



# Coronavirus disease 2019 and neurodegenerative disease: what will the future bring?

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## Purpose of review

Over 70 million people worldwide, including those with neurodegenerative disease (NDD), have been diagnosed with coronavirus disease 2019 (COVID-19) to date. We review outcomes in patients with NDD and COVID-19 and discuss the hypothesis that due to putative commonalities of neuropathogenesis, COVID-19 may unmask or trigger NDD in vulnerable individuals.

## Recent findings

Based on a systematic review of published literature, patients with NDD, including dementia, Parkinson's disease, and multiple sclerosis (MS) make up a significant portion of hospitalized COVID-19 patients. Such patients are likely to present with altered mental status or worsening of their preexisting neurological symptoms. Patients with NDD and poor outcomes often have high-risk comorbid conditions, including advanced age, hypertension, diabetes, obesity, and heart/lung disease. Patients with dementia including Alzheimer's disease are at higher risk for hospitalization and death, whereas those with preexisting Parkinson's disease are not. MS patients have good outcomes and disease modifying therapies do not increase the risk for severe disease. Viral infections and attendant neuroinflammation have been associated with the pathogenesis of Alzheimer's disease, Parkinson's disease, and MS, suggesting that COVID-19 may have the potential to incite or accelerate neurodegeneration.

## Summary

Since patients with Alzheimer's disease are at higher risk for hospitalization and death in the setting of COVID-19, additional precautions and protective measures should be put in place to prevent infections and optimize management of comorbidities in this vulnerable population. Further studies are needed to determine whether COVID-19 may lead to an increased risk of developing NDD in susceptible individuals.

## Keywords

Alzheimer's disease, coronavirus disease 2019, neurodegenerative disease, Parkinson's disease, severe acute respiratory syndrome coronavirus 2

## INTRODUCTION

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has swept across the world and caused a devastating pandemic. SARS-CoV-2 causes the syndrome known as coronavirus disease 2019 (COVID-19). Neurodegenerative diseases (NDDs) encompass both dementia syndromes and other autoimmune, genetic, and sporadic conditions. Broadly, NDDs are characterized by the progressive degeneration of the central nervous system and/or peripheral nervous system. Many patients with NDD are older with comorbidities and others are on immunosuppressive therapies. Older patients and those with comorbidities such as hypertension, diabetes, obesity, immunosuppression, and heart/lung disease are at increased risk for poor outcomes related to COVID-19 [1<sup>••</sup>,2]. High levels of inflammatory cytokines and chemokines

develop in COVID-19 and are predictive of disease severity and survival [3,4]. Several cytokines and chemokines have been identified, including IL-2, IL-6, IL-7, IL-10, interferon-inducible protein-10 (IP-10), IFN-I, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 $\alpha$ , and TNF- $\alpha$  [5,6<sup>••</sup>]. Here we provide a review of outcomes in patients with COVID-19 and NDD. In addition, we explore the hypothesis that COVID-19 may lead to a

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## KEY POINTS

- Patients with NDD may present with atypical symptoms or worsening of preexisting neurological deficits.
- Patients with Alzheimer's disease or dementia are at high risk for poor outcomes and should take additional precautions to prevent infection.
- Patients with Parkinson's disease and MS are not at increased risk for poor outcomes despite disease modifying therapy.
- Few cases of new onset NDD after COVID-19 have been reported.
- It is possible severe acute respiratory syndrome coronavirus 2 and the related inflammation could induce the onset of NDD.

dysregulated immune and inflammatory response that puts patients at higher risk of developing or accelerating NDD.

## METHODS

In September of 2020, we performed a systematic review of literature published since January 2020 using PubMed and Google Scholar. We sought to identify clinical studies reporting outcomes on patients who contracted COVID-19 and were known to have an NDD or who developed NDD during or after their COVID-19 course. In addition, we sought to identify articles discussing viral infections as causative agents of NDD to highlight potential mechanisms SARS-CoV-2 may use to trigger NDD.

Our search terms included: 'neurodegenerative disease'; 'neurodegeneration'; 'COVID-19'; 'SARS-CoV-2'; 'dementia'; 'Parkinson's disease'; 'Alzheimer's disease'; 'multiple sclerosis'; 'Lewy body dementia'; 'vascular dementia'; 'corticobasal degeneration'; 'frontal temporal dementia'; 'multiple system atrophy'; 'progressive supranuclear palsy'; 'amyotrophic lateral sclerosis'; 'Charcot-Marie-Tooth'; 'Huntington's disease'; 'prion disease'; 'spinal muscular atrophy'; 'spinocerebellar ataxia'; 'mitochondrial disease'.

