NEUROLOGICAL AND NEUROSCIENTIFIC EVIDENCE IN AGED COVID-19 PATIENTS

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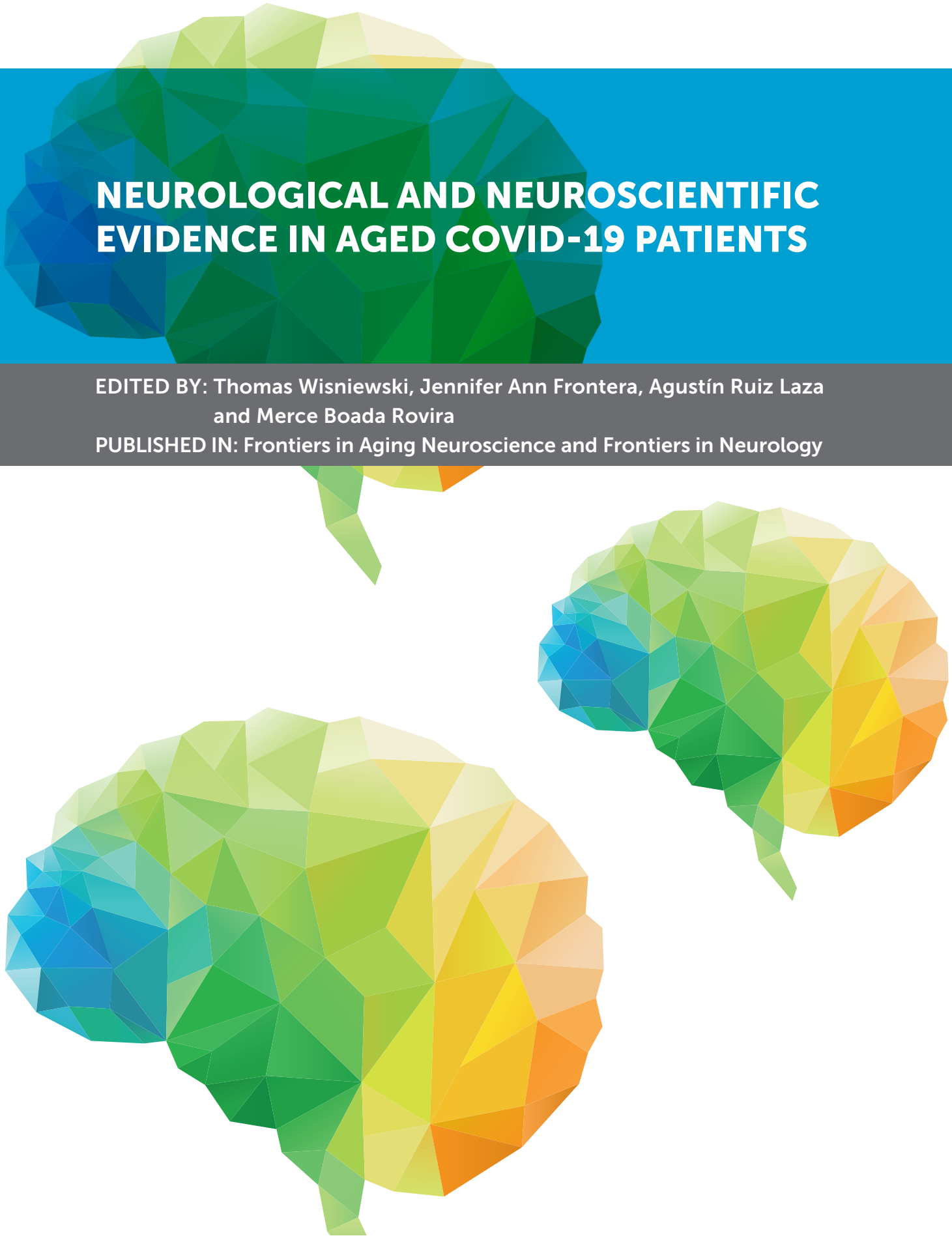
PUBLISHED IN: Frontiers in Aging Neuroscience and Frontiers in Neurology



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ISSN 1664-8714
ISBN 978-2-88971-838-2
DOI 10.3389/978-2-88971-838-2

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NEUROLOGICAL AND NEUROSCIENTIFIC EVIDENCE IN AGED COVID-19 PATIENTS

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Citation: Wisniewski, T., Frontera, J. A., Laza, A. R., Rovira, M. B., eds. (2021). Neurological and Neuroscientific Evidence in Aged COVID-19 Patients. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88971-838-2

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frontiers in Aging Neuroscience

EDITORIAL
published: 18 October 2021
doi: 10.3389/fnagi.2021.774318

Editorial: Neurological and Neuroscientific Evidence in Aged COVID-19 Patients

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Keywords: COVID-19, SARS-CoV-2, aging, dementia, neurodegeneration

Editorial on the Research Topic

Neurological and Neuroscientific Evidence in Aged COVID-19 Patients

The COVID-19 pandemic has touched hundreds of millions of lives worldwide and has had a particularly devastating effect on the elderly, those with pre-existing dementia or neurodegenerative disease and their caregivers. In this special Research Topic of *Frontiers in Aging Neuroscience*, we focus on the epidemiology and mechanisms of new or worsened cognitive impairment following SARS-CoV-2 infection and the implications of post-acute cognitive sequelae of COVID.

In comprehensive reviews, Kalra et al., and Alonso-Bellido et al. outline the spectrum of acute neurological events that have been reported among COVID-19 patients ranging from rare occurrences of acute disseminated encephalomyelitis, myelitis, or Guillain Barre Syndrome and its variants, to more commonly reported events of ischemic or hemorrhagic stroke. In a similar vein, Pavlov et al. report three typical cases of intracerebral hemorrhage following SARS-CoV-2 infection. In a retrospective review of prospectively collected data, Dhillon et al. identified 23/1,243 (2.3%) hospitalized COVID-19 patients with neurological disorders including confusion/delirium, seizures, stroke, movement disorders, peripheral nervous system disorders, and exacerbations of underling neurological conditions, such as multiple sclerosis.

The prevalence of specific acute neurological events appears to vary by age. In a systematic review and meta-analysis, Sullivan and Fischer evaluated 239 articles including 2,307 laboratory confirmed COVID-19 patients, 20% of whom had asymptomatic or mild disease. The most common new neurological events in individuals over age 50 were cerebrovascular events (50%), followed by smell/taste disorders in 24%. In contrast, patients aged 19–50 were most likely to experience smell/taste disorders (78%), with cerebrovascular events occurring in only 11%. Pediatric patients (aged $<$ 19 years) developed smell/taste disorders in 45%, CNS inflammatory disease in 18% and cerebrovascular events in 13%. Similarly, in an observational, retrospective cohort study of 148 COVID-19 patients, Davidescu et al. reported that symptoms of stroke and confusion were more common in those aged $\geq$ 65 years, while headache was the most common complaint among those <65 years old. Higher death rates were reported in older individuals.

Aside from age, underlying dementia plays a role in the types of neurological complications encountered in COVID-19. Alonso-Lana et al. note in their review that dementia patients often present with atypical COVID symptoms including worsening of baseline confusion/disorientation or functional status or new or worsened behavioral symptoms. Indeed, increased confusion may be the first symptom of COVID-19 among demented patients. In a multicenter, observational, case-control study, Pisaturo et al. matched 23 COVID-19 patients with dementia to 46 non-demented COVID-19 controls who were similar in age, sex, PaO_2/FiO_2 ratio and number of comorbidities. Sixty percent of patients with pre-existing dementia exhibited signs and symptoms of delirium,

Edited and reviewed by:
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Received: *11 September 2021*
Accepted: *23 September 2021*
Published: *18 October 2021*

Citation:
Frontera JA and Wisniewski T (2021) Editorial: Neurological and Neuroscientific Evidence in Aged COVID-19 Patients. Front. Aging Neurosci. 13:774318. doi: 10.3389/fnagi.2021.774318

compared to only 2% of non-dementia controls ($P < 0.001$). Dementia patients were more likely to have severe COVID disease and die in-hospital than controls.

In the post-acute setting, neuropsychiatric and cognitive complications of COVID-19 can persist for months. A review by Alonso-Lana et al. highlights the frequent occurrence of persistent post-acute sequelae including anxiety, depression, sleep impairment and post-traumatic stress disorder among survivors of hospitalization for COVID. In a cross-sectional survey of 999 adults across the U.S., 8% reported having COVID (none were hospitalized) and 25% of these patients reported having prolonged COVID-19 symptoms lasting a median of 4 months (range 1–13 months), according to a report by Frontera et al. Among those with a history of long COVID, the most common persistent neuropsychiatric symptoms were anxiety (53%), brain fog/difficulty concentrating/forgetfulness (47%), and headache (47%). However, symptoms of anxiety, headache, brain fog, fatigue, depression, and difficulty sleeping were also reported in >20% of patients *without* a history of COVID. Furthermore, low self-reported scores on NIH Neuro-Quality of Life Metrics for cognition, fatigue, anxiety, depression and sleep occurred in ∼30% of COVID-negative respondents, underscoring the contribution of pandemic related stressors to symptomatology. Indeed, 68% of respondents reported at least one socio-economic stressor in the prior month (most commonly social isolation, financial insecurity, fear of illness, and political conflict with family/friends) and 29% of respondents reported serious pandemic-related stressors (including unemployment, financial insecurity, food insecurity, or homelessness). In multivariable analysis, after adjusting for demographics and socio-economic stressors, respondents with a history of COVID still had significantly worse Neuro-QoL scores for subjective cognitive dysfunction compared to COVID-negative respondents, highlighting the relationship between SARS-CoV-2 and protracted cognitive abnormalities. No differences were identified in multivariable analyses for Neuro-QoL scores for anxiety, depression, fatigue, or sleep based on COVID status.

While indirect COVID-19 pandemic-related stressors appear to affect a wide age spectrum of the population, the impacts of social isolation, limited access to medical support systems, and financial strain, are particularly severe for dementia patients and their caregivers even in the absence of SARS-CoV-2 infection. In a survey of 4,913 COVID-negative patients with Alzheimer's dementia, dementia with Lewy bodies, frontal-temporal dementia, and vascular dementia, Rainero et al. report worsening cognitive function in 55% of patients and aggravation of behavioral symptoms in 52% of patients, underscoring the deleterious effects of quarantine. In a review by Hu et al. the authors point out that that pandemic-related safety and logistical issues have compromised diagnostic testing, clinical trial participation and access to therapeutics among those living with neurodegenerative diseases. Similarly, caregivers of dementia patients have reported increased anxiety, depression and distress. In a report by Zucca et al., 90% of caregivers reported at least one symptom of stress and 30% reported four or more symptoms. Risk factors for caregiver burnout were primarily related to relationship conflicts with the patient and pandemic-related interruptions in medical assistance. Compounding these issues, community stressors can lead to sleep deprivation, circadian rhythm disruption and reduced sleep quality, all of which impair immune responses and place older patients and those with underlying sleep disorders, such as obstructive sleep apnea, at higher risk for contracting or dying from SARS-CoV-2, according to a review by Pires et al.

In order to prevent or treat cognitive sequelae from SARS-CoV-2 infection, it is important to understand risk factors and underlying mechanisms of neurovirulence, particularly among vulnerable populations including the elderly and those with underlying neurodegenerative disease. Mainali and Darsie reviewed risk factors for death among older COVID-19 patients and identified pre-existing chronic neurological illness, sleep disturbance, anxiety, depression, immunosenescence, and inflammaging (i.e., increased susceptibility to hyperinflammation with age) as major contributors to COVID severity in the elderly. In a systematic review of neuroimaging and neuropathological findings among older COVID-19 patients (aged > 60 years), Manca et al. noted prominent imaging and pathological evidence of cerebrovascular injury, hypoperfusion, inflammation and cellular damage, particularly along white matter tracts, in the brainstem and frontal-temporal regions. Ganji and Reddy contributed a review addressing the contribution of virus-related mitochondrial injury to disease severity in older individuals. The ACE-2 receptor, which the SARS-CoV-2 virus utilizes for cell entry, is instrumental for mitochondrial function. A paucity of available ACE-2 receptors due to SARS-CoV-2 binding correlates with decreased ATP production. As mitochondria divert to production of radical oxygen species (ROS) in response to viral invasion, this stimulates additional downstream inflammatory responses, cell membrane permeability, and eventual apoptosis. As individuals age, the normal breakdown of mitochondria (mitophagy) occurs less frequently, leading to an accumulation of aged mitochondria that no longer produce energy efficiently. Without mitophagy, levels of ROS rise contributing to oxidative stress, tissue damage and hyperinflammation, which can exacerbate the hyperinflammatory response already present with COVID. Mitochondrial iron storage is also imbalanced in the context of SARS-CoV-2-induced elevated ferritin levels. Raha et al. have further explored the relationship of iron homeostasis and its relationship to SARS-CoV-2 susceptibility. The authors specifically evaluated hepcidin, a hormone involved in systemic iron homeostasis, which also has a role in innate immune responses against viruses. In their study of serum and post-mortem brain samples, they identified co-localized hepcidin and IL-6 in epithelial cells of the choroid plexus, meningeal macrophages and in astrocytes near the endothelium of brain blood vessels of AD and Down's syndrome patients. The authors hypothesized that these patients may be at higher risk for SARS-CoV-2 infection due to imbalanced iron homeostasis and failure of amyloid clearance, leading to neuro-inflammation.

In conclusion, while this topic broadly covers the current COVID-19 literature related to neurological events in the aging and dementia, in this rapidly changing field new

discoveries are emerging on a daily basis. The full spectrum of post-acute neurological and cognitive sequelae of COVID-19 and mechanisms of neurological injury are still being elucidated. As our understanding of the neurovirulence of SARS-CoV-2 evolves, it will be important to contextualize the impact of COVID in vulnerable populations, such as the elderly and those with neurodegenerative diseases. Understanding trajectories of cognitive recovery or decline may help guide therapeutic interventions and identify specific targets of pharmacological and rehabilitative interventions.

AUTHOR CONTRIBUTIONS

JF drafted the manuscript. TW critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

JF and TW received funding from NIH/NIA grant P30AG066512-01S1 to study neurodegenerative serum biomarkers in hospitalized COVID-19 patients. Dr. Frontera receives funding from NIH/NHLBI 1OT2HL161847-01 and NIH/NINDS 3U24NS11384401S1 for COVID-19 related research.

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frontiers in Aging Neuroscience

CASE REPORT
published: 22 October 2020
doi: 10.3389/fnagi.2020.600172

COVID-19-Related Intracerebral Hemorrhage

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Intracerebral hemorrhage (ICH) is a common and severe neurological disorder and is associated with high rates of mortality and morbidity. ICH is associated with old age and underlying conditions such as hypertension and diabetes mellitus. The COVID-19 pandemic is associated with neurological symptoms and complications including ICH. For instance, the mechanisms by which COVID-19 may contribute to hemorrhagic stroke may include both depletion of angiotensin converting enzyme 2 (ACE2) receptor and overactive immune response. In this study, we herein report three patients (0.25%) out of 1200 admissions with COVID-19 to our center between 1 May and August 4, 2020, who developed ICH. In addition, we will briefly discuss the possible pathophysiological mechanisms of COVID-19 infection in patients with ICH.

Keywords: COVID-19, intracerebral hemorrhage, pathophysiological mechanisms, neurological consequences, complications

OPEN ACCESS

Edited by:
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Received: *29 August 2020*
Accepted: *28 September 2020*
Published: *22 October 2020*

Citation:
Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A and Aliev G (2020) COVID-19-Related Intracerebral Hemorrhage. Front. Aging Neurosci. 12:600172. doi: 10.3389/fnagi.2020.600172

INTRODUCTION

Coronavirus infection 2019 (COVID-19) is a dangerous infectious disease that occurs as an acute respiratory viral infection with specific complications, which may include pneumonia, which leads to acute respiratory distress syndrome or respiratory failure with a high risk of death. Among the main complications of COVID-19 on the nervous system are encephalopathy, encephalitis, acute disseminated encephalomyelitis, meningitis, ischemic stroke, and intracerebral hemorrhage (ICH) and other diseases (Kannan et al., 2020). A growing number of case reports and series have been published describing the clinical characteristics of patients with ICH and COVID-19 (**Table 1**). The clinical course of COVID-19 is most severe in the elderly, and in patients with concomitant diseases such as hypertension and diabetes mellitus (DM), which are known to be the main factors in the development of ICH (Divani et al., 2020). Stroke has been reported as a complication of COVID-19. Most strokes among COVID-19 patients are arterial ischemic, though ICH has also been reported. We present three cases of ICH among patients hospitalized with COVID-19 from 1 May to August 4, 2020. ICH represented an infrequent complication among patients hospitalized with COVID-19 at our center, and patients with COVID-19 and ICH had other risk factors for ICH. However, our patients along with others in the literature suggest that several mechanisms may contribute to ICH in the setting of COVID-19.

TABLE 1 | Summary of published cases of COVID-19-related ICH.

Study	Total COVID-19, n	Patients with ICH, n	Vascular risk factors	Mortality rate,%
Reddy et al., 2020	47	1	Hypertension	0%
Li et al., 2020	221	1	Not reported	100%
Morassi et al., 2020	6	2	Hypertension and thrombocytosis	100%
Al-olama et al., 2020	1	1	Meningoencephalitis	100%
Bao et al., 2020	1	1	None	0%
Benger et al., 2020	5	5	Hypertension, IHD, T2DM, and anticoagulant therapy	0%
Sharifi-Razavi et al., 2020	1	1	Not reported	Not Reported
Haddadi and Shafizad, 2020	1	1	Hypertension and diabetes	0%
Khattar et al., 2020	1	1	Hypertension	100%
Kvernland et al., 2020	4071	16	Hypertension, and anticoagulant therapy	63%
Daci et al., 2020	1	1	None	100%
Poyiadji et al., 2020	1	1	Not reported	Not Reported
Hernández-Fernández et al., 2020	1683	5	Hypertension, dyslipidemia, and T2DM	20%
Shahjouei et al., 2020	26,175 (156 stroke patients)	25	Hypertension, IHD, and T2DM	Not Reported
Ghani et al., 2020	3	3	Hypertension, anticoagulant therapy and T2DM	100%
Al-Dalahmah et al., 2020	1	1	Not Reported	100%
Gogia et al., 2020	1	1	Hypertension and dyslipidemia	100%
Nawabi et al., 2020	18	6	Hypertension and diabetes	Not Reported
Kim et al., 2020	1	1	Hypertension	0%
Dogra et al., 2020	755	33	Hypertension, dyslipidemia, T2DM, and anticoagulant therapy	42%

ICH, intracerebral hemorrhage; IHD, Ischemic heart disease; T2DM, Type 2 diabetes mellitus.

MATERIALS AND METHODS

Ethics Approval and Consent to Participate

The study protocol was approved by the Hospital COVID-19 Clinics BSMU in Ufa, Russia. (Within the department of Neurosurgery), Clinic of the Bashkir State Medical University, Ufa, Republic of Bashkortostan, Russia. All research was performed in accordance with Bashkir State Medical University guidelines and regulations, and the respective authors declare a statement confirming that informed consent was obtained from all of the participants' parents and/or their legal guardians. In addition to the guidelines described above, the authors of these manuscripts dealing with human transplantation research attesting that no organs/tissues were procured from prisoners.

Human and Animal Rights

No animals were used for studies that are base of this research. All the humans used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013[1].

We performed a retrospective chart review of all hospitalized cases with confirmed COVID-19 infection and ICH between May 1 and August 4, 2020 seen at Hospital COVID-19 Clinics BSMU in Ufa, Russia. Diagnosis of ICH was confirmed on neuroimaging with computed tomography (CT) of the brain. COVID-19 infection nucleic acid tests were performed on nasopharyngeal swabs using quantitative real-time polymerase chain reaction (qRT-PCR). Patients were included in the case series if they had tested positive for COVID-19 prior to their ICH and had continuing clinical features related to COVID-19. Inclusion criteria were defined as patients with acute ICH on CT neuroimaging and additional radiological assessment of the chest who were positive for COVID-19 and suffered from acute neurological symptoms during a hospital stay. Each of the scans had an electronic clinical and, if applicable, pathology report associated with it. Electronic reports were reviewed to extract clinical, laboratory, pathology, and demographic data. Patients were excluded if they had a secondary ICH from the hemorrhagic transformation of ischemic infarction, brain tumor, cerebral aneurysm, or vascular malformation. Baseline patient characteristics were retrieved from medical records, including symptom onset, Glasgow Coma Scale (GCS), and modified Rankin Scale (mRS) at last medical evaluation or at discharge. Additionally, vascular risk factors (hypertension, dyslipidemia and DM), laboratory parameters (C-reactive protein, D-dimer, etc.), and invasive procedures such as craniotomy from patients' clinical records and follow-up CT were obtained. Any missing or uncertain records were collected and clarified through direct communication with health care clinicians.

RESULTS

A total of 1200 patients with COVID-19 were hospitalized during the 65-day study; of these, we identified three patients (0.25%) who presented with radiographic evidence of ICH and qRT-PCR-confirmed COVID-19 infection. We describe their clinical

[1]http://ethics.iit.edu/ecodes/node/3931

characteristics, laboratory data, imaging findings, and clinical course (**Table 2**).

CASE PRESENTATION

Patient 1

A 50- year-old male with well-controlled hypertension presented with a 2-week history of cough, fever and fatigue. A CT chest study demonstrated bilateral ground-glass opacities consistent with COVID-19 pneumonia (**Figure 1A**). One week post-admission, he became drowsy with new severe headache, right-sided hemiplegia, and right-sided hemihypesthesia. A CT head examination demonstrated an ICH in the parietal-occipital region on the left with a breakthrough of blood into the ventricular system requiring craniotomy and evacuation (**Figure 1D**). An intracranial CT angiogram (CT-A) was normal. At the time of ICH detection, INR, APTT, platelets and fibrinogen were normal, and the patient was receiving a prophylactic dose of low molecular weight heparin (LMWH). After a 3-week admission, patient was discharged to a rehabilitation center for further therapy.

Patient 2

A 64-year-old male was hospitalized for COVID-19 pneumonia (7 days history of cough, fever and fatigue) treatment. A CT chest showed typical COVID-19 pneumonia changes (**Figure 1B**). He had a history of multiple, hypertension and type 2 diabetes mellitus. On day three of hospitalization, he developed left hemiparesis. He had a GCS score of 13 and a blood pressure of 210/90. CT of the brain showed ICH in the projection of the basal ganglia on the right, which did not require surgical intervention (**Figure 1E**). CT-A of the brain was normal. The patient was admitted to the hyper-acute stroke unit (HASU) for further care. After a 2-week admission, he was discharged to a rehabilitation center for further therapy.

Patients 3

A 60-year-old male with a history of hypertension, type 1 diabetes mellitus and hyperlipidemia, presented with a 5 days

TABLE 2 | Baseline characteristics of patients COVID-19 with new onset of ICH during infection.

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	56	64	60
Sex	Male	Male	Male
Smoking history	Yes	Yes	No
Blood pressure (mm Hg) (at the time of ICH detection)	160/80	210/90	165/89
Blood glucose (4.0–5.4 mmol/L)	6.0	11.0	16.8
Red blood cells count (4.5–5.7 $\times$ 10^{12}/L)	3.8	3.0	2.8
Hemoglobin (115–160 g/L)	96	68	75
Erythrocyte Sedimentation Rate (ESR) (<20 mm/h)	18	27	21
White blood cells count (4.0–11.0 $\times$ 10^{9}/L)	14.8	15.0	15.2
Neutrophils (1.8–7.5 $\times$ 10^{9}/L)	12.5	12.3	14.8
Lymphocytes (1.5–4.0 $\times$ 10^{9}/L)	1.8	1.6	3.8
Eosinophils (0.0–0.4 $\times$ 10^{9}/L)	0.0	0.0	0.1
Monocytes (0.2–0.8 $\times$ 10^{9}/L)	1.2	0.6	0.5
Basophils (0.0–0.15 $\times$ 109/L)	0.0	0.1	0.0
Platelet count (150–450 $\times$ 109/L)	220	334	480
Creatinine (45–120 mmol/L)	66	138	130
Bilirubin, total (3–20 umol/L)	18	12	37
Total cholesterol (<5.2 mmol/L)	4.8	3.5	8.2
High-density lipoprotein (HDL) (>1 mmol/L)	1.3	1.1	1.8
Low-density lipoprotein (LDL) (<3.4 mmol/L)	2.8	3.5	5.17
D-Dimer (<500 ng/mL)	1820	2580	4000
Fibrinogen (2.0 to 4.0 g/L)	2.8	3.6	6.5
Activated partial- thromboplastin time (aPTT) (20–35 s)	22	25	21
International Normalized Ratio (INR) (0.85–1,15 ratio)	1.0	1.1	1.1
C-reactive protein (<5 mg/L)	88	120	189
Type of patients with COVID-19 (severe/non-severe)	Severe	Severe	Severe
Risk factors	Hypertension	Type 2 diabetes, hypertension	Hypertension, type 1 diabetes, high cholesterol,
The time between the onset of COVID-19 infection and onset of ICH (days)	21	10	12
Location of hematoma	Parietal-occipital region on the left with a breakthrough of blood into the ventricular system	In the projection of the basal ganglia on the right	In the projection of the basal ganglia on the right with a breakthrough into the ventricular system and a median dislocation to the left
Modified Rankin Scale (mRS, 0–6) (discharge)	4	2	5

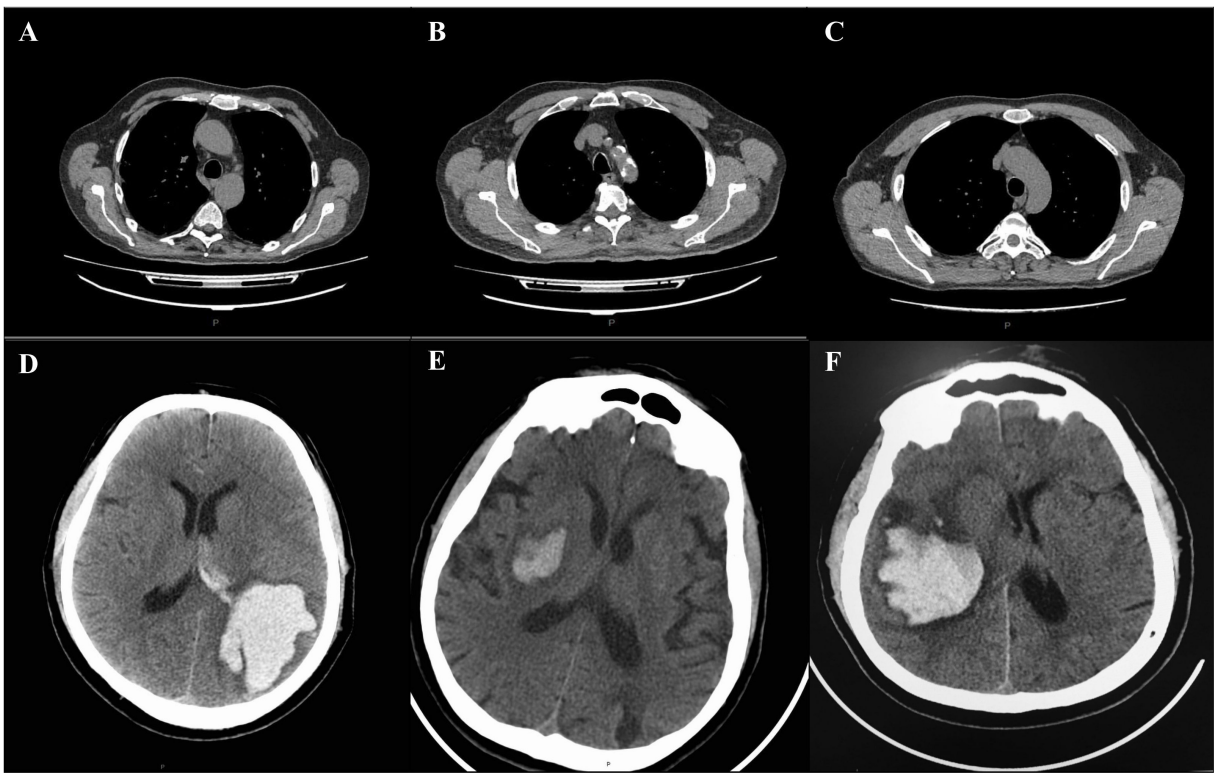

FIGURE 1 | CT changes of lung and brain in patients with COVID-19 complicated with ICH **(A–F)**. Chest and brain CT examination of patient 1 showing bilateral consolidations and ground-glass opacities of the lungs **(A)**, and hemorrhage in the parietal- occipital region on the left with a breakthrough of blood into the ventricular system **(D)**. Chest and brain CT examination of patient 2, showing diffuse bilateral ground-glass opacities involving both lungs **(B)** and hemorrhage in the projection of the basal ganglia on the right **(E)**. Chest and brain CT examination of patient 3, demonstrating bilateral ground-glass opacities **(C)** and hemorrhage in the projection of the basal ganglia on the right with a breakthrough into the ventricular system **(F)**. P = posterior.

history of shortness of breath, cough, fevers, and pleuritic chest pain. A CT chest study demonstrated bilateral ground-glass opacities consistent with COVID-19 pneumonia (**Figure 1C**). Clinical and laboratory evaluation showed moderate respiratory distress (PaO2/FiO2 190). The respiratory function progressively worsened during the following days and, on day six, he was transferred to an intensive care unit (ICU) for invasive ventilation. The next day, the patient was found with bilaterally fixed and dilated pupils, with a GCS of 3. Brain CT examination showed a new ICH in the projection of the basal ganglia on the right with a breakthrough into the ventricular system requiring craniotomy and evacuation (**Figure 1F**). The ventricles were displaced across the midline. CT-A of the brain was normal. Coagulation tests were normal. A total of 6 weeks post-admission the patient remains on ICU, receiving multiple organ support.

DISCUSSION

We report three cases with severe COVID-19 infection who developed an ICH. Therefore, the question is whether COVID-19 infection is the cause of ICH, or is it a coincidence with ICH. All patients had risk factors for ICH like hypertension and DM. During the penetration of COVID-19 into the cells of the body, angiotensin-converting enzyme 2 (ACE2) plays a crucial role (Weimar and Kleine-Borgmann, 2017). Through ACE2, not only does the viral infection penetrate into the cell, but with COVID-19, the expression of ACE2 decreases, which leads to dysfunction of the renin-angiotensin-aldosterone system (RAAS) and damage to the lungs and other organs and systems (Weimar and Kleine-Borgmann, 2017). A decrease in ACE2 expression can increase the risk of ICH in several ways: (1) a decrease in ACE2 expression can increase local Angiotensin II (Ang II) levels, which, acting on AT1 receptors, can increase blood pressure; (2) ACE2 deficiency in the CNS can lead to endothelial dysfunction in the cerebral vessels, leading to an increase in the risk of a cerebral hemorrhage; (3) A decrease in ACE2 expression will also lead to a decrease in Ang (1–7) generation and depression of Ang (1–7)/MasR signaling, thereby preventing its vasodilatory, neuroprotective, and antifibrotic effects (Weimar and Kleine-Borgmann, 2017; Benger et al., 2020; South et al., 2020). Therefore, it is reasonable to conclude that COVID-19 may exacerbate hypertension and increase the risk of ICH in patients.

Diabetes mellitus is also an independent risk factor for the development of ICH. Several biological mechanisms could explain the observed association between high glucose and ICH. High glucose could impair normal endothelial function, and subsequently lead to brain small vessel disease (SVD).

Degenerative changes in the walls of brain small vessels could cause ICH (Boulanger et al., 2016). Moreover, the rate of ICH in DM patients with the hypertension is higher than those without hypertension (Benger et al., 2020). Both hyperglycemia and hypertension can induce the risk factors to act on the brain vessels and to make them easy to be ruptured. DM is a chronic inflammatory condition characterized by multiple metabolic and vascular disorders that can influence our response to infection pathogens, in particular COVID-19 (Boulanger et al., 2016). Hyperglycemia and insulin resistance increase the synthesis of proinflammatory cytokines, oxidative stress, and stimulate the production of adhesion molecules that mediate tissue inflammation (Tadic et al., 2020). This inflammatory process may be one of the main mechanisms that lead to a higher propensity for COVID-19, with worse consequences in DM patients (Tadic et al., 2020). Indeed, the available data indicate that DM ranks second after hypertension among confirmed COVID-19 cases with major chronic diseases (Tadic et al., 2020).

Additionally, all of our patients had elevated D-dimer and C-reactive protein (CRP) on admission in the setting of COVID-19. The most common pattern of coagulopathy observed in patients hospitalized with COVID-19 infection is characterized by elevations in fibrinogen and D-dimer levels (Becker, 2020). In fact, patients with severe COVID-19 were reported to have increased D-dimer and tissue plasminogen activator (tPA) plasma levels, both of which are associated with an increased propensity for hemorrhagic complications (Becker, 2020; Divani et al., 2020). Therefore, it is possible that a coagulopathy in the setting of activation of intrinsic and extrinsic fibrinolytic processes predisposed these patients to ICH. The serum inflammatory factors, such as CRP play a great role in the process of the vascular damage (Boulanger et al., 2016). Early stage COVID-19 CRP levels are known to positively correlate with lung involvement and may reflect disease severity (Wang, 2020). Some researchers found that the incidence of ICH was significantly higher in the high CRP group than in the low CRP group (Liu et al., 2014). It indicates that CRP may influence the incidence of ICH in COVID-19 patients.

CONCLUSION

While it remains to be confirmed whether there is a causal relationship between COVID-19 infection and ICH, these three cases, along with others in the literature, support that COVID-19 patients with severe illness are at risk for ICH.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Hospital COVID-19 Clinics BSMU in Ufa, Russia (within the Department of Neurosurgery), Clinic of the Bashkir State Medical University, Ufa, Republic of Bashkortostan, Russia, and Bashkir State Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

VP contributed to conception and organization of research project, drafted the main manuscript text. OB and IG performed the experiments and acquired the data. LT and AS were involved in study conception, participated in design and coordination, and helped to draft the manuscript. GA was responsible for data acquisition, writing – review and editing, analysis and interpretation of data, wrote the manuscript, and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work supported by Russian Academic Excellence project "5–100" for the Sechenov University, Moscow, Russia, GALLY International Biomedical Research Institute, San Antonio, TX, United States, and Human Photosynthesis Study Center, Aguascalientes, México.

ACKNOWLEDGMENTS

We thank all participants of the underlying studies.

