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COVID-19: Brain Effects

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Neuropsychiatry • Long COVID • Neuroinvasion
• Neuroinflammation • Immunosenescence

KEY POINTS

- The underlying mechanisms by which severe acute respiratory syndrome coronavirus 2 affects the brain may include mechanisms related to inflammation, neuroinvasion, microvascular injury, and hypoxia.
- Brain effects may manifest as neurologic and neuropsychiatric symptoms in the acute and postacute phases of coronavirus disease, and the elderly are most vulnerable to these sequelae.
- Future research is needed to identify prevalence among other vulnerable groups, potential prognostic indicators, preventative measures, and therapeutic interventions.

INTRODUCTION

The global impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for the COVID-19 pandemic, has been particularly profound and enduring for the elderly. Since the beginning of the pandemic, organizations, such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), have warned about the elevated risk of severe illness and death due to COVID-19 in the aging population.[1,2] The elderly, defined by the WHO as age 60 and older and by the CDC as age 65 and older, have the highest rates of morbidity and mortality following infection from COVID-19.[2,3] The elderly are most vulnerable to adverse outcomes due to medical comorbidities and age-related physiological changes in the brain and immune system.[4–7] Although the focus here will be on the neurobiological mechanisms and increased viral susceptibility with age, it is important to recognize the influence that racial, ethnic, cultural, and socioeconomic disparities may have on worsening health outcomes in this age demographic.[8–10]

As ongoing research continues to unfold, there is growing evidence that COVID-19 causes pathological changes in the brain and alters cellular functioning via neuroinvasion, inflammation, microvascular injury, and hypoxia.[4,11–15] Emerging data reveal that

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neuropsychiatric manifestations of COVID-19 occur in both the acute and postacute phases of illness, and for some these symptoms persist for weeks to months after recovering from COVID-19 illness.[15,16]

This reality has broader implications for the pathogenicity of the SARS-CoV-2 virus when considering the increased vulnerability of the brain with aging, especially in those with premorbid cognitive impairment and dementia.[6–8,17–20] Epidemiological studies illustrate that acute manifestations of neurological and neuropsychiatric disease occur in up to 80% of hospitalized cases.[13,21] In milder cases of COVID-19, these symptoms occur in the absence of typical respiratory symptoms[4,5,13] In the elderly, postmortem histological and radiological studies reveal morphological changes in brain structure in addition to evidence of neurovascular injury within the central nervous system (CNS), suggesting potentially irreversible damage to the brain.[5,15,22–28]

Here, we summarize the most updated evidence underlying the proposed neuropathological and immunological processes by which COVID-19 impacts the brain. Given the rapid growth of knowledge being disseminated on this topic, we recognize that some of the proposed mechanisms have still to be fully elucidated and understood. First, we give a brief overview of some of the known characteristics of SARS-CoV-2 that have been proposed to facilitate inflammation and neuronal injury leading to direct brain effects. We discuss the mechanisms by which the elderly may be more vulnerable to these potentially indelible effects. Then, we highlight the neurological and neuropsychiatric symptoms that have been reported in the literature and review the potential brain regions that may be implicated in some of the long-term sequelae. We conclude with a summary of the current recommendations for the prevention and treatment of COVID-19 in addition to a discussion of areas for future research and development.

Proposed Mechanisms: What Is it and How Does it Infect the Brain?

Similar to other strains of coronaviruses, such as the Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome-Coronavirus, SARS-CoV-2 is hypothesized to enter the CNS by a variety of mechanisms.[11,15,29] The former viruses have demonstrated an ability to enter the brain stem and replicate, however, to date, there is insufficient data to support the ability of SARS-CoV-2 to do the same.[6,30]

SARS-CoV-2 is part of a family of enveloped, positive-sense, single stranded RNA viruses with viral spike (S) protein that bind to host cell entry receptors, namely, angiotensin converting-enzyme 2 (ACE2).[4,13–15] It has been proposed that ACE2 is the key transmembrane receptor on host endothelial cells to which the S-protein binds.[4,11,31] The fusion of cell and viral membranes is further enabled by cleavage of the S-protein attached to ACE2 by the host cell transmembrane protease, serine 2, allowing the virus to enter cells.[4,11,31]