The following inclusion and exclusion criteria were used to identify appropriate articles. A breakdown of the articles reviewed is detailed in Fig. 1. Out of 242 articles reviewed for inclusion, 66 were included in the final review.

Inclusion:

- (1) Patients with confirmed SARS-CoV-2 or high suspicion of clinical COVID-19
- (2) Patients with an NDD

- (3) Patients who developed symptoms or signs of an NDD during or after a COVID-19 course

Exclusion:

- (1) Articles which proposed hypotheses regarding NDD and COVID-19
- (2) Studies focusing on adapting care management of patients with NDD but without COVID-19
- (3) Preprint publications
- (4) Quantitative outcomes not provided

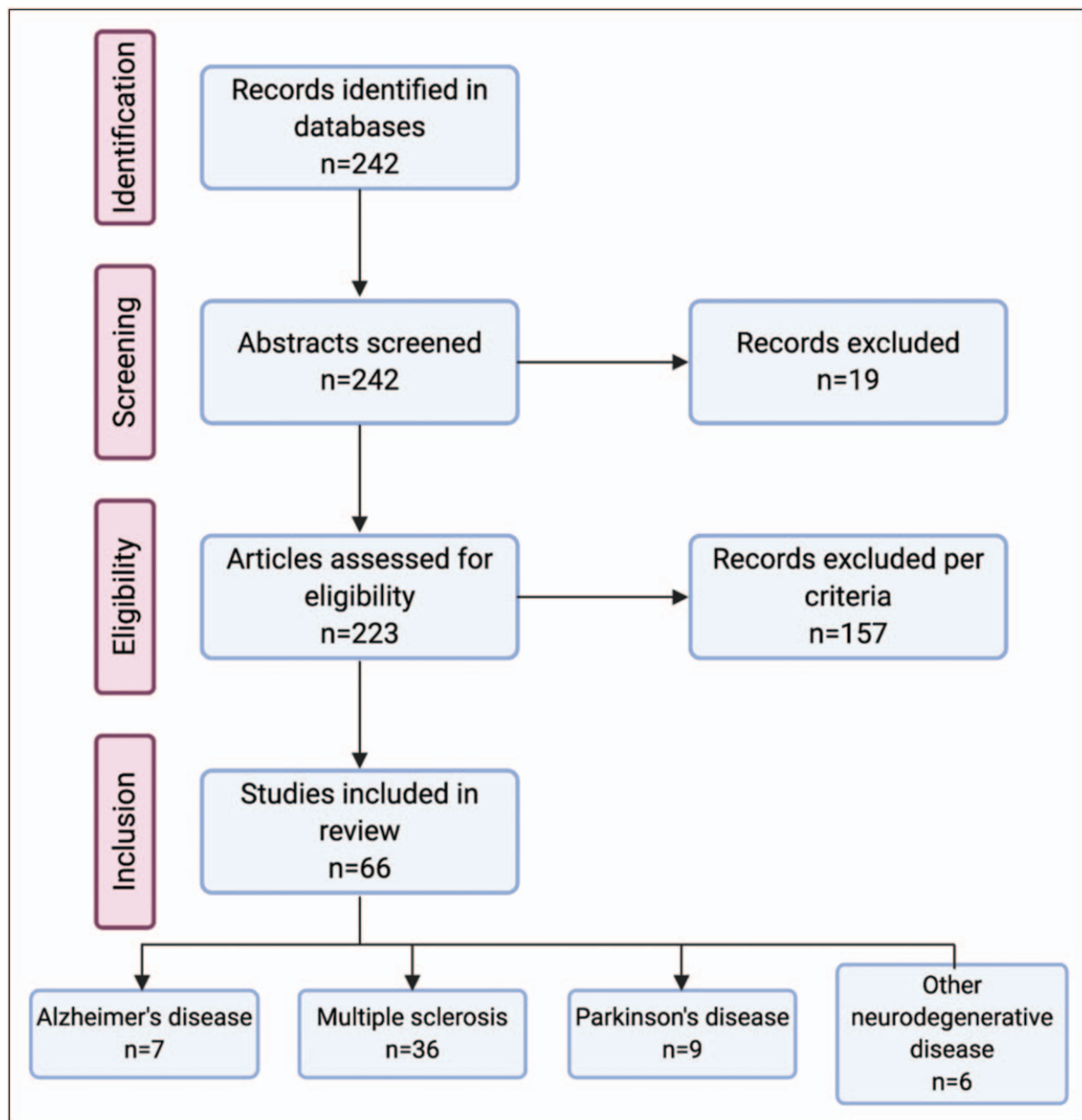
## CLINICAL REPORTS OF NEURODEGENERATIVE DISEASE AND CORONAVIRUS DISEASE 2019 IN THE LITERATURE TO DATE

