegeneration, which could potentially lead to AD [37, 42].

Furthermore, as previously mentioned, aggregating shreds of evidence suggests that Olfactory dysfunction (OD) is one of the most common signs of Covid 19 [15,16]. This olfactory dysfunction leads to anosmia. Anosmia, the inability of detecting smell or taste, is a hallmark of Covid 19 [11, 12]. Anosmia or its relevant marker hyposmia, lowered sensitivity to detect smell or taste, is also a hallmark of AD [11, 13]. The relationship between Covid 19 and AD does not stop at similarities of their neurological effects: the symptoms and social implications of AD affects Covid 19 and vice versa:

The symptoms of AD can be directly seen in affecting the transmission of Covid 19. As previously mentioned, AD is the most common form of dementia. This is important due to the fact that People with dementia are particularly vulnerable to being infected by and

spreading SARS-CoV-2 because they may not adequately comprehend, execute, or recall any of the suggested public health measures (eg, physical distancing, use of face masks): those with agitation, wandering, or disinhibition are probably at even higher risk of catching and spreading the infection[17]. Moreover, physical distancing is not feasible for those who are dependent on others for performing their basic activities of daily living (ADL; eg, bathing), such as those with more severe dementia[17].

The social implications of the Covid 19 pandemic has also had a negative effect on the mental health of the people with AD. To assess the effects of Covid 19 on the mental health of participants with AD who live in retirement homes, a study was conducted in France in which 58 participants consented to participate in the study: the participants rated their depression and anxiety during and before the Covid 19 crisis [18]. Participants reported higher depression ( $p = .005$ ) and anxiety ( $p = .004$ ) during than before the Covid 19 crisis: these increases can be attributed to the isolation of the residents and/or to the drastic changes in their daily life and care they receive[18].

It is interesting to note that there is a possibility of AD being a protective factor against severe Covid 19 symptoms. A retrospective cohort study of the clinical data of 19 AD patients with Covid 19 pneumonia, compared with 23 non-AD Covid 19 patients admitted at the same time showed that AD patients with Covid 19 were in milder conditions with a better prognosis than non-AD patients. AD patients who had adequate access to healthcare showed resilience to Covid 19 with shorter hospital stays[14]. However, other studies that have been published in literature found that AD patients could be more susceptible to severe Covid 19 [37]. More research is necessary in this respect in order to deduce the true interaction of Covid 19 in patients with AD or a related dementia.

Age is the best established risk factor both for AD and for symptomatic and severe illness and mortality from Covid 19 [34]. This is illustrated by the situation in Italy where over a third of confirmed cases and approximately 9 of 10 deaths are occurring in individuals 70 years and older. Beyond age, increased morbidity and mortality is expected in patients with AD due to the association of ADRD with physical comorbidities and other features of AD. Individuals with dementia are more likely to have cardiovascular disease, diabetes, and pneumonia compared to individuals of the same age without dementia [32, 35]. These conditions have been associated with poorer outcomes including death, in individuals with Covid 19 [32, 36]. Among 1,099 cases of laboratory-confirmed Covid 19 in China, pneumonia occurred in over 90% of cases [32]. Absent the pandemic, mortality from

pneumonia has been reported to be twice higher in individuals with dementia compared to those without dementia[32, 33].

There does seem to be an association between Covid 19 and the AD, this may be due in part to the fact that both diseases have been identified to be neuroinvasive, however it is also clear that the social implications of Covid 19 have also had an effect on the health of AD patients. Moreover it is evident that more research needs to be done to verify and ascertain the effects that Covid 19 has had on AD.

## **NEURODEGENERATIVE EFFECTS OF COVID 19**

Interestingly, studies have surfaced consolidating the link between patients suffering from severe form of covid 19 and dementia-like cognitive impairment. In a network-based, multimodal omics comparison of Covid 19 and neurologic complications, researchers found significant network-based relationships between Covid 19 and neuroinflammation and brain microvascular injury pathways and processes which are implicated in AD [27].

The researchers also detected aberrant expression of AD biomarkers in the cerebrospinal fluid and blood of patients with Covid 19. While transcriptomic analyses showed relatively low expression of SARS-CoV-2 entry factors in the human brain, neuroinflammatory changes were pronounced [27]. In addition, single-nucleus transcriptomic analyses showed that expression of SARS-CoV-2 host factors and antiviral defense genes was elevated in brain endothelial cells of AD patients and healthy controls relative to neurons and other cell types, suggesting a possible role for brain microvascular injury in Covid 19 mediated cognitive impairment [27].