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Conflict of Interest: GA employed by GALLY International Biomedical Research LLC. All of other authors declared no conflict of interest.

frontiers in Aging Neuroscience

REVIEW
published: 26 October 2020
doi: 10.3389/fnagi.2020.588872

Cognitive and Neuropsychiatric Manifestations of COVID-19 and Effects on Elderly Individuals With Dementia

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The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide and has had unprecedented effects in healthcare systems, economies and society. COVID-19 clinical presentation primarily affects the respiratory system causing bilateral pneumonia, but it is increasingly being recognized as a systemic disease, with neurologic manifestations reported in patients with mild symptoms but, most frequently, in those in a severe condition. Elderly individuals are at high risk of developing severe forms of COVID-19 due to factors associated with aging and a higher prevalence of medical comorbidities and, therefore, they are more vulnerable to possible lasting neuropsychiatric and cognitive impairments. Several reports have described insomnia, depressed mood, anxiety, post-traumatic stress disorder and cognitive impairment in a proportion of patients after discharge from the hospital. The potential mechanisms underlying these symptoms are not fully understood but are probably multifactorial, involving direct neurotrophic effect of SARS-CoV-2, consequences of long intensive care unit stays, the use of mechanical ventilation and sedative drugs, brain hypoxia, systemic inflammation, secondary effects of medications used to treat COVID-19 and dysfunction of peripheral organs. Chronic diseases such as dementia are a particular concern not only because they are associated with higher rates of hospitalization and mortality but also because COVID-19 further exacerbates the vulnerability of those with cognitive impairment. In patients with dementia, COVID-19 frequently has an atypical presentation with mental status changes complicating the early identification of cases. COVID-19 has had a dramatical impact in long-term care facilities, where rates of infection and mortality have been very high. Community measures implemented to slow the spread of the virus have forced to social distancing and cancelation of cognitive stimulation programs, which may have contributed to generate loneliness, behavioral symptoms and worsening of cognition in patients with dementia. COVID-19 has impacted the functioning of Memory Clinics, research programs and clinical trials in the Alzheimer's field, triggering the

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Edited by:
Panteleimon Giannakopoulos, Université de Genève, Switzerland

Reviewed by:
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Received: *29 July 2020*
Accepted: *05 October 2020*
Published: *26 October 2020*

Citation:
Alonso-Lana S, Marquié M, Ruiz A and Boada M (2020) Cognitive and Neuropsychiatric Manifestations of COVID-19 and Effects on Elderly Individuals With Dementia. Front. Aging Neurosci. 12:588872. doi: 10.3389/fnagi.2020.588872

implementation of telemedicine. COVID-19 survivors should be periodically evaluated with comprehensive cognitive and neuropsychiatric assessments, and specific mental health and cognitive rehabilitation programs should be provided for those suffering long-term cognitive and psychiatric sequelae.

Keywords: COVID-19, SARS-CoV-2, pandemics, cognition, neuropsychiatry, dementia, Alzheimer

INTRODUCTION

In late December 2019, China reported a cluster of cases of pneumonia caused by a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the subsequently named coronavirus disease 2019 (COVID-19). Since then, positive cases and deaths rapidly began to rise and spread worldwide, and the World Health Organization (WHO) declared the outbreak as a pandemic on 11 March 2020. Currently, as of 27 September 2020, the WHO has reported more than 32 million laboratory-confirmed positive cases and 991,224 deaths for COVID- 19 worldwide, half of them in the Americas followed by Europe (World Health Organization, 2020).

SARS-CoV-2 infection primarily affects the respiratory system, being fever and cough two of the most common acute symptoms in those symptomatic (Borges Do Nascimento et al., 2020; Lechien et al., 2020), but around 20% of individuals can suffer a more severe disease with critical and life-threatening respiratory complications (Wu and McGoogan, 2020). Besides, COVID-19 is increasingly being recognized as a systemic disease, and multiple neurologic manifestations have been reported in around 35.6% of cases (Tsai et al., 2020). They encompass non-specific symptoms, mainly headache and myalgia, along with hyposmia and dysgeusia, but there is also evidence of more severe complications such as neuroinflammatory syndromes, encephalopathies, ischemic strokes or Guillain-Barré syndromes, that have also been described in relation to other respiratory viruses (Ellul et al., 2020; Paterson et al., 2020; Roman et al., 2020; Tsai et al., 2020). Severely ill patients present more frequently these neurologic manifestations (Pinzon et al., 2020). In a large cohort of 841 patients hospitalized due to COVID-19 from two clinical centers in Spain, neurological symptoms were present in 54.7% of cases, a rate that increased up to 64.7% in those with a severe infection (Romero-Sanchez et al., 2020). Altered levels of consciousness were the most common neurologic manifestation in this group (Romero-Sanchez et al., 2020). Moreover, these mild disorders of consciousness along with focal neurologic deficits were the reason for the initial consultation in 2.5% of the patients and neurological complication were the main cause of death in 4.1% of the total deceased patients (Romero-Sanchez et al., 2020).

Although COVID-19 may affect individuals from all ages, elderly population is disproportionately impacted by the pandemic. Hospitalization and mortality rates increase drastically after 65 years of age (Centers for Disease Control and Prevention, 2020; Goujon et al., 2020) and current evidence points to age along with male sex and the presence of comorbid medical conditions as factors of poor prognosis and higher risk of death (Lu et al., 2020; Martin-Sanchez et al., 2020; Williamson et al., 2020). Moreover, elderly people with chronic diseases such as dementia often present atypical symptoms at onset of COVID-19 such as altered mental status (including confusion, agitation, disorientation, refusal of care, disorientation, and loss of appetite) (Bianchetti et al., 2020; Isaia et al., 2020; Ward et al., 2020). This atypical presentation may delay appropriate diagnosis and treatment and consequently, it may worsen their prognosis and survival.

Thus, elderly population is not only more likely to suffer a more severe illness from COVID-19 but also, they are more vulnerable to possible persisting health consequences. Long-term complications in those patients who have survived are currently unknown. However, as it has been seen in similar viral infection and survivors of critical illness, some of these patients might show neurological sequelae in the next months and years in form of lasting neuropsychiatric and cognitive impairment (Lam et al., 2009; Desai et al., 2011; Herridge et al., 2016; Troyer et al., 2020). Therefore, in this study we review the evidence regarding the neuropsychiatric and cognitive manifestations of COVID-19 as well as its direct and indirect consequences in survivors, especially in elderly individuals with dementia.

NEUROPSYCHIATRIC MANIFESTATIONS OF COVID-19

Manifestations such as insomnia, anxiety, post-traumatic stress symptoms (PTSD), psychosis and mood disorders have been described in several reports (see **Table 1**; Dinakaran et al., 2020; Liguori et al., 2020; Nalleballe et al., 2020; Rogers et al., 2020; Romero-Sanchez et al., 2020; Vindegaard and Benros, 2020). A study that retrieved data from a global health collaborative platform that included medical records of 40,469 COVID-19 positive cases, mostly from the United States (US) (76%), found that 22.5% had neurological and/or psychiatric manifestations, being anxiety and related disorders the most prevalent (4.6%) (Nalleballe et al., 2020).

A surveillance study in the United Kingdom (UK) showed that 39 cases of a cohort of 125 COVID-19 hospitalized patients with neurological manifestations presented with altered mental status, with encephalopathy in 16 and neuropsychiatric syndromes in 23 of them, mostly new-onset psychosis (n = 10) or other related psychiatric disorders (n = 7) (Varatharaj et al., 2020). In line with this evidence, in a retrospective descriptive study from a hospital in Madrid, Spain, 10 patients with a lab-confirmed diagnosis of COVID-19 and new-onset psychotic symptoms were identified among 10,000 patients with symptoms compatible with COVID-19 assessed between March and April 2020 in the emergency department (Parra et al., 2020). They had a mean age of 54.1 years, and psychiatric symptoms, mainly delusion,

TABLE 1 | Neuropsychiatric manifestations of COVID-19.

Study	Type of COVID-19 sample	Country	N	Sex (M/F)	Age mean (SD)	Type of assessment	Results
Cai et al., 2020	Cured COVID-19 patients in quarantine after discharge from hospital	China	126	60/66	45.7 (14.0)	Online questionnaire consisting of self-report scales: – Post-traumatic stress disorder self-rating scale (PTSD-SS) – Self-rating depression scale (SDS) – Self-rating anxiety scale (SAS)	Percentage of subjects who met the cut-off value of the scale: – Overall: 54.8% – Depression: 38.1% – PTSD: 31% – Anxiety: 22.2% – Anxiety and depression: 11.9%
Dinakaran et al., 2020	Review of 12 studies: – 9 case report and series – 1 observational study – 2 case control studies	Global: China: 4 studies US: 3 studies Others: France, Japan, Saudi Arabia, Spain and Perú	–	–	–	–	Evidence of neuropsychiatric manifestations: – Delirium: 4 studies – Psychosis: 2 studies – Mood swings: 1 study – Increased psychological distress in individuals with pre-existing epilepsy and psychiatric disorders: 2 studies
Helms et al., 2020	Patients admitted to an ICU with ARDS due to COVID-19	France	58	–	63 (median)	Confusion Assessment Method for the ICU (CAM-ICU)	Prevalence of symptoms: – Positive CAM-ICU: 65% – Agitation: 69%
Liguori et al., 2020	Hospitalized patients due to COVID-19	Italy	103	59/44	55 (14.65)	Anamnestic interview	Prevalence of symptoms: – Sleep impairment: 49.51% – Depression: 37.86% – Anxiety: 33.01% – Confusion: 22.33%
Nalleballe et al., 2020	Data retrieved from a platform that included medical records of COVID-19 positive cases	Global (76% US)	40,469	18,364/22,063	–	ICD-10 diagnosis for neurological and psychiatric symptoms during or within 1 month after COVID-19 diagnosis	Prevalence of manifestations: – Overall: 22.5% – Anxiety and other related disorders: 4.6% – Mood disorders: 3.8% – Sleep disorder: 3.4% – Emotional state symptoms and signs: 0.8% – Suicidal ideation: 0.2%
Parra et al., 2020	COVID-19 patients with new-onset psychotic symptoms	Spain	10	6/4	54.1 (10.67)	–	Prevalence of symptoms: – Delusions: 100% – Orientation/attention disturbances: 60% – Auditory hallucinations: 40% – Visual hallucinations: 10%

(Continued)

TABLE 1 | Continued

Study	Type of COVID-19 sample	Country	N	Sex (M/F)	Age mean (SD)	Type of assessment	Results
Rogers et al., 2020	Review of 12 studies (including 7 preprints)	Global China: 10 studies Others: France, Japan	–	–	–	–	Evidence of neuropsychiatric manifestations: – Confusion: 5 studies – Anxiety and depression: 2 studies – Insomnia: 1 study
Romero-Sanchez et al., 2020	Hospitalized patients with COVID-19	Spain	841	473/368	66.42(14.96)	–	Prevalence of symptoms: – Insomnia: 13% – Anxiety: 8.1% – Depression: 5.2% – Psychosis: 1.3%
Varatharaj et al., 2020	CoroNerve Platform COVID-19 hospitalized patients with neurological manifestations	UK	125	73/44 *(36 not reported)*	–	–	Prevalence of manifestations: – Psychosis: 8% – Other psychiatric disorders: 5.6%
Vindegaard and Benros, 2020	Review of 43 studies: – *2 studies* of COVID-19 patients – 41 studies of health care workers, general public and psychiatric patients without COVID-19	Global	–	–	–	–	Evidence of neuropsychiatric manifestations: – High prevalence of PTSD in COVID-19 patients – Prevalence of depression higher in COVID-19 patients than in individuals under quarantine – Worsening of psychiatric symptoms in patients with pre-existing psychiatric disorders – Increased psychiatric symptoms in health care workers – Lower psychological well-being and higher scores in anxiety/depression scales after pandemic
Yuan et al., 2020	Cured COVID-19 patients in quarantine after discharge from hospital Subsample of Cai et al., 2020	China	96 (42 self-reported depression, 54 control group)	Depression group: 20/22 Control group: 27/27	Depression group: 49.6 (13.2) Control group: 45.2 (13.2)	Online questionnaire consisting of SDS scale:	Increased immune response (white blood cells count, neutrophil count and neutrophil-to-lymphocyte ratio) in the depression group in comparison to the control group
Zhang et al., 2020	COVID-19 patients in comparison to individuals under quarantine and general public	China	57 COVID-19 patients 50 individuals under quarantine 98 general public	29/28	46.9 (15.37)	App-based questionnaire – 9-item Patient Health Questionnaire (PHQ-9) – 7-item Generalized Anxiety Disorder Scale (GAD-7)	Percentage of subjects with COVID-19 who met the cut-off value of the scales: – Depression: 29.2% – Anxiety: 20.8% – Depression and anxiety: 21.1% Prevalence of depression was higher in COVID-19 patients than individuals under quarantine

ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit; ICD-10, 10th Revision of the International Statistical Classification of Diseases and Related Health Problems; PTSD, Post-traumatic stress disorder; UK, United Kingdom; US, United States.

orientation/attention disturbances and auditory hallucination (in 10, 6, and 4 cases, respectively), appeared primarily after the first typical COVID-19 symptoms and were resolved in less than 2 weeks (Parra et al., 2020). These episodes were considered atypical since patients had no familiar history of psychiatric disorders, no substance use disorders, had an atypical age of onset, and presented a fast recovery (Parra et al., 2020). Authors suggested that these atypical psychotic episodes may be explained by systemic inflammatory responses, based on analytical and complementary tests findings, or by side effects associated with COVID-19 treatment (Parra et al., 2020).

Critically ill patients with COVID-19 who require Intensive Care Unit (ICU) admission are also at most at risk of developing delirium, which is further exacerbated by the frequent need for high doses of sedation, elderly age and the presence of multiple comorbidities (Cipriani et al., 2020). In an observational study in France, 40 out of 58 (69%) COVID-19 patients attended in the ICU showed agitation and 26 of them confusional state (Helms et al., 2020). Brain imaging found bilateral frontotemporal hypoperfusion in eleven patients and larger leptomeningeal spaces in eight of them (Helms et al., 2020).

There is also evidence of prevalent depressive symptoms in those already recovered from COVID-19 (Cai et al., 2020; Yuan et al., 2020; Zhang et al., 2020). A study of 126 COVID-19 survivors in convalescence from Shenzhen, China, showed that self-reported anxiety and depression were common after discharge from hospital (Cai et al., 2020) and moreover, depressive symptoms were associated with immune systemic suppression, based on increased white blood cells and inflammatory factors measures (Yuan et al., 2020).

Despite this preliminary evidence, most of the findings came from self-reported scales, without clinical diagnostic assessments, and further examinations and follow-ups are needed to determine not only if these symptoms are related to the infection itself, secondary immune responses, side effects of treatments or psychologic stressors, but also if they improve, remain or worsen over time.

COGNITIVE MANIFESTATIONS OF COVID-19

There are very few studies reporting cognitive symptoms related to COVID-19 (see **Table 2**). Data from 431,051 participants of the United Kingdom Biobank prospective study show that several psychosocial factors were associated with the risk of being hospitalized due to COVID-19, but after controlling for other relevant variables (sociodemographic, socioeconomic, psychological, lifestyle factors, and medical comorbidities), the only significant factor associated with the risk of the infection was a lower cognitive function (Batty et al., 2020). However, the causality and mechanisms involved in such association remain to be elucidated. In a retrospective study carried out in Chicago, United States, of 50 hospitalized patients with COVID-19 who were admitted to a neurology unit or presented neurological symptoms, 24% of them had short-term memory loss (Pinna et al., 2020). A surveillance study in the United Kingdom showed that 6 cases of a cohort of 125 COVID-19 hospitalized patients with neurological manifestations presented a neurocognitive disorder (Varatharaj et al., 2020).

There is also preliminary evidence of cognitive impairment after hospital discharge. In this sense, in an observational study in France, over one third (15/45) of patients showed evidence of cognitive impairment at discharge from ICU, especially in the form of dysexecutive syndrome characterized by inattention, disorientation and poorly organized movements in response to commands (Helms et al., 2020). In a case series of 4 severe COVID-19 patients who required ICU admission, cognitive impairment, identified as memory deficit and frontal syndrome, was detected after discharged but remitted after 5 days of immunoglobulin therapy (Chaumont et al., 2020). Besides, in a sample of 71 COVID-19 hospitalized patients, those who were diagnosed with delirium during their hospitalization (42%) had lower cognitive scores on a telephone screening interview after 4 weeks of discharge, although the between-group comparison did not reach statistical significance ($p = 0.06$) (McLoughlin et al., 2020).

The lack of more precise information regarding cognitive symptoms in COVID-19 patients may be explained by the impact that the pandemic has had on healthcare systems and also, in severe cases, the difficulty to carry out a comprehensive neuropsychological assessment. However, this information will be of great value in order to identify risk factors related to the acute cognitive symptoms associated to the disease, both in people with or without pre-existing cognitive impairment, and to shed light on their underlying mechanisms. It will also be necessary to offer neuropsychological rehabilitation to those who need it. It is essential and urgent to minimize the potential negative effects on cognitive and psychosocial functioning and quality of life on survivors.

POTENTIAL COVID-19 COGNITIVE AND NEUROPSYCHIATRIC LONG-TERM COMPLICATIONS

Long-term complications in those patients who survived the disease are currently unknown but are expected to appear in the next months and years, as it was seen in past pandemics caused by influenza or similar coronaviruses such as MERS-CoV and SARS-CoV (Rogers et al., 2020; Troyer et al., 2020) and also in survivors of critical illness who required ICU support (Desai et al., 2011; Herridge et al., 2016; Marra et al., 2018).

In a systematic review and meta-analysis carried out by Rogers et al. (2020) regarding the acute and post-illness neuropsychiatric manifestations of coronavirus infections, 72 studies were evaluated, including SARS-CoV ($n = 47$), MERS-CoV ($n = 13$) and the current SARS-CoV-2 ($n = 12$) and the hospitalized patients' ages ranged from 12 to 68 years (Rogers et al., 2020). SARS-Cov and MERS-CoV were associated with prevalent neuropsychiatric symptoms both in the acute phase and after recovery (Rogers et al., 2020). Results from the meta-analysis carried out showed that after recovery, the estimated prevalence for PTSD was 32.2% (mean follow-up of 33.6 months)

TABLE 2 | Cognitive manifestations of COVID-19.

Study	Type of COVID-19 sample	Country	N	Sex (M/F)	Age mean (SD)	Type of assessment	Results
Batty et al., 2020	UK Biobank data of COVID-19 hospitalized patients	UK	908 individuals with hospitalization due to COVID-19 430,143 no COVID-19	COVID-19 group: 506/402 No COVID-19 group: 193,820/236,323	COVID-19 group:57.27 (8.99) No COVID-19 group: 56.36 (8.10)	Computerized cognitive assessment at baseline (2006-2010)	Risk of COVID-19 hospitalization related to (after controlling for all covariates) cognitive function at baseline (verbal and numerical reasoning): Odds ratio 1.31
Chaumont et al., 2020	COVID-19 patients with ARDS and neurological manifestations admitted to an ICU	France	4	4/0	range 50-72	–	Prevalence of cognitive impairment: 100%
Helms et al., 2020	Patients admitted to an ICU with ARDS due to COVID-19	France	58	–	63 (median)	–	Prevalence of dysexecutive syndrome at discharge: (14/39) 36%
McLoughlin et al., 2020	COVID-19 hospitalized patients	UK	71 (16 no delirium, 31 delirium, 24 no assessment). 26 patients with a 4-week follow-up	51/20	61 (range 24-91)	Telephone assessment: – Telephone Instrument for Cognitive Status (TICS-m)	Cognitive performance at 4-week follow-up: Delirium group TICS-m mean score: 34.5/53 No delirium group TICS-m mean score: 41.5/53
Pinna et al., 2020	COVID-19 Hospitalized patients admitted to a neurology unit or with neurological symptoms	US	50	29/21	59.6 (14.3)	–	Prevalence of short-term memory loss: 24%
Varatharaj et al., 2020	CoroNerve Platform COVID-19 hospitalized patients with neurological manifestations	UK	125	73/44 *(36 not reported)*	–	–	Prevalence of neurocognitive disorder: 4.8%

ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit; UK, United Kingdom; US, United States.

and prevalence of anxiety and depression disorders was 15% (mean follow-up of 11.6 and 22.6 months, respectively) (Rogers et al., 2020). Measures of health-related quality of life were significantly lower in patients compared to the control group and 76.9% (range: 66–93%) had returned to work after a mean of 3 years of follow-up (range: 1–144 months) (Rogers et al., 2020). As noted by the authors, most of the peer-reviewed studies included in the systematic review were considered either of low (32/65) or medium (30/65) quality due to limited assessment of previous psychiatric symptoms in the patients and lack of control group in many of them in order to distinguish symptoms related to the viral infection from the psychiatric impact these epidemics may had in the general population (Rogers et al., 2020). However, results from one of the longitudinal studies included in this review, with a sample of 181 individuals who had been infected by SARS-CoV-1, indicated that while only 3.3% of patients had a previous history of psychiatric disorder before the viral infection, after a mean follow-up of 3.4 years, 42.5% met clinical criteria of at least one psychiatric illness, being PTSD the most prevalent disorder (54.5%) followed by depression (39%) (Lam et al., 2009). Likewise, 70.8% of confirmed MERS-CoV cases developed psychiatric symptoms and 40% of them met clinical psychiatric diagnosis during hospital admission, while none of the suspected cases who were quarantined but tested negative for the virus showed any psychiatric symptoms (Kim et al., 2018). This evidence therefore suggests the possible role of coronavirus infections in inducing brain changes related to these psychiatric symptoms.

Moreover, ICU admission and invasive treatments such as ventilation and sedation following acute respiratory distress syndrome (ARDS) are risk factors for cognitive decline (Sasannejad et al., 2019). In the current pandemic caused by SARS-CoV-2, a retrospective case series study of 1591 COVID-19 patients admitted to ICU in Italy found that 88% required mechanical ventilation (Grasselli et al., 2020) and in a smaller study from an ICU in Washington, United States, 71% of 21 critically ill patients developed ARDS and required mechanical ventilation (Arentz et al., 2020). Data of long-term outcomes in adults requiring mechanical ventilation showed cognitive impairment in attention, memory, verbal fluency, processing speed or executive function in 78 and 47% of the patients after 1 and 2 years of discharge, respectively (Hopkins et al., 1999, Hopkins et al., 2005). A total of 15 patients in this study also underwent brain imaging and, in comparison to an age and sex-matched control group, they had significantly larger ventricular and temporal horn volumes (Hopkins et al., 2006). Even after 5 years of follow-up, 20% of survivors of ARDS showed cognitive sequelae in a wide variety of cognitive domains (Herridge et al., 2016).

MECHANISMS INVOLVED IN COGNITIVE AND NEUROPSYCHIATRIC MANIFESTATIONS OF COVID-19

The underlying causes for these symptoms related to COVID-19 and the mechanisms involved in potential long-lasting impairments are currently not fully understood but are probably multifactorial. These factors include direct viral infection of the nervous system, the systemic inflammatory response to the virus, cerebrovascular ischemia due to endothelial dysfunction or severe coagulopathy, the ARDS presented in severe cases, the use of invasive ventilation and sedation along with side effects of drugs used to treat COVID-19, and peripheral organ dysfunction (see **Figure 1**; Sasannejad et al., 2019; Heneka et al., 2020; Ogier et al., 2020).

SARS-CoV-2, similarly to other coronaviruses, shows certain neurotropism. Two potential methods for coronaviruses intracranial spread have been hypothesized: direct hematogenous attack and retrograde ascent via peripheral nerve fibers of the upper respiratory tract (Zubair et al., 2020). SARS-CoV-2 uses the SPIKE proteins located on its surface to bind the angiotensin-converting enzyme 2 (ACE2) receptor on mammalian host cells (Hoffmann et al., 2020). The ACE2 receptor has been found to be expressed widespread in neurons and glial cells (Xia and Lazartigues, 2008). There is evidence of neuronal death after brain infection by SARS-CoV-1 via the olfactory bulb in animal models (Netland et al., 2008).

To date there is little evidence of direct brain infection related to COVID-19. Results from reverse transcription polymerase chain reaction (RT-PCR) assays of cerebrospinal fluid (CSF) samples carried out in a few COVID-19 cases with neurological manifestations have been negative for SARS-CoV-2 (Chaumont et al., 2020; Helms et al., 2020).

Sparse neuropathological data of COVID-19 cases are available and mostly show hypoxic changes and demyelinating lesions (Coolen et al., 2020; Reichard et al., 2020; Solomon et al., 2020). An autopsy series from Germany detected SARS-CoV-2 viral load in brain along kidneys, liver, heart and blood, although in lower levels that in the respiratory system (Puelles et al., 2020). Further studies are needed to determine whether these lesions are due to SARS-CoV-2 infection or caused by illness-related secondary conditions. A recent systematic review that included 26 neuroimaging studies, most of them case series of COVID-19 patients who underwent brain imaging examination due to neurological symptoms, found that 34% (124/361) of the cases presented brain lesions probably attributable to COVID-19 and among them, the most common finding was diffuse subcortical and deep white matter abnormalities. Other common findings, although less prevalent, were microhemorrhages, hemorrhages, and infarcts (Rita Egbert et al., 2020).

Even in the absence of direct brain infection, severe systemic infection may be also involved by precipitating neuroinflammatory responses that may promote subsequent brain tissue damage (Frank-Cannon et al., 2009; Dantzer, 2018; Rea et al., 2018). In severe cases, the virus may trigger an exacerbated and dysregulated host response called "cytokine storm" that involves increased levels of pro-inflammatory cytokines such as necrosis tumoral factor (TNF) and interleukin-6 (IL-6), among others. If this response persists over time it creates a state of systemic inflammation, resulting in disruption of blood-brain barrier and neural and glial cells damage that can be involved in long-term sequelae in survivors. Current evidence related to SARS-CoV-2 shows that usually the most

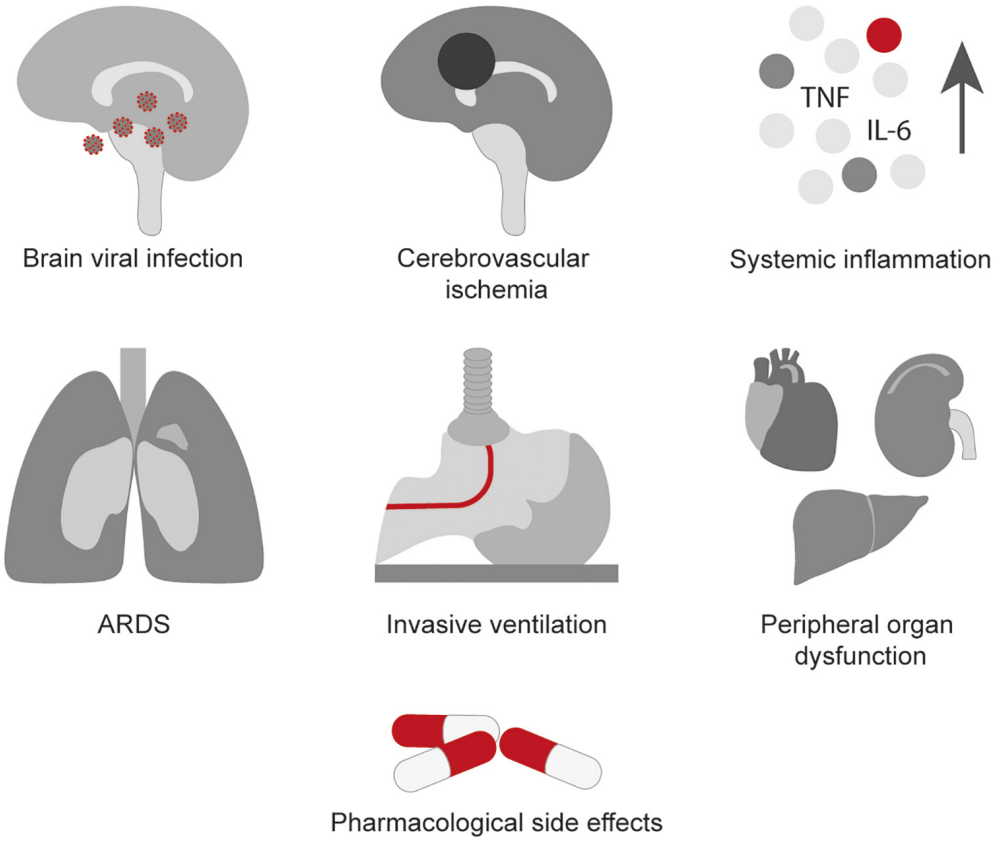

FIGURE 1 | Possible mechanisms involved in the neurological manifestations of COVID-19.

severely affected patients presented increased levels of pro-inflammatory cytokines (Chen et al., 2020; Huang et al., 2020; Yang et al., 2020).

Chronic systemic inflammation has been also studied as one of the underlying pathogenic mechanisms involved in neurodegenerative disease such as Alzheimer's disease (AD) (Akiyama et al., 2000). In a sample of 12,336 participants with a mean age of 56.8 years, systemic inflammation was studied using a composite score of blood biomarkers, and results indicated a significant association between baseline inflammation and accelerated cognitive decline after a follow-up of 20 years (Walker et al., 2019). The inflammation related to viral infection significantly worsens tau-related pathology and results in impairment of spatial memory (Sy et al., 2011). The hippocampus, region involved in memory formation, is an especially vulnerable area to respiratory viral infections, as shown in animal models (Jacomy et al., 2006). Short-term deterioration in hippocampus-dependent learning and reduced long-term potentiation associated with impairment in spatial memory were observed in mice infected with the influenza virus (Hosseini et al., 2018). Also, in the presence of pro-inflammatory cytokines the microglial cells lose its capacity to phagocyte β-amyloid that can be related to the accumulation of amyloid plaques, one of the hallmarks of AD (Koenigsknecht-Talboo and Landreth, 2005).

The APOE-ε4 gene allele, the strongest genetic risk factor for AD, has been found to be linked to increased risk of infection and mortality due to COVID-19, although the biological mechanisms involved in this association remain to be known (Kuo et al., 2020). However, ACE2 expression has been reported to be reduced in mid-frontal brain tissue in AD patients, particularly in those carrying an APOE ε4 allele, and this reduction was negatively correlated with Aβ and phosphorylated tau pathology (Kehoe et al., 2016). It is also worth noting that in a study of 46 AD patients and 44 non-AD elderly individuals, the APOE-ε4 allele was overrepresented in AD patients positive for herpes simplex virus type 1 (HSV1) in the brain in comparison to those negative for the virus and even to non-AD patients positive for HSV1, with an OR of 16.8 (Itzhaki et al., 1997). Authors argued that APOE-ε4 could promote vulnerability to viral infection and neurodegeneration, participating in the extent of cells infected by the virus or in the extent of repair after HSV1-induced damage. Thus, viral infection may be an aggravating factor for neurodegeneration in individuals with susceptible genetic variants.

Despite this preliminary evidence related to COVID-19, further studies are needed in order to ascertain the underlying causes for these symptoms and the mechanisms involved in potential long-lasting impairments, and furthermore,

whether this coronavirus might precipitate or exacerbate neurodegenerative diseases.

COVID-19 MANIFESTATIONS IN PATIENTS WITH DEMENTIA

Elderly people with chronic diseases such as dementia develop more serious and often lethal forms of COVID-19 (Bianchetti et al., 2020; Hwang et al., 2020; Miyashita et al., 2020). People with dementia are likely unable to follow the recommendations from public health systems to reduce the transmission of the virus (such as physical distancing, frequent hand washing, and use of facial masks) (Suzuki et al., 2020), exposing them to a higher chance of infection. A review of 627 patients admitted to an acute medical ward with COVID-19 pneumonia in Italy revealed that those with dementia (n = 82, 13.1%) had a significantly higher mortality rate compared to those cognitively unimpaired (62.2% vs. 26.2%, $p < 0.001$) (Bianchetti et al., 2020). The diagnosis of dementia was independently associated with a higher mortality, with an odds ratio of 1.84 (Bianchetti et al., 2020). In the largest population-based study carried out to date and including 17,278,392 probable COVID-19 cases from England, previous history of stroke or dementia was associated with increased risk of death after 90 days, with an adjusted hazard ratio of 2.16 (Williamson et al., 2020). Similarly, in a nursing facility located in Washington, United States (US), among 101 residents who were positive for COVID-19, the case fatality rate (CFR, proportion of deaths from the total number of people diagnosed) associated was dramatically high (33.7%) (McMichael et al., 2020). Something to take into account is that given the rapid evolution of COVID-19 cases that have required medical attention, there is concern that older people with dementia may have been largely excluded from resources such as hospital admission and/or access to ICUs in favor of younger individuals or those with less comorbidities. This could partly explain the high mortality rates in this population and particularly, in long-term care and nursing home facilities (Cipriani and Fiorino, 2020).

Moreover, patients with dementia often present atypical symptoms, such as altered mental status (including confusion, agitation, disorientation, refusal of care, disorientation, and loss of appetite) as the initial COVID-19 manifestation, even without fever and cough (Isaia et al., 2020; Ward et al., 2020), along with worsening of baseline functional status (Bianchetti et al., 2020). Thus, waiting for typical respiratory symptoms to appear would delay appropriate diagnosis and treatment. Indeed, the Alzheimer's Association advises caregivers to be alert to the presence of confusion as it is might be the first symptom of a possible COVID-19 infection in individuals with dementia (Alzheimer's Association, 2020).

When treating COVID-19 in patients suffering from AD, drug interactions should be taken into account (Balli et al., 2020). Cholinesterase inhibitors (ChEIs) levels may increase during chloroquine (CQ), hydroxychloroquine (HCQ) and lopinavir/ritonavir treatment, due to effects on cytochrome P450. Cardiac adverse events can be related to both Azithromycin, CQ, HCQ, and ChEIs, so frequent electrocardiography monitoring is advised. Memantine has a low risk of pharmacokinetic interactions and may be a safer alternative when using drugs to treat COVID-19 in AD patients. Antipsychotics and antidepressants, used frequently in dementia, have potential interactions with Azithromycin, CQ, HCQ and lopinavir/ritonavir. Lastly, Tocilizumab, ribavirin and favipiravir show no potential interactions with AD treatments (Balli et al., 2020; University of Liverpool, 2020).

COVID-19 INDIRECT EFFECTS IN PATIENTS WITH DEMENTIA

The COVID-19 pandemic further exacerbates the vulnerability of elderly patients with cognitive impairment, especially those who depend on family or caregivers for their daily care. This is due to the increased morbidity and mortality caused by the infection but also to the indirect effects of the pandemic on the healthcare system that they depend on (Brown et al., 2020). Medical resources have been diverted away from patients with chronic conditions, such as dementia, to attend COVID-19 cases. People with dementia are at risk of discontinuing their treatment during lockdown, especially those who depend on external help for reminders or assistance (Brown et al., 2020).

Most COVID-19-related deaths have occurred in long-term care facilities, where patients with dementia are a significant part of the residents and require close contact for assistance in their daily care (Blackman et al., 2020; Cordasco et al., 2020). Blackman et al. (2020) reported the rapid evolution of COVID-19 in a long-term care facility with 150 beds for individuals with dementia, where despite the preventive measures developed, within 3 weeks of the first confirmed COVID-19 case, 30 residents had died and more than 50 were confirmed cases or were having symptoms compatible for the disease. It is thus of crucial importance to equip these facilities with appropriate preventive measures and rapid detection capacity to avoid transmission and protect this already fragile population as much as possible.