According to recent studies, a large proportion of patients with COVID-19 have underlying NDDs, 9–16% [7,8]. Based on our selection criteria, 66 articles were included in the review. Nineteen articles report on patients with Alzheimer's disease or dementia, 36 on multiple sclerosis (MS), 10 on Parkinson's disease, and six on rare diseases or NDD in general.

### Alzheimer's disease

Alzheimer's disease affects an estimated 5 million Americans and is the most common form of dementia [9]. Patients with Alzheimer's disease may be more likely to present with atypical COVID-19 symptoms, such as diarrhea, altered mental status, poor functional status, or worsening preexisting neurologic deficits [10,11]. Up to 20% of older adults can present with altered mental status as the primary COVID-19 symptom [12]. Alzheimer's disease and patient with other types of dementia are also at higher risk for hospitalization and death according to numerous studies [11,13–21]. Most Alzheimer's disease patients have one or more high-risk comorbid medical conditions, which significantly contributes to increased risk of poor outcomes [13,14]. Even Alzheimer's disease patients who do not contract COVID-19 are at risk for worsening of neuropsychiatric symptoms during the pandemic due to isolation, psychosocial stressors, and lack of optimal care [22].

Significantly, an 18F-FDG PET study in two patients with prolonged anosmia demonstrated hypometabolism in the amygdala, hippocampus, parahippocampus, cingulate cortex, and pre/post-central gyrus. These findings are concerning since hypometabolism in these same areas is commonly seen in mild cognitive impairment and Alzheimer's disease [23]. In addition, hyposmia can be an early sign of Alzheimer's disease and is a prominent



**FIGURE 1.** PRISMA flow diagram of articles reviewed and included.

feature of COVID-19. The timing of Alzheimer's disease onset is affected by numerous genetic and environmental factors as well as oxidative stress, vascular disease, and neuroinflammation [24]. COVID-19 is associated with endotheliopathy and neuroinflammation in at least some individuals, though whether COVID-19 can precipitate or facilitate the onset of Alzheimer's disease in susceptible individuals is unknown.

### Parkinson's disease

Parkinson's disease is a common neurodegenerative condition that affects approximately 1 million

people in the United States [25]. Several patients with comorbid Parkinson's disease and COVID-19 have been reported in the literature [26–28]. Parkinson's disease patients have been found to exhibit atypical symptoms, such as poor mood, fatigue, anosmia, flushing, and joint pain, and in some cases may mimic a Parkinson's disease exacerbation [29]. Overall, the consensus is that Parkinson's disease patients with COVID-19 are at higher risk for significant worsening of motor symptoms and may require up-titration of their dopaminergic regimen [29,30,31,32]. However, preexisting Parkinson's disease alone does not impart an increased risk of hospitalization or death [13]. Only one study

reported a high mortality rate (40%) in an older patient cohort (mean 78 years old). Parkinson's disease patients with other comorbidities such as obesity, chronic obstructive pulmonary disease, and low vitamin D were also at higher risk [33].

One patient in the literature developed a parkinsonian syndrome associated with COVID-19 [34<sup>□</sup>]. The 58-year-old man had hyposmia as an initial symptom along with fever, cough, and dyspnea. Subsequently, he developed an asymmetric hypokinetic-rigid syndrome with generalized myoclonus, fluctuating mental status, and opsoclonus. MRI of the brain was normal, but a dopamine transport single photon emission computed tomography (DaT-SPECT) scan showed decreased presynaptic dopamine uptake asymmetrically in bilateral putamina. In Parkinson's disease patients, the DaT-SPECT typically shows decreased dopamine uptake and nigrostriatal cell loss along the nigrostriatal pathway in the substantia nigra pars compacta (SNc) and striatum [35]. This patient developed dysfunction of the nigrostriatal pathway at its termination in the putamen. The myoclonus resolved without treatment and his parkinsonism improved, but did not completely resolve at the time of publication [34<sup>□</sup>].