Although the ACE2 receptor has a wide distribution of systemic tissue expression, there is a high ACE2 receptor density in the cerebral microcirculation.[15] The high burden of neurological and neuropsychiatric symptoms observed in COVID-19 suggests a particular viral tropism favoring entry through the CNS or the peripheral nervous system.[14,30] SARS-CoV-2 has high affinity for ACE2 receptors in cerebral microcirculation and it has been proposed that the virus may travel via nerves innervating the respiratory tract, a primary site for replication.[11,15] Specifically, CNS invasion of cranial nerves via axonal transport, such as on olfactory nerve endings, have been described in the literature.[14,15,32] Alternatively, SARS-CoV-2 may bind ACE2 receptors on olfactory epithelial cells and enter via tight junctions. In addition to viral tropism, it has been suggested that SARS-CoV-2 is capable of hematogenous spread, enabling disruption of the blood–brain barrier (BBB) or the blood–cerebrospinal fluid

barrier (B-CSFB).[11,15] Regardless of the precise route of viral cell entry, the resulting endothelial cell damage triggers a neuroinflammatory response that is thought to be responsible for microvascular injury, leading to stroke, vasculitis, organ failure, and effects on the brain.[9,11,15,33,34] The influx of inflammatory mediators known as "cytokine storm" and upregulation of the coagulation cascade are implicated in the activation of microglial cells.[4,7,11,14,15] There is subsequent neurotransmission dysfunction and neuronal cell loss resulting in neurological and neuropsychiatric symptoms.[4,7,11,14,15,35] **Fig. 1** is a schematic illustration summarizing the proposed mechanisms.[4,11,13,14,33–35]

Mechanisms of severe acute respiratory syndrome coronavirus 2 neuroinvasion[4,11,13,14,33–35]

1. *Infection*: SARS-CoV-2 respiratory droplets enter sustentacular cells of the olfactory epithelium. Hematogenous transmission is via ACE2 receptor binding to vascular endothelium. Endothelial damage triggers microthrombus formation, increased von Willebrand factor (vWF), fibrin deposition, and platelet activation. Systemic infection leads to oxidative stress, hypoxia, and a hyperinflammatory state.
2. *Neuronal transmission:* Neuronal injury and infection trigger recruitment and activation of immune cells, including glial cells, astrocytes, macrophages, and T-lymphocytes. SARS-CoV-2 neuroinvasion causes neuroinflammation by way of cytokine storm [production and release of tumor necrosis factor-alpha, interleukin-6 (IL-6), IL-10, and IL-1β] that directly induces microglial activation and indirectly triggers coagulation cascade (which leads to further microglial activation).
3. *CNS pathophysiology:* Microglial activation leads to increased kynurenine production, which increases quinolinic acid (increases glutamate and upregulates N-methyl-D-aspartate receptors) and depletes neurotransmitters (serotonin, dopamine, and norepinephrine). Altered neurotransmission and excitotoxicity by increased glutamate and hypoxic injury contribute to neuronal dysfunction and cell death. Demyelination (due to oligodendroglial cell death) leads to neuronal excitotoxicity, hypoxia, and synaptic alterations. Cytokine storm leads to neuroinflammation, increased vascular permeability, dysfunction of BBB and BCSFB, and subsequent neurodegeneration. Coagulation cascade and elevation of vWF lead to thrombotic events. Hypercoagulation increases D-dimer, fibrinogen and thrombus formation.

Neurologic and Neuropsychiatric Manifestations

During the COVID-19 pandemic, the nomenclature has emerged to identify neurologic and neuropsychiatric symptoms as they related to specific periods of time during COVID-19 illness. Acute symptoms have been reported in the literature to last up to approximately 4 weeks and include delirium, encephalitis, stroke, and psychiatric disorders.[13,20,33,34,36,37] For the purposes of this article, the term *postacute* will refer to chronic or long-term neuropsychiatric symptoms lasting any time beyond 4 weeks after acute infection. In the published literature to date, many refer to long-term neuropsychiatric symptoms that continue for 12 weeks or more, after one has recovered from COVID-19 illness.[38] The term "long COVID" is gaining recognition as a way to identify some of the symptoms that have lasting effects on individuals long after their recovery from acute infection.[15,38,39] There is little understood as of the writing of this article the exact etiologies or risk factors for this condition, especially as symptom development does not correlate with the severity of COVID-19 illness.[15,38,39] The constellation of symptoms associated with long COVID is also sometimes referred