The COVID-19 pandemic forced Memory Clinics worldwide to close their face-to-face consultations and non-pharmacological interventions for dementia, such as cognitive therapy, exercise and socialization, have been suddenly stopped during lockdown (Benaque et al., 2020; Brown et al., 2020). Many centers, though, took action and implemented telemedicine in order to continue assisting patients during the pandemic, both for their scheduled follow-up visits but also for urgent consultations (Benaque et al., 2020; Ousset and Vellas, 2020; Padala et al., 2020). This continued care during the pandemic has been especially important for those patients and caregivers in a more vulnerable situation. The transformation of medical care, though, posed a challenge for many patients, especially elderly individuals with cognitive, visual and/or hearing impairment, those living alone, and those from a low socio-economic status or living in rural areas with limited access to technology. From the clinical point of view, safety and legal concerns about privacy and data protection had to be addressed, and some tests from the neuropsychological batteries had to be adapted to be performed in a virtual way (Bilder et al., 2020). After this experience, it is likely that telemedicine

TABLE 3 | Neuropsychiatric and cognitive manifestations in dementia patients during confinement.

Study	Country	Participants	Male/Female	Age mean (SD)	Assessment	Results
Lara et al., 2020	Spain	40 – Mild AD: 20 – MCI: 20	16/24	77.4 (5.25)	Phone interview after 5 weeks of home confinement: – NPI – EuroQol-5D	Significant worsening in neuropsychiatric symptoms after confinement (NPI score baseline: 33.75 vs. confinement: 39.05) No changes in quality of life (0.66 vs. 0.62)
Canevelli et al., 2020	Italy	139 – Dementia: 96 – MCI: 37 – SCD: 6	55/84	79	Telephone survey in patients or caregivers	Percentage of individuals with reported worsening: – Behavioral: 54.7% – Neuropsychiatric symptoms: 54.68% – Cognition: 31.65% – Functional decline 13.67% – Required adjustment/introduction of pharmacological treatments: 7.2%
Boutoleau-Bretonniere et al., 2020	France	38 individuals with probable AD	15/23	71.89 (8.24)	Caregivers phone interview: – NPI	Prevalence of neuropsychiatric worsening (mean duration of confinement: 27.37 days): 26.31% Worsening associated with lower general cognitive functioning before confinement (2-4 months before).
Goodman-Casanova et al., 2020	Spain	93 individuals with MCI or mild dementia	33/60	73.34 (6.07)	Telephone-based survey in patients or caregivers	Prevalence of mental health and well-being status reported: – Sleep quality maintained: 70% – Well: 61%* – Sad: 29%* – Anxious: 24%* – Sleep quality altered: 24%* – Worried: 22% – Bored: 14% – Afraid: 11% – Calm: 9%
Capozzo et al., 2020	Italy	32 individuals with frontotemporal lobar dementia	18/14	66.25 (9.76)	Telemedicine assessment Structured clinical questionnaire in caregivers	Prevalence of individuals with reported worsening: – Cognitive function: 53% – Behavior: 56% – Language: 47% – Sleep disturbances: 25%

*AD, Alzheimer's disease; EuroQol-5D, European Quality of Life-5 Dimensions; MCI, Mild cognitive impairment; NPI, Neuropsychiatric inventory; SCD, Subjective cognitive decline; *, Significant differences between those living alone (n = 24) vs. living with others.*

will continue to have an important role in the evaluation of patients with cognitive impairment even after the COVID-19 pandemic is contained.

Community measures implemented to slow the spread of COVID-19 have forced to social distancing and self-isolation, and this may have contributed to generate feelings of loneliness and behavioral changes in patients with cognitive impairment (Canevelli et al., 2020). A significant proportion of patients with dementia reside in long-term care and nursing home facilities, which have been quarantined in many countries, prohibiting family members to visit residents or them to get outside. Factors such as solitariness and social isolation should not be underestimated, since they have been consistently found to be related to increased risk of medical health problems, including cardiovascular disease, depression or dementia (Holwerda et al., 2014; Courtin and Knapp, 2017), and higher mortality risk, even after controlling for relevant variables such as health status (Holt-Lunstad et al., 2015).

In this sense, there is evidence of cognitive, neuropsychiatric and functional worsening in this population during confinement periods implemented in several countries (see **Table 3**). A study from a cognitive disorders unit in Spain evaluating 40 patients with mild AD dementia and mild cognitive impairment (MCI) that attend a cognitive stimulating program reported that their neuropsychiatric symptoms significantly worsened after 5 weeks of lockdown (mainly apathy, anxiety, agitation and aberrant motor behavior) (Lara et al., 2020). Likewise, a report of 139 patients with dementia, MCI and subjective cognitive decline from a dementia center in Rome, showed worsening or onset of behavioral disturbances in 54.7% (mostly agitation/aggression, apathy, and depression) after 1 month of lockdown (Canevelli et al., 2020). In 7.2% of cases, these symptoms required adjustments or introduction of pharmacological treatments, mostly antipsychotics (Canevelli et al., 2020). Worsening of neuropsychiatric symptoms has been found particularly associated with significant lower general cognitive functioning before confinement in a sample of 38 patients with a clinical diagnosis of probable AD (Boutoleau-Bretonniere et al., 2020). In a sample of 93 older adults with MCI or mild dementia, those living alone reported significantly a decrease in their well-being, more anxiety and sleeping problems (Goodman-Casanova et al., 2020). Also, in a study with a smaller sample of 32 individuals with frontotemporal lobar dementia from a dementia care center in Tricase (Italy), caregivers were interviewed by telephone using a structured clinical assessment and reported that, compared to their last visit (mean of 6.78 months), 53% of patients showed significant worsening in cognitive function, particularly in memory, along with worsening in behavior and language function during COVID-19 confinement (Capozzo et al., 2020).

Another concern is the effect that this pandemic could have on those individuals at the preclinical stage of dementia or those experiencing subtle cognitive changes. After 6 months with the healthcare systems worldwide on edge, referrals to Memory Clinics and timely diagnosis and interventions will probably be delayed. Prevention is the most important strategy in potentially slowing the progression of neurodegenerative disorders and given the increased risk of negative health outcomes in older people, it is important to examine and determine whether COVID-19 may trigger or aggravate neurodegenerative processes in this vulnerable group.

COVID-19 EFFECTS ON DEMENTIA RESEARCH AND CLINICAL TRIALS

A recent survey among 267 researchers and clinicians specialized in dementia identified 9 priorities in research for older people, including management of COVID-19 and its complications and outcomes in this population, and the need to include older people in research studies to design safe and adequate interventions (Richardson et al., 2020). However, while clinical trials should be designed to enable inclusion of elderly individuals due to the increased morbidity and mortality caused by the infection in this population, a recent review reported that over a third of COVID-19-related clinical trials registered as of 16th March 2020 excluded participants over 75 years of age (Lithander et al., 2020).

The closure of Memory Clinics due to the lockdown measures imposed by governments worldwide has had a negative effect on dementia clinical research as well. Although some procedures could be still performed through telemedicine such as clinical

TABLE 4 | Summary of considerations for dementia management and research in relation to COVID-19.

Health and social care	**Implement telemedicine to continue consultations and non-pharmacological interventions**
Health and social care	Implement technology solutions to facilitate communication with family members during quarantine or confinement periods.
	Facilitate solutions to continue pharmacological treatment to those who depend on external help for reminders or assistance during quarantine and confinement periods
Health and social care	Continue the assessment of individuals with cognitive complaints to facilitate early diagnosis and interventions as prevention of neurodegenerative progression
Prevention	Equip long-term facilities with appropriate preventive measures and rapid detection capacity to avoid COVID-19 transmission
Prevention	Be aware of the onset of COVID-19 as atypical symptoms/worsening of baseline status
Treatment	Take into account pharmacological interactions when treating for COVID-19 in this population
Treatment	Perform follow-up evaluations to COVID-19 survivors and provide mental health support and cognitive rehabilitation when necessary
Research and clinical trials	Include older people in research studies to design safe and adequate interventions
Research and clinical trials	Continue research funding in dementia
Research and clinical trials	Continue dementia clinical trials, considering testing for SARS-CoV-2 prior to the onset of treatment.
Research and clinical trials	Perform follow-up evaluation to COVID-19 survivors to examine the presence of long-term neuropsychiatric and cognitive complications

evaluations and neuropsychological testing, this type of research usually requires the presence of patients to undergo blood draw, lumbar puncture or neuroimaging, among others.

Basic laboratories conducting experimental research in the Alzheimer's field have also been affected by COVID-19, as the sudden lack of staff due to lockdown forced ongoing experiments to be stopped and transgenic animals to die, with the resulting loss of valuable data (Bostanciklioglu, 2020). Besides, research funding is currently being diverted into COVID-19 research, leaving dementia researchers with less funding opportunities to continue their projects. Also, until movement restriction measures among countries are lifted, international students and researchers will not be allowed to continue or start new positions in foreign countries.

The COVID-19 pandemic has compelled most ongoing clinical trials in the AD field to be put on hold for a few months, affecting participants' recruitment, administration of medication infusions and follow-up visits (Weinberg et al., 2020). This has caused a significant disruption in the management of clinical trials, with the need of protocol amendments to deal with missing data, deviations, loss of participants and allowing the use of telemedicine. In the United States, the Food and Drug Administration (FDA) issued on April 2nd a document entitled "Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic" (The Food and Drug Administration, 2020), encouraging sponsors to use their best judgment to decide the continuance of the clinical trial during the pandemic. Lastly, the clinical trials disruption has especially affected patients and their families in a personal manner, as they trusted pharmacological research to fight against this disease, faced great uncertainty and helplessness regarding their future, but in general were eager to continue their treatment once it was safe (Geerts and van der Graaf, 2020; Weinberg et al., 2020).

Something to be considered is the need for SARS-CoV-2 RT-PCR testing prior to the onset of treatment once participants are allowed to reinitiate their participation in clinical trials, as some novel drugs being tested against Alzheimer have immune-mediated mechanisms (Perez-Grijalba et al., 2019) and COVID-19 should to be ruled out for safety reasons.

Given the impact that this pandemic is having on elderly people with dementia and based on the evidence reviewed and existing to date, a summary of relevant considerations to take into account for this population is presented in **Table 4**.

CONCLUSION

The current COVID-19 pandemic is having a significant impact on many health, economic and social aspects worldwide. Elderly population, and especially those with comorbidities such as dementia, is a vulnerable group at risk of contracting the disease and presenting more severe forms and worse outcomes, including mortality. In this regard, long-term care facilities have been specially hit by the pandemic, showing high rates of infection and mortality. Memory Clinics attending patients with dementia have been forced to cancel their face-to-face appointments, while research and clinical trials in the field of Alzheimer's disease have also suffered the negative consequences of the pandemic.

At this point, it is of crucial relevance to perform follow-up evaluations to COVID-19 survivors using comprehensive cognitive and neuropsychiatric assessments along with brain imaging if appropriate, especially to those who have suffered severe forms of the disease with ICU-care level and neurological manifestations during the acute phase. It is necessary to rule out long-term sequelae and provide mental health support and cognitive rehabilitation to minimize the potential negative effects on psychosocial functioning and quality of life of survivors. Given the increased risk of negative health outcomes in older individuals, it is important to examine and determine whether COVID-19 may trigger or aggravate neurodegenerative processes in this vulnerable group, as an early diagnosis and intervention are the most important strategies to slow the progression of neurodegenerative disorders. Importantly, clinical trials and research studies related to COVID-19 should be designed to enable inclusion of elderly individuals.

AUTHOR CONTRIBUTIONS

SA-L and MM equally contributed to the scientific literature review and wrote the manuscript. SA-L designed the figure. AR and MB have supervised the study and have critically revised and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study has been funded by Instituto de Salud Carlos III (co-funded by European Regional Development Fund/European Social Fund "Investing in your future") Sara Borrell Contract (CD19/00232) awarded to SA-L, by Instituto de Salud Carlos III (ISCIII) Acción Estratégica en Salud, integrated in the Spanish National R+D+I Plan and financed by ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER-Una manera de hacer Europa) grant PI17/01474 awarded to MB, grants AC17/00100 and PI19/01301 awarded to AR, and grant PI19/00335 awarded to MM, and by the European Union Joint Programme – Neurodegenerative Disease Research (JPND) Multinational research projects on Personalised Medicine for Neurodegenerative Diseases/Instituto de Salud Carlos III grant AC19/00097 awarded to AR.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

REVIEW
published: 12 January 2021
doi: 10.3389/fnagi.2020.614650

Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases

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The coronavirus disease 2019 (COVID-19) has become a deadly pandemic with surging mortality rates and no cure. COVID-19 is caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) with a range of clinical symptoms, including cough, fever, chills, headache, shortness of breath, difficulty breathing, muscle pain, and a loss of smell or taste. Aged individuals with compromised immunity are highly susceptible to COVID-19 and the likelihood of mortality increases with age and the presence of comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, or chronic obstructive pulmonary disease. Emerging evidence suggests that COVID-19 highjacks mitochondria of immune cells, replicates within mitochondrial structures, and impairs mitochondrial dynamics leading to cell death. Mitochondria are the powerhouses of the cell and are largely involved in maintaining cell immunity, homeostasis, and cell survival/death. Increasing evidence suggests that mitochondria from COVID-19 infected cells are highly vulnerable, and vulnerability increases with age. The purpose of our article is to summarize the role of various age-related comorbidities such as diabetes, obesity, and neurological diseases in increasing mortality rates amongst the elderly with COVID-19. Our article also highlights the interaction between coronavirus and mitochondrial dynamics in immune cells. We also highlight the current treatments, lifestyles, and safety measures that can help protect against COVID-19. Further research is urgently needed to understand the molecular mechanisms between the mitochondrial virus and disease progression in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, Alzheimer's disease, diabetes, obesity, immune response, mitochondrial dynamics, lifestyle

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Edited by:
Thomas Wisniewski,
New York University, United States

Reviewed by:
Amandine Grimm,
University of Basel, Switzerland
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Received: *06 October 2020*
Accepted: *16 December 2020*
Published: *12 January 2021*

Citation:
Ganji R and Reddy PH (2021) Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases. Front. Aging Neurosci. 12:614650. doi: 10.3389/fnagi.2020.614650

INTRODUCTION

Coronaviruses are viruses that come from the *coronaviridae* family and *Nidovirales* order (Vallamkondu et al., 2020). When viewed with electron microscopy, coronaviruses have a crown-like appearance caused by the spike glycoproteins on their envelopes (**Figure 1**; Vallamkondu et al., 2020). Coronaviruses can use human lung alveolar epithelial cells as host cells for their survival and replication. In 2019, a novel coronavirus emerged, referred to as Severe Acute

Respiratory Syndrome coronavirus type-2 (SARS-CoV-2). It caused a worldwide pandemic with its disease, named by the World Health Organization (WHO) as the novel coronavirus disease discovered in 2019, or COVID-19.

COVID-19 causes a range of respiratory symptoms, varying with patient demographic makeup and medical history. These symptoms include sore throat, cough, fever, chills, headache, shortness of breath, difficulty breathing, muscle pain, and a loss of smell or taste (Huang et al., 2020; Li et al., 2020). It is transmitted *via* respiratory droplets and has a reproductive quotient (R0) of 2.2, meaning that a person infected with SARS-CoV-2 infects roughly 2.2 new individuals (Kandimalla et al., 2020). As of December 2020, there have been nearly 70 million cases worldwide and upwards of 1.5 million deaths [World Health Organization (WHO), 2020], and while many medications are being tested for efficacy, none have proven to be a one-for-all solution yet (Bhatti et al., 2020). Patients that are more likely to present with symptoms of COVID-19 are older individuals; the likelihood increases with age and with the presence of comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, or chronic obstructive pulmonary disease (Yang et al., 2020; Zhang et al., 2020), as well as obesity or dementia (Holder and Reddy, 2020). Those with the highest mortality rate seem to be older, male patients with various comorbidities (Onder et al., 2020).

Given the prevalence of older individuals among those who acquired COVID-19, it is necessary to explore the mechanisms that could encourage a link between aging and COVID-19 so that treatment formation may be better directed, and health professionals can better assess risks in these patients. As humans age, the speed and strength of their immune response weaken due to the loss of certain immune tissues such as the thymus, as well as poorer energy metabolism at the cellular level with mitochondria. The energy in the cell comes in the form of adenosine triphosphate (ATP) and is made by mitochondria when the cell is fueled with oxygen, as well as by glycolysis in the absence of oxygen. Mitochondria are also known to interact with viral particles when they infect human host cells, engaging interferon and cytokine release, stimulating inflammation, and influencing viral survival and replication (Khan et al., 2015; Tiku et al., 2020). Studying mitochondrial-based immunity against the SARS-CoV-2 may give insight into why older individuals, with lessened mitochondrial efficiency, maybe worse equipped to face COVID-19.

The purpose of our study is to explore the molecular link between mitochondria in aged individuals and SARS-CoV-2. Furthermore, we also highlighted the role of various age-related comorbidities such as diabetes, obesity, and neurological illnesses in increased mortality rates amongst the elderly with COVID-19.

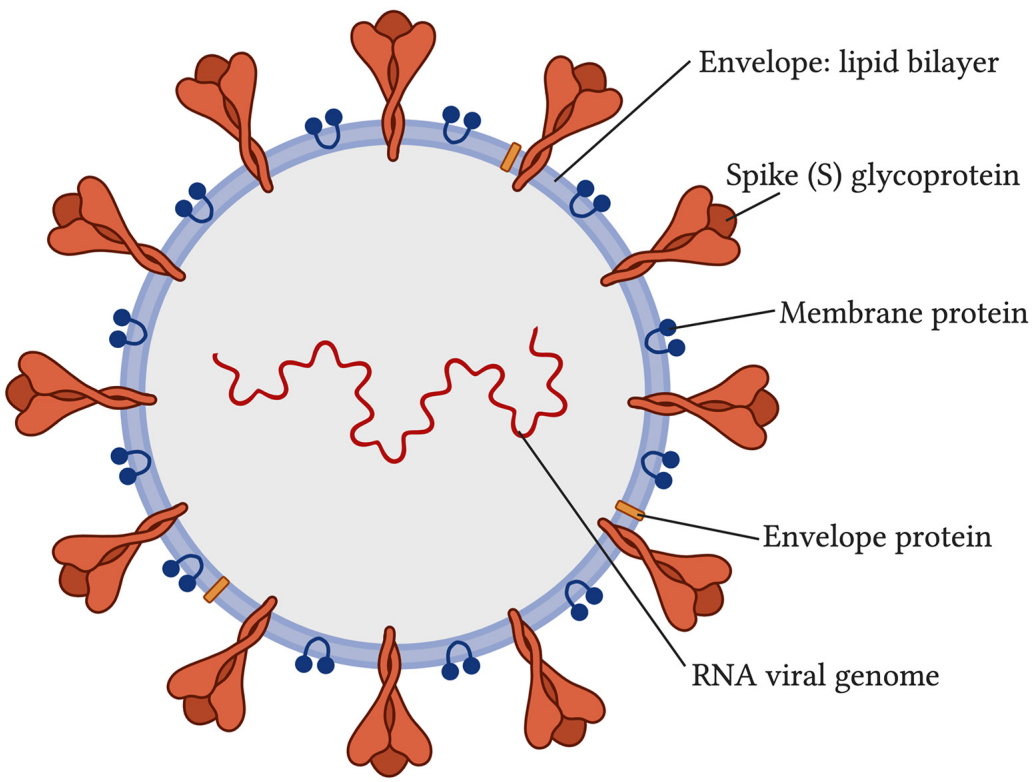

FIGURE 1 | Structure of severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2; Vallamkondu et al., 2020).

We also explore current treatments, lifestyles, and safety measures that can help protect against COVID-19.

MITOCHONDRIA AND IMMUNITY

Mitochondria are organelles with a double membrane that serves as a cell's primary source of energy production in the form of ATP and contribute to homeostasis, cell proliferation, cell death, and synthesis of amino acids, lipids, and nucleotides. In the event of an infection, mitochondria contribute to immunity by engaging the interferon system, altering their structure, and inducing programmed cell death (apoptosis; Ohta and Nishiyama, 2011).

Interferon Signaling and Mitochondria

Upon viral infection, the host's innate immune system recognizes certain patterns, such as viral nucleic acid sequences or viral proteins, when they attach to receptors on host cellular membranes, intracellularly and extracellularly. Their recognition activates signaling pathways that lead to the inflammatory response. There are different types of receptors that these viral components attach to, including toll-like receptors and retinoic acid-inducible gene-I-like receptors (RLRs; Takeuchi and Akira, 2009). Toll-like receptors are involved in activating type-I interferon, an inflammatory cytokine, and chemokine production and are found on the cell surface, endosome, and endoplasmic reticulum membranes (Takeuchi and Akira, 2009). RLRs are the cytosolic receptors that start the production of type-I interferon in nonimmune cells (Takeuchi and Akira, 2009) and can be found on mitochondria (Tal and Iwasaki, 2009).

These RLRs detect viral RNA in the cytoplasm and are involved in the recognition of RNA viruses such as paramyxoviruses, Japanese encephalitis virus, influenza virus, and picornaviruses (Kato et al., 2006). However, certain subtypes of RLRs may be involved in the detection of certain DNA viruses as well. For example, adenovirus and Herpes Simplex Virus Type 1 have a DNA-dependent RNA polymerase III that affects RLRs and stimulates interferon-β production, and the Epstein-Barr virus produces small RNA fragments that can activate RLRs (Samanta et al., 2006; Cheng et al., 2007; Chiu et al., 2009).

A component of the signaling pathway stemming from RLR activation is a molecule known as mitochondrial antiviral signaling protein (MAVS; Kawai et al., 2005). MAVS is located on the outer mitochondrial membrane (OMM; Seth et al., 2005) and upon activation, triggers transcription factors that will result in additional interferon production (Zhang et al., 2014). In addition to MAVS, the mitochondria-associated protein called "stimulator of interferon genes" and the mitochondrial protein mitofusin 2 are also involved in RLR cascades or work with MAVS (Ishikawa and Barber, 2008; Yasukawa et al., 2009). This evidence goes to show that mitochondria are an important part of interferon signaling in the immune system. Some viruses alter MAVS levels to prevent interferon production; the influenza A virus (Varga et al., 2012), the measles virus (Xia et al., 2014), the Newcastle disease virus (Meng et al., 2014), and the Hepatitis C virus (Ohta and Nishiyama, 2011) reduce or degrade MAVS as a way to prolong survival by reducing interferon signaling.

Mitochondrial Fission and Fusion Modulation

Viruses can manipulate mitochondrial fission and fusion to benefit viral survival (Holder and Reddy, 2020). Mitochondria can alter their structure through fission and fusion of their OMM and inner mitochondrial membrane (IMM), by functions involving GTPases related to dynamin (Tiku et al., 2020). The fusion of the OMM is mediated by proteins Mitofusin 1 and Mitofusin 2 *via* GTP hydrolysis, and fusion of the IMM is mediated by the protein optic atrophy 1, which is a GTPase present in the IMM (Tiku et al., 2020). Mitochondrial fusion is needed for the exchange of mitochondrial DNA, proteins, and metabolites (Archer, 2013). On the other hand, fission of the OMM is mediated by the cytosolic GTPase dynamin-related protein 1 (Drp1) *via* GTP hydrolysis (Mears et al., 2011). Upon finding a mitochondrial scission site, Drp1 interacts with mitochondrial fission factor and mitochondrial dynamics proteins 49 and 51 to constrict and cut the OMM (Mears et al., 2011; Loson et al., 2013). The mechanisms of mitochondrial fission are not well understood. Fission is needed for removing damaged parts of mitochondria to be cleared by mitophagy (autophagy of the mitochondria) and is needed during cell cycle replication (Mao and Klionsky, 2013). Thus, enhanced fission usually leads to increased mitophagy.

Some viruses may promote mitochondrial fusion to reduce the interferon pro-inflammatory response against viruses through a mechanism that involves mitofusin 2 inhibition of MAVS. For example, the dengue virus stimulates mitochondrial fusion *via* its nonstructural protein NS4B (Barbier et al., 2017), and HIV enhances fusion *via* its envelope protein gp120 (Fields et al., 2016). The SARS coronavirus (SARS-CoV-1) enhances fusion *via* its virulence factor ORF-9b (Shi et al., 2014). These virulence factors reduce the levels of Drp1, the fission-inducing protein, thus leading to unbalanced mitochondrial fusion, which is driven by mitofusin 2. As mitofusin 2 interacts with and inhibits MAVS, which typically increases interferons (Yasukawa et al., 2009) this can hinder the interferon response. Interestingly, SARS-CoV-1 uses the same ORF-9b to also reduce levels of MAVS directly, which further lowers the interferon response (Shi et al., 2014).

Some viruses induce mitochondrial fission to enhance mitophagy and alter the rate of apoptosis, usually *via* up-regulation or activation of Drp1 and/or degradation or inhibition of MAVS (Khan et al., 2015). Among these is the Hepatitis C virus *via* its core proteins and proteins E1-E2 (Kim et al., 2014), the Human cytomegalovirus *via* viral protein vMIA (McCormick et al., 2003), and the Hepatitis B virus *via* viral protein HBx (Kim et al., 2013). Fission mediated by these three particular viruses leads to inhibition of apoptosis so that the virus may survive for longer and further replicate (McCormick et al., 2003; Kim et al., 2013, 2014).

Due to the modulation by viruses on mitochondrial fusion and fission, their presence may lead to altered energy levels

by way of mitochondrial count and form. Viruses that cause mitochondrial fission and lead to inhibition of apoptosis can allow viral particles to survive unharmed for longer. Many patients often feel weak from a lack of energy when infected with a viral illness. This may be due to the poorer mitochondrial energy production as a result of the increased fission.

Cell Death

Apoptosis, or programmed cell death, is another important function of the cell influenced by the mitochondria. There is an extrinsic pathway to activate apoptosis, controlled by certain ligands binding to "death" receptors, and an intrinsic pathway that is controlled by mitochondria (Brenner and Mak, 2009). In this intrinsic pathway, the mitochondrial membrane is permeated and the mitochondrial membrane potential (MMP) is disrupted as the intermembrane space proteins spill into the cytoplasm (Shawgo et al., 2008). These proteins include cytochrome *c* (Liu et al., 1996), caspase-9 (Du et al., 2000), and apoptosis protease activating factor 1 that work together to form an apoptosome, which stimulates the final caspases to carry out cell death procedure (Cain et al., 2002).

MMP destabilization, which leads to apoptosis, is thought to occur by various mechanisms. First, there is the mechanism of selective OMM permeabilization (Kuwana et al., 2002). Bax and Bak, proteins that make up the Bax proapoptotic subfamily of Bcl-2 proteins, serve as pores on the mitochondrial membrane to maintain the MMP as well as release cytochrome c and calcium from within the mitochondria (Nutt et al., 2002). When another proapoptotic subfamily known as the BH3-only subfamily attaches to activated Bax/Bak, they enhance permeability and increase the chance of apoptosis (Chen et al., 2005). On the other hand, the antiapoptotic Bcl-2 subfamily (including Bcl-2 and Bcl-xL) can attach to activated Bax/Bak proteins and inhibit Bax/Bak by forming an antiapoptotic complex and leading to decreased apoptosis (Shawgo et al., 2008). A second mechanism involves the lipid bilayer makeup of the mitochondrial membrane and involves Bax creating rapid reorganization of the lipids that leads to structural stress and hole formation (Terrones et al., 2004). The last mechanism involves the stimulation of the permeability transition pore complex (PTPC) in the IMM (Shimizu et al., 1999). This is triggered by an overabundance of calcium or reactive oxygen species (Deniaud et al., 2008) and can be influenced by proteins from all parts of the mitochondria.

Viruses can use viral proteins that mimic Bcl-2 family members and other factors that are involved in the apoptosis pathways to manipulate the cell's lifespan as they see fit. **Table 1** demonstrates some common examples to illustrate this point.

SARS-CoV-2 AND MITOCHONDRIA

The novel SARS-CoV-2 uses its spike glycoprotein on the angiotensin-converting enzyme-2 (ACE-2) host receptor (Cao et al., 2020) to enter human host cells and host transmembrane serine protease 2 (TMPRSS2) to prime the spike protein for attachment (Hoffmann et al., 2020; **Figure 2**). The virus particle enters the cell *via* endocytosis, and it has been proposed that the spike protein needs to be cleaved by host enzymes for viral entry to take place (Ou et al., 2020). ACE-2 influences mitochondrial functions and a lack of ACE-2 correlates with decreased ATP production and altered activation of NADPH oxidase 4 in the mitochondria, which is normally used for ROS production (Singh et al., 2020) that can both protect the cell by destroying pathogens or trigger the infected cell to go into apoptosis. With the SARS-CoV-2 virus using ACE-2 receptors for its entry, the availability of ACE-2 for its usual functions may be impaired and contribute to symptom development. Additionally, some studies have suggested that the TMPRSS2 from SARS-CoV-2 also influences mitochondrial function by acting on the estrogen-related receptor alpha, which is a nuclear receptor that regulates transcription of mitochondrial functions and energy homeostasis (Xu et al., 2018; Hoffmann et al., 2020; Singh et al., 2020).

Once inside the cell, SARS-CoV-2 triggers a massive inflammatory response. Through the innate immunity functions triggered upon viral infection detailed above, cytokines such as TNF-α, INF-γ, and interleukin-10 arrive at infected cells and cause an increase in mitochondrial ROS production through gene expression upregulation and electron transport chain modulation (Saleh et al., 2020). Mitochondrial ROS then stimulates additional proinflammatory cytokine production (Li et al., 2013) as the virus continues to persist, eventually leading to a "cytokine storm" in which over-inflammation can cause fatal harm if adaptive immunity does not take over in time. The immune response also causes the mitochondria to divert some energy away from ATP production to contribute to ROS production, which can harm the mitochondria in overwhelming amounts, leading to membrane permeabilization and apoptosis (Saleh et al., 2020). If severely damaged mitochondria release their contents into the cytosolic space, they stimulate the production of more cytokines such as IL-1β and IL-6 which are hallmarks for COVID-19 (Saleh et al., 2020).

Another mechanism of mitochondrial disruption employed by SARS-CoV-2 involves ferritin as evidenced by the high levels of ferritin in those with severe outcomes (Aguirre and Culotta, 2012). A normally functioning mitochondrion uses this iron to make heme, create iron-sulfur clusters, and store as mitochondrial ferritin (Saleh et al., 2020), but an overload of iron can lead to oxidative stress and impair mitochondrial function by reducing oxygen consumption by the mitochondria (Tang et al., 2020). Additionally, the ferritin overload can disrupt glucose tolerance in these cells with mitochondrial oxidative stress (Tang et al., 2020), which has implications for diabetic patients.

It is theorized that SARS-CoV-2 uses double-membrane vesicles derived from mitochondrial membranes to hide and protect itself inside the cell (Singh et al., 2020). This theory is based on evidence of HIV using ER-derived double-membrane vesicles (Somasundaran et al., 1994) and an observation that a point mutation in the coronavirus in rodents was shown to decrease ER-derived vesicles and increase localization of the virus to mitochondria at the same time (Clementz et al., 2008). Furthermore, a study found 5′ and 3′ untranslated regions on SARS-CoV-2 unique for mitochondrial localization, although further work needs to be done on this finding (Wu et al., 2020). When comparing SARS-CoV-1 and SARS-CoV-2, both are found to contain open reading frame ORF-9b, ORF-7a, and

TABLE 1 | Viral Effects on apoptosis *via* the internal mechanism of mitochondrial influence.

ANTI-APOPTOTIC **Virus; protein**	**Mechanism**	**Notes**
Adenovirus; E1B-19K	Bcl-2 mimic	Han et al. (1996)
African swine fever virus; A179L	Bcl-2 mimic	Brun et al. (1996)
Myxoma virus; M11L	Bcl-2 mimic	Douglas et al. (2007)
Epstein-Barr virus; BHRF1	Bcl-2 mimic	Hickish et al. (1994)
Human herpesvirus 8; Kaposi's sarcoma-associated Bcl-2	Bcl-2 mimic	Cheng et al. (1997)
Cytomegalovirus; vMIA	PTPC inhibition	Goldmacher (2002)
SARS-CoV-1; NSP15	Inhibited MAVS-induced apoptosis	Dose-dependent and with specificity as it did not inhibit staurosporine-induced apoptosis Lei et al. (2009).
PRO-APOPTOTIC **Virus; protein**	**Mechanism**	**Notes**
Human papillomavirus; E1 and E4	Disrupt the intracellular keratin network and cause mitochondria to accumulate next to the nucleus and lose MMP	Doorbar et al. (1991)
Vesicular stomatitis virus; matrix protein M	Interfere with the Bcl-2 family	Gadaleta et al. (2005)
Avian encephalomyelitis virus; 2C	Activates caspase-9	Liu et al. (2004)
Hepatitis C virus; NS4A	Disrupts MMP	Nomura-Takigawa et al. (2006)
Hepatitis C virus; NS3	Induces caspase-8	Prikhod'ko et al. (2004)
Influenza A; PB1-F2	Disrupts MMP	Chanturiya et al. (2004)
Human immunodeficiency virus type 1; Vpr	Rapid dissipation of the MMP and interaction with components of the PTPC	Jacotot et al. (2000)
SARS-CoV-1; gene 7a	Inhibit antiapoptotic Bcl-xL in cultured cells	Schaecher et al. (2007)
SARS-CoV-1; ORF-6	Induce caspase-3 mediated apoptosis	Ye et al. (2008)

ORF-8b, which localize to the mitochondria, in the case of SARS-CoV-1, to alter MAVS function and mitochondrial function (Chen et al., 2007; Shi et al., 2014). SARS-CoV-2 additionally had ORF-3a present but ORF-3b absent (Singh et al., 2020; **Figure 3**). By encouraging the formation of double-membrane vesicles from the mitochondrial membrane or even the ER membrane, SARS-CoV-2 can safely avoid attacks from ROS and host proteases that threaten its survival. Meanwhile, the ROS is lingering around and can attack healthy tissue.

There is evidence of the SARS-CoV-1 ORF-9b causing mitochondrial fusion by the degradation of Drp1 by proteasomes (Shi et al., 2014; Holder and Reddy, 2020), and given the similarities in the genome, it is likely that the SARS-CoV-2 ORF-9b is lowering the amount of Drp1 as well, leading to more fusion. Mitochondrial fusion, which partly occurs *via* mitofusin 2, may lead to a hindered interferon response *via* inhibition of MAVS (Yasukawa et al., 2009). While this suggests that the lowered interferon numbers may take away from interferon-induced apoptosis specifically (Chawla-Sarkar et al., 2003), we must consider that SARS-CoV-1 is known to induce apoptosis *via* other factors such as ORF-6 and -7a (Schaecher et al., 2007; Ye et al., 2008). Comparing both SARS viruses indicates that SARS-CoV-2 may induce apoptosis when its need for the human host cell is over. Additionally, there is some evidence for ferroptosis or ferritin-induced apoptosis with iron overload. Defective mitochondria cannot metabolize iron as they normally would, leading to iron buildup and ferroptosis (Saleh et al., 2020). This all implies a greater number of cell death with COVID-19.