Ultimately speaking, this study concluded that there is a significant mechanistic overlap between AD and Covid 19, centered on neuroinflammation and microvascular injury [27]. These results help improve our understanding of Covid 19-associated neurological manifestations and provide guidance for future development of preventive or treatment interventions [27].

Further studies have elaborated the fact that cognitive impairment following SARS-CoV-2 infection is being increasingly recognized as an acute and possibly also long-term sequelae of the disease [28]. Direct viral invasion through infected vascular endothelial cells directly to glial cells has also been described, as well as penetrance from the olfactory epithelium to the



olfactory bulb through retrograde axonal transport along the olfactory nerve in patients suffering neurological sequelae of the disease [29]. Biomarkers of Covid 19 induced cognitive impairment are currently lacking, but there is some limited evidence that SARS-CoV-2 could preferentially target the frontal lobes, as suggested by behavioral and dysexecutive symptoms, fronto-temporal hypoperfusion on MRI, EEG slowing in frontal regions, and frontal hypometabolism on 18F-FDG-PET [28].

Fascinatingly, immune responses and excessive inflammation in Covid 19 may also accelerate the progression of brain inflammatory neurodegeneration [30]. There is no question the viral neurotropism is important along factors intrinsic to the host, including genetics, innate immunity, the hyperactivation of the immune system, and the development of cytokine storm syndrome along with the immune previous status of the host to the Covid 19 encounter [31]. Patients with symptomatic or asymptomatic Covid 19 are fully expected to accelerate their progression of AD, based on their synergistic systemic and neuroinflammatory increases related to the virus itself and the ongoing air pollution related process. Children, young adults, and the elderly could present with progression of pre-existing or increased neuropsychological pathological outcomes [39-41]. Long-term neurodegenerative diseases ought to be in the mind of every neurologist across the world, with aberrant proteostasis, neuroinflammation, and abnormal immune responses being key factors for accelerating AD pathology [31].

Ultimately, we see that the evidence from the published literature strongly suggests that there may be a direct link between severe covid 19 infections and an accelerated onset of dementia like sequelae in patients prone to or susceptible to Alzheimer's disease.

## **DISCUSSION AND CONCLUSION**

Extensive analysis of literature yields a solid link to neurological manifestation of severe covid 19 illness in addition to the more commonly experienced pulmonary manifestations in patients suffering from covid 19. In a retrospective observational study that was done at 3 centers (Main District, West Branch, and Tumor Center) of Union Hospital of Huazhong University of Science and Technology (Wuhan, China), it was shown that 36.4% of patients with severe Covid 19 infections had neurological manifestations [19]. Furthermore, a case study from Japan in May of 2020, found an incident that describes the first case of a 24 year old male patient, who was brought in by the ambulance due to a convulsion accompanied by

unconsciousness which was later diagnosed with aseptic encephalitis with SARS-COV-2 RNA in cerebrospinal fluid [21]. Altered sense of smell and/or taste in uncomplicated early-stage Covid 19 patients is suggestive of a movement of the virus to the brain via the olfactory bulb, which enables the virus to reach and affect the brain [20]. From here we see that there is a definite link between severe Covid 19 cases and neurological implications.

In regards to Alzheimer's disease, it has already been established in literature that neurotropic viruses from the herpesviridae family, especially Human herpesvirus 1 (HHV-1), Cytomegalovirus (CMV), and Human herpesvirus 2 (HHV-2), can play a role in AD neuropathology [10]. Therefore, it should come as no surprise that with the newly emerging literature about Covid 19, it is apparent that there may be a connection between Covid 19 and AD. Published literature indicates that there may be a significant mechanistic overlap between AD and Covid 19, centered on neuroinflammation and microvascular injury [27]. With Covid 19, inflammatory mediators have been implicated in CNS manifestations, and immunological processes in peripheral nervous system (PNS) abnormalities, and plasma level of inflammatory cytokines had been reported to be associated with the status of AD progression and inversely related with immune response [11].

It is interesting to note that there is a possibility of AD being a protective factor against severe Covid 19 symptoms. A retrospective cohort study of the clinical data of 19 AD patients with Covid 19 pneumonia, compared with 23 non-AD Covid 19 patients admitted at the same time showed that AD patients with Covid 19 were in milder conditions with a better prognosis than non-AD patients. AD patients who had adequate access to healthcare showed resilience to Covid 19 with shorter hospital stays[14]. However, other studies that have been published in literature found that AD patients could be more susceptible to severe Covid 19 [37]. It's worth mentioning that the relationship between Covid 19 and dementia is unclear in literature at this time. More research is necessary in this respect in order to deduce that true interaction of Covid 19 in patients with AD or a related dementia.