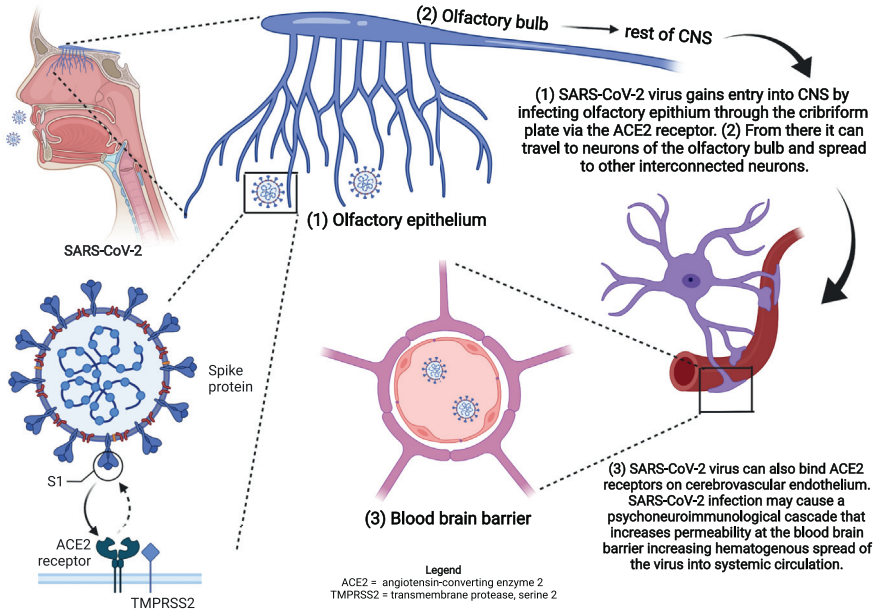

Fig. 1. A schematic summarizing the proposed mechanisms. ACE2, angiotensin converting-enzyme 2; TMPRSS2, transmembrane protease, serine 2. (Created with BioRender.com.)

to as the postacute sequelae of COVID-19 (PASC) and may be used interchangeably in this discussion.[40–42] The phenomenon of long COVID is unique in that it appears to represent a protracted course of neurologic and neuropsychiatric sequelae across all age groups. Long COVID has been reported to include a wide range of symptoms, including dyspnea, fatigue, sleep disturbances, and neuropsychiatric symptoms, such as headache, memory loss, concentration, and changes in mood.[2,13–16,38,40] One proposed mechanism for the lasting brain effects after recovering from acute illness is that SARS-CoV-2 remains dormant in neurons and the delayed effect of neuroinflammation leads to demyelination and neurodegeneration.[43]

Due to the increasing prevalence of these symptoms and their impact on daily functioning, there is still much to be learned and understood about what causes these sequelae and how they may be prevented or reversed.[32,33,38,40] Broadly, acute effects of viral infection can include acute stroke, neuromuscular dysfunction, demyelinating disorders, encephalopathy, confusion, emotional disturbances, and psychosis. Acute neurological events in individuals over age 50 most commonly include cerebrovascular events followed by anosmia/hyposmia, and hypogeusia, and those aged 65 and older more commonly present with confusion and stroke symptoms.[22,44–46]

Delirium is often multifactorial in nature and in the elderly, it may be the first acute presenting symptom of COVID-19, creating a diagnostic challenge and possible delays in care. There is some evidence that suggests individuals who experienced delirium during their acute illness were likely to be affected by PASC.[41]

Some of the postacute neuropsychiatric sequelae commonly noted in the literature include depression, anxiety, cognitive difficulties, including memory impairment, inattention, executive dysfunction, concentration difficulty as well as headache.[3,22,43] In