SARS-CoV-2 may also interfere with platelet count and coagulation, specifically with increasing coagulability and decreasing platelet count as the severity of COVID-19 increases (Tang et al., 2020; Terpos et al., 2020). Apart from the increasing risk of stroke, the increased coagulation and decreased platelets are impairing the cell's ability to undergo mitophagy (Lee et al., 2016). When platelets cannot undergo mitophagy, they undergo apoptosis, which leads to increased thrombus formation; this is especially true in diabetic patients who suffer from oxidative-stress destroying their mitochondria yet hindering mitophagy (Lee et al., 2016). COVID-19 patients suffer from hyper inflammation and iron buildup, both of which are stressful to platelets, and thus contribute to the decreased platelet count (Saleh et al., 2020).

Men have had more severe outcomes with COVID-19 than women. While the cause is unknown, it has been speculated that the TMPRSS2 receptor is involved (Singh et al., 2020). TMPRSS2 can be induced by androgen, but not estrogen, and localize to the mitochondria to regulate mitochondrial function (Singh et al., 2020). Older individuals have also had worse outcomes. Aging is accompanied by a decrease in mitochondrial function, which has been shown to worsen the severity of viral illness and is also linked to numerous age-related diseases.

MITOCHONDRIA AND AGING

Inflammation

"Inflammaging" is a phenomenon that describes worsened susceptibility to hyperinflammation among those who age (Hager et al., 1994; Soysal et al., 2016). Mitochondria may contribute to inflammaging when they release their intramitochondrial proteins and mitochondrial DNA (mtDNA) into cytosolic space upon membrane permeabilization, leading

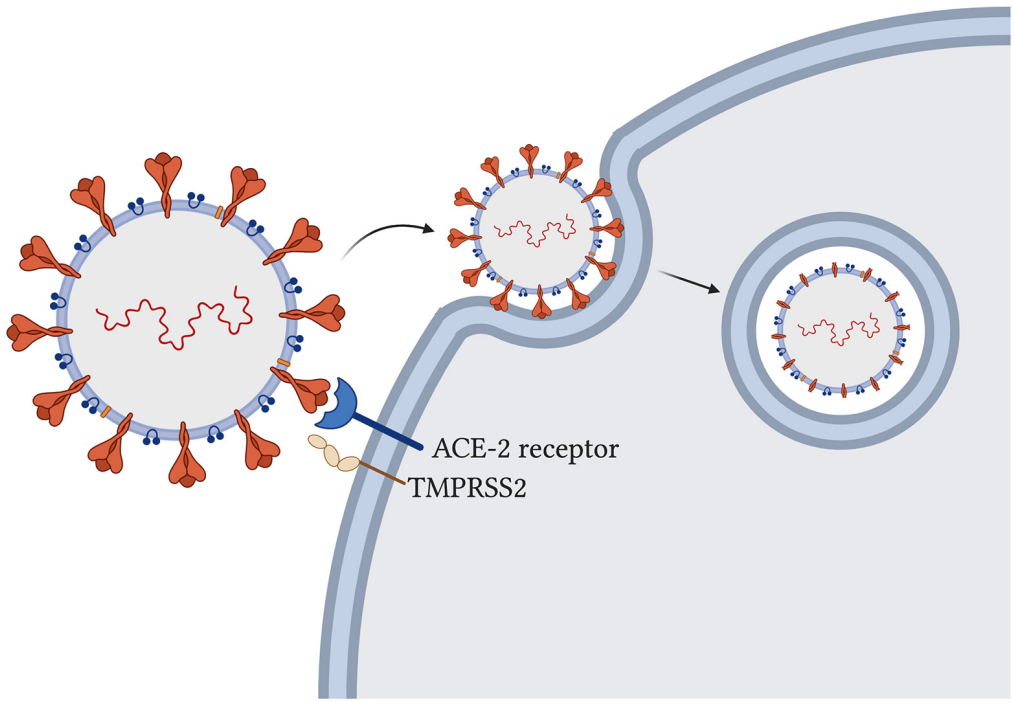

FIGURE 2 | SARS-CoV-2 entry into host cells in the lung. Spike glycoproteins on the SARS-CoV-2 particle attach to human angiotensin-converting enzyme-2 for entry (Hoffmann et al., 2020). Host transmembrane serine protease 2 primes the spike protein for attachment (Hoffmann et al., 2020). Virus particle enters through endocytosis and spike proteins are cleaved (Ou et al., 2020).

to recognition by intracellular immune receptors such as toll-like receptor-9 that activate neutrophil recruitment and cytokine production from monocytes (Jang et al., 2018). Moreover, levels of circulating mtDNA were found to steadily increase in individuals after 50 years of age (Pinti et al., 2014).

Inflammasomes, or multiprotein complexes that are a part of innate immunity signaling, are found to be involved in aging and particularly in age-related diseases through their ability to activate caspase-1 (Furman et al., 2017). Caspase-1 activation can be harmful to mitochondria, and MAVS, mitochondrial membrane cardiolipin, ROS, and mtDNA from damaged mitochondria were all found to activate inflammasomes (Jang et al., 2018). Furthermore, SARS-CoV-2 may activate inflammasomes (Shah, 2020), further putting the elderly at risk of hyperinflammation.

mtDNA Mutations and Increased ROS

Mitochondrial DNA sees more mutations than nuclear DNA, and age-related increases in mutated mtDNA and increased ROS levels have been causally connected (Reddy and Beal, 2005; Reddy, 2006; Kuka et al., 2013; Kang et al., 2016; Oliver D. M. A. and Reddy, 2019). This may be due to the findings that mtDNA is placed spatially close to the ROS-producing machinery of the respiratory chain (Chistiakov et al., 2014) and mutations in mtDNA can lead to increased ROS production and mitochondrial malfunction (Wallace, 2010). While the most widely accepted theories suggest that ROS only led to detrimental effects on mitochondrial health, there has also been evidence that some ROS is required to balance redox reactions and stimulate anti-oxidant functions to keep the cell alive—even contributing to longevity (Schulz et al., 2007; Yang and Hekimi, 2010). Nevertheless, ROS in amounts larger than necessary cause age-related cellular damage (Chistiakov et al., 2014). Seeing as SARS-CoV-2 invokes ROS production indirectly, an aged person's cells may face an even greater amount of ROS exposure upon infection with this virus compared to healthy young individuals.

Quality Control of Mitochondria

In combination with lessened ATP production, there is a decrease in mitophagy as a person ages (García-Prat et al., 2016), which not only contributes to unregulated inflammasome activity (Jang et al., 2018) but also an accumulation of mitochondria that may no longer produce energy efficiently. Mitophagy is a protective function of the cell that keeps inflammation at a manageable level by removing damaged mitochondria that could contribute to hyper inflammation, especially among already susceptible older patients. Without autophagy or mitophagy, levels of ROS rise and cause oxidative stress and related tissue damage (Yan and Finkel, 2017).

Mitochondrial fission and fusion are important functions that change with age and in neurodegenerative diseases

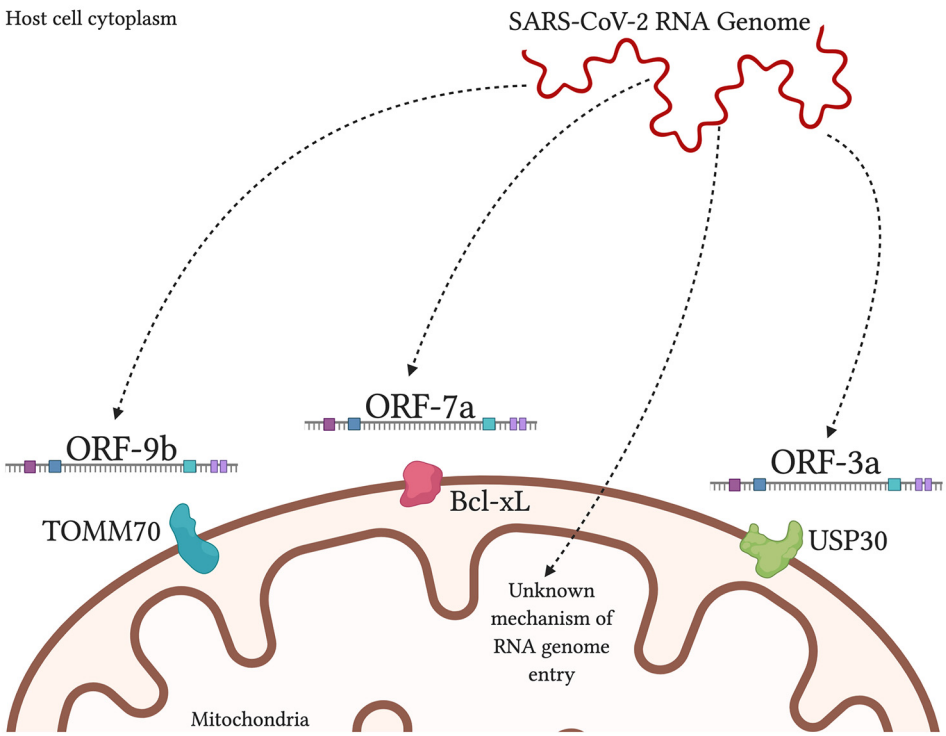

FIGURE 3 | SARS-CoV-2 products localize to the mitochondria inside human host cells. SARS-CoV-2 RNA genome has been shown to localize in the mitochondrial matrix through an unknown mechanism. Viral protein ORF-9b interacts with translocase of outer mitochondrial membrane-70 (TOMM70), a host receptor that may affect activation of the interferon response (Gordon et al., 2020). Viral ORF-7a localizes to transmembrane protein Bcl-xL on the OMM, causing the promotion of apoptosis (Schaecher et al., 2007). Viral ORF-3a is theorized to localize to ubiquitin-specific protease-30 (USP30), which is typically involved in mitochondrial fission/fusion and mitophagy; and the sequence of ORF-3a that interacts with USP30 has been found in SARS-CoV-2 (Singh et al., 2020).

(Reddy et al., 2011; Kandimalla and Reddy, 2016; Oliver D. and Reddy, 2019). Mitochondrial biogenesis occurs from growth to increase mass and division to increase the number (Chistiakov et al., 2014; Pradeepkiran and Reddy, 2020). Despite reduced mitophagy and dysfunctional mitochondria, the overall mitochondrial count decreases with age in skeletal muscle (Crane et al., 2010) and this may be due to decreased biogenesis (Chistiakov et al., 2014). The fission and fusion balance tend to fall off with age, with fission decreasing and leading to poorer quality control for the mitochondria as well as decreased mitophagy (Chistiakov et al., 2014). This may be due in part to dysregulation of proteins that are involved in fission, including DRP1 (Udagawa et al., 2014). While fusion has been found to protect mitochondria against starvation-induced autophagosomal degradation (Shi et al., 2014), an unbalanced ratio may be harmful. As the ratio for fusion increases, so does the difficulty for a cell to dispose of damaged, overlarge mitochondria. Improperly structured mitochondria become stressed and turn to increased ROS production (Chistiakov et al., 2014), adding to the initial problem (**Figure 4**). SARS-CoV-1 is observed to stimulate mitochondrial fusion (Shi et al., 2014), and SARS-CoV-2 can be expected to do the same given the genomic similarities. As an elderly person is already subject to increased mitochondrial fusion, they are in a worse position to fend off the additional burden of a virus with such capability. However, some studies indicate an increase in fission in elderly animal models (Chaudhari and Kipreos, 2017), so the evidence behind an increase in one function over the other is not complete and still requires further study and elaboration.

The impaired mitochondria quality through defective mitophagy and fusion/fission imbalance may contribute to a decrease in energy production with increasing age. A study on skeletal muscle found that mitochondrial respiration capacity declined by about 50% in older patients compared to young patients, with an accompanying decline in ATP (Conley et al., 2000). Aging was also shown to decrease ATP synthase activity (Frenzel et al., 2010). As fatigue and muscle weakness is among the symptoms of COVID-19, those with aged mitochondria are matched to this shortness of energy.

Oxidative Stress and Calcium Dyshomeostasis in Mitochondria

Another important factor to consider in the mitochondria's role in aging has to do with mitochondrial permeability transition pores (mPTP), which sit on the IMM and open up in response to excessive calcium in the mitochondria (Panel et al., 2018). The mPTP's sensitivity to calcium is increased when the cell is under oxidative stress

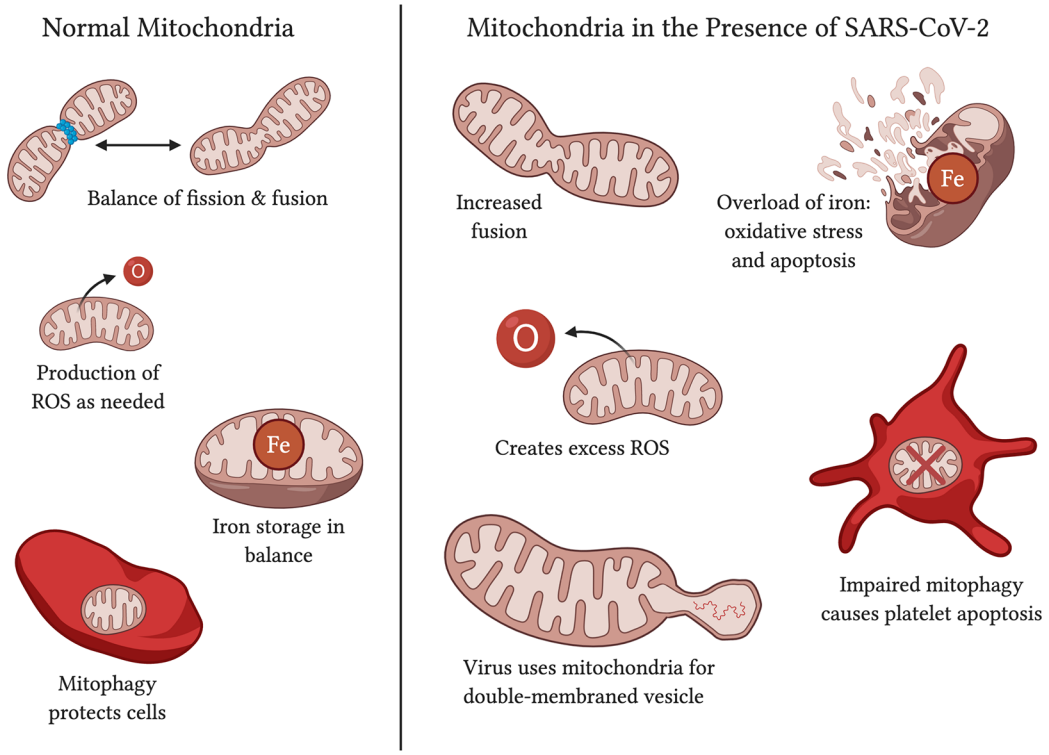

FIGURE 4 | Functions of normal mitochondria vs. effects on mitochondria in the presence of SARS-CoV-2. Normal mitochondria have a balance on fission and fusion, produce ROS only in quantities necessary, have balanced iron storage, and use mitophagy to upkeep functional mitochondria and protect the cell against damage. In the presence of SARS-CoV-2, mitochondria may have increased fusion (Shi et al., 2014; Zhang et al., 2020), an excess of ROS production (Kuka et al., 2013; Kang et al., 2016), too much iron in storage (Saleh et al., 2020), and impaired mitophagy that leads to platelet apoptosis (Lee et al., 2016; Tang et al., 2020). SARS-CoV-2 affects mitochondria may also serve as a source of double-membraned vesicles for the virus to travel in (Singh et al., 2020).

(Halestrap and Richardson, 2015). As humans age, basal calcium levels increase and affect mPTPs to open their pores more often (Panel et al., 2018). This is observed to have a more detrimental effect on cardiac muscle because calcium is used as a communication tool between the sarcoplasmic reticulum and mitochondria. Without the control of mPTPs in releasing calcium into the cytosol in regulated amounts, the failure of calcium transfer, decreased energy production, and increase in oxidative stress may altogether contribute to heart failure in older individuals (Szalai et al., 2000; Kohlhaas and Maack, 2013; Fernandez-Sanz et al., 2014). Myocardial infarctions, a type of heart attack, are also linked to mPTP activation; studies found that mPTP opening and apoptosis are increased in aged cardiac cells (Fernandez-Sanz et al., 2015), possibly as the result of oxidative stress in aging (Ferrara et al., 2008).

Neurological Diseases

The role of mutated mtDNA, oxidative damage, decreased energy production and increased ROS production all come together in age-related neurological diseases. Alzheimer's disease is associated with increased free radical production and oxidative stress, mitochondrial dysfunction, and impaired ATP production (Beal, 2005; Reddy and Beal, 2005, 2008). While definitive evidence for an increase in mtDNA changes has not yet surfaced, a few studies point in that direction (Coskun et al., 2004) as well as towards disrupted axonal transport of mitochondria in AD neurons (Stokin et al., 2005; Calkins et al., 2011). Alzheimer's causes a buildup of amyloid precursor protein and amyloid-beta, both of which are found on the mitochondrial membrane (Crouch et al., 2005; Manczak et al., 2004), where they induce increased free radical production, decrease cytochrome oxidase activity, and decrease ATP production (Parker et al., 1990; Smith et al., 1996; Gibson et al., 1998).

Parkinson's disease analysis shows disease-specific proteins in mitochondrial membranes and matrix (Reddy, 2009; Reddy and Reddy, 2011). Additionally, PINK1 protein overexpression disrupts the MMP which leads to impaired respiration (Reddy, 2009; Pradeepkiran and Reddy, 2020). Parkin is another protein, a ligase, that is associated with the OMM and induces free radical production (Reddy, 2009). Huntington's disease shows a mutated huntingtin protein bound to the OMM and also induces free radical production, and this disease shows the dysfunctional movement of mitochondria in cells affected by Huntington's (Reddy, 2009; Reddy et al., 2009; Reddy and Shirendeb, 2012). Normally functioning SOD1 proteins seek out and counteract ROS to protect cellular function, but in Amyotrophic Lateral Sclerosis (ALS), mutated SOD1 contributes to oxidative stress built up in free radicals and mitochondrial dysfunction (Reddy, 2009; Reddy and Reddy, 2011).

Given the evidence for mitochondrial involvement in both age-related diseases and SARS-CoV-2, it is not difficult to see how it is easier for the virus to induce more severe outcomes in those with compromised mitochondria, especially those with neurological diseases and diabetes.

SARS-CoV-2 and Aging

Older individuals lose acquired immunity as they age, and the innate immune system tries to compensate for that by increasing inflammation signals such as CRP-1, IL-6, and fibrinogen among others (Franceschi et al., 2007; Soysal et al., 2016). Notably, C-reactive protein and IL-6 are significantly increased in the response to SARS-CoV-2 in severely ill patients (Gong et al., 2020). Fibrinogen, which is involved in the coagulation process that contributes to thrombosis formation and vascular weakening, is also observed to be increased in response to SARS-CoV-2 (Tang et al., 2020; Terpos et al., 2020). Sustained inflammation can lead to cell destruction and apoptosis. SARS-CoV-2 can cause hyper inflammation, and in an elderly person prone to an over-stimulated inflammatory response, this combination can make them more susceptible to death by "cytokine storm" and offers a possible explanation for the increased mortality among the elderly population (Jeyaraman et al., 2020).

Aging cells embody senescence in part from an increase in mitochondrial dysfunction (Wiley et al., 2016). Given the negative effects on mitochondrial health by SARS-CoV-2 discussed previously, an aged person is starting with already weakened mitochondria and facing a disease that affects mitochondria. This progression can only lead to worsened outcomes. Senescence also affects macrophages, which have protective effects on the lungs during a SARS-CoV-2 infection; without properly functioning macrophages, the body's response to SARS-CoV-2 will be weaker (Liu et al., 2020). Older individuals were also found to have increased levels of mtDNA in the cytoplasm (Pinti et al., 2014), and due to mtDNA's role in inducing innate immunity and increasing inflammation, this is likely another mechanism that contributes to the lethal levels of inflammation seen in older COVID-19 patients (Singh et al., 2020).

Diabetes and Obesity in SARS-CoV-2

ACE-2 is an enzyme that serves in the renin-angiotensin system to adjust water volume as needed and holds the receptor for SARS-CoV-2 to enter in the lungs. ACE-2 works as a "negative" regulator by cleaving angiotensin II so that it does not overwhelm the body with increased blood pressure (Obukhov et al., 2020). Increasing age and uncontrolled diabetes both correlate with a decreasing amount of ACE-2 expression (Xie et al., 2006; Obukhov et al., 2020). The use of ACE-2 receptors for cell entry by SARS-CoV-2 can exacerbate the lower availability of the enzyme for its anti-inflammatory purposes and contribute to unchecked blood pressure and inflammation in diabetics.

Diabetics who control their condition with ACE-inhibitors and angiotensin II-blockers see some upregulation of ACE-2, although not likely to above-normal levels (AlGhatrif et al., 2020) but this could protect against severe COVID-19. Those who take the drug Metformin, usually for diabetes, have also seen less severe COVID-19 infections compared to those who did not (Scheen, 2020).

Those with obesity have increased adipose tissue which comes with associated meta-inflammation, a state of chronic, low-grade inflammation (Mauvais-Jarvis, 2020). This creates an environment that makes it more likely for SARS-CoV-2 to trigger a cytokine storm and cause the more severe, and sometimes lethal, consequences of COVID-19 (Mauvais-Jarvis, 2020). With the slightly lowered anti-inflammatory capabilities in diabetics *via* loss of ACE-2 receptors, the meta-inflammation of obese patients, and the lowered quality of mitochondrial function and protection in elderly patients, it can be theorized that older patients with comorbidities have a combination of risky features that make SARS-CoV-2 infection more likely to be severe.

TREATMENTS AND PREVENTION FOR SARS-CoV-2

Medications currently approved for use in COVID-19 patients include repurposed drugs such as hydroxychloroquine, ribavirin, lopinavir-ritonavir, darunavir, and cobicistat, favipiravir, arbidol, remdesivir, and combination therapies (Bhatti et al., 2020; Kandimalla et al., 2020), most of which are antivirals against other viruses. Vaccines against SARS-CoV-2 are still in their infancy and are variously targeting spike proteins (Kandimalla et al., 2020), but they may not be as effective in elderly patients due to the decline of adaptive immunity with age.

To target mitophagy, patients could use calorie restriction to conserve existing mitochondrial shape (Khraiwesh et al., 2014), or polyamine spermidine to increase autophagy/mitophagy (Eisenberg et al., 2016). Urolithin A, found in pomegranates, is also known to encourage mitophagy (Ryu et al., 2016). By improving mitophagy, we reduce inflammation and give the elderly a better chance of surviving the immune response. Experimentally, mitochondrial transfer from bone marrow stromal cells is effective in protecting against acute lung injury (Islam et al., 2012), and is a technique that can be used here, although there is not much evidence of current use.

Exercise has been shown to not only protect against mitochondrial decline but aging itself (Fiuza-Luces et al., 2013; Garatachea et al., 2015). Maintaining muscle mass and strong vasculature encourages the body to keep your mitochondria alive and well. Over years of exercise, your body adapts to become more stress-resistant, homeostatic, and protected against chronic illnesses and cancers (Nilsson et al., 2019). When it comes to the lungs, breathing exercises have been recommended to be useful in training your respiratory muscles and increase lung capacity; while there are yet to be any controlled experiments on the effectiveness of this method, physical therapists and physicians around the globe are recommending the preventative measure [Lien, 2020; American Lung Association (ALA), 2020].

Along those lines, consuming foods with high antioxidant properties, such as raw cacao, berries, matcha, pecans, artichokes, beets, kale, and spinach can help prevent the damage caused by ROS. Anti-inflammatory foods such as heart-healthy oils, fish,

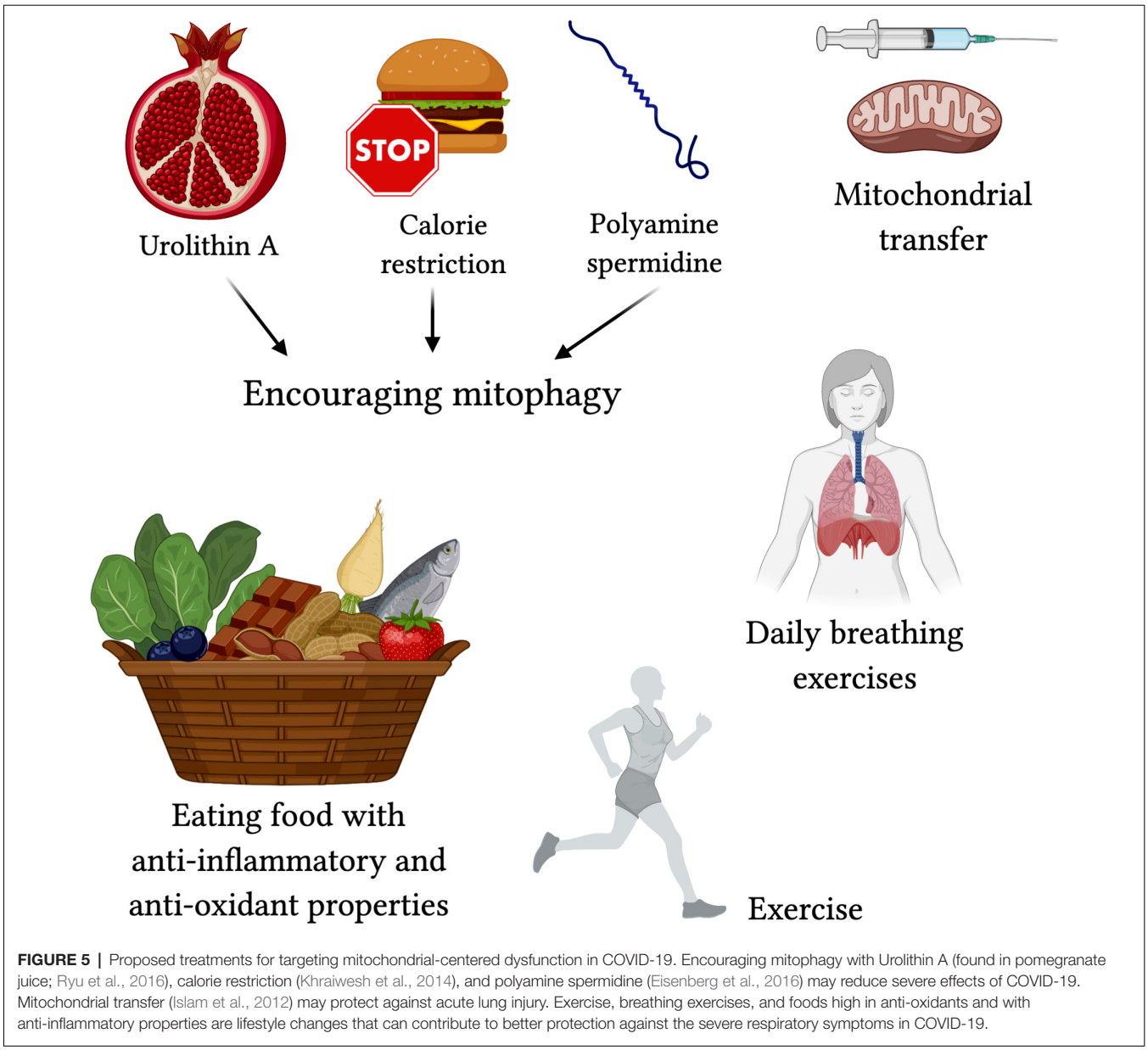

FIGURE 5 | Proposed treatments for targeting mitochondrial-centered dysfunction in COVID-19. Encouraging mitophagy with Urolithin A (found in pomegranate juice; Ryu et al., 2016), calorie restriction (Khraiwesh et al., 2014), and polyamine spermidine (Eisenberg et al., 2016) may reduce severe effects of COVID-19. Mitochondrial transfer (Islam et al., 2012) may protect against acute lung injury. Exercise, breathing exercises, and foods high in anti-oxidants and with anti-inflammatory properties are lifestyle changes that can contribute to better protection against the severe respiratory symptoms in COVID-19.

fruits, nuts, garlic, herbs, and chocolate do not go amiss either (**Figure 5**).

CONCLUSIONS AND FUTURE DIRECTIONS

There are many avenues involving mitochondria and their roles in inflammation that can offer answers as to why SARS-CoV-2 is impacting the elderly population so harshly, especially those that have comorbidities. Therefore, the role of mitochondria should not be ignored in the direction that treatment discovery takes. There are several links between aging mitochondria and weakened immunity; the avenues include over-stimulated or sustained inflammatory responses with interferon and cytokine release, regulation of fission and fusion, mitochondrial biogenesis, and interference of apoptosis and mitophagy. Many pathogens have shown a tendency to affect mitochondria as a way to influence host behavior once inside a cell by affecting these functions, from bacteria to parasites to viruses similar to the SARS-CoV-2.

SARS-CoV-2 enters the cell *via* the ACE-2 receptor and sends its genetic material towards the mitochondria to influence ROS production, mitophagy, iron storage, platelet coagulability, and cytokine production stimulation. These functions are already suffering in aging patients. In those with comorbidities, the impaired mitochondrial functions amplify other issues that contribute to severe outcomes, such as ferritin storage in diabetes and increased coagulability in heart disease. This could provide a reason as to why older, comorbid patients have the most severe

outcomes with COVID-19 and offer one direction for developing drug therapy.

While scientists around the world grapple with finding the definitive cure to the novel disease that is COVID-19, there are many things one can do at home to give themselves the best chance at survival. Apart from medications targeted at strengthening the mitochondria, exercise, fresh foods, breathing practices, and general preventative medicine practices can help the body protect itself.

AUTHOR CONTRIBUTIONS

PR contributed to the conceptualization and formatting of the article. RG and PR are responsible for writing, original draft preparation, and finalization of the manuscript. PR is responsible for funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

The research presented in this article was supported by the National Institutes of Health (NIH) grants AG042178, AG047812, NS105473, AG060767, AG069333, and AG066347.

ACKNOWLEDGMENTS

We sincerely thank Ms. Hallie Morton for the critical reading of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 18 January 2021
doi: 10.3389/fnagi.2020.625781

The Impact of COVID-19 Quarantine on Patients With Dementia and Family Caregivers: A Nation-Wide Survey

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OPEN ACCESS

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Received: 03 November 2020
Accepted: 21 December 2020
Published: 18 January 2021

Citation:
Rainero I, Bruni AC, Marra C, Cagnin A, Bonanni L, Cupidi C, Laganà V, Rubino E, Vacca A, Di Lorenzo R, Provero P, Isella V, Vanacore N, Agosta F, Appollonio I, Caffarra P, Bussè C, Sambati R, Quaranta D, Guglielmi V, Logroscino G, Filippi M, Tedeschi G, Ferrarese C and the SINdem COVID-19 Study Group (2021) The Impact of COVID-19 Quarantine on Patients With Dementia and Family Caregivers: A Nation-Wide Survey. Front. Aging Neurosci. 12:625781. doi: 10.3389/fnagi.2020.625781

Introduction: Previous studies showed that quarantine for pandemic diseases is associated with several psychological and medical effects. The consequences of quarantine for COVID-19 pandemic in patients with dementia are unknown. We investigated the clinical changes in patients with Alzheimer's disease and other dementias, and evaluated caregivers' distress during COVID-19 quarantine.

Methods: The study involved 87 Italian Dementia Centers. Patients with Alzheimer's Disease (AD), Dementia with Lewy Bodies (DLB), Frontotemporal Dementia (FTD), and Vascular Dementia (VD) were eligible for the study. Family caregivers of patients with dementia were interviewed by phone in April 2020, 45 days after quarantine declaration. Main outcomes were patients' changes in cognitive, behavioral, and motor symptoms. Secondary outcomes were effects on caregivers' psychological features.

Results: 4913 patients (2934 females, 1979 males) fulfilled the inclusion criteria. Caregivers reported a worsening in cognitive functions in 55.1% of patients, mainly in subjects with DLB and AD. Aggravation of behavioral symptoms was observed in 51.9% of patients. In logistic regression analysis, previous physical independence was

associated with both cognitive and behavioral worsening (odds ratio 1.85 [95% CI 1.42–2.39], 1.84 [95% CI 1.43–2.38], respectively). On the contrary, pandemic awareness was a protective factor for the worsening of cognitive and behavioral symptoms (odds ratio 0.74 [95% CI 0.65–0.85]; and 0.72 [95% CI 0.63–0.82], respectively). Approximately 25.9% of patients showed the onset of new behavioral symptoms. A worsening in motor function was reported by 36.7% of patients. Finally, caregivers reported a high increase in anxiety, depression, and distress.

Conclusion: Our study shows that quarantine for COVID-19 is associated with an acute worsening of clinical symptoms in patients with dementia as well as increase of caregivers' burden. Our findings emphasize the importance to implement new strategies to mitigate the effects of quarantine in patients with dementia.

Keywords: quarantine, COVID-19, dementia, Alzheimer's disease, BPSD, caregiver burden

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is, nowadays, a global public health emergency (Palacios Cruz et al., 2020). By December 8, 2020, over 66 million confirmed cases of COVID-19 with more than 1.530.000 deaths worldwide have been reported to the World Health Organization. Older adults and patients with certain comorbidities, many of whom are of advanced age, are particularly susceptible to more severe consequences of the disease (Shahid et al., 2020). The impact of the pandemic to the healthcare systems has been disruptive, and prevention as well as treatment services for patients with non-communicable diseases have been severely reduced.

Trying to slow down the spread of pandemic, several governments launched mitigation strategies, based mainly on quarantine. Quarantine is efficacious in reducing incidence and mortality during outbreaks of infectious diseases, and preliminary indications suggest that this strategy is effective also in the COVID-19 pandemic (Nussbaumer-Streit et al., 2020). However, home confinement is an unpleasant experience, due to the significant limitations in physical, cognitive, and social activities. Studies related to the 2003 outbreak of severe acute respiratory syndrome (SARS) in China and Canada, as well as the 2014 Ebola outbreak in Africa, showed that quarantine is associated with several negative psychological effects, like depression, irritability, anger, and insomnia (Hawryluck et al., 2004; Barbisch et al., 2015; Brooks et al., 2020; Gualano et al., 2020). Deaths by suicide increased in older adults during the SARS epidemic in Hong Kong (Cheung et al., 2008). In addition, long-lasting psychiatric effects of quarantine have been reported (Mak et al., 2009).

