

Short Communication

Neurologic and Immunologic Complications of COVID-19: Potential Long-Term Risk Factors for Alzheimer's Disease

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Abstract. The COVID-19 pandemic has been met with studies on risk factors, characteristics, and clinical course. Among these characteristics are neurologic symptoms, which may provide improved insight into the mechanisms of this novel virus and the brain's susceptibility to infectious diseases. This article aims to discuss 1) findings related to neurologic complications, 2) how they connect to and are bidirectionally impacted by bioimmunology, 3) how this combination of biological mechanisms impact and are impacted by psychosocial stressors, and 4) the importance of considering potential neurodegenerative consequences of COVID-19. Longitudinal studies on neuropathology and cognition are critical to avoiding premature conclusions related to long-term neurologic effects.

Keywords: Alzheimer's disease, coronavirus disease 2019 (COVID-19), immunology, neurobiology, stress

Much will be discovered over time regarding long-term outcomes of coronavirus disease 2019 (COVID-19) exposure. While focus is primarily on pulmonary function, extrapulmonary dysfunction such as neurologic manifestations are gaining attention as we continue to witness otherwise healthy individuals being impacted. While older adults are still considered at increased risk of severe and potentially fatal consequences of the pandemic due to comorbidities and otherwise compromised immune function, there should be elevated concern related to

long-term neurologic effects of COVID-19 exposure and recovery for both young and older populations. The question, then, is not whether or not these are age-related risk factors for COVID-19 or health concerns that will persist upon COVID-19 remission, but whether or not patients will be at greater risk for neurodegenerative processes, specifically Alzheimer's disease (AD), during and subsequent to recovery.

Central nervous system (CNS) manifestations are arguably most concerning as it relates to populations at risk for AD, particularly those who are treated and subsequently recover. While there is still much to learn about COVID-19's effects on the brain, it is worth considering how this may impact one's risk of AD given the overlap in noted neurologic and immunologic alterations. Mao and colleagues

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engaged in a retrospective, observational case series that focuses on neurologic manifestations of hospitalized patients with COVID-19 [1]. Approximately 36.4% of the sample of 214 patients presented with neurologic manifestations, with severe cases being more likely to experience these symptoms than non-severe cases ($p=0.02$). This has been the starting point of evidence of COVID-19 ramifications outside of the respiratory and cardiovascular systems.

Some of the earliest neurologic findings were in those experiencing COVID-19-related anosmia and dysgeusia [2]. Important to this equation is that COVID-19 may prove to be a risk factor for future neurodegenerative disorders, beyond that which would be expected in the context of other comorbidities and genetic predispositions. Anosmia and the biological processes resulting in this symptom contribute to grey matter loss in cortical regions [3], which is similar to where pathognomonic amyloid plaques are often discovered [4]. Olfactory dysfunction has also been found to be associated with the graduation from mild cognitive impairment (MCI) to AD, serving as a potential identifier for pre-clinical stages [5]. Our concern with a rapid increase in AD patients due to the sheer size of the Baby Boomer generation may be extended if AD pathogenesis is altered or increased in progression rate by a novel virus. The median duration of viral shedding (20 days) for survivors [6] does not necessarily imply that neurologic damage is also transient, which is likely dependent on infection course, treatment, and recovery. Pleasure and colleagues [7] reported that stroke and alterations of consciousness often occur not only in the context of severe acute respiratory syndrome but also later in the recovery process. However, this article also suggested that COVID-19 may be drawing closer attention to underlying conditions and risk factors rather than serving as a risk factor in itself. While this could be argued based on temporal association of events, those who move on to return home at their perceived physical baselines may not be facing the same trajectory moving forward.

Premature immunosenescence plays a putative role in AD pathogenesis, such that lymphocytic changes in distribution and levels may impact AD risk [8]. This is in alignment with findings in COVID-19-positive patients in Wuhan [1]. Further, blood urea nitrogen and creatinine kinase levels in severe COVID-19 cases have been observed as significantly altered [1], consistent with studies on blood-cerebrospinal fluid barrier (BCSFB) function and neurodegeneration that suggest a seem-

ingly important alteration in BCSFB permeability in those with AD [9]. Muscular injuries, irrespective of COVID-19 severity, have been highlighted as presenting with elevated neutrophil counts compared to those without injury [1]. These heterogeneous neutrophils play a critical role in immune response and inflammation due to threat to maintain homeostasis, but when this inflammation is due to injury, neutrophils can result in substantial tissue damage, acquire a toxic phenotype within the CNS, and introduce new molecules that can impact AD risk [10].