### Multiple sclerosis

MS is a neurodegenerative, autoimmune disease that affects nearly 1 million people in the United States [36]. It is common for MS patients to experience worsening of their preexisting neurological deficits in the setting of infection, and this has been reported in COVID-19 [37,38]. However, MS patients with severe disease requiring hospitalization during COVID-19 were more likely to have comorbid medical conditions, advanced age, obesity, significant disability, or progressive disease [38,39<sup>□□</sup>]. Early in the pandemic, there was a concern that MS patients immunosuppressed by disease modifying therapies (DMTs), would be at higher risk of poor outcomes related to COVID-19. Fortunately, this has not been borne out. Numerous case reports have demonstrated patients on rituximab or ocrelizumab, an anti-CD20 B-cell depleting mAb therapies, have better outcomes, experience mild-to-moderate symptoms, and rarely require hospitalization [40–49]. Significantly, several case reports have also demonstrated MS patients on ocrelizumab clear SARS-CoV-2, but do not always produce a measurable antibody response [41,47,50,51]. A few patients have been reported to mount IgG or IgA antibodies on anti-CD20 therapies [52,53]. Two case reports have described patients taking natalizumab who also experienced mild COVID-19 courses [54,55].

Generally, as reported to date in the literature, MS patients have experienced mild-to-moderate COVID-19 disease course and without evidence that DMT use increases the risk of hospitalization or death [38,56]. In fact, evidence showed MS patients on DMTs had milder symptoms compared with MS patients not on DMTs [39<sup>□□</sup>]. However, this finding may be skewed by the fact that patients who have discontinued DMT are more likely to have primary and secondarily progressive MS and greater baseline disability. Several case reports described severe disease in patients on fingolimod requiring hospitalization and respiratory support [37,57,58]. Significantly, one patient recovered well after tocilizumab administration and another patient's COVID-19 symptoms worsened significantly when fingolimod was stopped [58]. Only one report of two young patients, 22 and 26 years old, described asymptomatic COVID-19 infections while taking fingolimod [59]. One study reported severe COVID-19 symptomatology in the setting of alemtuzumab and cladribine when compared with interferon or glatiramer acetate [60]. However, two other case reports showed patients on alemtuzumab and cladribine who recovered without complication [61,62].

There have been several cases of demyelinating disease in the setting of COVID-19 reported in the literature, but only one case of MS diagnosis after a COVID-19 infection has been described [63<sup>□</sup>,64–66]. A 29-year-old female with COVID-19 presented with right optic neuritis and was found to have numerous demyelinating lesions of various ages. It was hypothesized that the patient's SARS-CoV-2 infection unmasked a case of undiagnosed MS, in turn leading to an MS flare.

### LINKS TO NEURODEGENERATIVE DISEASE PATHOGENESIS

The literature on NDD and COVID-19 will likely become more robust with time. It is important for all NDD patients to optimize their comorbidities to reduce the risk of severe disease. Patients with dementia are at particularly high risk for morbidity and mortality. It is vital to put new policies and produces in place to protect this vulnerable population. Significantly, Parkinson's disease and MS patients are generally not at high risk for severe disease, but COVID-19 may provoke new onset parkinsonism and demyelinating disease in rare cases. Given less than a year has passed since the pandemic started, it is too early to detect the onset of NDD due to COVID-19 patients; however, previously viral infections and inflammation have been strongly linked to the pathogenesis of Alzheimer's disease, Parkinson's disease, and MS.

## Alzheimer's disease

It is well known that both severe systemic and central nervous system infections can lead to permanent neurologic deficits. Memory, cognitive, and learning deficits, as well as behavioral changes have been reported following arboviral infections [67]. Severe sepsis in older adults is associated with a significant decline in cognitive function and functional status [68]. The extent of systemic inflammation correlates strongly with cognitive deficits. In the 6 months after an infection, TNF- $\alpha$ , a proinflammatory cytokine that is significantly elevated in severe COVID-19, has been associated with a two-fold increase in cognitive decline [69]. Another key inflammatory marker in COVID-19, IL-6, is significantly associated with hippocampal atrophy [70]. Analysis of the cerebrospinal fluid in patients with COVID-19 has revealed markedly elevated inflammatory levels, including IL-6, IL-8, IL-10, IP-10, and TNF- $\alpha$  [71,72]. The severe inflammation in COVID-19 is likely to impart long-lasting detrimental effects, similar to other causes of severe sepsis.