Individuals with Alzheimer's disease and other dementias are among the most vulnerable persons in the society, and the COVID-19 outbreak is likely to have further exacerbated their frailty (Wang et al., 2020). Quarantine effects in dementia patients and family caregivers have never been adequately investigated. All the negative effects of quarantine previously reported may be exacerbated in individuals with dementia, whose physical and social isolation may amplify the functional limitations and the pre-existing conflicts within the family. Patients with dementia living at home significantly depend on family caregivers for assistance, and caring for dementia patients causes a significant burden in caregivers (Chiao et al., 2015; Raggi et al., 2015; Brown et al., 2020). Higher levels of cognitive, behavioral and motor impairment in patients with dementia are associated with greater burden and distress in their caregivers (Black et al., 2018; Yang et al., 2019; Xiong et al., 2020). Therefore, there is an urgent need to investigate clinical and psychological changes due to quarantine in patients with dementia and their caregivers.

This study aimed at evaluating the effects of quarantine in Italian patients with different types and severity of dementia and their caregivers. Approximately 45 days after quarantine declaration by the Italian government, we interviewed the family caregivers of persons with dementia referring to several Italian Centers for Cognitive Disorders and Dementia (CDCDs), investigating patients' variations in cognitive, behavioral, and motor symptoms. Besides, we evaluated the changes in prescribed medications, caregiver's burden, and changes in health services provided by the Italian National Health Service.

MATERIALS AND METHODS

Study Design, Centers and Participants

This is a multicentric, nation-wide survey. Eighty-nine Italian CDCDs were initially recruited for the study. First of all, a semi-structured questionnaire (see **Supplementary Material**) was administered to the Director of each Centre in order to evaluate its qualitative and quantitative characteristics, and variations in clinical activities after quarantine declaration. Due to the quarantine rules, all the out-patients visits were stopped. Therefore, the clinical staff members of each CDCD consecutively contacted by phone the family caregivers of patients registered in the waiting list. After an oral consent, a semi-structured, self-made interview gathering demographic and clinical data on the patient and the caregiver was administered (see **Supplementary Material**). Inclusion criteria were a diagnosis of one of the most common forms of dementias including: (1) Alzheimer's Disease (AD), (2) Dementia with Lewy Bodies (DLB), (3)

Frontotemporal Dementias (FTD), and (4) Vascular Dementia (VD). Exclusion criteria included current or previous diagnosis of other forms of dementias, mild cognitive impairment, and subjective cognitive complaints.

Description of the Survey

We collected all the socio-demographic characteristics of patients. The stage of dementia was assessed using the Clinical Dementia Rating (CDR) (Morris et al., 1997) scale. Furthermore, we investigated the patient's variation in his/her clinical status, analyzing cognitive, psychological, behavioral, and motor symptoms during the quarantine period. Briefly, the following cognitive features were investigated: changes in memory, spatial and temporal orientation, language, attention, and perception. Questions about patient's awareness of the pandemic were administered. In addition, we acquired data regarding variations in behavioral and psychological symptoms of dementia (BPSD, i.e., irritability, apathy, agitation, anxiety, depression, sleep change, aggressiveness, wandering, appetite change, hallucinations, and delusions), reporting for these symptoms both a worsening and/or a new onset that occurred during the quarantine period. Further questions about the need for modifying therapy because of BPSD changes were administered. Finally, we investigated the changes in patients' motor activity, evaluating through a 5-point ordinal scale specific question if the subject walked better from the beginning of the quarantine period, remained stable, walked slower, became wheelchair, or became confined to bed.

Caregivers' Socio-Demographic Characteristics

Caregivers' were asked about the cohabitation with the patient, composition of the family, and own work activity. Other questions concerned the impact of the quarantine period on caring for a person with dementia on their caregivers' lives, investigating both social and psychological effects (changes in caregiver's life, change in the relationship with the patient, concern for the pandemic, changes in therapeutic assistance, need to seek help from the emergency department, use of telemedicine, need to support during quarantine, own feeling of depression, anxiety, irritability, distress, overwhelm, and abandonment). Further details are available at **Supplementary Material.**

Statistical Analysis

We performed statistical analysis using SPSS software, version 21, and the R statistical computing environment, version 3.6.2 (IBM Corp, 2012; R Core Team, 2013). Due to the low rate of missing data (<1%) no imputation was made. Firstly, we performed a descriptive analysis of all the demographic and clinical data. Then, we performed univariable and multivariable logistic regression of the dependent variables (outcomes in clinical symptoms, all described by binary variables) on the collected independent variables, using mixed effects logistic regression (as implemented in the lme4 R package) with the center as a random effect and all other regressors as fixed effects. Regressors with significant p (<0.05) in univariable logistic regression were included in multivariable regression. Bonferroni correction was applied to all the p-values of multivariable analysis, considering all outcomes together, as multivariable analysis is considered as our final result. We controlled for caregiver stress by including it in the multivariable analysis as a confounder, as a numerical fixed effect. The level of statistical significance was set at $p < 0.05$.

Ethical Standards

The study was initially approved by the Ethics Committee of the Coordinating Centre (University of Torino on April 7, 2020, n.00150/2020) and then by the local ethics boards. Caregivers gave first oral and then written fully informed consent to the study.

RESULTS

Changes in Health Services

The response rate of CDCDs to the proposed questionnaires was 98%. Only two CDCDs were excluded because they did not recruit patients. The final 87 recruiting Centers were homogeneously distributed throughout the Italian territory (**Figure 1**).

Thirty-two percent of patients with dementia were recruited in Northern, 32% in Central, and 36% in Southern Italy. Thirty percent of CDCDs was based at university hospitals, 34% to general hospitals, and 36% to territorial based health services. In the pre-COVID-19 pandemic period, each Center followed a mean of 160 dementia patients per month. After the quarantine declaration, 85% of the CDCD suspended medical and psychological appointments, and visits were restricted to emergencies. Different forms of telemedicine (from phone calls to videoconferencing) were activated in 78% of Centers. One out of two Center provided on-line psychological support for caregivers. All the randomized clinical trials were stopped. Finally, 94% of support activities for dementia patients (Alzheimer's café, Day Center, etc.) were closed.

Caregivers

The Survey response rates of the family caregivers ranged from 91.3 to 99.1%, according to different dementia Centers. We interviewed 5321 caregivers of patients regularly followed at different CDCDs. After data cleaning, the information collected from 4913 family caregivers (women 2934, mean age $\pm$ SD = 58.2 $\pm$ 12.0 years; men 1979, mean age $\pm$ SD = 60.7 $\pm$ 13.9 years) were analyzed. Fifty-nine % were cohabitants with the patients, and 36% were spouses of the dementia care recipient. Approximately half of the caregivers reported that quarantine induced a significant change in their lifestyle, with 30.3% complaining a reduction in time devoted to their own activities, and 15.5% reporting an increase in intrafamilial psychological conflicts. Caregivers reported a significant increase in anxiety (45.9%), depression (18.6%), irritability (26.2%), and distress (28.9%). Finally, 80.8% of the caregivers reported that telemedicine has been of help during quarantine.

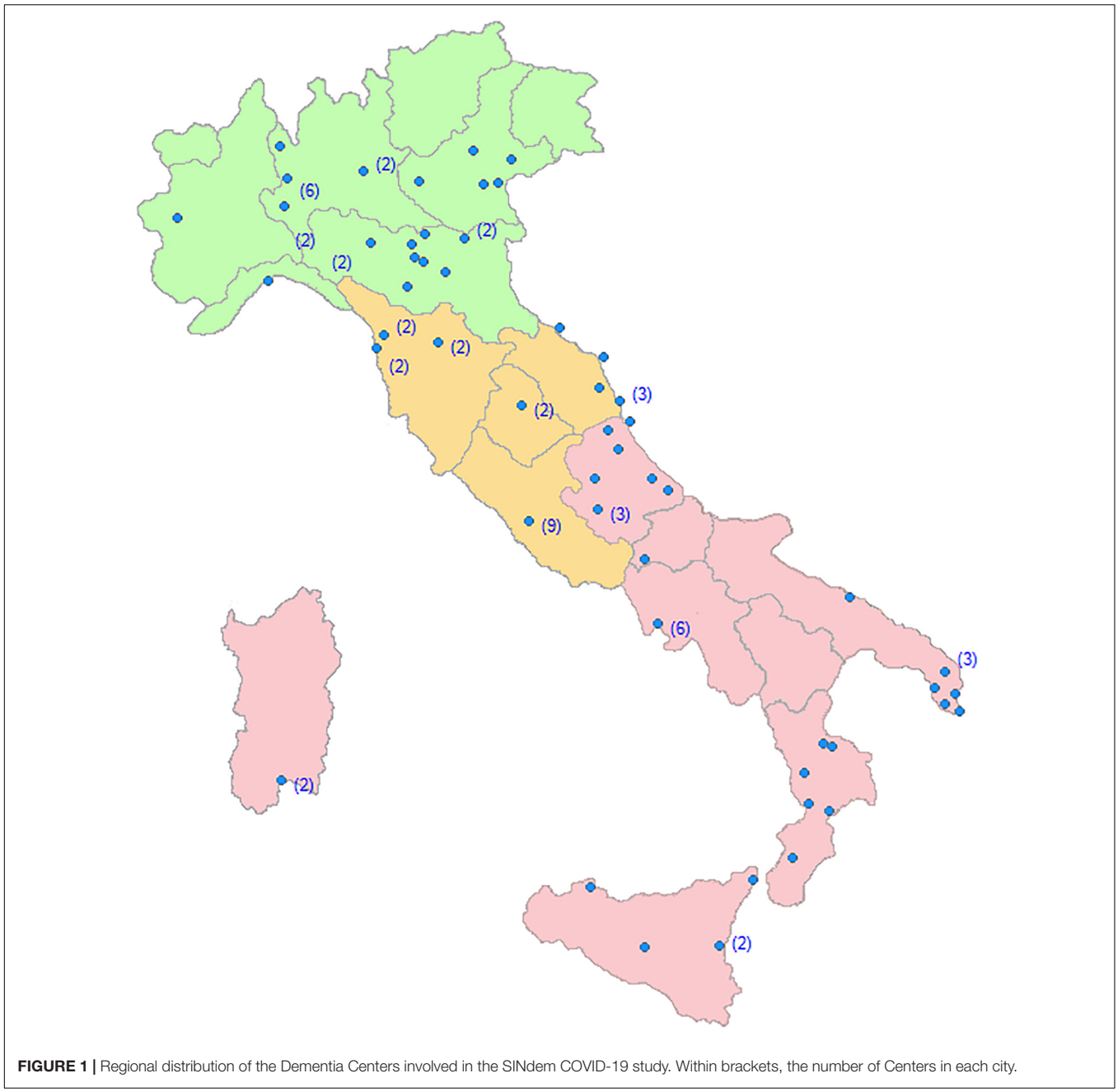

FIGURE 1 | Regional distribution of the Dementia Centers involved in the SINdem COVID-19 study. Within brackets, the number of Centers in each city.

Dementia Patients

From April 14 to April 27, 2020, we collected data regarding 4913 patients with dementia (2934 females, mean age ± *SD* = 78.9 ± 8.2 years; 1979 males, mean age ± *SD* = 77.2 ± 8.0 years) regularly followed at CDCDs. Demographic and clinical characteristics of dementia patients are shown in **Table 1**.

Family caregivers reported that, after a quarantine period of approximately 47 days, dementia patients showed a worsening in cognitive symptoms (+55.1%), and behavioral symptoms (+51.9%), the onset of new behavioral symptoms (+25.9%), and an increase in motor symptoms (+36.7%). According to caregivers, 40.1% of patients were totally aware of quarantine declaration, 36.0% were only partially aware, while 23.9% were totally unaware. Awareness of the quarantine varied significantly among the dementia subgroups, with DLB patients showing the highest degree (69.8%) of partial of total unawareness of pandemic.

Changes in Cognitive Symptoms

Caregivers reported a worsening in cognitive symptoms in approximately 60% of dementia participants. About 37% of dementia participants showed worsening in two or more cognitive domains. Deficits more often reported as increased

TABLE 1 | Demographic and clinical characteristics of study participants.

Patients	Total (*n* = 4913)	AD (*n* = 3372)	DLB (*n* = 360)	FTD (*n* = 415)	VD (*n* = 766)
Age (years, mean ± SD)	78.3 ± 8.2	78.3 ± 8.0	78 ± 7.3	72.3 ± 8.9	81.6 ± 7.0
Sex (female, %)	59.7	63.5	42.2	46.7	58.4
Duration of the disease (years, mean ± SD)	4.5 ± 3.1	4.6 ± 3.1	4.5 ± 3	4.8 ± 3.2	4.1 ± 2.9
Regional distribution					
North (%)	32.2	26.5	35.3	47.5	47.8
Centre (%)	31.5	34.1	36.4	21.2	23.4
South - Islands (%)	36.3	39.4	28.3	31.3	28.8
CDR Stage (%)					
1	25.0	24.3	26.3	23.4	28.4
2	47.8	49.2	41.9	48.6	43.8
3	27.2	26.5	31.8	28.0	27.8
Duration of the quarantine (days, mean ± SD)	47.2 ± 6.4	47.2 ± 6.5	46.6 ± 5.6	46.4 ± 5.3	47.8 ± 6.8
Changes in cognitive symptoms (Yes, %)	55.1	55.7	59.6	48.3	54.2
Sex (female, %)	58.4	63.0	36.3	44.7	55.2
Changes in BPSD (Yes, %)	51.9	50.5	63.8	55.3	50.3
Sex (female, %)	57.9	62.9	38.4	45.4	55.1
New onset BPSD (Yes, %)	25.9	26.7	23.3	21.9	25.6
Sex (female, %)	56.7	59.8	41.7	41.8	56.1
Changes in motor symptoms (Yes, %)	36.7	33.2	52.8	40.2	42.3
Sex (female, %)	58.6	65.0	44.7	43.1	52.5
Caregivers					
Age (years, mean ± SD)	59.3 ± 13	59.3 ± 13.1	60.7 ± 12.7	59.1 ± 13.6	60 ± 12.4
Sex (female, %)	53.9	51.2	66.4	55.4	59.4
Cohabitant caregiver (%)	58.9	58.1	63.5	69.6	54.4
Degree of kinship					
Spouses (%)	36.0	35.0	43.1	54.8	26.9
Son/daughter (%)	54.5	55.5	48.7	37	62.5
Others (%)	9.5	9.5	8.2	8.2	10.6
Increase in anxiety (%)	45.9	46.1	43.4	44.2	47.4
Increase in depression (%)	18.6	17.2	21.3	24.3	20.3

AD, Alzheimer's disease; DLB, Dementia with Lewy Bodies; FTD, frontotemporal dementia; VD, vascular dementia; CDR, Clinical Dementia Rating; BPSD, Behavioral and Psychological symptoms of dementia.

were: forgetfulness (68%), confusion (67.9%), and temporal disorientation (37%). **Figure 2** displays the frequency distribution of cognitive symptoms worsened during quarantine.

When we examined diagnostic subgroups, we found a worsening of cognitive symptoms mainly in patients with DLB (59.6%) and AD (55.7%), followed by VD (54.2%), and FTD (48.3%) patients. Thirty-eight % of patients with AD showed a worsening in memory functions, 37.5% presented an increase in confusion, and 21.1% showed a worsening in temporal disorientation. The same effects were observed in patients with DLB, showing a worsening in memory functions in 26.1%, an increase in confusion in 40.3%, and in temporal disorientation in 20.3%. Patients with FTD showed mainly a worsening in language functions (25.5%). After multivariable analysis, the increase of cognitive symptoms in the overall group of patients with dementia was not associated with age, gender, duration of quarantine, disease severity, and changes in caregivers' psychological features. Contrariwise, an inverse relationship between the aggravation of cognitive symptoms and the duration of the dementia was found ($p < 0.001$).

Interestingly, the pre-existing total or partial independence in motor function represents a risk factor for the worsening of cognitive functions (OR 1.85 [95% CI 1.42–2.39], $p < 0.001$; and OR 2.08 [95% CI 1.68–2.57], $p < 0.001$, respectively). Contrariwise, total awareness of quarantine was a protective factor against cognitive worsening (OR 0.68 [95% CI 0.57–0.81], $p < 0.001$) (**Table 2**).

Changes in Behavioral Symptoms

During the quarantine period, BPSD worsened in approximately half of the patients with dementia. The most frequently worsened BPSD were irritability (40%), followed by apathy (35%), and agitation (31%) (**Figure 3**).

Examining subgroups, we found an increase in the number of symptoms mainly in patients with DLB (63.8%), followed by FTD (55.3%), AD (50.5%), and VD (50.3%). The increase of neuropsychiatric symptoms in patients with dementia was associated with moderate disease severity (CDR 2, $p = 0.009$), but not remained significant after applying Bonferroni correction. The worsening of BPSD was associated with pre-existing total

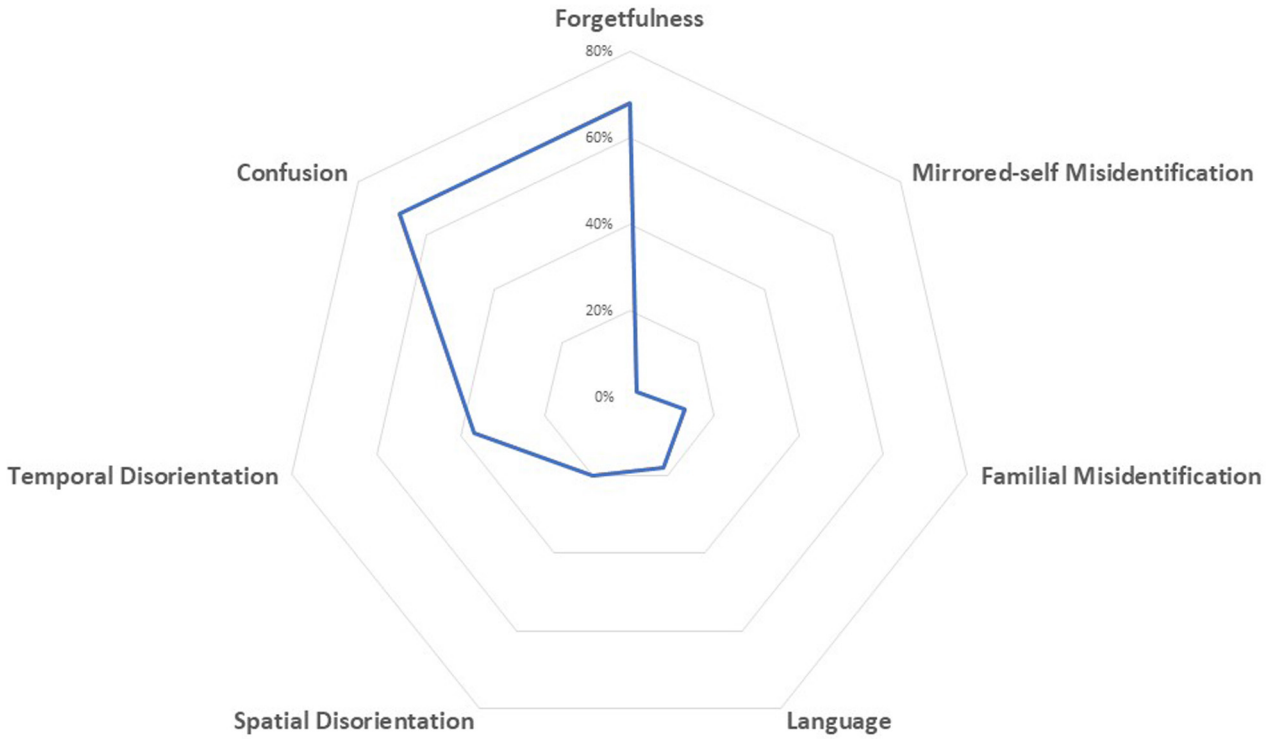

FIGURE 2 | Spider-plot of changes in cognitive function during quarantine; dots mark the mean proportion of each symptom.

TABLE 2 | Univariable and multivariable analysis of risk and protective factors for cognitive and motor changes during quarantine in patients with dementia.

	Univariable analysis		Multivariable analysis		
	Crude OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**	***P*-value after Bonferroni correction**
Changes in cognitive symptoms					
Age	1.00 (0.99 – 1.00)	0.24			
Sex (men vs. women)	1.15 (1.01 – 1.30)	0.03	1.13 (0.99 – 1.29)	0.07	1
Duration of the disease (years)	0.95 (0.93 – 0.97)	<0.001	0.94 (0.92 – 0.97)	<0.001	<0.001
Duration of quarantine (days)	1.00 (0.99 – 1.01)	0.97			
Disease severity – CDR 2	1.29 (1.11 – 1.50)	<0.001	1.19 (1.00 – 1.42)	0.05	1
Disease severity – CDR 3	1.02 (0.86 – 1.21)	0.81	0.93 (0.74 – 1.17)	0.52	1
Total physical independence	1.74 (1.40 – 2.16)	<0.001	1.85 (1.42 – 2.39)	<0.001	<0.001
Partial physical independence	2.19 (1.80 – 2.67)	<0.001	2.08 (1.68 – 2.57)	<0.001	<0.001
Total awareness of pandemic	0.74 (0.65 – 0.85)	<0.001	0.68 (0.57 – 0.81)	<0.001	<0.001
Partial awareness of pandemic	1.39 (1.18 – 1.64)	<0.001	1.20 (1.00 – 1.43)	0.05	1
Changes in motor symptoms					
Age	1.03 (1.02 – 1.04)	<0.001	1.02 (1.01 – 1.03)	<0.001	0.001
Sex (men vs. women)	1.11 (0.98 – 1.25)	0.12			
Duration of the disease (years)	1.05 (1.03 – 1.07)	<0.001	1.00 (0.98 – 1.03)	0.86	1
Duration of quarantine (days)	1.00 (0.99 – 1.01)	0.99			
Disease severity – CDR 2	1.94 (1.65 – 2.29)	<0.001	1.29 (1.07 – 1.56)	0.009	0.29
Disease severity – CDR 3	3.08 (2.56 – 3.70)	<0.001	1.60 (1.26 – 2.02)	<0.001	0.004
Total physical independence	0.32 (0.25 – 0.40)	<0.001	0.49 (0.37 – 0.64)	<0.001	<0.001
Partial physical independence	0.93 (0.77 – 1.12)	0.44	1.06 (0.86 – 1.30)	0.59	1
Total awareness of pandemic	0.44 (0.38 – 0.51)	<0.001	0.76 (0.64 – 0.91)	0.003	0.10
Partial awareness of pandemic	0.75 (0.64 – 0.88)	<0.001	0.93 (0.78 – 1.10)	0.39	1

OR, Odds ratio; 95% CI, 95% confidence interval; CDR, Clinical Dementia Rating.

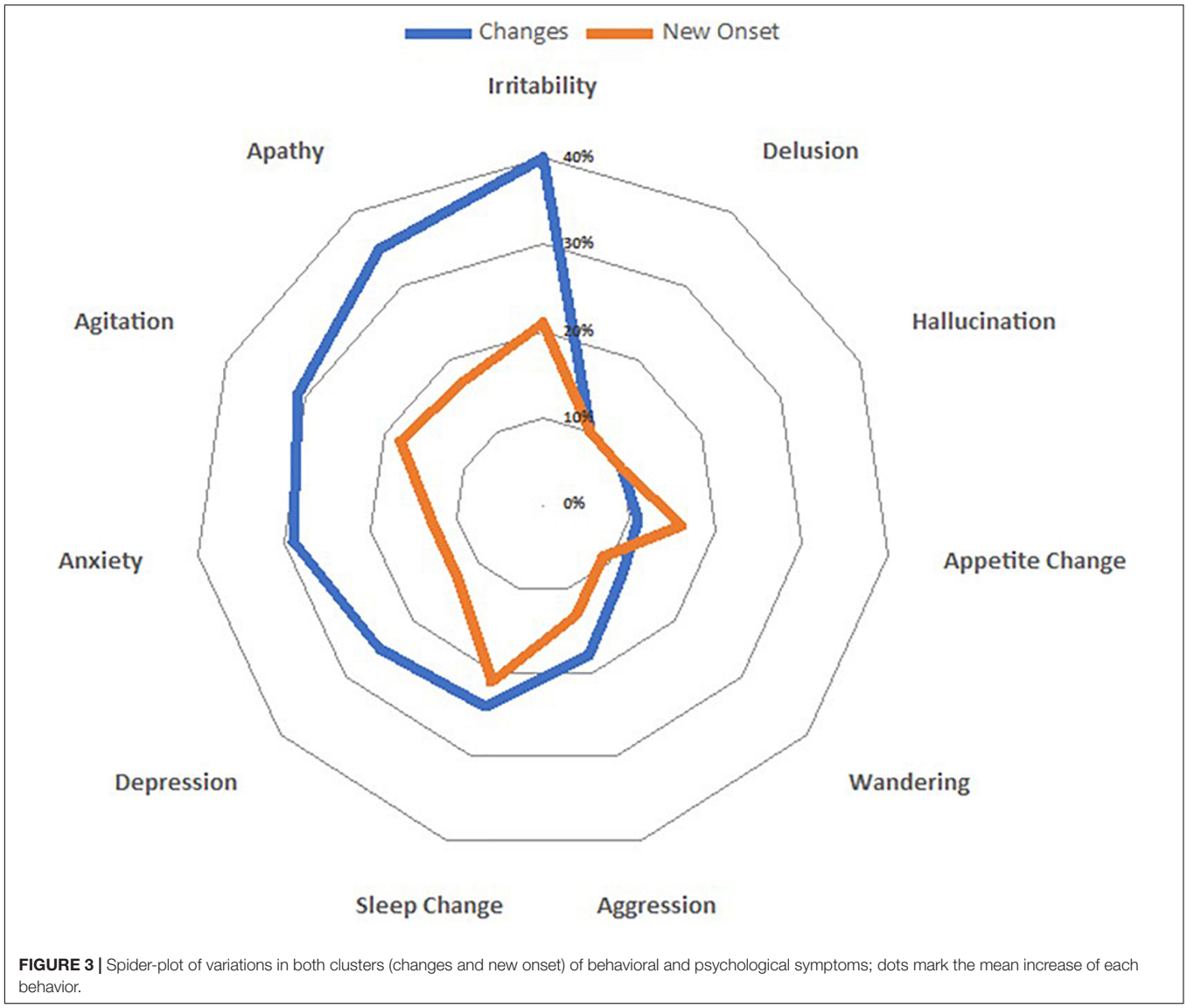

FIGURE 3 | Spider-plot of variations in both clusters (changes and new onset) of behavioral and psychological symptoms; dots mark the mean increase of each behavior.

or partial autonomy in motor function (totally independent OR 1.84 [95% CI 1.43–2.38], $p < 0.001$; partially dependent OR 1.88 [95% CI 1.53–2.31], $p < 0.001$). After multivariate analysis, the worsening of BPSD was not associated with age, gender, duration of quarantine, disease severity, duration of disease, and changes in caregivers' psychological features. On the contrary, total awareness of the pandemic was inversely related to worsening of BPSD (OR 0.75 [95% CI 0.63–0.89], $p = 0.03$) (**Table 3**).

New BPSD occurred in approximately a quarter of the dementia patients. There was a different increase in the frequency of BPSD across groups. The most frequently reported new symptom was irritability (21.3%), followed by sleep change (21%), and agitation (18%) (**Figure 2**), which required therapy adjustments. The highest increase was observed in AD (26.7%), intermediate in VD and DLB (25.6 and 23.3%, respectively), and the lowest increase in FTD (21.9%). No suicide attempts were reported. The onset of new BPSD was associated with the total or partial physical independence ($p < 0.001$ and $p = 0.01$, respectively). Total awareness of the pandemic was inversely related to onset of new BPSD (OR 0.74, [95% CI 0.62–0.88], $p = 0.03$).

Changes in Motor Symptoms

Increased motor dysfunction, mainly characterized by walking difficulties, was reported by caregivers in 36.7% of the patients. There was an increase mainly in patients with DLB (52.8%), followed by VD (42.3%), FTD (40.2%), and AD (33.2%). Age and disease severity were associated with an increase of motor dysfunction ($p < 0.001$) during quarantine, whereas full physical autonomy before quarantine was a positive predictor against worsening in motor functions (OR 0.49 [95% CI 0.37–0.64], $p < 0.001$).

The increased prevalence of cognitive, behavioral and motor symptoms was not influenced either by regional distribution of different CDCD or by the regional prevalence of COVID-19 at the time of the study.

TABLE 3 | Univariable and multivariable analysis of risk and protective factors for increase in BPSD and onset of new BPSD during quarantine in patients with dementia.

	Univariable analysis		Multivariable analysis		
	Crude OR (95% CI)	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**	***P*-value after Bonferroni correction**
Increase in BPSD					
Age	0.99 (0.98 – 0.99)	<0.001	0.99 (0.98 – 0.99)	0.005	0.16
Sex (men vs. women)	1.17 (1.04 – 1.32)	0.008	1.12 (0.99 – 1.28)	0.08	1
Duration of the disease (years)	0.98 (0.96 – 0.99)	0.04	0.97 (0.95 – 0.99)	0.01	0.48
Duration of quarantine (days)	0.99 (0.99 – 1.01)	0.66			
Disease severity – CDR 2	1.33 (1.15 – 1.54)	<0.001	1.26 (1.06 – 1.49)	0.009	0.30
Disease severity – CDR 3	1.32 (1.12 – 1.56)	0.001	1.21 (0.97 – 1.52)	0.09	1
Total physical independence	1.56 (1.26 – 1.93)	<0.001	1.84 (1.43 – 2.38)	<0.001	<0.001
Partial physical independence	1.90 (1.57 – 2.30)	<0.001	1.88 (1.53 – 2.31)	<0.001	<0.001
Total awareness of pandemic	0.72 (0.63 – 0.82)	<0.001	0.75 (0.63 – 0.89)	<0.001	0.03
Partial awareness of pandemic	1.25 (1.07 – 1.45)	0.005	1.20 (1.01 – 1.42)	0.04	1
Onset of new BPSD					
Age	1.00 (0.99 – 1.00)	0.32			
Sex (men vs. women)	1.19 (1.04 – 1.36)	0.01	1.10 (0.95 – 1.27)	0.21	1
Duration of the disease (years)	0.99 (0.97 – 1.01)	0.41			
Duration of quarantine (days)	1.00 (0.99 – 1.01)	0.72			
Disease severity – CDR 2	1.14 (0.96 – 1.35)	0.13			
Disease severity – CDR 3	1.08 (0.89 – 1.32)	0.41			
Total physical independence	1.69 (1.30 – 2.18)	<0.001	1.92 (1.45 – 2.55)	<0.001	<0.001
Partial physical independence	1.59 (1.26 – 2.02)	<0.001	1.55 (1.22 – 1.99)	<0.001	0.01
Total awareness of pandemic	0.78 (0.67 – 0.92)	0.003	0.74 (0.62 – 0.88)	<0.001	0.03
Partial awareness of pandemic	1.17 (0.99 – 1.39)	0.07	1.10 (0.92 – 1.32)	0.29	1

BPSD, Behavioral and Psychological Symptoms of Dementia; OR, Odds ratio; 95% CI, 95% confidence interval; CDR, Clinical Dementia Rating.

DISCUSSION

Our study shows that quarantine due to COVID-19 pandemic is associated with a dramatic increase in clinical symptoms of patients with dementia. According to family caregivers, social isolation and physical restraint caused a worsening in cognitive function, an aggravation of several behavioral symptoms, and a worsening in motor function. These effects were observed in all forms of dementia, but patients with DLB and AD showed the highest increase in cognitive and behavioral symptoms. In addition, the quarantine period was associated with an increase of caregiver's burden, mainly characterized by anxiety.

To the best of our knowledge, this is the first nation-wide study that investigated the effects of quarantine in patients with dementia. Our data confirm the results of a previous, small study that investigated the effects of COVID-19 outbreak in patients with MCI and dementia (Canevelli et al., 2020). To evaluate factors associated with the quarantine-related clinical worsening, we performed extensive statistical analyses, and the most consistent relation was observed with the pre-pandemic physical status. Patients still able to walk unassisted or accompanied, after an acute interruption of physical activity, showed the greater worsening in clinical symptoms. Sex, age, duration of the disease, and disease severity had small and inconsistent effects. Several studies showed that physical activity has a positive impact on cognition of elderly adults (Fratiglioni et al., 2004; Bherer, 2015; Forbes et al., 2015; Young et al., 2015) and provided evidence that in patients with dementia there is an inverse relationship between physical activity, abnormal behavior, and cognitive decline (Nelson and Tabet, 2015; Karssemeijer et al., 2017). Patients physically more independent and, probably, with a more active life, enriched with a variety of social contacts and cognitive stimulation, are those most affected by the negative effects of confinement. Our study highlights the importance of maintaining physical activity in patients with dementia, and suggests the need for additional investigations to better understand this phenomenon.

Our study showed that 40% of the examined patients were totally aware of the COVID-19 pandemic and of social and physical restrictive measures planned to control virus transmission. Intriguingly, we found that patients with dementia still able to completely understand the need of quarantine, and therefore able to adopt adequate strategies to face the stress, had a significantly lower impairment in cognitive, behavioral and motor function. Contrariwise, less aware patients failed in creating new adaptive procedures to quarantine. Awareness of quarantine varied significantly among dementia subgroups and DLB patients showed the highest degree of partial and total degree of awareness. Taken together, the results of our study suggested that DLB patients are the most vulnerable to acute stress among the patients with dementia.

The neurobiological basis of the observed phenomenon has never been investigated. Examining subgroups of patients with dementia, we found an increase mainly of the core symptoms that characterize different types of dementing illness. This finding

suggests that the observed phenomenon is not disease-specific but is more likely attributable to stress-induced changes. Studies in experimental animals showed that exposure to both acute and chronic stress evokes chemical changes in brain that impair the higher cognitive functions (Arnsten et al., 1999; Yamada et al., 2003). Uncontrollable, acute stress induces a diffuse increase in brain glucocorticoids and a specific catecholamine release in prefrontal cortex, impairing spatial memory tasks (Arnsten, 2015; Bahtiyar et al., 2020). Intriguingly, in animal models of acute physical and social restraints, an impairment of serotonin metabolism in the central nervous system was reported, with an alteration of immune response (Medina-Martel et al., 2013). In humans, stress drives several diseases, including cognitive disorders such as AD (Canet et al., 2019). Acute stress induces a neuroinflammatory response characterized by the release of several pro-inflammatory molecules and microglial activation that is a common feature of several neurodegenerative diseases (Sharma and Kanneganti, 2016). Finally, worsening of sleep, frequently reported in our study, is an additional explanation of our findings. Poor sleep is strongly associated with risk of multiple types of dementia and, via modulation of β-amyloid secretion, is directly involved in AD pathogenesis (Vanderheyden et al., 2018). Further studies are warranted to better elucidate the neurobiological mechanisms underlying the reported worsening of patients with dementia during quarantine and to provide therapeutic strategies.