Table 1
Neurologic and neuropsychiatric manifestations

	Acute Coronavirus Disease	Postacute Coronavirus Disease
Neurologic symptoms	Anosmia, hyposmia Hypogeusia, dysgeusia Encephalitis Stroke Neuromuscular dysfunction Demyelinating disorders Acute encephalopathy[a]	Anosmia Encephalopathy Encephalitis Stroke Headache Neurodegeneration Demyelination Neuropathy
Neuropsychiatric symptoms	Psychiatric Disorders Mood disorders Catatonia Anxiety Insomnia Psychosis Neurocognitive Disorders Delirium[a] Major/minor neurocognitive disorder	Psychiatric Disorders Mood disorders Anxiety Insomnia Psychosis Post-traumatic stress disorder Neurocognitive disorders Cognitive impairment—memory deficits, inattention, executive dysfunction

[a] Interchangeable per updated nomenclature guidelines in Slooter et al.

those hospitalized due to COVID-19, anxiety, depression, sleep impairment, and post-traumatic disorder comprised the longstanding PASC **Table 1**.[33]

Neurological symptoms

- CNS effects: anosmia, ageusia, stroke—hemorrhagic and ischemic, CNS vasculitis, acute inflammation of brain, spinal cord, meninges leading to encephalitis or encephalopathy.[47]
- PNS effects: neuromuscular disorders, such as Guillain–Barré syndrome, Miller Fisher variant, Bell's palsy, and other demyelinating neuropathies, epilepsy (direct versus indirect cause; secondary to cytokine storm). Nonspecific neurological manifestations include headache, fatigue, and myalgias.[30,47]

Neuropsychiatric symptoms

- Neuropsychiatric symptoms secondary to excitotoxicity and hypoxic injury and differ depending on the Brodmann area involved.
- Acute psychiatric symptoms include depression, anxiety, insomnia, memory impairment, psychosis, and delirium/encephalopathy (acute confusion and agitation).[47] Many of these may persist as late neuropsychiatric sequelae, including depression, suicidal behavior, anxiety, psychosis, seizures, insomnia, fatigue, post-traumatic stress, attention deficits, memory impairment and irritability, encephalitis lethargica (caused by 1918 influenza pandemic), and limbic encephalitis.[34]

What does neuroimaging research reveal about brain changes due to coronavirus disease?. The literature concerning the effects of the SARS-CoV-2 virus on the brain continues to expand and there is no exception when reviewing neuroimaging research

available on this topic. As we enter the third year of the pandemic, the data collected and analyzed have also evolved. Earlier radiological studies aimed at characterizing abnormal neuroimaging findings on MRI and computed tomography (CT) scans in COVID-19-infected individuals, including cerebral microhemorrhages, acute spontaneous intracranial hemorrhage, acute and subacute infarcts, and encephalitis or encephalopathy.[48] Subsequent systematic reviews with meta-analysis of MRI, PET, and CT studies have revealed specific brain regions that may be structurally and functionally affected in COVID-19, such as the olfactory cortex extending to prefrontal and limbic regions.[28]

Many of these neuroimaging studies have suggested COVID-19 brain-related pathologies in the elderly (age > 60 years) in the brain stem and frontotemporal regions, including cerebrovascular injury, hypoperfusion, evidence of inflammation, and cellular damage along white matter tracts.[22,44–46] Such investigations have identified risk factors that contribute to the severity of COVID-19 illness, such as pre-existing neurological illness, psychiatric illness, sleep disturbance, immunosenescence, and hyperinflammatory states with age. However, investigations thus far have been unable to isolate the direct impact of pathogenicity of SARS-CoV-2 infection in the brain.

More recently, the UK Biobank COVID-19 re-imaging case-control study has been the first and largest of its kind to elucidate statistically significant longitudinal changes in the brain due to SARS-CoV-2 infection by comparing neuroimaging scans from affected individuals both pre- and post- COVID-19 infection.[5] Early evidence from this study suggests a greater reduction in global brain size, the possibility of the left cerebral hemisphere being more strongly associated with SARS-CoV2 infection, and longitudinal limbic olfactory brain changes involving functionally connected regions of anterior cingulate cortex, orbitofrontal cortex, amygdala, hippocampus, and parahippocampal gyrus.[5]

Primary brain regions demonstrating altered structure or function on neuroimaging include the olfactory cortex and subsequent projection areas, such as the orbitofrontal cortex, amygdala, insula, entorhinal cortex, and hippocampus.[28] Neuroimaging findings involving brain regions implicated in COVID-19 infection are summarized in **Table 2**, which summarizes findings derived from a review of case series, cohort studies, and systematic reviews.[13]