Many viruses have been implicated in  $\beta$ -Amyloid-42 (A $\beta$ 42) accumulation and other neuropathological features of Alzheimer's disease, including herpes simplex virus-1 (HSV-1), HSV-2, cytomegalovirus, Epstein-Barr virus (EBV), varicella zoster virus, hepatitis C virus, human herpes viruses-6 (HHV-6), and HHV-7 [73]. A $\beta$ 42 is a peptide with antimicrobial and antiviral properties. Majde *et al.* proposed a 'hit and run' mechanism where an infection activates astrocytes and induce microglia to release proinflammatory cytokines and chemokines, which then stimulates A $\beta$ 42 release [74,75]. At some point, the inflammatory response becomes dysregulated and A $\beta$ 42 misfolds and accumulates. Misfolded A $\beta$ 42 and antigen from a new viral infection can bind to and activate microglia leading to additional proinflammatory cytokine and chemokine release. This creates a positive feedback cycle that stimulates chronic neuroinflammation and further neuronal damage and loss [75,76]. On pathology, HHV-6 and HHV-7 has been detected at higher levels in the brains of Alzheimer's disease patients compared with controls suggesting chronic infection is present in many individuals [77].

Heneka *et al.* [78] hypothesize that the dramatic inflammation of COVID-19 strongly induces the neurodegenerative process through the upregulation of the NLRP3 inflammasome-mediated pathway, a component of the innate immune system. The NLRP3 inflammasome leads to the accumulation of A $\beta$ 42 and formation of neurofibrillary tangles and has been proposed as a disease modifying target for both Alzheimer's disease and Parkinson's

disease prevention [78,79]. The NLRP3 inflammasome is also a suspected culprit in propagating the cytokine storm seen in COVID-19 and could also contribute Alzheimer's disease pathogenesis in patients with severe disease [80,81]. In addition, patients with *apoE4* gene have an increased risk for developing Alzheimer's disease and a vulnerability to HSV-1 infections and patients with both are at significantly increased risk for developing Alzheimer's disease [76,82]. This suggests that the interplay between genes, infections, and neuroinflammation is critical to the pathogenesis of Alzheimer's disease. It is unknown based on current studies whether COVID-19 may trigger the onset of NDD in susceptible individuals, but neuroinflammation may be a trigger for some of the pathogenetic pathways that eventually manifest as Alzheimer's disease.

## Parkinson's disease

Several viruses have been implicated in the pathogenesis of Parkinson's disease, including influenza, coronavirus, herpes viruses, coxsackievirus, Japanese encephalitis virus, St. Louis encephalitis virus, West Nile virus, and HIV [83]. Hawkes *et al.* [84] hypothesize that Parkinson's disease patients undergo a 'dual-hit', where a neuroinvasive virus enters the nervous system and triggers immune dysregulation and propagation of abnormal protein accumulation.  $\alpha$ -Synuclein ( $\alpha$ Syn) is an antimicrobial peptide that is secreted in response to infection and along with its infectious target can be transported retrograde from an infected organ into the central nervous system along cranial nerves, including the olfactory and vagus nerves. Cell autophagy and lysosomal degradation are critical components of the innate immune system and viruses often target this pathway to impair the cell's ability to degrade or recycle pathogenic or cellular materials [85]. By hijacking this pathway, viruses can cause the inadvertent aggregation of intracellular proteins, such as  $\alpha$ Syn, which over time may lead to NDD. Genetic and environmental factors predispose certain patients to develop Parkinson's disease [86].

It is plausible that systemic and neuroinflammation and altered immune response associated with COVID-19 could induce Parkinson's disease in susceptible patients. Parkinson's disease has been found in 'clusters' of persons living or working in close quarters, suggestive of a shared infectious insult [83]. In fact, antibodies to common coronaviruses have been detected at significantly higher levels in the cerebrospinal fluid of Parkinson's disease patients compared with controls [87]. In murine models, H5N1 influenza virus induced

microglial activation followed by  $\alpha$ Syn aggregation and significant loss of SNc dopaminergic neurons [88]. The 1918 influenza A pandemic was followed by an outbreak of encephalitic lethargica, parkinsonian type, which is characterized by resting tremor, bradykinesia, and catatonia. Amantadine and memantine, NMDA receptor antagonists and antiviral agents, have long been used to treat the tremor of Parkinson's disease. In an observational study, five Parkinson's disease patients taking adamantanes who tested positive for SARS-CoV-2 had asymptomatic courses and no change in neurologic symptoms, suggesting a possible protective effect of adamantanes against COVID-19 [28]. The regular use of NSAIDs was also found to be protective against developing Parkinson's disease [89]. Inflammatory mediators associated with onset and progression of Parkinson's disease include IL-1, IL-2, IL-4, IL-6, IL-10, TNF- $\alpha$ , IFN- $\gamma$ , transforming growth factor- $\alpha$ , IL-6, MMP-3, IL-17, and IL-18, many of which are elevated in COVID-19 [90]. High concentrations of IL-1 $\beta$  and TNF- $\alpha$  have been shown to be toxic to the SNc and therapies targeting TNF- $\alpha$  have been proposed to treat Parkinson's disease [91].