Caregiving of dementia patients is associated with a higher prevalence of depressive and anxiety disorders, and impairments in physical health. Data from our study clearly showed that, as previously observed in the general population after SARS and Ebola outbreaks, quarantine is associated with increase in anxiety and depression. New health policies should be planned in the post-COVID-19 era to help family caregivers in delivering effective care. Finally, dementia Centers need to implement new strategies, as telemedicine (Goodman-Casanova et al., 2020; Hollander and Carr, 2020), in order to assist frailty people and support family members.

Some limitations of our study should be acknowledged. We examined dementia patients living at home and our data cannot be generalized to institutionalized patients with dementia. Then, we performed a cross-sectional study and, at present, it is unclear whether the observed clinical worsening is a transient or long-lasting phenomenon. Finally, all the clinical data regarding patient's symptoms were collected from family caregivers as, due to quarantine rules, it was not possible to administer face-to-face standardized neuropsychological tests. However, previous studies showed that BPSD can be adequately evaluated by family caregivers and demonstrated that symptoms reported can be used in the clinical staging of dementia (Kwok et al., 2011; Yuan et al., 2020). Therefore, in order to evaluate if there is a time-effect, we have planned a new follow-up interview to the same caregivers. Finally, the major strength of our study is the high number of caregivers that have been interviewed in a relatively small amount of time and their reliability, having this role from the onset of dementia.

CONCLUSION

In conclusion, interviewing family caregivers, we investigated for the first time the acute effects of quarantine in a large Italian population of patients with dementia, and we found that restrictive public health measures, are associated with an increase of dementia symptoms. These findings are important from a health policy perspective and suggest the need of new health care strategies to target patients with dementia during pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Interaziendale di Torino. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IR, AB, CM, AC, LB, CC, and VL designed the study and planned center recruitment. AC, CM, ER, and AB wrote the report. RDL and PP did the statistical analyses. ER, AV, VI, NV, FA, IA, PC, CB, RS, DQ, VG, GL, MF, GT, and CF contributed to the interpretation and discussion of results and reviewed the manuscript. The collaborating authors contributed to the collection of clinical data. All the authors and the collaborating authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Ministero dell'Istruzione, dell'Universitá e della Ricerca and MIUR project "Dipartimenti di Eccellenza 2018–2022" to Department of Neuroscience "Rita Levi Montalcini".

ACKNOWLEDGMENTS

We thank all the patients and caregivers involved in the study for their kind collaboration. In addition, we thank Gabriele Bartalini, Laura Franci, and Barbara Frati for the technical assistance in collecting the data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2020.625781/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Neurology

ORIGINAL RESEARCH
published: 19 February 2021
doi: 10.3389/fneur.2021.640017

Neurological Disorders Associated With COVID-19 Hospital Admissions: Experience of a Single Tertiary Healthcare Center

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Background: Early reports have detailed a range of neurological symptoms in patients with the SARS-CoV-2 infection. However, there is a lack of detailed description and incidence of the neurological disorders amongst hospitalized COVID-19 patients. We describe a range of neurological disorders (other than non-specific neurological symptoms), including their clinical, radiological, and laboratory findings, encountered in our cohort of COVID-19 patients admitted to a large tertiary institution.

Methods: We reviewed our prospectively collated database of all adult Neurology referrals, Neurology and Stroke admissions and Neurological multi-disciplinary team meetings for all hospitalized patients with suspected or proven COVID-19 from 17 March 2020 to 31 August 2020.

Results: Twenty-nine of 1,243 COVID-19 inpatients (2.3%) presented with COVID-19-related neurological disorders. The mean age was 68.9 ± 13.5(SD) years, age range of 34–97 years, and there were 16 males. Twenty two patients had confirmed, five were probable and two had suspected COVID-19 infection according to the WHO case classification. Eight patients (27%) required critical care admission. Neurological symptoms at presentation included acute confusion and delirium, seizures, and new focal neurological deficits. Based on the pre-defined neurological phenotype, COVID-19 patients were grouped into four main categories. Sixteen patients had cerebrovascular events (13 with acute ischemic stroke and three had hemorrhagic features), seven patients were found to have inflammatory, non-inflammatory and autoimmune encephalopathy (including two with known Multiple Sclerosis), whilst disorders of movement and peripheral nervous system were diagnosed in three patients each.

Conclusion: Although the exact prevalence and etiology remain unclear, new onset of neurological disorders, in addition to anosmia, is non-sporadic during the acute COVID-19-infection. Longitudinal follow-up of these patients is required to determine the clinical and functional outcome, treatment response and long-term effects of the SARS-CoV-2 infection.

Keywords: COVID-19, neurology, delirium, stroke, encephalitis

OPEN ACCESS

Edited by:
Peter R. Williamson, National Institutes of Health (NIH), United States

Reviewed by:
Tory P. Johnson, Johns Hopkins University, United States
Seher Anjum, National Institutes of Health (NIH), United States

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Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: *11 December 2020*
Accepted: *26 January 2021*
Published: *19 February 2021*

Citation:
Dhillon PS, Dineen RA, Morris H, Tanasescu R, Nikfekr E, Evans J, Constantinescu CS and Hosseini AA (2021) Neurological Disorders Associated With COVID-19 Hospital Admissions: Experience of a Single Tertiary Healthcare Center. Front. Neurol. 12:640017. doi: 10.3389/fneur.2021.640017

INTRODUCTION

The coronavirus disease 2019 (COVID-19), a manifestation of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on 11 March 2020 (1, 2). At present, the COVID-19 incidence in the United Kingdom (UK) is one of the highest in the world with 3,443,431 cases (95,675,708 globally) and 90,033 deaths (2,043,806 globally), accurate as of 19 January 2021 (3). Early reports from Wuhan, China detailed a range of neurological symptoms seen in patients with the SARS-CoV-2 infection (4). Recent isolated case reports have also described some of these manifestations, which include acute cerebrovascular disorders [CVD] (5–7), encephalopathy or encephalitis, acute demyelinating encephalomyelitis (ADEM), as well as peripheral neurological associations such as Guillain-Barre syndrome (GBS) (8, 9). Some of the proposed mechanisms underlying the increased prevalence of neurological disorders in COVID-19 include widespread systemic inflammatory and cytokine responses, diffuse intravascular coagulation and/or critical illness-related coagulopathy, direct neuronal injury, immune-mediated disorders and hemodynamic alterations (8–14).

Many reports have detailed a range of presenting neurological symptoms in patients with the SARS-CoV-2 infection, including headache, delirium, seizures, and altered mental status. However, there is often a lack of detailed description and incidence of the neurological disorders amongst hospitalized patients with COVID-19. Herein, we solely include neurological disorders, instead of non-specific neurological symptoms such as headache, dizziness and anosmia. We describe a range of neurological disorders causing neurological deficits, including their clinical, radiological and laboratory findings, encountered in our cohort of patients with COVID-19 admitted to a large tertiary institution.

METHODS

This study was registered with and approved by the East Midlands-Derby Research Ethics Committee (Ref:18/EM/0292, Major amendments) and individual patient consent was waived (15). We reviewed our prospectively collated database of all inpatient Neurology referrals, Neurology and Stroke admissions and Neurological multi-disciplinary team (MDT) meetings for all hospitalized patients with suspected or proven COVID-19 from 17 March 2020 (when national lockdown was declared in the UK) to 31 August 2020, at our institution. Each case, including the clinical, laboratory, and imaging findings, was discussed and a consensus of the underlying COVID-19 associated neurological syndrome was reached amongst the Neurology or Stroke physicians. Cases without definite neurological deficits, symptoms or signs, no clinical/radiological suspicion of COVID-19, or other more likely alternate diagnoses were excluded from our study cohort.

Patients presenting with symptoms and/or signs indicative of COVID-19 and the associated positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) status from the naso-pharyngeal swab test, were classified according to the WHO COVID-19 case definition (16), into confirmed, probable and suspected cases. Further case definitions for the association of COVID-19 with neurological disease were defined based on our local MDT consensus and adapted from Ellul et al.'s compilation panel of published information (14). These included cerebrovascular disease, encephalitis, myelitis, or meningitis, and acute disseminated encephalomyelitis or acute neuropathies associated with the SARS-CoV-2 infection. Some findings of four patients from our cohort were described in a recent correspondence by the respective clinicians/authors: (Patients 21 and 22) by Hosseini et al. (17) and (Patients 18 and 28) by Dhillon et al. (18).

RESULTS

Our tertiary institution holds a capacity of ∼1,700 hospitals beds and provides services to over 2.5 million residents. During the study period, our institution reported 1,243 COVID-19 admissions, of which 29 patients (2.3%) with neurological disorders associated with COVID-19 were identified in our study. The 29 patients included had a mean age of 68.9 ± 13.5 (SD) years, age range of 34–97 years, and there were 16 males. There were 27 Caucasian patients (92%), and only two were from the Black, Asian or Minor Ethnicity groups (BAME; one Black and one Asian). According to the WHO COVID-19 case classification, 22 patients were deemed to have confirmed COVID-19, five were probable and two had suspected COVID-19 infection. Eight patients (27%) required critical care admission, six of whom needed invasive ventilation. There was an array of neurological symptoms at presentation, namely, reduced consciousness, acute confusion, behavioral change and seizures, acute motor or sensory neurological deficits, and acute onset of movement disorders. The onset of neurological symptoms was between 9 days before to 15 days after the diagnosis or symptoms onset of COVID-19. The mean number of admission days was 25 and the range was 1–107 days. Based on the pre-defined neurological phenotype, COVID-19 patients were grouped into four main categories: 16 patients diagnosed with a cerebrovascular event (acute ischemic or hemorrhagic), seven patients with inflammatory, non-inflammatory, and autoimmune encephalopathy (including one case of transverse myelitis and two cases with known Multiple Sclerosis), three patients with movement disorders, and three patients peripheral nervous system syndromes.

Cerebrovascular Event

Acute Ischaemic Stroke: (Patient 1, 2, 3, 4, 6, 10, 11, 12, 15, 16, 25, 29, 30)

Thirteen of the 28 patients (46%) with an age range of 66–97 years, and seven females, were diagnosed with acute ischemic stroke, five of which were large vessel occlusions involving the middle cerebral artery (MCA) (**Table 1**). Only one patient presented with a posterior circulation stroke whilst two had multifocal infarcts. All but one patient had at least one known cardiovascular risk factor. Eleven of the 13 patients had pulmonary features consistent with COVID-19. Two patients

TABLE 1 | Sixteen patients with cerebrovascular events (13 Ischaemic stroke and 3 Hemorrhagic).

Patient	**1**	**2**	**3**	**4**	**6 (Figure 1)**
Age, M/F, ethnicity, COVID-19 diagnosis	97, F, White, Definite	90,F, White, Definite	66,F, White, Definite	85, M, White, Probable	71, M, White, Definite
Stroke type, Thrombolysis/ Thrombectomy	Left ICA/MCA infarct; Thrombolysis	Left partial anterior circulation stroke (PACS)	Left ICA/MCA infarct; Mechanical thrombectomy	Right MCA infarct; Thrombolysis	Right MCA infarct
Presenting symptoms/ signs	Right hemiparesis	Right hemiparesis and dysphasia	Right hemiparesis, hemianopia and dysphasia	Left hemiparesis	GCS 3
Blood results at admission:	Hemoglobin 136 g/l lymphocyte count 1.39 neutrophil count 3.41 platelet count 207 CRP 6 mg/L D-dimer; NR Ferritin; NR Creatinine 66 umol/L PT 12.6 s	Hemoglobin 125 g/l lymphocyte count 0.98 neutrophil count 10.98 platelet count 421 **CRP 276** mg/L **ESR mm/h: 116** D-dimer; NR Ferritin; NR Creatinine 59 umol/L PT 11.1 s	Hemoglobin 131 g/l lymphocyte count 2.91 neutrophil count 9.74 platelet count 400 **CRP 62** mg/L **D-dimer ug/l; 3144** Ferritin; NR Creatinine 64 umol/L PT 11.6 s	Hemoglobin 140 g/l **lymphocyte count 0.92** neutrophil count 5.53 platelet count 231 **CRP 23** mg/L D-dimer; NR Ferritin; NR Creatinine 89 umol/L PT 11.9 s	Hemoglobin 106 g/l **lymphocyte count 0.15** neutrophil count 2.81 **platelet count 38** **CRP 298** mg/L D-dimer; NR Ferritin; NR Creatinine 119 umol/L PT 11.9 s
Brain Imaging	CT: Acute thrombus within the left ICA and MCA consistent with an acute infarct	CT: No acute abnormality. Severe small vessel disease	CT: Left MCA territory infarct, with associated mass effect	CT: Right MCA territory infarct	CT: Massive acute right MCA territory infarct with mass effect and shift of midline structures
Outcome status	Died	Full recovery	Continued recovery in rehabilitation; mRS 5	Full recovery	Died

10	**11**	**12**	**15**	**16**	**25**
88, F, White, Definite	69, F, White, Probable	78, M, White, Suspected	66, M, White, Definite	89, M, White, Definite	78, F, White, Definite
Right PCA Infarct	Left ACA infarct	Right MCA infarct	Right MCA infarct	Right MCA/ACA infarct	Left MCA infarct; Mechanical Thrombectomy
Left hemiparesis	Right hemiparesis and dysphasia	Left hemiparesis and confusion	GCS 3	Left hemiparesis	Right hemiparesis and dysphasia
Hemoglobin 113 g/l **lymphocyte count 0.80** neutrophil count 6.82 platelet count 296 **CRP 30** mg/L D-dimer; NR Ferritin 126 ug/l Creatinine 62 umol/L PT; NR	Hemoglobin 108 g/l **lymphocyte count 0.76** neutrophil count 11.27 platelet count 196 **CRP 74** mg/L D-dimer; NR Ferritin; NR Creatinine 34 umol/L PT 12.1 s	Hemoglobin 145 g/l **lymphocyte count 0.49** neutrophil count 8.14 platelet count 332 **CRP 132** mg/L D-dimer; NR Ferritin 38 ug/l Creatinine 81 umol/L PT 13 s	Hemoglobin 117 g/l **lymphocyte count 0.87** neutrophil count 10.72 platelet count 352 **CRP 296** mg/L D-dimer; NR Ferritin; NR Creatinine 84 umol/L PT 10.9 s	Hemoglobin 136 g/l **lymphocyte count 0.82** neutrophil count 7.87 platelet count 335 **CRP 345** mg/L D-dimer; NR Ferritin; NR **Creatinine 118** umol/L PT 14.4 s	Hemoglobin 105 g/l lymphocyte count 1.19 neutrophil count 8.49 platelet count 362 CRP 8 mg/L D-dimer; NR Ferritin; NR **Creatinine 106** umol/L PT 12.6 s
MRI: Acute right PCA infarct	CT: Acute left ACA territory infarct	CT: Small cortical infarcts involving the right pre-central gyrus	CT: Large acute right MCA territory infarct with mass effect	CT; Acute thrombus within the terminal segment ICA, M1/M2 segments of the right MCA and the proximal right A1 ACA segment	CT: Left MCA thrombus and infarct
Continued recovery in rehabilitation; mRS 3	Full recovery	Continued recovery in rehabilitation; mRS 3	Died	Died	Full recovery

28 (Figure 1)	**18 (Figure 1)**	**24**	**29**	**30**
65, M, White, Definite	49, M, White, Definite	56, F, Black, Suspected	34, F, White, Definite	68, M, Definite
Isolated intraventricular hemorrhage	1. Isolated Intraventricular hemorrhage 2. Unilateral hearing loss (new)	Cerebral microbleeds, suspected CAA	Multifocal cerebral and cerebellar infarcts	Multifocal cerebral and cerebellar infarcts
Reduced consciousness despite sedation hold	Reduced consciousness despite sedation hold	Recurrent seizures	Dysphasia and dysarthria	GCS 3
Hemoglobin 127 g/l **lymphocyte count 0.17** neutrophil count 3.99 platelet count 228 **CRP 158** mg/L **D-dimer 8645** ug/l **Ferritin 758** ug/l **Creatinine 128** umol/L PT 10.8 s	Hemoglobin 141 g/l **lymphocyte count 0.52** neutrophil count 3.51 platelet count 170 **CRP 171** mg/L D-dimer; NR **Ferritin 2132** ug/l Creatinine 91 umol/L PT 11.4 s	Hemoglobin 147 g/l **lymphocyte count 0.86** neutrophil count 6.02 platelet count 202 CRP <5 mg/L D-dimer; NR Ferritin; NR Creatinine 95 umol/L PT 12.9 s	Hemoglobin 91 g/l **lymphocyte count 0.94** neutrophil count 5.87 platelet count 455 **CRP 263** mg/L **D-dimer 6358** ug/l **Ferritin 2986** ug/l **Creatinine 286** umol/L PT 11.4 s	Hemoglobin 132 g/l **lymphocyte count 0.66** neutrophil count 9.35 platelet count 412 **CRP 342** mg/L D-dimer; NR **Ferritin 3712** ug/l Creatinine 75 umol/L **PT 13.1** s
CT; Small volume intraventricular hemorrhage in the left occipital horn of the lateral ventricle	CT and MRI: Small volume intraventricular hemorrhage layering in both occipital horns	MRI; Micro-hemorrhagic changes in both cerebral hemispheres	CT and MRI: Multiple bilateral white matter and left cerebellar tiny foci of infarction	CT; Multifocal supra- and infra-tentorial infarcts
Full recovery	Recovery with slight disability; mRS 1	Full recovery	Died	Died

M, male; F, female; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; GCS, Glasgow Coma Scale; CAA, cerebral amyloid angiopathy; NR, no result; CRP, C-Reactive protein; ESR, Erythrocyte sedimentation rate; mRS, modified Rankin Score; PT, Prothrombin time; CT, computed tomography. MRI, magnetic resonance imaging; Lymphocyte, neutrophil and platelet count; numbers x 10 E9/L. The bold values highlight abnormal values.

were admitted in the intensive care unit for management of a malignant MCA syndrome. All patients underwent a computed tomography (CT) and/or an magnetic resonance imaging (MRI) of the head at presentation (representative examples in **Figure 1**). Only two patients were given intravenous (IV) thrombolysis and two underwent mechanical thrombectomy (MT). Four patients recovered fully, three survived with disability and six patients died within days of their diagnosis due to a combination of the underlying stroke and/or COVID-19 pneumonia.

Hemorrhagic Stroke: (Patient 18, 24, 28)

Two male patients with COVID-19, Patients 18 and 28 (aged 48 and 65 years respectively), had isolated intraventricular hemorrhage demonstrated on the CT scan of the head, performed due to reduced level of consciousness despite a sedation hold, during their prolonged critical care admission (**Table 1**). The MRI of the head from the 48-year-old patient showed cerebral microbleeds in the splenium of the corpus callosum and subcortical white matter (**Figure 1**). Both patients were placed on continuous veno-venous hemofiltration, but neither required extracorporeal membrane oxygenation (ECMO). The platelet count level, prothrombin and activated partial thromboplastin times were within the normal referenced ranges.

The third patient (Patient 24) was a 55 year-old female who presented with recurrent seizures. The MRI of the head also revealed cerebral microbleeds, with features suggestive of cerebral amyloid angiopathy. No critical care admission was required and the prothrombin time was normal. Two patients (Patient 24 and 28) made an uneventful recovery. However, patient 18 reported unilateral hearing impairment following hospital discharge.

Inflammatory, Non-inflammatory, and Autoimmune Encephalopathy

Limbic encephalitis (Patient 21); Inflammatory encephalopathy (Patient 22); ADEM (Patient 27); Transverse myelitis (Patient 5); Non-inflammatory encephalopathy (Patient 9) (**Table 2**).

Three patients (aged between 46 to 79 years, three females) demonstrated a range of inflammatory encephalopathies. Patient 21 was diagnosed with limbic encephalitis, patient 22 with inflammatory encephalopathy, patient 27 with ADEM. Patient 9 was diagnosed with non-inflammatory encephalopathy and Patient 5 with transverse myelitis. Whilst four patients (9, 21, 22, and 27) presented with acute-onset delirium and altered mental status, patients 21 and 22 also suffered from status epilepticus, cognitive impairment (scored 19 and 20 on the Montreal Cognitive Assessment, respectively) and amnesia. Patient 5 presented with quadriparesis and altered sensation at the cervical level. In Patient 27, three white cells were found in the cerebrospinal fluid (CSF) on the first day of admission, prior to

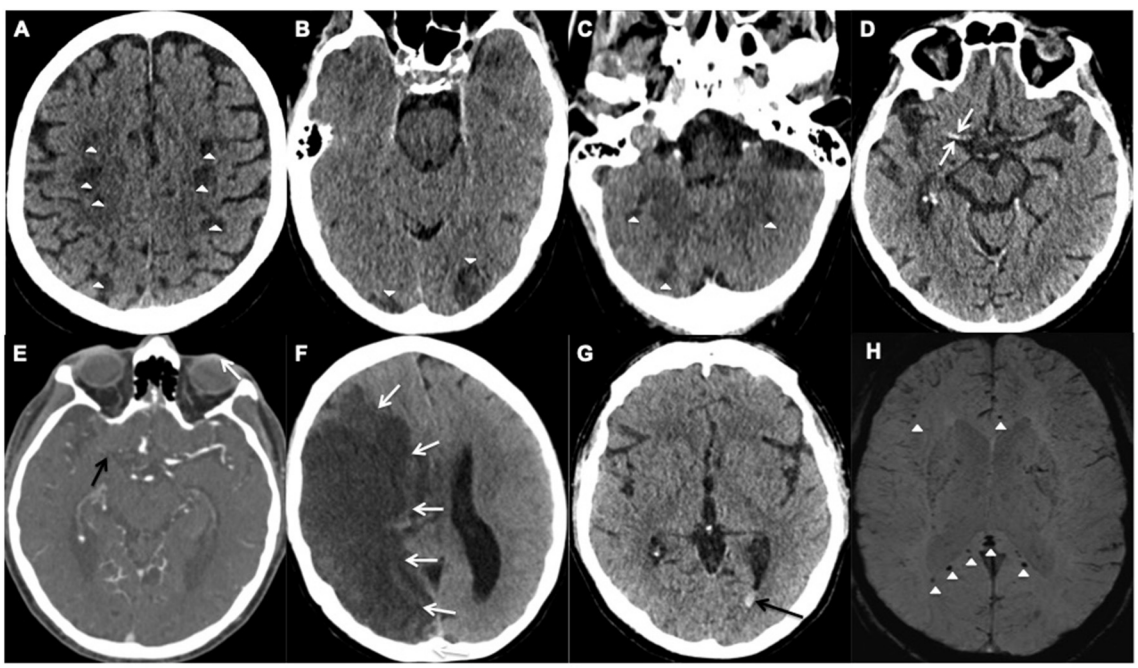

FIGURE 1 | Representative examples of cerebrovascular events; **(A–F)** acute ischemic stroke and **(G,H)** hemorrhagic events. **(A–C)** Axial unenhanced CT images of Patient 28 demonstrate multifocal infarcts (white arrowheads) bilaterally along the **(A)** centrum semiovale, **(B)** Occipital lobes, and **(C)** Cerebellar hemispheres. **(D,E)** Axial CT images of Patient 25 demonstrates the **(D)** hyperdense right middle cerebral artery (MCA) sign (white arrows) and **(E)** corresponding filling defect on the CT angiogram confirming an occlusive thrombus (black arrow). **(F)** Axial unenhanced CT image of Patient 6 shows a large right MCA territory infarct (white arrows) with mass effect in keeping with an MCA malignant syndrome. **(G,H)** Axial images of Patient 18. **(G)** unenhanced CT demonstrates hyperdense layering in the occipital horn of the left lateral ventricle (black arrow) in keeping with isolated intraventricular hemorrhage (IVH), **(H)** Susceptibility weighted imaging confirms the IVH bleed within the left occipital horn (white arrow) and shows microbleeds at the splenium and genu of the corpus callosum, and subcortical white matter (white arrowheads).

TABLE 2 | Seven patients with inflammatory, non-inflammatory or autoimmune encephalopathy, including two patients with known multiple sclerosis (MS), and one patient with transverse myelitis.

Patient	**27 (Figure 2)**	**21 (Figure 2)**	**22**	**5**	**9**	**8**	**14**
Age, M/F, ethnicity, COVID-19 diagnosis	68, F, White, Definite	79, F, White, Definite	46, M, Asian, Definite	69, M, White, Probable	55, F, White, Definite	65, M, White, Definite	56, M, White, Definite
Final neurological diagnosis (impression)	Acute demyelinating encephalomyelitis (ADEM)	Limbic encephalitis associated with SARS-CoV2	Inflammatory encephalopathy associated with SARS-CoV2	Transverse myelitis	Non-inflammatory encephalopathy associated with SARS-CoV2	Relapse in an advanced Secondary Progressive MS	Relapse in a known Multiple Sclerosis
Key neurological signs	Delirium, limb weakness, ataxia, visual hallucination,	Delirium, New onset generalized seizure/status epilepticus, dysphagia, cognitive impairment, amnesia	Delirium, New onset generalized seizures, disinhibition and cognitive impairment	Quadriparesis and sensory loss at cervical level	Headache, delirium, reduced conscious level, confusion and behavioral change	Delirium, reduced consciousness	Worsening limb weakness and dysarthria
Blood results at admission	Hemoglobin 124 g/l **Lymphocyte count 0.55** Neutrophil count 9.11 Platelet count 336 **CRP 262 mg/L** ESR 10 mm/hr D-dimer; NR Ferritin; NR Creatinine 94 umol/L PT 10 s	Hemoglobin 132 g/l **Lymphocyte count 0.39** Neutrophil count 5.83 Platelet count 313 **CRP 31** mg/L **D-dimer 3748** ug/l Ferritin; NR Creatinine 65 umol/L PT 13.7 s	Hemoglobin 147 g/l **Lymphocyte count 0.89** Neutrophil count 3.6 Platelet count 133 **CRP 149** mg/L **ESR 90** mm/hr **D-dimer 1659** ug/l **Ferritin; 1328** ug/l Creatinine 88 umol/L PT 11.9 s	Hemoglobin 120 g/l Lymphocyte count 1.1 Neutrophil count 8.9 Platelet count 407 **CRP 24 mg/L** D-dimer; NR Ferritin; NR Creatinine 53 umol/L PT; NT	Hemoglobin 132 g/l Lymphocyte count 1 Neutrophil count 9.1 Platelet count 203 **CRP 47 mg/L** D-dimer; NR Ferritin; NR Creatinine 67 umol/L PT; NR	Hemoglobin 147 g/l **Lymphocyte count 0.46** Neutrophil count 6.4 Platelet count 154 **CRP 168** mg/L **D-dimer 3748** ug/l Ferritin; NR Creatinine 69 umol/L PT 10.4 s	Hemoglobin 132 g/l **Lymphocyte count 0.76** Neutrophil count 3.67 Platelet count 153 **CRP 62** mg/L **D-dimer 5422** ug/l Ferritin 381 ug/l Creatinine 64 umol/L PT 11.2 s
Brain imaging	MRI; Multiple patchy, asymmetric periventricular and subcortical white matter lesions in bilateral cerebral hemispheres, midbrain, dorsal pons, right middle cerebellar peduncle, medulla and right cerebellar hemisphere. Mixed diffusivity exhibited. Radiological progression on subsequent imaging during hospital admission	MRI; Lesions in the limbic system, predominantly in the left amygdala and hippocampus with partial restricted diffusion	MRI; White matter lesions in the left anterior limbic structures with foci of increased diffusivity suggesting cellular inflammation	MRI; Restricted diffusion in the inferior medulla with enhancement. Small area of restricted diffusion in left middle cerebellar peduncle. MRI spine; Extensive spinal cord abnormality predominantly involving the cervical and lower thoracic regions including the conus in keeping with transverse myelitis	MRI; No acute abnormality. Marked parenchymal atrophy with medial bitemporal predominance	CT: No acute abnormality	MRI: Progression of inflammatory demyelinating plaques since 2015

(Continued)

TABLE 2 | Continued

Patient	27 (Figure 2)	21 (Figure 2)	22	5	9	8	14
CSF examination	White cells 3 per μl (first day of admission), White cells 8 lymphocytes per μl (14 days after admission), red cells 1, **protein 45.1 mg/dl,** glucose 4.1, Paired serum glucose 5.6 mmol/L. **Oligoclonal bands** present. Viral PCR for SARS-CoV-2/enterovirus/HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative, paraneoplastic anti-neuronal antibodies negative, anti-MOG and AQP4 negative	White cell none, Red cells 9, protein; protein 340 mg/dl, glucose 4.1, Paired serum glucose 5.4 mmol/L. Oligoclonal bands negative. Viral PCR for SARS-CoV-2/enterovirus /HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative, paraneoplastic anti-neuronal antibodies negative	White cell none, Red cells 25, **protein 98.7 mg/dl**, glucose 4.5, Paired serum glucose 5.8 mmol/L. **Oligoclonal bands** present. Viral PCR for SARS-CoV-2/enterovirus /HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative, paraneoplastic anti-neuronal antibodies negative	White cell 1, red cells 0, **protein 51.4 mg/dl**, glucose 3.1 mmol/L. **Oligoclonal bands** present (identical to serum). Viral PCR for SARS-CoV-2/enterovirus /HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative, paraneoplastic anti-neuronal antibodies negative	Not performed (known early-onset advanced Alzheimer's Dementia with further cognitive decline)	Not performed	Not performed
Neurological treatments; recovery	Corticosteroids; Intravenous Methylprednisolone	Benzodiazepine, Levetiracetam IV & maintenance	Intubation and sedation for status epilepticus, Empirical aciclovir, antibiotics until CSF results available. IV valproate & maintenance	Intravenous Methylprednisolone	Supportive	Supportive and antibiotics (due to advanced disorder, osteomyelitis and pressure sores)	Glatiramer acetate injections 3 times/weekly
Outcome status	Recovery with mild neurological deficits; mRS 1	Partial recovery with mild neurological deficits; mRS 1	Full clinical recovery	Partial recovery with neurological deficits; Moderate disability mRS 4	Partial recovery with neurological deficits; Severe disability mRS 5	Died	Partial recovery with moderate disability; mRS 3

M, male; F, female; NR, no result; CRP, C-Reactive protein; mRS, modified Rankin Score; ESR, Erythrocyte sedimentation rate; PCR, polymerase chain reaction; NMDA-R, N-methyl-D-aspartate Receptor antibodies; LGi-1, Leucine-rich glioma inactivated-1; CASPR2, contactin-associate protein-like 2; MOG, myelin oligodendrocyte glycoprotein; AQP4, Aquaporin-4; PT, Prothrombin time. Paraneoplastic anti-neuronal antibodies including GABA-B; γ-Aminobutyric acid-B receptor; AMPA; GluR1 and GluR2 subunits of the AMPA receptor. CT, computed tomography. MRI, magnetic resonance imaging, Lymphocyte, neutrophil and platelet count, numbers x 10 E9/L. The bold values highlight abnormal values.

commencement of steroid treatment. A repeat lumbar puncture on Day 14 was performed after a course of corticosteroid treatment (intravenous Methylprednisolone 1 gram per day for three days followed by oral Prednisolone 60 milligrams per day). The second CSF examination revealed 8 lymphocytes per μl. There was no evidence of pleocytosis in Patient 21 (12 days after admission) or Patient 22 (two days after admission). Oligoclonal bands and mildly raised proteins were detected in the CSF of Patients 5, 22, and 27, whilst intrathecal SARS-CoV-2, paraneoplastic and autoimmune encephalitis antibodies (including N-methyl-D-aspartate Receptor, Leucine-rich glioma inactivated-1, contactin-associate protein-like 2, γ-Aminobutyric acid-B receptor, GluR1 and GluR2 subunits of the AMPA receptor) were negative in all three patients. Patient 9 had a pre-morbid diagnosis of Early Onset Alzheimer's Dementia, and missed out on a diagnostic lumbar puncture due to the time's real-life challenges and the guidelines that were based on uncertainties and lack of knowledge on SARS-CoV2 transmission routes.

The MRI of the head showed partial diffusion restriction in the limbic system of Patient 21 (**Figure 2**) and persistent diffusion-weighted hyperintensities without overt restriction in Patient 22, suggestive of cellular inflammation. Patient 27 had progressive patchy, asymmetric periventricular and subcortical white matter hyperintense foci with diffusion restriction in the cerebral hemispheres, right cerebellar hemisphere and brainstem, which are features consistent with ADEM (**Figure 2**). The MRI of the spine in Patient 5 showed extensive spinal cord abnormality involving the cervical, lower thoracic, and conal regions that were supportive of transverse myelitis. Small regions of diffusion restriction were also identified in the medulla and middle cerebellar peduncle. Patient 22 required a brief critical care admission for four days to control seizures, Patients 5 and 27 were given a course of intravenous (IV) followed by oral corticosteroids. Patient 22 was considered, but did not receive corticosteroid treatments as he had a rapid recovery after seizure-control and was discharged from the intensive care unit. During the first peak of COVID-19 in the UK, the evidence on the use of corticosteroids during acute phase of SARS-CoV-2 infection, particularly during intensive care admissions, was controversial (19). All five patients recovered from their acute respiratory illness sufficiently for hospital discharge. However, only Patient 22 made a full neurological recovery, whilst the remaining patients were identified as having persistent neurological disability at discharge.