Considerations for coronavirus disease in persons with dementia. Early during the COVID-19 pandemic, the elderly were identified as the most vulnerable population to SARS-CoV-2 infection due to the increased burden of pre-existing medical comorbidities, frailty, and age-related immune system dysfunction known as immunosenescence.[4,49] Further review of literature on effects of COVID-19 in the elderly reveals an atypical course of symptom presentation, which may include no fever or low-grade fever and the absence of common respiratory symptoms, such as dyspnea and cough, which may lead to delayed diagnosis of COVID-19 in the geriatric population.[3]

Atypical symptom presentation is also common in persons with dementia who contract COVID-19 and may manifest as exacerbation of cognitive decline, impairment in activities of daily living, or worsening behavioral and psychological symptoms of dementia (BPSD). However, delirium is commonly the first presenting symptom in persons with dementia with acute SARS-CoV-2 infection.[34] Using a validated measurement tool for detecting delirium, such as the Confusion Assessment Method, is recommended but there is currently no existing equivalent tool for detecting long COVID or post-acute sequelae of COVID (PASC).

Underlying cognitive impairment is known to be associated with higher rates of delirium due to medical illness and it is well known that delirium may be protracted in individuals with dementia. Therefore, not surprisingly, persons with mild cognitive

Table 2
Neuroimaging findings on the brain regions implicated in severe acute respiratory syndrome coronavirus 2

	Brain Regions	Imaging Findings	Studies	Imaging Modalities	Study Design
Cortical regions	Anterior cingulate cortex (PFC)	Impairments in connectivity and signal intensity (functional MRI), fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Orbitofrontal cortex prefrontal cortex (PFC)	Greater reduction in gray matter thickness and tissue-contrast (MRI)	Douaud et al,[5] 2022	MRI, functional MRI	Case control cohort study
		Fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Olfactory cortex (limbic)	Greater changes in markers of tissue damage (functional MRI)	Douaud et al,[5] 2022	MRI, functional MRI	Case control cohort study
		Altered cortical volume, thickness and hypometabolism	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Insula (limbic)	Low gray matter volume/ reduced cortical thickness (MRI)	Douaud et al,[5] 2022	MRI, functional MRI	Case control cohort study
		Fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Superior temporal gyrus (limbic)	Reduced cortical thickness	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Parahippocampal gyrus (limbic)	Greater reduction in gray matter thickness and tissue contrast	Douaud et al,[5] 2022	MRI, functional MRI	Case control cohort study
		Fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis

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Table 2
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	Brain Regions	Imaging Findings	Studies	Imaging Modalities	Study Design
Subcortical regions	Entorhinal cortex	Greater changes in markers of tissue damage (functional MRI)	Douaud et al,[5] 2022	MRI, functional MRI	Case control cohort study
	Thalamus	Fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Amygdala (limbic)	Fluorodeoxyglucose hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Hippocampus (limbic)	Low gray matter volume/ reduced cortical thickness, decreased cerebral blood flow (MRI)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Corpus callosum	Increased diffusivity indicating tissue damage, white matter abnormalities due to microhemorrhage (MRI)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis
	Brain stem	White matter and volume abnormalities due to microhemorrhage (MRI) FDG hypometabolism (PET)	Najt et al,[28] 2021	MRI, PET, computed tomography	Systematic review and meta-analysis

mpairment or dementia who contract the SARS-CoV-2 virus are at greater risk of severe illness and are more vulnerable to long-term neuropsychiatric sequelae.[22,34,44–46] Specifically, persons with dementia due to underlying neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease, may experience an exacerbation of preexisting BPSD due to COVID-19; therefore, monitoring for changes can be essential for early detection of acute infection. Symptom overlap with BPSD and long-term neuropsychiatric sequelae, such as agitation, apathy, and aberrant motor activity, presents a challenge to those caring for persons with dementia.[30]