Many have highlighted the hyposmia link between Parkinson's disease and COVID-19 [92-94]. Anosmia or hyposmia is characteristic of early Parkinson's disease and a prevalent symptom in COVID-19 [86,93]. It is hypothesized that SARS-CoV-2 can enter the central nervous system via the olfactory nerve [94]. An MRI study of a patient with anosmia in the setting of COVID-19 showed a subtle hyperintensity of the olfactory bulb when symptomatic [95]. One month later the hyperintensity resolved and the olfactory bulbs were notably smaller, providing evidence for resolved edema and possible viral invasion. Another study noted hyperintensity of the olfactory bulb on MRI in five patients with COVID-19. Only three of the patients had anosmia, which suggests neuroinflammation or neuroinvasion may be present without hyposmia. It is currently unknown whether inflammation and/or damage to the basal ganglia associated with COVID-19 predisposes patients to develop Parkinson's disease.

### Multiple sclerosis

There is a strong correlation between viral infections and new onset MS as well as MS flares [96,97]. HHVs, including EBV and HHV-6, have been shown to increase the risk of developing MS in vulnerable individuals [98]. Human coronavirus, HCoV-OC43 specifically, has been found in the cerebrospinal fluid and brains of MS patients at significantly higher rates than controls [99,100]. The pathogenesis of MS is still unknown, but the heterogeneity

seen both clinically and pathologically alludes to multiple possible mechanisms of immune dysfunction. The 'bystander' theory hypothesizes the secretion of proinflammatory cytokines and upregulation of inflammation during a viral infection may be neurotoxic and inadvertently lead to demyelination [99]. Coronaviruses have been shown to stimulate astrocytes and microglia to produce inflammatory mediators, including IL-6 and TNF- $\alpha$  [101]. The molecular mimicry theory hypothesizes viruses share epitopes which cross react with myelin stimulating autoreactive T-cell and/or B-cell production and ultimately leading to demyelination [102]. Autoreactive T cells in MS patient have been shown to cross-react with both HCoV-OC43 antigen and myelin basic protein validating this theory [103]. In addition, antibodies in MS patients have been shown to cross react with EBV antigen and myelin basic protein and to reliably trigger experimental autoimmune encephalitis in murine models [104]. The presence of persistent virus or viral proteins may continue to stimulate the immune system and perpetuate chronic demyelination.

Several cases of demyelinating disease have been reported in connection with COVID-19. To date, it is unclear whether COVID-19 can predispose patients to relapsing-remitting and progressive MS or whether it only triggers monophasic demyelinating events such as postviral transverse myelitis and acute demyelinating encephalomyelitis. Further studies elucidating the pathophysiology of COVID-19 and central nervous system demyelination will be critical in preventing neurologic damage in susceptible individuals.

### STRENGTHS AND LIMITATIONS

The current review is based on a comprehensive and systematic review of the literature available to date. The review is limited by the number of cases reported, the lack of systematic studies to date, and the short-term follow-up of individuals with acute COVID-19 given the recent onset of the pandemic. Longitudinal systematic studies and disease registries to examine the long-term neurologic effects of acute COVID-19 are warranted to fully understand the implications of COVID-19 for the development and progression of neurodegenerative diseases.

### CONCLUSION

The findings of this systematic review suggest that patients with underlying dementia who contract COVID-19 are at high risk for hospitalization and death. Additional precautions and protective

measures should be put in place to prevent infections and optimize aggressive COVID-19 care for this vulnerable population. In addition, it will be important to address modifiable comorbidities in these patients to reduce the risk of severe disease. Lastly, viral infections and the related inflammation have been associated with the pathogenesis of Alzheimer's disease, Parkinson's disease, and MS, suggesting potential links between COVID-19 and the risk of developing NDD in susceptible individuals. Further research and longitudinal studies are needed to determine if COVID-19 can trigger Alzheimer's disease, Parkinson's disease, or MS in the postinfectious period.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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