Demyelination: (Patient 8, 14)

Two male patients (Patients 14 and 8), with known advanced Multiple Sclerosis (MS) (aged between 56 to 65 years, respectively), presented with symptoms consistent with, and were diagnosed with COVID-19 (**Table 2**). Patient 8 presented with acute delirium whilst Patient 14 was hospitalized due to the MS relapse associated with worsening of his baseline MS-related limb

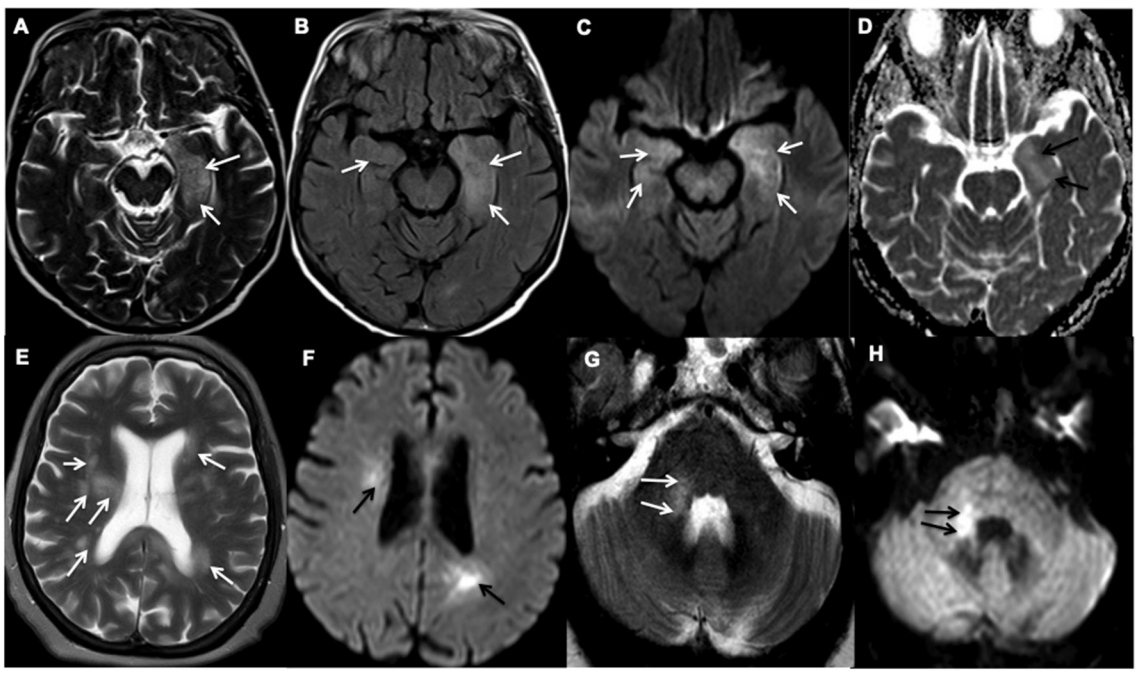

FIGURE 2 | Representative examples of inflammatory encephalopathy. **(A–D)** Axial MR images of Patient 21 demonstrate limbic encephalitis. **(A)** T2-weighted and **(B)** Fluid attenuated inversion recovery (FLAIR) imaging demonstrate hyperintensity in both medial temporal lobes, but predominantly in the left amygdala and hippocampus (white arrows), **(C)** Diffusion-weighted imaging (white arrows) and **(D)** Apparent diffusion coefficient (ADC) show corresponding partial diffusion restriction (black arrows). **(E–H)** Axial MR images of Patient 27 demonstrate acute demyelinating encephalomyelitis. **(E)** T2-weighted imaging demonstrates patchy and asymmetric white matter hyperintensities within the periventricular and subcortical regions and **(G)** right middle cerebellar peduncle (white arrows). **(F,H)** Diffusion-weighted imaging shows corresponding high diffusion signal (black arrows).

weakness and dysarthria during the admission. The MRI of the head performed showed progression of the inflammatory plaques since 2015 in Patient 14 but no acute changes were identified on the CT scan of the head obtained from Patient 8. None of them were admitted to the intensive care unit. Only Patient 14 survived with ongoing disability, whilst Patient 8 succumbed to septicaemia.

Movement Disorders

Myoclonus ± Opsoclonus (Patients 7, 19, 20)

Movement Disorders were seen in three patients with COVID-19 (Patients 7, 19 and 20; aged between 57 to 86 years, two males) (**Table 3**). Patient 7 suffered from mild rest myoclonus of the arm, Patient 20 had a generalized rest myoclonus and Patient 19 was diagnosed with opsoclonus-myoclonus syndrome. No other neurological symptoms or signs were identified. The CT/MRI of the head demonstrated no acute abnormality in all patients. There was elevated CSF protein in Patients 19 and 20, with otherwise normal CSF constituents (including no detectable intrathecal SARS-CoV-2). Normal electroencephalography (EEG) record was demonstrated in Patient 20. All patients were treated with benzodiazepines and two patients made a full recovery at the time of discharge from hospital while Patient 19 had residual symptoms. Only Patient 7 required critical care admission for pulmonary symptoms of COVID-19.

Peripheral Nervous System Disorders

Acute Inflammatory Demyelinating Polyneuropathy (Patient 13, 23); Brachial Plexopathy (Patient 26)

Two patients with COVID-19 (Patient 13 and 23) presented with ascending peripheral weakness and diagnosed with acute inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome (**Table 4**). The ascending distal limb weakness in Patient 23 was associated with seizures and an atypical acute inflammatory demyelinating polyneuropathy was diagnosed. The nerve conduction studies confirmed features in keeping with segmental demyelinating peripheral neuropathy in Patient 13 and axonal neuropathy (motor and sensory) in Patient 23. Elevated CSF protein with otherwise normal CSF constituents was identified in both these patients. Patient 26 who presented with left upper limb weakness was diagnosed with brachial plexopathy.

Patient 13 was treated with intravenous immunoglobulin (IVIG). Patients 23 and 26 required a short period of critical care admission and all patients made a partial recovery. Patient 26 reported bilateral hearing loss following hospital discharge and has been referred for further investigation.

DISCUSSION

We report a variety of neurological disorders with a clinical impact in patients with COVID-19 infection admitted in a large tertiary institution during the "first wave" of the COVID-19 pandemic in the UK. There have been isolated reports of various neurological disorders associated with previous outbreaks of the severe acute respiratory syndrome (SARS) and Middle East acute respiratory syndrome (MERS) (20, 21). Similarly, our cohort of cases demonstrates a wide range of COVID-19 related neurological disorders, ischemic and hemorrhagic cerebrovascular events, inflammatory and non-inflammatory encephalopathy syndromes, transverse myelitis, movement disorders, and acute inflammatory demyelinating polyneuropathy with additional neurological manifestations. Excluding anosmia, the cumulative incidence of disorders is in 2.3% of our hospitalized patients with COVID-19, with 27% of them requiring critical care admission. The diagnosis of each of the neurological disorders was made in conjunction with a positive diagnosis of COVID-19, suggesting their association may not be fortuitous. Whilst recent case reports/series have described a range of neurological symptoms during the ongoing COVID-19 pandemic, there is often a lack of detailed clinical, radiological and laboratory findings of the neurological disorders amongst hospitalized patients with COVID-19, which reflect the challenge of studying the natural history of COVID-19 complications in this patient cohort.

Evidence from our cohort and recent studies have included non-specific initial presentations such as altered mental status or delirium, features commonly seen in the critically unwell with sepsis and hypoxemia, as well as being potential early signs of dementia. The neurological disorders have been reported in patients who present solely with neurological signs and symptoms as well as those with established systemic or pulmonary illness related to COVID-19. These neurological features may precede or occur days after the onset of pulmonary symptoms. Hence, the variable and non-specific nature of the presentation and onset of the illness creates a diagnostic and therapeutic dilemma. Furthermore, the occasional delay of presentation and hospital admission during the first peak of the pandemic due to patients' fear, isolation or shielding, may have lead to an increase in severity of the illness and neurological disorders at the point of diagnosis. Interestingly, there was no increased incidence or severity of the COVID-19 infection or neurological disorders amongst the BAME groups in our cohort. However, this could be due to the relatively small number of BAME communities in our geographical region. Additionally, during the first wave that peaked in May 2020, patients with acute SARS-CoV-2 infection did not receive corticosteroids or anti-viral therapy as part of standard treatment. Whilst some patients may have been recruited to the RECOVERY trial (22), which included dexamethasone and anti-viral therapy arms, none of the patients in this case series were involved.

There has been a reported increase in the incidence and severity of cerebrovascular disease associated with COVID-19, particularly in a younger cohort (6, 23). Our cohort demonstrated a high percentage of patients with acute ischemic stroke and up to 38% of these had a large vessel occlusion. Some of the acute ischemic cerebrovascular events with multifocal infarcts may be cardioembolic in nature, due to associated cardiovascular risk factors, but coagulopathy, vasculitis and viral endothelialitis have also been reported as potential causes of multi-vessel stroke in patients with COVID-19 (23, 24). The hyper-inflammatory syndrome or "cytokine storm" strongly associated with severe COVID-19 infection could also contribute to the underlying etiology (13).

TABLE 3 | Three patients with movement disorders.

Patient	7	19	20
Age, M/F, ethnicity, COVID-19 diagnosis	57, M, White, Definite	86, F, White, Definite	86, M, White, Probable
Final neurological diagnosis	Myoclonus	Opsoclonus myoclonus	Generalized rest myoclonus affecting lower face and whole body
Blood results at admission	Hemoglobin 104 g/l **Lymphocyte count 0.56** Neutrophil count 3.22 Platelet count 223 **CRP 409** mg/L **D-dimer; 17390** **Ferritin; 916** Creatinine 84 umol/L PT 12.5 s	Hemoglobin 109 g/l **Lymphocyte count 0.86** Neutrophil count 10.2 Platelet count 271 CRP 5 mg/L D-dimer; NR Ferritin; NR Creatinine 80 umol/L PT; NR	Hemoglobin 97 g/l **Lymphocyte count 0.76** Neutrophil count 4.51 Platelet count 302 **CRP 35** mg/L**, ESR 105** mm/hr D-dimer; NR Ferritin; NR Creatinine 139 umol/L PT; NR
Brain imaging	CT: No acute abnormality	MRI: No acute abnormality	MRI: No acute abnormality Electroencephalography: Normal
CSF examination	Not performed	White cell none, red cell none, protein; 46.8 mg/dl, glucose; 3.9 mmol/L. paired serum glucose; NR. Viral PCR for SARS-CoV-2/enterovirus/HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative	White cell none, red cells 265, **protein; 166.7 mg/dl**, glucose 3.6 mmol/L, paired serum glucose; NR. **Oligoclonal bands** present in serum and CSF. Viral PCR for SARS-CoV-2/enterovirus/HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative
Neurological treatments; recovery	Diazepam	Levetiracetam and clonazepam	Clonazepam
Outcome status	Full recovery	Partial recovery with neurological deficits; Moderate disability mRS 3	Full recovery

M, male; F, female; NR, no result; CRP, C-Reactive protein; mRS, modified Rankin Score; NMDA-R, N-methyl-D-aspartate Receptor antibodies; ESR, Erythrocyte sedimentation rate; PCR, polymerase chain reaction; LGi-1, Leucine-rich glioma inactivated-1; CASPR2, contactin-associated protein-like 2. PT, Prothrombin time; CT, computed tomography. MRI, magnetic resonance imaging, Lymphocyte, neutrophil and platelet count, numbers x 10 E9/L. The bold values highlight abnormal values.

Thrombotic microangiopathy and endothelial dysfunction, also evident in multiple organ systems related to COVID-19, may be contributory factors in sepsis/critical illness-related cerebral microbleeds (24, 25). The SARS-CoV-2 has been shown to preferentially bind to the angiotensin converting enzyme (ACE)-2 receptors that can be found in the endothelial lining, leading to the breakdown of the blood-brain barrier (8). However, cerebral microbleeds have similarly been reported in acute respiratory distress syndrome patients with a resemblance seen in cerebral microbleeds-related high altitude exposure, sharing a common underlying etiology of hypoxemia (26). This could likewise explain the findings in our cases with hemorrhagic neurological manifestations in COVID-19. Interestingly, both patients with isolated intraventricular hemorrhage had normal coagulation parameters, and the observed cerebral microbleeds were atypical for hypertensive or amyloid angiopathy causes. Other variables that may influence the presence and/or extent of microhemorrhage in patients with COVID-19 include therapeutic anticoagulation and raised cerebral venous pressure secondary to ventilator measures in optimizing patient oxygenation in the critical care setting (18).

The neurotropic potential of COVID-19 via direct viral axonal injury has been alluded to following scarce reports of the SARS-CoV-2 being detected in the CSF of patients with meningo-encephalitis and in animal models (27, 28). Similarly, a large case series of brain autopsies in patients with COVID-19 revealed the detection of the SARS-CoV-2 RNA and proteins in up to 53% of patients, although its presence was not associated with the severity of the immuno-pathological findings (29). Furthermore, few case reports have demonstrated imaging features of direct neuronal injury of the olfactory pathway in COVID-19 patients presenting with anosmia, adding strength to this potential mechanism (30). Nonetheless, no detectable intrathecal coronavirus strain was identified in our patients who presented with encephalopathy. Recent CSF-based studies in patients with COVID-19 also failed to detect any evidence of SARS-CoV-2 intrathecally (31). However, it remains unclear if this reflects the poor sensitivity of the RT-PCR assay in CSF resulting in a possible false negative result, or if other (indirect) immune-mediated mechanisms are responsible for the neurological changes (32).

Interestingly, two patients who required critical care admission reported new onset hearing loss following hospital discharge, despite no acute abnormality on their MRI of the head during the hospital stay. A recent case report also described a possible association between sensorineural hearing impairment and COVID-19 in the critical care setting (33). It is postulated that such an observation could be due to the underlying hyperinflammatory process and/or the neuro-invasive potential

TABLE 4 | Three patients with disorders of the peripheral nervous system.

Patient	13	23	26
Age, M/F, ethnicity, COVID-19 diagnosis	67, M, White, Definite	58, F, White, Probable	58, M, White, Definite
Final neurological diagnosis	Guillain-Barré syndrome	Atypical acute inflammatory demyelinating polyneuropathy	Brachial plexopathy 2. Bilateral hearing loss
Blood results at admission	Hemoglobin 133 g/l **Lymphocyte count 0.93** Neutrophil count 3.81 Platelet count 242 **CRP 112** mg/L D-dimer; NR Ferritin; 295 Creatinine 58 umol/L PT; NR	Hemoglobin 85 g/l **Lymphocyte count 0.48** Neutrophil count 5.19 Platelet count 178 **CRP 16** mg/L D-dimer; NR Ferritin 340 ug/l **Creatinine 140** umol/L PT 11.4 s	Hemoglobin 101 g/l Lymphocyte count 1.24 Neutrophil count 16.36 Platelet count 224 **CRP 351** mg/L **D-dimer 9251** ug/l **Ferritin 800** ug/l Creatinine 62 umol/L PT 11.5 s
Brain imaging	Not performed	MRI Brain and spinal cord: No acute abnormality	CT brain: No acute abnormality
Nerve conduction study	Segmental demyelinating peripheral neuropathy	Sensory and motor axonal neuropathy	Not performed during the acute SARS-CoV2 infection
CSF examination	Red cells: 1770, white cells: none; **protein; 155.6 mg/dl**, glucose; 4.2, Paired blood glucose; 6.6 mmol/L; Viral PCR for enterovirus/HSV negative	Red cells 8; White cells: none, **protein; 340.1 mg/dl**, glucose; 4.2, Paired blood glucose; 6.6 mmol/L; Oligoclonal bands negative. Viral PCR for SARS-CoV-2/enterovirus/HSV negative. NMDA-R/CASPR2/LGi-1/Glycine receptor antibodies all negative	Not performed
Neurological treatments; recovery	Intravenous Immunoglobulin	Intravenous Methylprednisolone, Levetiracetam & Sodium Valproate (seizures)	No specific treatment administered (neurological disorder identified after ventilation support in critical care)
Outcome status	Recovery with slight disability; mRS 1	Partial recovery with neurological deficits; mRS 4	Partial recovery with slight disability; mRS 2

M, male; F, female; NR, no result; CRP, C-Reactive protein; mRS, modified Rankin Score; NMDA-R, N-methyl-D-aspartate Receptor antibodies; PCR, polymerase chain reaction; LGi-1, Leucine-rich glioma inactivated-1; CASPR2, contactin-associated protein-like 2. PT, Prothrombin Time; CT, computed tomography. MRI, magnetic resonance imaging; Lymphocyte, neutrophil and platelet count, numbers x 10 E9/L. The bold values highlight abnormal values.

of the SARS-CoV-2 against the auditory nervous system. Hence, it will be important to consider screening patients with severe COVID-19 infection for hearing impairment during the hospital admission.

An immunological response secondary to the SARS-CoV-2, resulting in cerebral inflammation and edema with clinical encephalopathic features may offer an alternative explanation for the incidence of inflammatory and auto-immune encephalopathy disorders (14, 34). Antibodies against neuronal synaptic proteins have been demonstrated in autoimmune encephalitis, and there have been increased numbers of antibodies reported against other coronavirus strains, suggesting a possible association between auto-immune or inflammatory encephalopathic disorders and the COVID-19 infection (35, 36). Furthermore, the presence of both intrathecal and serum oligoclonal bands in two patients with acute encephalopathy and a patient with ADEM suggests that the immune-mediated response is not restricted to the intrathecal production of immunoglobulins. Post-infectious autoimmune disorder is also demonstrated in our case cohort of acute inflammatory demyelinating polyneuropathy, whereby the onset of neurological symptoms followed an initial period of illness related to COVID-19. Expected electrophysiological changes in keeping with demyelinating peripheral neuropathy were confirmed in one patient and the anticipated response to the IV immunoglobulin therapy was observed.

Limitations of our study include its lack of pathological evidence to prove causality. Furthermore, we only included hospitalized patients with COVID-19 in our study, thereby potentially underestimating the true incidence of the neurological associations in patients in the community. There were also inherent drawbacks in the sensitivity and specificity of the available RT-PCR swab tests during the study period, which may have underestimated the incidence of COVID-19 in the patient population (37).

Although the exact mechanism and possible causality of the SARS-CoV-2 infection associated with each of the presented neurological disorders remains unclear, it is likely that shared pathophysiological mechanisms are responsible for the various neurological manifestations of COVID-19. Our study lends further support to the growing body of evidence, aiding better understanding of the neurological features and optimizing management strategies using an approach guided by the evolution of clinical, laboratory and imaging features.

Longitudinal follow-up of these patients is required to determine the long term effects, treatment response and outcome of the SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by East Midlands-Derby Research Ethics Committee (Ref:18/EM/0292, Major amendment). The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

AH conceptuated and designed the study, prospectively screened, identified, collected and registered patients with neurological COVID-19. AH and RD held multidisciplinary meetings to discuss patients with COVID-19. RT and EN registered a prospective clinical audit to identify patients. PD and AH applied for ethical approval. PD, AH, HM, and RT obtained clinical information from medical records. AH, RT, and CC described neurological phenotype. PD described radiological features and wrote the manuscript. AH edited versions and revised the final manuscript. All co-authors edited the manuscript.

FUNDING

AH was partly funded by the Medical Research Council (MRC) United Kingdom.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

MINI REVIEW
published: 23 March 2021
doi: 10.3389/fnagi.2021.648662

Neurologic and Neuroscientific Evidence in Aged COVID-19 Patients

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The COVID-19 pandemic continues to prevail as a catastrophic wave infecting over 111 million people globally, claiming 2. 4 million lives to date. Aged individuals are particularly vulnerable to this disease due to their frailty, immune dysfunction, and higher rates of medical comorbidities, among other causes. Apart from the primary respiratory illness, this virus is known to cause multi-organ dysfunction including renal, cardiac, and neurologic injuries, particularly in the critically-ill cohorts. Elderly patients 65 years of age or older are known to have more severe systemic disease and higher rates of neurologic complications. Morbidity and mortality is very high in the elderly population with 6–930 times higher likelihood of death compared to younger cohorts, with the highest risk in elderly patients ≥85 years and especially those with medical comorbidities such as hypertension, diabetes, heart disease, and underlying respiratory illness. Commonly reported neurologic dysfunctions of COVID-19 include headache, fatigue, dizziness, and confusion. Elderly patients may manifest atypical presentations like fall or postural instability. Other important neurologic dysfunctions in the elderly include cerebrovascular diseases, cognitive impairment, and neuropsychiatric illnesses. Elderly patients with preexisting neurologic diseases are susceptibility to severe COVID-19 infection and higher rates of mortality. Treatment of neurologic dysfunction of COVID-19 is based on existing practice standards of specific neurologic condition in conjunction with systemic treatment of the viral illness. The physical, emotional, psychologic, and financial implications of COVID-19 pandemic have been severe. Long-term data are still needed to understand the lasting effects of this devastating pandemic.

Keywords: COVID-19, SARS-CoV-2, neurologic complications, elderly, aged adults, older patients, neurologic manifestations, neuro

OPEN ACCESS

Edited by:
Jennifer Ann Frontera,
New York University, United States

Reviewed by:
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Received: *01 January 2021*
Accepted: *23 February 2021*
Published: *23 March 2021*

Citation:
Mainali S and Darsie ME (2021) Neurologic and Neuroscientific Evidence in Aged COVID-19 Patients. Front. Aging Neurosci. 13:648662. doi: 10.3389/fnagi.2021.648662

INTRODUCTION

Over the course of one year, the novel SARS-CoV-2 virus has wreaked havoc globally accounting for over 111 million documented infections with a vast toll of death and disability. Although the proportion of severe cases is likely to depend on the study population and epidemiological behavior of the infection in each country or geographic region, current evidence suggests that older individuals and those with compromised immune systems are more likely to develop severe forms of COVID-19. In a large Chinese case series of 72,314 cases, older adults were more susceptible to the virus with case fatality rate of 8.0% in patients aged 70–79 years and 14.8% in patients aged ≥80 years (Wu and McGoogan, 2020). Some studies have reported age >65 years as an independent

predictor of mortality (Wu et al., 2020). Countries like Italy that have endured severe effects of the pandemic have also experienced highest morbidity and mortality in the elderly population, particularly those with underlying comorbidities (Livingston and Bucher, 2020). In fact, Italy has one of the world's oldest population, with 23% of people ≥65 years, which is likely the reason for Italy's high case fatality rate (7.2%) compared to other countries (Onder et al., 2020). In the United States (U.S.), although infection is most prevalent in the 18–29 age group (23%), elderly patients ≥65 years are 5–13 times more likely to be hospitalized and have 9–630 times higher likelihood of death; with the highest rate of hospitalization and death among patients ≥85 years of age (Centers for Disease Control Prevention, 2020). Per the National Vital Statistics System data on the demographic and geographic trends of COVID-19 in the U.S between May 1 and August 31, 78.2% of deaths occurred predominantly in men (53.3%) aged ≥65 years (Gold et al., 2020). Neurologic dysfunctions of COVID-19 are also more common in the elderly population (Frontera et al., 2020), and the presence of neurologic dysfunction has been identified as an independent predictor of mortality in hospitalized COVID-19 patients (Aggarwal et al., 2020; Frontera et al., 2020; Pranata et al., 2020).

As neurologic complications are often associated with disease severity and mortality, characterization of neurologic dysfunction and accurate prognostication is crucial. Here we briefly discuss common neurologic dysfunctions of COVID-19 in the elderly, possible determinants of disease severity in this age group, outcomes, and treatment.

NEUROLOGIC ASSOCIATIONS AND COMPLICATIONS IN AGED COVID-19 PATIENTS

The most commonly reported symptoms of COVID-19 are fever, dry cough, fatigue, and dyspnea (Siordia, 2020). Elderly patients are likely to present with atypical symptoms such as falls, postural instability, or delirium (Steinmeyer et al., 2020). The pulmonary manifestations of COVID-19 drive most hospitalizations worldwide, more commonly in patients ≥65 years and those with comorbidities like diabetes and hypertension (Xu et al., 2020). Critically-ill COVID-19 patients frequently develop multi-organ dysfunction including arrhythmias, myocardial injury, heart failure, arterial and venous thrombosis, disseminated intravascular coagulation (DIC), dysregulated immune response, and neurologic complications (DeKosky et al., 2020; Guzik et al., 2020; Ortiz-Prado et al., 2020). Preexisting vascular disease is known to predispose individuals to severe COVID-19 infection, with aged individuals being more susceptible to more severe courses (Guzik et al., 2020; Li et al., 2020).

Neurologic complications are noted to be more common in patients with severe respiratory illness (Mao et al., 2020). Furthermore, neurologic dysfunctions can also lead to longer duration of mechanical ventilation in critically-ill patients (Helms et al., 2020). Neurologic dysfunctions of COVID-19 span a spectrum of mild symptoms like headache, anosmia, ageusia to severe complications including stroke, meningitis, encephalitis, and status epilepticus (DeKosky et al., 2020; Iadecola et al., 2020; Mao et al., 2020; Paterson et al., 2020). Heterogeneity in reports related to data elements, population, study design, analysis, and associated comorbidities have precluded a robust systematic analysis of neurologic dysfunctions of COVID-19. A qualitative, systematic review on clinical features of COVID-19 specifically in the elderly cohort has reported several neurologic manifestations including headache, fatigue, myalgias, dizziness, gait disturbances, confusion, and delirium (Neumann-Podczaska et al., 2020). The severity of COVID-19 illness and associated neurologic complications are known to be more prevalent in persons with preexisting comorbidities such as cerebrovascular and cardiovascular diseases, hypertension, diabetes, obesity, respiratory diseases, and malignancy (Worldometer, 2020; Zádori et al., 2020).

Acute encephalopathy has been reported as a common neurologic complication of COVID-19, particularly in elderly patients and those with severe diseases (Garg et al., 2020; Helms et al., 2020). Across the literature, various terms have been used to describe altered cognition including acute encephalopathy, delirium, altered mental status, acute confusional state, acute brain dysfunction, acute brain failure, etc. Lack of standard nomenclature with varied reporting practices related to conceptual or semantic disparities across different medical disciplines has made it difficult to pool data for evaluating the true global prevalence and impact of encephalopathy related to COVID-19. Although a consensus statement of 10 critical care societies was published in early 2020 proposing the standard nomenclature (Slooter et al., 2020), existing literature on COVID-19-related-encephalopathy remain tainted with a variety of terms and reporting practices. Historically, delirium has been noted in about 10–15% of elderly patients presenting to the hospital and diagnosed in up to one-third of general medical patients ≥70 years (Marcantonio, 2017). However, it is much more common in critically-ill patients. Although reports are variable across studies, one multicenter study reported a delirium prevalence of up to 73% in intubated patients with ARDS (Hsieh et al., 2015). In comparison, published reports have suggested increased prevalence of delirium in COVID-19 patients presenting to the emergency department with estimates of around 28% and much higher rates in critical care cohorts of up to 84.3% (Helms et al., 2020; Kennedy et al., 2020; Liotta et al., 2020). In particular, elderly patients with comorbidities are particularly vulnerable, with delirium at presentation noted in up to 36.8% of elderly patients (Poloni et al., 2020). This apparent increase in the prevalence of delirium during the COVID-19 pandemic is likely to be due to both infectious as well as environmental factors such as social isolation (LaHue et al., 2020). Moreover, while acute encephalopathy is more common in older COVID-19 patients with medical comorbidities, when controlled for age and comorbidities, the presence of acute encephalopathy was still noted to be a predictor of critical care need, intubation, and 30-day mortality (Shah et al., 2020).

Acute stroke is another commonly reported neurologic complication of COVID-19, particularly in the elderly population (Berardelli et al., 2020; Josephson and Kamel, 2020). Li et al. reported a 5% risk of ischemic stroke and a 0.5% risk of

cerebral hemorrhage in 221 patients with COVID-19 infection from Wuhan, with the highest prevalence in aged individuals with underlying vascular and thrombotic risk factors such as hypertension, diabetes, and elevated plasma D-dimer levels (Li et al., 2020). Recent systematic reviews report stroke incidence of 1–2% in COVID-19 patients, which is significantly higher than historical controls, including a cohort with seasonal influenza (Fridman et al., 2020; Katsanos et al., 2020; Merkler et al., 2020; Nannoni et al., 2020). Mortality among hospitalized COVID-19 patients with acute stroke is also extremely high. Reports have noted mortality rates of 31.5–34.4%, with highest impact in older patients (Fridman et al., 2020; Nannoni et al., 2020). Elderly stroke survivors are also at increased risk of severe infection and suffer from higher mortality, likely related to their underlying comorbidities and swallowing complications (Aggarwal et al., 2020; Pranata et al., 2020). A recent meta-analysis of 39 studies on COVID-19-associated stroke suggested a mean age of 63.4 ± 13.1 years with male predominance and clinical findings of elevated D-dimer, elevated fibrinogen, and the presence of antiphospholipid antibodies (Tan et al., 2020). Although many other neurologic and neuropsychiatric symptoms have been reported, focused reports on elderly is generally sparse.

AGING PROCESS, COVID-19 DISEASE SEVERITY AND NEUROLOGIC IMPAIRMENT: SOCIAL AND PATHOPHYSIOLOGICAL DETERMINANTS

Multiple postulations have been made regarding mechanisms of disease severity in the elderly, including higher rates of neurologic complications of COVID-19 (Banerjee and Viswanath, 2020; Chen et al., 2020; Connors and Levy, 2020; Mehta et al., 2020; Paniz-Mondolfi et al., 2020; Sardu et al., 2020; Zhang et al., 2020). Investigators have recently performed integrative analyses of single-cell atlases in the lung and airways and across tissues to identify cell types and tissues that have the key molecular machinery required for SARS-CoV-2 infection (Muus et al., 2020). They further examined the relationship between specific cell types and three key covariates of disease severity including age, sex, and smoking status. The investigators noted increasing trends of double-positive $ACE2^{+}TMPRSS2^{+}$ cell proportions with *increasing age* which could be one of the reasons for disease severity in the elderly. Investigators also noted the presence of these receptors in tissues beyond the respiratory system, including oligodendrocytes in the brain. Furthermore, myelin proteins were noted to be co-expressed in numerous $ACE2^{+}TMPRSS2^{+}$ cells across various organs, which may suggest the potential for neurologic autoimmunity through the invasion of $ACE2^{+}TMPRSS2^{+}$ cells in organs such as the lungs and gut.

Frailty is common among the elderly (Bhaskar et al., 2020). It is characterized by declining function across several homeostatic systems leading to increased vulnerability to stressors and increased risk of adverse health outcomes (Maltese et al., 2020). Studies have shown that progressive physical frailty in the elderly is strongly correlated with declining cognition, which may in part be due to a common pathologic basis (Buchman et al., 2014; Wallace et al., 2019). Elderly patients with macroinfarcts, Alzheimer's disease, and Parkinson's disease pathology show independent association with the rate of change of both physical frailty and cognition (Buchman et al., 2014), placing these individuals at higher risk of COVID-19 disease severity.

The presence of chronic neurologic diseases (CND) has been reported to be an independent predictor of COVID-19 related death when controlled for confounding variables including, age, sex, baseline function, hypertension, diabetes, smoking, cardiac disease, pulmonary disease, and malignancy (García-Azorín et al., 2020). In a Spanish study, patients with CND were noted to be older with higher baseline disability, had more vascular risk factors, and exhibited fewer typical clinical symptoms of COVID-19, such as cough or malaise. Of the CND, elderly patients more commonly have preexisting neurovascular and neurodegenerative conditions, which in turn predisposes them to COVID-19 infection. Patients with neurodegenerative conditions like Parkinson's disease are vulnerable to severe COVID-19 illness due to older age, bulbar symptoms, respiratory dysfunction, frailty, and cognitive impairment. Similarly, patients with Alzheimer's disease and related dementias are at increased COVID-19 infection risk with a higher likelihood of morbidity and mortality (Brown et al., 2020).

Older patients are particularly vulnerable to the psychological burden of COVID-19. A recent report of a cross-sectional survey from Greece involving participants over the age of 60 years reported high rates of disrupted sleep (37.9%), moderate to severe depression (81.6%), and moderate to severe anxiety (84.5%) (Parlapani et al., 2020). Loneliness related to quarantine and social isolation has significantly impacted mental health outcomes in the elderly (Okruszek et al., 2020). Patients with CND are particularly vulnerable to social isolation. A recent nation-wide multi-center caregiver survey evaluated acute psychological effects of quarantine in frail elderly subjects with diagnoses of Alzheimer disease, dementia with Lewy bodies, frontotemporal dementia, and vascular dementia (Cagnin et al., 2020). This study including survey from 4,913 caregivers showed that quarantine induced a rapid increase of behavioral and psychological symptoms in ∼60% of patients and stress-related symptoms in two-thirds of caregivers. Most common symptoms included irritability, apathy, agitation anxiety, and sleep disorder (Cagnin et al., 2020). Similarly, a Spanish study using online survey of PD patients showed that 67.5% patients perceived worsening symptoms during the quarantine period (Santos-García et al., 2020).

Furthermore, older adults have aging immune systems characterized by two main processes including immunosenescence and inflammaging (Mueller et al., 2020; Thomas et al., 2020). Immunosenescence is a process of gradual decline in innate (ineffective pathogen recognition or macrophage activation and reduction in natural killer cell cytotoxicity) and adaptive (thymic hypoactivity and reduction in the accumulation of anergic memory lymphocytes) immune functions leading to impairment in pathogen recognition, alert signaling, and clearance. Inflammaging is characterized by a hyperactive yet ineffective alert system with age-related process

of systemic inflammation and autoimmune predisposition (Thomas et al., 2020). Emerging literature suggests that chronic systemic comorbidities and aging (known risk factors for severe COVID-19 disease) are associated with upregulation of inflammation and predisposition to neuroinflammatory and neurodegenerative conditions (Bossù et al., 2020; Scheiblich et al., 2020). Neuroinflammation also results from sustained anti-viral immune response with propagation of inflammation from the periphery to the brain through various pathways as previously described (Dantzer et al., 2008; Capuron and Miller, 2011). Moreover, neuroinflammation may alter integrity of the blood brain barrier, further enabling entry of circulating immune cells to the brain resulting in various neuropathological processes such as anxiety, depression, fatigue, psychomotor slowing, anorexia, cognitive dysfunction, and sleep impairment (Capuron and Miller, 2011), all of which are commonly reported with COVID-19.

Another hypothesis regarding T-cell paucity is related to exhaustion of immune system driven by repeated exposures to viruses over one's lifespan. This has been noted in patients with cytomegalovirus (CMV) seropositivity where cycles of reemergence is associated with immune remodeling and exhaustion of $CD8^+$-T-cells leading to higher mortality in the elderly population (Olsson et al., 2000; Pawelec, 2014). Some other studies have indicated that T-cell depletion in elderly is likely related to cumulative exposure to various pathogens over the years (Ongrádi and Kövesdi, 2010; Bartlett et al., 2012). At the chromosomal level, the age-related immunomodulation is likely due to telomere shortening in viral-specific memory $CD8^+$-T-cells, leading to a state of cell cycle arrest and hyper-inflammation, thereby limiting the ability to mount appropriate immune response against novel viral infections such as SARS-CoV-2 (Bellon and Nicot, 2017). Due to the neuroinflammatory state, patients with CND may be particularly challenged in this aspect. There are other reports of vascular inflammation with increased oxidative stress and endothelial dysfunction leading to microvascular disease which may play a role in increased incidence of COVID-19-related cerebrovascular diseases in the elderly (Ungvari et al., 2018). Studies have also reported that aging expands clonal populations of $CD8^+$-T-cells restricting their diversity, while $CD4^+$-T-cells retain the T-cell receptor reserve but suffer from activation deficits (Salam et al., 2013; Yoshida et al., 2017). A recent study on supercentenarians (>110 years) using single-cell transcriptome analysis of 61,202 peripheral blood mononuclear cells (PBMCs), showed that supercentenarians have an unusual population of cytotoxic $CD4^+$-T-cells whose activation doesn't decline with age and can take on the effector functions normally performed by $CD8^+$-T-cells (Hashimoto et al., 2019). Preservation of immunity through this mechanism might explain why some very old individuals with COVID-19 infection survive the pandemic.

Multiple other postulations regarding COVID-19 disease severity and increased mortality in the elderly have been proposed including age-related epigenetic changes, inflammasome activity, covalent modifications of human, and viral proteins etc. (Mueller et al., 2020). Further research is needed to understand the key factors leading to the vulnerability of the elderly population especially in regards to its intersection with aging and neuroscience.