Treatment Recommendations

There is currently limited published data to support the use of any specific agent for the treatment or prevention of neuropsychiatric sequelae of COVID-19. Multiple national organizations, such as the WHO and CDC, and The National Institutes of Health, have highly recommended vaccination for all eligible elderly to prevent and reduce the risk of severe illness.[2] As of the time of this writing, The National Institutes of Health COVID-19 Treatment Guidelines Panel continues to update its Web site regarding the therapeutic management of hospitalized and nonhospitalized adults. The guidance on clinical management of COVID-19 inpatients changes rapidly as we gain a better understanding of the virus. Current knowledge about SARS-CoV-2 has enabled the use of therapeutic agents, such as antivirals, like remdesivir, and immunomodulators, such as corticosteroids and monoclonal antibodies.[31,49] There is some hope that an improved understanding of the mechanisms of these drugs will inspire future research and development of immunotherapeutic agents that can potentially mitigate the acute and postacute brain effects of COVID-19. In the absence of a more novel approach, for now, the use of pre-existing evidence-based treatments and standards of care will continue to be employed for treating the neurologic and neuropsychiatric symptoms that emerge from COVID-19. For the treatment of delirium, there is no clinical consensus; however, there is a growing body of data that supports the efficacy of using low-dose neuroleptics and alpha-adrenergic blockers for managing symptoms.[2,50,51] However, the ever-present challenge in the pharmacological treatment of delirium in the elderly with COVID-19 will be to carefully avoid adverse events due to drug interactions, or medical contraindications and to weigh the risks versus benefits of those agents known to be potentially harmful in the elderly.[52]

SUMMARY

In conclusion, the long-term effects of COVID-19 on the brain have left an indelible imprint on the global community. Whether acute or postacute, brain effects have impacted individuals across all age groups, irrespective of the severity of COVID-19 illness. The knowledge regarding the neuropathology of the virus suggests that by way of neuroinvasion and hyperinflammation, neurologic and neuropsychiatric symptoms may emerge and persist for an extended period, well after one has recovered from COVID-19. Data also suggest that a major risk factor for lasting brain effects is age, and the neuropsychiatric sequelae present a greater burden on the elderly, especially those with premorbid cognitive impairment.[8,18,20,33,46] Detecting delirium or changes in baseline behavior in the elderly may be an early key finding in the acute phase of illness, given the propensity for atypical COVID-19 presentations in this age group.

As the current understanding of the neurochemical and immunological processes underlying the brain effects of COVID-19 continues to evolve, lessons learned up to this point during the pandemic will undoubtedly pave the way for future research

and innovation. By applying the current knowledge about how the brain and immune system respond to acute COVID-19 infection, we will hopefully soon identify other risk factors and prognostic indicators in a variety of other populations. Areas of need for further research include epidemiological studies that identify the true prevalence and incidence of long COVID across the life span and any potentially irreversible sequelae. It will be equally important to ensure such studies not only look at all age groups and at people who have been both vaccinated and unvaccinated, but also at individuals of diverse backgrounds and geographical regions. Given the existing health care disparities related to race, ethnicity, and socioeconomic status, the pandemic presents an opportunity for a critical look at how biopsychosocial factors might influence the development of future vaccines and immunotherapies.[2]

CLINICS CARE POINTS

- Severe acute respiratory syndrome coronavirus 2 infection causes acute and postacute neurologic and neuropsychiatric symptoms, some of which persist for weeks to months, and is known as long coronavirus disease (COVID-19) or post-acute sequelae of COVID-19 (PASC).
- Neuropathological mechanisms have been hypothesized to trigger neuroinflammation, causing downstream effects on neurotransmitters and leading to a myriad of symptoms.
- Increased vulnerability of the brain with aging places the elderly, especially those with cognitive impairment, at an increased risk for neuropsychiatric sequelae from COVID-19.
- People with dementia may have atypical presentations of COVID-19, which lead to delays in diagnosis and increased risk of severe illness and death.
- People with dementia are at an increased risk of persistent postacute neuropsychiatric sequelae, which may be difficult to differentiate from worsening dementia.
- In caring for people with dementia, monitoring for changes in baseline mentation (delirium) or worsening of pre-existing behavioral disturbances may be the earliest way to detect acute COVID-19 infection.
- A better understanding of the mechanisms by which COVID-19 affects the brain will pave the way for future research and the development of potential preventative and therapeutic approaches.

DISCLOSURE

The authors have nothing to disclose.

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