From here we see that patient's already suffering from AD may experience less severe Covid 19 symptoms. This is in contrast to patients without AD who seem to experience more severe Covid 19 symptoms, however, more research should be done in this respect to deduce the reason as to why the findings are the way they are.

There does seem to be an association between Covid 19 and the AD, this may be due in part to the fact that both diseases have been identified to be neuroinvasive, however it is also clear

that the social implications of Covid 19 have also had an effect on the health of AD patients. Moreover it is evident that more research needs to be done to verify and ascertain the effects that Covid 19 has had on AD.

Further studies have surfaced consolidating the link between patients suffering from severe form of covid 19 and dementia-like cognitive impairment. In a network-based, multimodal omics comparison of Covid 19 and neurologic complications, researchers found significant network-based relationships between Covid 19 and neuroinflammation and brain microvascular injury pathways and processes which are implicated in AD [27]. The researchers also detected aberrant expression of AD biomarkers in the cerebrospinal fluid and blood of patients with Covid 19. While transcriptomic analyses showed relatively low expression of SARS-CoV-2 entry factors in the human brain, neuroinflammatory changes were pronounced [27]. In addition, single-nucleus transcriptomic analyses showed that expression of SARS-CoV-2 host factors and antiviral defense genes was elevated in brain endothelial cells of AD patients and healthy controls relative to neurons and other cell types, suggesting a possible role for brain microvascular injury in Covid 19 mediated cognitive impairment [27].

Ultimately speaking, this study concluded that there is a significant mechanistic overlap between AD and Covid 19, centered on neuroinflammation and microvascular injury [27]. These results help improve our understanding of Covid 19-associated neurological manifestations and provide guidance for future development of preventive or treatment interventions [27].

Published literature has also found a potential link that cognitive impairment following SARS-CoV-2 infection is being increasingly recognized as an acute and possibly also long-term sequelae of the disease [28]. Researchers have found in patients suffering neurological sequelae of the disease a direct viral invasion through infected vascular endothelial cells directly to glial cells has also been described, as well as penetrance from the olfactory epithelium to the olfactory bulb through retrograde axonal transport along the olfactory nerve [29]. It has also been discovered that there is some limited evidence that SARS-CoV-2 could preferentially target the frontal lobes, as suggested by behavioral and dysexecutive symptoms, fronto-temporal hypoperfusion on MRI, EEG slowing in frontal regions, and frontal hypometabolism on 18F-FDG-PET [28].

Fascinatingly, immune responses and excessive inflammation in Covid 19 may also accelerate the progression of brain inflammatory neurodegeneration [30]. There is no question the viral neurotropism is important along factors intrinsic to the host, including genetics, innate immunity, the hyperactivation of the immune system, and the development of cytokine storm syndrome along with the immune previous status of the host to the Covid 19 encounter [31]. Patients with symptomatic or asymptomatic Covid 19 are fully expected to accelerate their progression of AD, based on their synergistic systemic and neuroinflammatory increases related to the virus itself and the ongoing air pollution related process. Children, young adults, and the elderly could present with progression of pre-existing or increased neuropsychological pathological outcomes [39-41]. Long-term neurodegenerative diseases ought to be in the mind of every neurologist across the world, with aberrant proteostasis, neuroinflammation, and abnormal immune responses being key factors for accelerating AD pathology [31].

In this review, we sought to provide an overview on the relationship between AD and Covid 19, focusing on the potential role of biomarkers, which could represent a precious tool for early identification of Covid 19 patients at high risk of developing AD [37]. Neurological sequelae, including the cognitive impairment leading to AD, could represent an important complication of Covid 19. Further detailed clinical, laboratory, and neuropathological studies will help to elucidate the underlying pathophysiological mechanisms of the Covid 19 neurological complications [37]. A longitudinal follow-up of Covid 19 patients, especially older adults and severe cases, is required to detect the potential long-term neurological consequences of SARS-CoV-2 infection [37]. In such a scenario, biomarkers represent reliable tools for early monitoring of Covid 19 patients and early detection of those at high risk of developing neurological sequelae, such as AD.

The published literature indicates that there definitely is a connection between Covid 19 and AD. It seems as though patients prone/susceptible to AD may experience an earlier onset of AD symptoms after a severe Covid 19 illness. The lines between Covid 19 interaction in patients with dementia is unclear in literature at this time. It seems as though AD patients who had adequate access to healthcare showed resilience to Covid 19 with shorter hospital stays [14] yet other studies that have been published in literature found that AD patients could be more susceptible to severe Covid 19 [37]. More research is necessary in this regard in order to deduce the true interaction of Covid 19 in patients with AD or a related dementia.

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