It has become clear that many age-related conditions are found among those testing positive for COVID-19, though some of these are also related to lifestyle and family history. For example, Zhou and colleagues [6] found that hypertension, diabetes, and coronary artery disease were the most common comorbidities in a sample of 191 COVID-19-positive patients (median [IQR] age = 56.0 [46.0 to 67.0] years). Systolic hypertension in midlife, rather than only late life, is associated with 18% and 25% increased risk of AD, respectively [11]. COVID-19 deaths have also been associated with an odds ratio of 18.42 when d-dimer levels are greater than $1 \mu\text{g/mL}$ [6], which is a biomarker involved in AD that complicates diabetes, particularly in the context of carotid artery plaques [12]. Diabetes and obesity, which can result in cardiovascular events and diseases, are also modifiable risk factors of AD that can alter blood-brain barrier permeability of immune-related cells and, thus, impact inflammation [13]. These cardiovascular risk factors are directly related to cerebrovascular consequences, such as hypoperfusion, a symptom strongly associated with MCI and AD [14]. Plasma exchange and albumin for AD patients with hypoperfusion, for example, has been shown to improve cognitive deficits and initiate cerebrospinal fluid (CSF) amyloid- β ($A\beta$) [15]. These albumin levels are a concern for COVID-19 patients as well, such that nephritis and other complications could be similarly treated [16]. Family history also extends to AD, such that $A\beta$ -positive individuals are not only more likely to have a family history of dementia but are also more likely to carry at least one apolipoprotein E (*APOE*) $\epsilon 4$ allele [17]. Thus, it may be clinically inappropriate to view comorbidities as a function of age but, instead, family history because it encompasses a broader view of the situation at-hand.

Behavioral and psychological symptoms of dementia (BPSD), found in approximately 90% of AD patients [18], cannot be neglected in the context of the COVID-19 pandemic. Frontline healthcare

workers are at increased risk for anxiety, depression, and stress, with some concern related to posttraumatic stress symptomatology [19]. Along with the clinical phenotypes that define BPSD, the recursive effects over time are arguably more important to pathogenesis than mere presence. The serotonergic alterations that both result in and are altered by BPSD are critical components of disease trajectory. For example, affective symptoms are found to increase the risk of premature mortality, particularly as a function of time, attenuated most strongly by existing health conditions [20]. Therefore, it is reasonable to suspect that a highly stressful and uncertain situation could significantly impact disease course in not only those at risk, but those who were not initially at risk for AD. It is important to consider the bidirectional nature of biological mechanisms related to psychosocial stress responses. Evidence is not lacking in terms of purported mechanistic relationships between stress- and trauma-related events and dysregulation of immune response to inflammation [21]. The observed microglial dysregulation during stressful events is that which is implicated in AD pathogenesis due to the preferential expression of microglia by identified risk genes [22]. Acute necrotizing encephalopathy, a potential complication of viral infections, can further impact the breakdown of blood-brain-barrier functionality and the start of cytokine storms [23]. This immune response is potentially why convalescent plasma has proven to be a viable treatment option for COVID-19 [24, 25]. Stroke is another known adverse event associated with COVID-19, yet this relationship is not fully understood at present [26]. Thus, it should not go unnoticed that AD patients are at a greater risk of hemorrhagic stroke than controls [27] and that cardiorespiratory state impacts this stroke risk [28].

Future research, tailored to the brain, would allow us to better understand COVID-19 over the course of symptoms and in the context of viral shedding, as well as the potential risks it may pose in the future. For example, A β positron emission tomography (PET) for those without cognitive impairment or MCI, tau PET using ^{18}F -RO-948 for those with cognitive deficits [29], and CSF tau [30] should be collected along with *APOE* genotyping. Regions of interest should be created to ensure that results approximate the original development of the Braak system for tau pathology [31]. These variables are commonly collected in AD studies, particularly within the National Alzheimer's Coordinating Center (NACC), and are interrelated to a degree that warrants ongoing collec-

tion. Neuropsychological measures should be utilized to gauge cognitive performance both at baseline and over time in relation to these noted AD biomarkers [32].

The monitoring of COVID-19 patients for both clinical and research purposes is of utmost importance. It is likely that some of the complications, depending on age and medical history, will require substantial follow-up following viral shedding. There will also be behavioral and psychological consequences that should be carefully considered even when not spontaneously endorsed by patients. Thus, research could be conducted in the context of routine clinical work to avoid other patient-specific barriers related to travel and time. Given the extent of ramifications following the spread of COVID-19 across the globe, it would behoove both the public and scientific community to ensure that we understand the connections between future AD risk and COVID-19. This information would arguably prove invaluable should another pandemic arise or, even with COVID-19, a new spike in the coming months.

There are meaningful connections between the neurologic and immunologic complications of COVID-19 and those that impact neurodegeneration and AD pathogenesis. It would be a missed opportunity for neurologists to move into position to accept neurologic presentations under the assumption that a history of COVID-19 does not have a lasting impact. Whether or not this question is clinically meaningful is currently premature—considering the importance of ongoing research that follows these individuals over time is both apropos and a scientific obligation. Premature conclusions can logically affect our understanding of neurodegenerative processes, such that meaningful factors are lost in translation or ignored altogether for the sake of taking a presentation at face-value. COVID-19 may offer unique insights into AD neuropathology through the brain's susceptibility to certain viruses and other infectious agents.

Human and animal rights in informed consent

In this article, the cited articles contain studies with human and/or animal work approved by institutional review boards prior to publication.

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CONFLICT OF INTEREST

The author discloses no conflicts of interest, competing interests, or potential financial interests.

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