TREATMENT AND TREATMENT RESPONSE OF AGED COVID-19 PATIENTS

As we approach one year since the World Health Organization's (WHO) initial declaration of the novel coronavirus pandemic, limited evidence-based therapies specific to COVID-19 are available with management primarily focused on treatment of associated complications and supportive care. As of early December 2020, the only antiviral agent to receive FDA approval for the treatment of COVID-19 is remdesivir [National Institute of Health (NIH), 2020]. The primary benefits are shortened time to recovery and reduction in the progression of disease in individuals at high risk of hyper-inflammation, who are diagnosed early (≤10 days of illness) and require supplemental oxygen (Young et al., 2021). The WHO and National Institutes of Health also recommend the use of dexamethasone, after the RECOVERY Trial demonstrated improved survival in hospitalized patients requiring supplemental oxygen [National Institute of Health (NIH), 2020]. Regarding management of neurologic complications of COVID-19, existing evidence-based therapies are used for specific neurologic conditions, in conjunction with systemic treatment with antivirals, corticosteroids, and immunomodulators, as appropriate.

Delirium management has long been a priority in the care of older adults. Multidisciplinary care focused on prevention of delirium using non-pharmacologic strategies, is the best practice (Oh et al., 2017). Non-pharmacologic interventions include patient-centered care with frequent re-orientation, regular visits from family and friends, optimization of hearing and vision by ensuring access to hearing aids and glasses, adequate hydration, adequate sleep, early mobilization, and minimization of unnecessary lines, tubes, polypharmacy, and precipitating medications (Oh et al., 2017; Kotfis et al., 2020). In centers with pandemic-related visitation restrictions, care teams can help meet the emotional needs by displaying family photos, facilitating the use of technology to connect patients with their families, and assessing patients' desire to access spiritual care. Early mobilization is the single intervention with the strongest evidence of decreasing the incidence and the length of delirium (Marra et al., 2017). Pre-COVID literature suggests that delirium can be prevented with appropriate in-hospital multimodal approach in about 30% of cases (Siddiqi et al., 2016). Regular clinical assessments for pain, agitation, and delirium with validated screening tools can help with early recognition and management (Oh et al., 2017; Kotfis et al., 2020). As delirium/acute encephalopathy is a common manifestation of COVID-19, it is important to establish a baseline mental status for all hospitalized COVID-19 patients (Oh et al., 2017). Upon diagnosing delirium in hospitalized COVID-19 patients, attempts should be made to identify and address any underlying precipitating factors (e.g., dehydration, untreated pain, alcohol or benzodiazepine withdrawal, renal dysfunction with delayed medication clearance, etc.) (Marra et al., 2017; Oh et al.,

2017). To date, no pharmacological agent has received FDA approval for the prevention or treatment of delirium. However, typical and atypical antipsychotics, benzodiazepines, propofol, and dexmedetomidine, among others, are frequently used to treat hyperactive delirium (Marra et al., 2017; Oh et al., 2017; Kotfis et al., 2020). Anecdotal observations have suggested association of COVID-19 delirium with myoclonus, rigidity, alogia, and abulia, suggesting a dopamine-depletion state or catatonia-spectrum condition, hence pragmatic, individualized step-wise treatment approach is prudent (Baller et al., 2020).

Acute stroke is another commonly reported neurologic dysfunction of COVID-19. The American Heart Association released emergency guidance at the beginning of the pandemic that recommended adherence to standard treatment guidelines whenever possible (On Behalf of the AHA/ASA Stroke Council Leadership, 2020). All patients with ischemic stroke should continue to be evaluated for potential treatment with standard-dose thrombolytics or endovascular thrombectomy (Dafer et al., 2020). While older COVID-19 patients with stroke have worse outcomes than younger cohorts, there is no evidence to suggest that it is due to a difference in therapeutic response. Given concerns for enhanced inflammation and hypercoagulability with COVID-19, there has been significant interest in using empiric therapeutic anticoagulation in place of standard chemoprophylaxis. However, trials have shown futility or even harm with empiric anticoagulation in COVID-19 patients (Lynn et al., 2021). Adhering to pre-pandemic treatment protocols is the practice standard in the management of stroke.

Patients on immunosuppressants and those with neuroinflammatory diseases like multiple sclerosis should continue treatment of their underlying illness while applying precautions to prevent viral spread and ensuring access to healthcare via teleneurology (Josephson and Kamel, 2020).

DISCUSSION

Elderly patients with COVID-19 are susceptible to neurologic conditions like acute stroke, acute encephalopathy, neuropsychiatric manifestations, and complications related to underlying CND. Reports from heavily affected countries like China, Italy, and the U.S. have informed that elderly population suffer a high rate of COVID-19-associated mortality (Centers for Disease Control and Prevention (CDC), 2020; Marcon et al., 2020; Wu and McGoogan, 2020). As neurologic dysfunctions of COVID-19 lead to increased morbidity and mortality, systematic studies on acute and long-term implications of neurologic complications of COVID-19 are imperative.

One of the biggest concerns of the COVID-19 pandemic is the tendency to periodically overwhelm hospitals and medical centers at the local, regional, and national level. A finite supply of healthcare resources led healthcare leaders to craft directives that address scarce resource allocation (Farrell et al., 2020a). The Italian Society of Anesthesiology, Analgesia, Resuscitation, and Intensive Care (SIAARTI) published guidelines that informed care during the outbreak in Northern Italy in March-2020 (Cesari and Proietti, 2020; Farrell et al., 2020a). Although this policy was criticized for overreliance on chronologic age and resource prioritization for younger patients, it prompted a search for more equitable criterias (Cesari and Proietti, 2020). Numerous national and international societies have released policy recommendations to guide resource allocation which involves a few common themes. First, it is inappropriate to use chronological age alone as an exclusion criteria (Farrell et al., 2020a; Montero-Odasso et al., 2020). Second, given the heterogeneity in the baseline health status of aged adults, use of objective measures such as the Clinical Frailty Scale or Sequential Organ Failure Assessment are thought to be valid and equitable alternatives in assessing potential benefit of therapeutic intervention (De Smet et al., 2020; Farrell et al., 2020b; Montero-Odasso et al., 2020). Third, implementation of protocols to prioritize advanced care planning is not only an integral component of patient-centered care but may also help in allocation of limited resources by promptly identifying patients who opt not to be intubated or resuscitated (Farrell et al., 2020a,b; Montero-Odasso et al., 2020). In one study, only 2.9% of COVID-19 patients older than 80 years survived to hospital discharge after receiving cardiopulmonary resuscitation (Hayek et al., 2020). Hence early discussions regarding goals of care is important, particularly in patients with neurologic dysfunctions. Depending on the type and severity of the disease, neurologic conditions often hold a grave prognosis, reduce life expectancy, or are associated with difficult to control pain and depression (Boersma et al., 2014; Creutzfeldt et al., 2018). Additionally, caregivers of patients with neurologic conditions are known to have similar rates of distress and burnout as that of cancer patient caregivers (Kim and Schulz, 2008). In severely ill patients with persistent encephalopathy or coma requiring full time care, burden of disease is tremendous from clinical, social, and economic standpoint. Given the high burden of disease both on patients and caregivers, early goals of care discussions become extremely important in patients with neurologic dysfunction. Lastly, healthcare systems need to work on facilitating access to in patient and outpatient palliative care and hospice services for COVID-19 patients.

Strained healthcare systems and rising healthcare costs are global problems predating the coronavirus pandemic. With the additional economic burden related to severe COVID-19 illness and the short and long-term disability associated with neurologic complications, the financial hit is likely to be staggering. For perspective, the estimated annual direct and indirect costs for ∼795,000 strokes in the U.S. from 2014 to 2015 was $45.5 billion, while healthcare cost related to delirium alone was $164 billion in 2011 (Inouye et al., 2014; Virani et al., 2020). Although the actual economic impact of COVID-19 and related neurologic complications is yet to be determined, it is likely to have profound financial implications for an extended period of time.

The scientific community is only beginning to evaluate the long-term effects of the pandemic. Robust long-term data are lacking, especially pertaining to neurologic complications. One of the first studies to focus on outcomes after hospitalization for COVID-19 found that 44% of Italian patients rated their quality of life as worse (≥10 point difference on a scale of 100) since contracting COVID-19. Though patients were assessed

at a mean of 60.3 days since symptom onset, 87.4% reported at least one ongoing COVID-19-related symptom, particularly dyspnea and fatigue (Carfì et al., 2020). Prolonged symptoms are also reported among those with mild COVID-19 infections. In a telephone survey of American adults with mild COVID-19 illness conducted 14–21 days after a positive PCR test, 47% of respondents aged ≥50 years reported ongoing symptoms (Tenforde et al., 2020). Data on COVID-19-associated neurologic conditions including inflammatory, vascular, autoimmune, and neurodegenerative diseases are urgently needed (Wang et al., 2020). Similarly, neuropsychiatric conditions related to social isolation are only just beginning to surface and are likely to have significant long-term implications.

In conclusion, COVID-19 has been a catastrophic pandemic, particularly for the elderly, who tend to suffer from neurologic complications as well as a very high rate of morbidity and mortality. The physical, emotional, psychological, and financial implications of this disease have been severe. Long-term data are still needed to understand the lasting complications of this devastating pandemic.

AUTHOR CONTRIBUTIONS

SM: substantial contributions including conception and design of the work, literature review, interpretation and summarization of data, drafting the complete manuscript, revising it critically for important intellectual content, and final approval of the manuscript to be published. MD: contribution including conception and design of the work, literature review, interpretation and summarization of the data, drafting of critical portion of the manuscript, critical revision for important intellectual content, and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

MINI REVIEW
published: 06 April 2021
doi: 10.3389/fnagi.2021.632673

The Other Side of SARS-CoV-2 Infection: Neurological Sequelae in Patients

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the globe causing coronavirus disease 2019 (COVID-19). Because it affects the respiratory system, common symptoms are cough and breathing difficulties with fever and fatigue. Also, some cases progress to acute respiratory distress syndrome (ARDS). The acute phase of COVID-19 has been also related to nervous system symptoms, including loss of taste and smell as well as encephalitis and cerebrovascular disorders. However, it remains unclear if neurological complications are due to the direct viral infection of the nervous system, or they appear as a consequence of the immune reaction against the virus in patients who presented pre-existing deficits or had a certain detrimental immune response. Importantly, the medium and long-term consequences of the infection by SARS-CoV-2 in the nervous system remain at present unknown. This review article aims to give an overview of the current neurological symptoms associated with COVID-19, as well as attempting to provide an insight beyond the acute affectation.

Keywords: coronavirus, COVID-19, SARS-CoV-2, neurological, nervous system

OPEN ACCESS

Edited by:
Jennifer Ann Frontera, New York University, United States

Reviewed by:
Annelise Emily Barron, Stanford University, United States
Jin Jun Luo, Temple University, United States

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Received: *23 November 2020*
Accepted: *12 March 2021*
Published: *06 April 2021*

Citation:
Alonso-Bellido IM, Bachiller S, Vázquez G, Cruz-Hernández L, Martínez E, Ruiz-Mateos E, Deierborg T, Venero JL, Real LM and Ruiz R (2021) The Other Side of SARS-CoV-2 Infection: Neurological Sequelae in Patients. Front. Aging Neurosci. 13:632673. doi: 10.3389/fnagi.2021.632673

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly caused a pandemic, only a few months after the first cases reported in December 2019. Although some infected individuals are asymptomatic, manifestations of the SARS-CoV-2 disease (coronavirus disease 2019, COVID-19) are cough, breathing difficulty (dyspnea) with fever, and fatigue (asthenia). However, some cases show severe bilateral pneumonia and progress to acute respiratory distress syndrome (ARDS) and multiorgan failure (Chen et al., 2020; Dhama et al., 2020; Huang et al., 2020; Zhang J. J. Y. et al., 2020).

Recent works have described neurological manifestations that ranged from mild to fatal in both asymptomatic and symptomatic patients infected by SARS-CoV-2 (Helms et al., 2020; Kremer et al., 2020; Mao et al., 2020; Oxley et al., 2020). Some frequently reported symptoms are not severe (such as headache, malaise, dizziness, loss of taste and smell; Mao et al., 2020), but other most

severe brain conditions such as stroke and encephalitis are also common (Paterson et al., 2020; Varatharaj et al., 2020). These observations have highlighted the need to deeply describe the clinical and epidemiological characteristics of these conditions including their long-term consequences in infected individuals as well as the possible mechanisms involved.

This review article aims to give an overview of those neurological symptoms associated with COVID-19 (**Figure 1**), attempting to provide an insight beyond the acute affectation.

NERVOUS SYSTEM DISEASES RELATED TO SARS-CoV-2 INFECTION

Viral Encephalitis (VE)

Viral encephalitis (VE) is a syndrome caused by neurotropic viruses (Tyler, 2018) characterized by altered mental status. The symptoms consist of a combination of acute fever, seizures, neurologic deficits, cerebrospinal fluid (CSF) pleocytosis, and neuroimaging and electroencephalographic (EEG) abnormalities. Clinical cases of VE in COVID-19 patients have been reported (Etemadifar et al., 2020; Moriguchi et al., 2020; Paniz-Mondolfi et al., 2020; Ye et al., 2020; Zhou F. et al., 2020), suggesting a potential invasion capacity of this virus into the Central Nervous System (CNS), as shown by other members of the Coronaviridae family (Xu et al., 2005; Morfopoulou et al., 2016; Nilsson et al., 2020). Neurological complications induced by respiratory viruses from the Coronaviridae family, such as HCoV-OC43, HCoV-229E, and SARS-CoV-1, have been already reported (Sharifian-Dorche et al., 2020).

The mechanisms by which SARS-CoV-2 causes encephalitis are poorly understood due to the low number of reported cases. It is speculated that the infection might occur after an inflammatory injury, rather than direct viral infection (Zhou Z. et al., 2020). However, given the high homology of SARS-CoV-2 with SARS-CoV-1, direct damage to the CNS cannot be ruled out. Similarly, the infection with HCoV-OC43, a coronavirus that presented a particular tropism for neurons and can produce direct neuronal death, also causes encephalitis that can be enhanced by the host immune responses (Butler et al., 2006). Intranasal administration of SARS-CoV-2 plaque-forming units in K18-hACE2 mice have demonstrated the capacity of neuroinvasion of SARS-CoV-2 causing encephalitis symptoms, including cytokine and chemokine production, leukocyte infiltration, hemorrhage, and neuronal cell death (Kumari et al., 2021). Moreover, in this mouse model, the onset of the severe disease was correlated with the maximal viral levels in the brain (Kumari et al., 2021). Also, findings in mice show that those that survived acute encephalitis induced by HCoV-OC43 infection, developed long-term sequelae, such as hypo-activity in the open field test

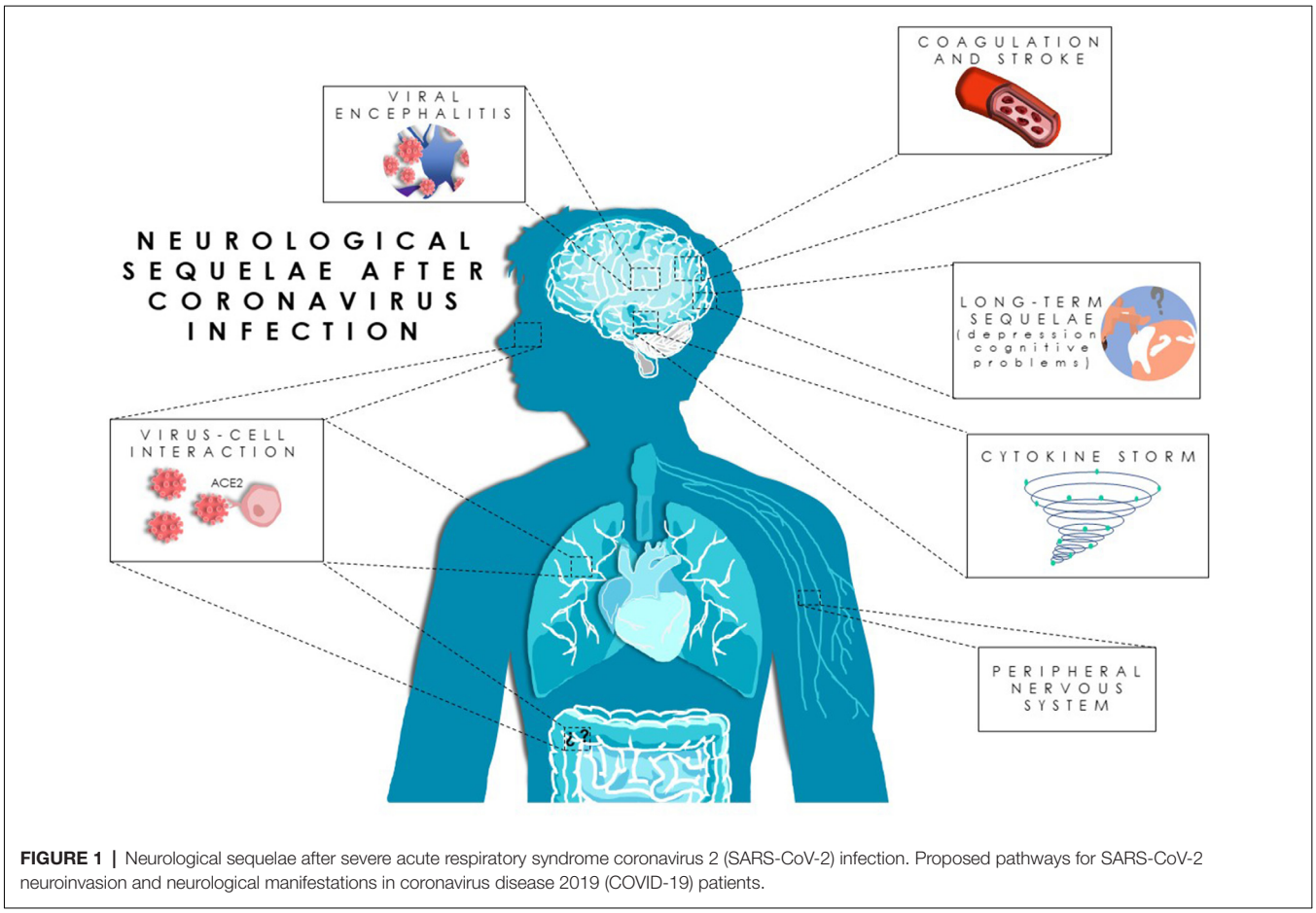

FIGURE 1 | Neurological sequelae after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Proposed pathways for SARS-CoV-2 neuroinvasion and neurological manifestations in coronavirus disease 2019 (COVID-19) patients.

and decreased hippocampal excitability with concomitant neural loss in CA1 and CA3 hippocampal regions (Divani et al., 2020). However, most of the reported cases of COVID-19 patients with the manifestation of encephalitis do not have detectable SARS-CoV-2 RNA in CSF samples, which does not necessarily exclude direct CNS infection (Divani et al., 2020). In fact, experience with other infections, such as tick-borne encephalitis, suggests that there is no correlation between viral load, the timing of viremia, and clinical severity (Umapathi et al., 2020). Not surprisingly, diagnostic criteria for viral encephalitis do not require demonstration of viral particles in CSF or blood (Umapathi et al., 2020). Nevertheless, diagnosis currently relies heavily on virus isolation in the CSF. Diagnosis of COVID-19-related encephalitis can be extremely challenging, as the definitive diagnosis is highly dependent on CSF virus isolation. This trouble becomes difficult in COVID-19 patients because the dissemination of SARS-CoV-2 is transient and its titer in CSF can be extremely low (Haider et al., 2020). Further studies, both, in patients and animal models, are required to precisely determine the extent of neurological sequelae of SARS-CoV-2-related encephalitis.

To summarize, the lack of continuity and consistency in encephalopathies in COVID-19 patients leaves us without a clear picture of where the neurological abnormalities may come from. Therefore, more in deep studies are necessary to clarify the exact role of SARS-CoV-2 in this disease.

Peripheral Nervous System Disease

Coronavirus family also affects the peripheral nervous system (PNS) which could be caused directly by the virus or by the body's innate and adaptive immune responses to infection. The Guillain-Barré syndrome (GBS) is an autoimmune neurologic disease of PNS caused by an infection leading to an autoimmune response, which produces demyelination and injury of axons. The disease symptoms begin with weakness and tingling in the extremities leading to rapidly progressive, symmetrical limb weakness, areflexia on examination, sensory symptoms, and, in some patients, facial weakness, although several variants exist (Willison et al., 2016). The first case of COVID-19 initially associated with acute GBS was reported by Zhao et al. (2020). To date, 50 GBS patients, or its variants, and COVID-19 have been reported (for review, see Katyal et al., 2020; Satarker and Nampoothiri, 2020; Sriwastava et al., 2020). The mean latency between infection and GBS symptoms ranged between 11 and 13 days (Sriwastava et al., 2020). It has been hypothesized that the various mechanisms by mean of SARS-CoV-2 trigger GBS: (i) cross-reactivity between the viral protein (viral spike (S) protein)—associated gangliosides containing sialic acid residues, including the GalNAc residue of GM1 (Ahmed et al., 2020; Baig et al., 2020; Caress et al., 2020; Dalakas, 2020; Sriwastava et al., 2020; Zhou Z. et al., 2020) and peripheral nerve gangliosides as the result of molecular mimicry. Serum ganglioside antibodies were found in 7% of described COVID-19-GBS patients (for review, see Sriwastava et al., 2020). (ii) T-cell activation and release of inflammatory mediators as cytokine storms induce nerve damage and, therefore trigger GBS in COVID-19 patients. Interestingly, none of the reported patients had positive PCR for SARS-CoV-2 in the CSF (Sriwastava et al., 2020) but the damage could be produced by the breakdown of the blood-brain barrier rather than direct intracranial viral invasion (Ahmed et al., 2020; Zhou F. et al., 2020). Although a direct effect of the virus on the PNS could not be ruled out, probably, the cytokine storm described in a proportion of the most severe COVID-19 patients triggers the neurological symptoms, including GBS, as has been proposed for some other viral infectious diseases (Chousterman et al., 2017). However, a more in-depth study would need to unequivocally demonstrate the relationship of GSB with SARS-CoV-2 infection, despite the low proportion of COVID-19 patients presenting GBS.

Acute Cerebrovascular Disease

Acute cerebrovascular disease is caused by the blood supply disruption in the brain under ischemic or hemorrhagic conditions, such as thrombotic or embolic occlusion. The brain responds to this blood disruption altering the metabolism, the microvascular hemodynamics, and the collateral flow interactions. These responses may result in brain damage and even death (Gaddi et al., 2003; Donahue and Hendrikse, 2018). Beyond the motor impairment observed in stroke patients, the long-term neurological manifestations include depression and cognitive impairment followed by dementia, recurrent strokes, epilepsy, bleeding and also, death (Singh et al., 2018).

It is known that between 0.2 and 1% of COVID-19 patients undergo ischemic strokes (Altable and De La Serna, 2020), and it is thought to be caused by the prothrombotic effect as a consequence of the inflammatory response (for review, see Abou-Ismail et al., 2020). COVID-19 patients with a historical cerebrovascular disease (CVD), may present increased severity. Besides, patients with severe infection are more prone to display a CVD rather than the ones with less severe infection (Li et al., 2020). Moreover, other comorbidities, such as diabetes mellitus, high coagulation and hypertension, and aging enhance the CVD in COVID-19 patients (Goldberg et al., 2020; Larson et al., 2020).

There are several mechanisms by which the SARS-CoV-2 virus might cause brain stroke (Trejo-Gabriel-Galan, 2020), including: (i) invasion of vascular walls by directly joining angiotensin-converting enzyme 2 (ACE2) receptors located on the surfaces of the endothelial cells; (ii) coagulopathy associated with COVID-19: produced by the cytokine storm that increases the D-dimers levels [the fibrin degradation products found in the blood after blood clots degradation which is associated to high mortality in COVID-19 patients (Rostami and Mansouritorghabeh, 2020)]; (iii) myocardial damage with cerebral embolism: SARS-CoV-2 could damage the heart, which in turn causes a cardioembolic stroke, measured by increased troponin levels (Huang et al., 2020; Zhou F. et al., 2020); and, (iv) destabilization of a pre-existing atheroma plaque: systemic inflammation might break the fibrous cap of the atheroma and the thrombogenic material can be released to the blood, leading to a coagulation cascade and recruitment of inflammatory cells and circulating platelets (Badimon and Vilahur, 2014). However, the exact mechanism by which SARS-CoV-2 could be involved in the CVD needs further investigation.

Cognitive Decline After Overcoming Acute SARS-CoV-2 Infection in COVID-19

Neurological effects have been associated with COVID-19 including confusion, disorientation, agitation, and drowsiness (Helms et al., 2020; Heneka et al., 2020). In fact, a total of 33% of the discharged patients presented mental alterations and motor deficiencies (Helms et al., 2020). These symptoms could be caused by the dysfunction of peripheral organs, encephalitis, systemic inflammation, and cerebrovascular alterations. These conditions would expose COVID-19 survivors at risk of long-term neurological consequences, either by aggravating a pre-existing disorder or by initiating them (Heneka et al., 2020). Therefore, it has been suggested that individuals who survive the most severe COVID-19 are at high risk to develop neurological diseases, and in particular, Alzheimer's disease (Tejera et al., 2019). So far, it seems unlikely that the virus has a role in causing or exacerbating Parkinson's disease, but the aggravation of specific motor and non-motor symptoms has been recently discussed (Sulzer et al., 2020). Whether or not, these complications are directly produced by the virus or indirectly enhanced by the cytokine storm displayed by the immune system or both remains unknown due to the scarcity of histopathological evidence available. Thus, it has been reported that strokes appear to be more related to hypercoagulability and endothelial injury than to the direct SARS-CoV-2 vasculitis affecting the brain (Iadecola et al., 2020). However, there is evidence of brain infection by SARS-CoV-2 (Deigendesch et al., 2020; Moriguchi et al., 2020; Paniz-Mondolfi et al., 2020) that deserves special attention in this review article.

POTENTIAL NEURO-INVASIVE MECHANISMS OF SARS-CoV-2

Experimental and clinical studies have demonstrated a neuro-invasive potential of human and animal coronaviruses (Pennisi et al., 2020). A recent report by Mao et al. (2020) described that 36.4% of the 214 total patients with SARS-CoV-2 infection exhibited neurological symptoms, suggesting its neuro-invasive potential, especially in the most severe cases (Helms et al., 2020; Paterson et al., 2020; Varatharaj et al., 2020). Moreover, there are reports of the presence of SARS-CoV-2 in brains or CSF from COVID-19 patients (Deigendesch et al., 2020; Moriguchi et al., 2020; Paniz-Mondolfi et al., 2020).

Although the precise mechanism by which SARS-CoV-2 can reach the CNS has not yet elucidated, based on previous knowledge about the infection mechanisms of other coronaviruses, two hypotheses emerge as the potential routes of how SARS-CoV-2 enters into the brain: (i) through retrograde axonal transport; and/ or (ii) hematogenous spread from systemic to the cerebral circulation.

Within the first alternative, SARS-CoV-2 could infect the peripheral neurons in the olfactory tract and might reach the brain through retrograde axonal dissemination. The olfactory bulb is connected through the cribriform plate with the olfactory receptor neurons (van Riel et al., 2015). It is well known that ACE2 receptors are the key molecules to allow the entry of the virus into cells. These receptors are expressed not only on the epithelial cells of the mucosa (Xu et al., 2020) but also in glial cells, neurons, and in endothelial and arterial smooth muscle cells (Baig et al., 2020; Deigendesch et al., 2020; Xu and Lazartigues, 2020). This fact could enhance viral dissemination. This hypothesis was previously tested for SARS-CoV infection using a human transgenic mouse model for ACE2 receptors (Netland et al., 2008). The authors showed that the virus infected the olfactory bulb and spread reaching the brain and causing neuronal death, especially affecting those neurons located in the cardiorespiratory centers. Although this mechanism could explain the loss of smell and taste in COVID-19 patients (Giacomelli et al., 2020), the retrograde axonal transport hypothesis needs to be investigated for SARS-CoV-2.

Additionally, COVID-19 patients also present gastrointestinal alterations (Silva et al., 2020). As already described in MERS-CoV infection (Zhou et al., 2017), a new potential route for viral neuroinvasion has been proposed for SARS-CoV-2 (Esposito et al., 2020). *In vitro* experiments, using human small intestine and brain organoids, and histological characterizations for human intestine samples, have demonstrated the capacity of SARS-CoV-2 to infect the gastrointestinal tract (Lamers et al., 2020; Zhang H. et al., 2020; Silva et al., 2020; Kumari et al., 2021). This invasion may activate the enteric glial cells inducing the cytokine storm observed in COVID-19 patients (Esposito et al., 2020). Moreover, enteric glial cells are crucial regulators of gut-brain signaling and their activation has been related to the viral infection by HIV-1 Tat-associated gastrointestinal and neurological impairments (Esposito et al., 2017).

The second hypothesis is based on the hematogenous dissemination of the virus from the systemic to the cerebral circulation. In this route, the virus might extend to the brain by binding to ACE2 receptors present on the endothelial cells and smooth muscles in the cerebral microvasculature, inducing BBB disruption. This possible way is supported by the high expression of ACE2 receptors and associated proteases in the vascular endothelium, suggesting that these cells could be also targeted by the SARS-CoV-2 (Monteil et al., 2020). Besides, and based on other coronavirus studies, cytokines might be playing a fundamental role inducing neuroinflammation. In fact, one of the major manifestations in COVID-19 severe patients is the cytokine storm (Qin et al., 2020; Wang et al., 2020). It could also alter the BBB, enabling the viral entry into the brain through the hematogenous way (Pellegrini et al., 2020). Furthermore, cytokine storm in response to viral infections induces clotting in the cerebral vasculature (Mizuguchi et al., 2007) also recently described in a clinical case of a severe COVID-19 patient (Muhammad et al., 2020). For this reason, the anticoagulant medication appears as a promising treatment in severe COVID-19 patients associated with coagulopathy (Tang et al., 2020). Interestingly, SARS-CoV-2 particles have been found in brain microvascular endothelial cells in the neural niche (Paniz-Mondolfi et al., 2020). Nevertheless, the hematogenous alternative needs to be demonstrated.

Nonetheless, the exact mechanism by which SARS-CoV-2 leads to neurological symptoms is still undetermined and requires further investigations.

CONCLUSION

The clinical manifestations of SARS-CoV-2 infection are in the early phase prominent in the lungs where ACE2 is highly expressed. However, apart from the lungs and intestines, ACE2 is expressed in venous and arterial endothelial cells and arterial smooth muscle cells in most of the organs (Hamming et al., 2004), which could open up for COVID-19 to become a systemic disease. The nervous system is not unfamiliar with the influence of the virus and two non-exclusive pathways of viral neuroinvasion have been postulated: (i) through retrograde axonal transport, and/or (ii) hematogenous spread from systemic to the cerebral circulation. Data on the infection of the olfactory bulb enabling access to the brain through retrograde axonal dissemination in SARS-CoV infection (Netland et al., 2008) and experiments showing the infection of choroid plexus cells in human brain organoids (Pellegrini et al., 2020) strongly suggest the existence of these two pathways. Independently of the pathways that SARS-CoV-2 uses to reach the CNS if the immune response against the virus is not contained and feedback loop mechanisms non-functional, which are otherwise exquisitely regulated under physiologic conditions, detrimental hyperinflammation/SIRS can occur. This affectation allows an aberrant deleterious response, causing a cytokine storm with severe multiorgan manifestations including those of the CNS, favoring the disruption of the BBB and the infiltration of different immune cells, such as cytotoxic T lymphocytes and monocytes with profound proinflammatory potential. This scenario is the ground to pro-atherogenic manifestations, such as CVD including stroke, but also encephalitis, affectations of the peripheral nervous system or different grades of cognitive decline after overcoming the primary SARS-CoV-2 infection. In the absence of effective antivirals, therapeutic efforts have to be paid to decrease this aberrant immune response, trying to apply immunomodulators that balance the antiviral effect of the immune system without producing and aberrant autoimmune hyper-inflammatory response, in order to decrease neurological sequelae associated to COVID-19. However, if the infection of the nervous system by SARS-CoV-2 is confirmed, a new challenge would appear in the battle against the COVID-19 disease.

AUTHOR CONTRIBUTIONS

RR and LR conceptualized, designed, and drafted the manuscript. IA-B, SB, GV, LC-H, EM, and ER-M were involved in the literature search and drafted the manuscript. The image was made by IA-B, following the guidelines of SB. TD and JLV critically revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

REVIEW
published: 08 April 2021
doi: 10.3389/fnagi.2021.664965

Impact of COVID-19 Pandemic on Patients With Neurodegenerative Diseases

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COVID-19 pandemic has already produced great impacts on global health security and social-economy. Elderly, particularly those with underlying diseases, are suffering from higher fatality rate. Neurodegenerative diseases are a group of incurable neurological disorders of loss of neuron and/or myelin sheath, which affect hundreds of millions of elderly populations and usually need long-term care. Older population is one of the most vulnerable to COVID-19 pandemic. In this report, we reviewed the current status of COVID-19 on the patients with several neurodegenerative diseases, particularly Alzheimer's disease, Parkinson's disease, prion disease, and amyotrophic lateral sclerosis. Meanwhile, the potential mechanisms of SARS-CoV-2 infection in the pathogenesis of neurodegenerative diseases were also summarized.

Keywords: coronavirus disease 2019, severe acute respiratory syndrome-associated coronavirus 2, Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease

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Edited by:
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Received: *06 February 2021*
Accepted: *17 March 2021*
Published: *08 April 2021*

Citation:
Hu C, Chen C and Dong X-P (2021) Impact of COVID-19 Pandemic on Patients With Neurodegenerative Diseases. Front. Aging Neurosci. 13:664965. doi: 10.3389/fnagi.2021.664965

INTRODUCTION

As of March 12, 2021, coronavirus disease 2019 (COVID-19) has affected 224 countries, areas or territories, more than 118,000,000 confirmed cases and 2,600,000 deaths has been reported worldwide (WHO, 2021). The COVID-19 pandemic is disrupting the health systems and threatening the lives and health of people worldwide in an unprecedented way. Severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is able to trigger cytokine storm in infected individuals leading to malignant outcomes (Mehta et al., 2020). Although all populations are susceptible to SARS-CoV-2, COVID-19 causes obviously higher fatality rate among the elderly and individuals with weakened immune systems, especially those with underlying diseases (The Editors of Alzheimer's & Dementia, 2020). Study have shown that SARS-CoV-2 can invade central nervous system (CNS) and further lead to neurological dysfunction in a significant proportion of affected patients, and individuals with COVID-19 can develop acute CNS-related symptoms (Mao et al., 2020). During the acute phase of SARS-CoV-2 infection, neurological symptoms occur in approximately 36% of cases, 25% of which can be attributed to direct involvement of CNS (Heneka et al., 2020). It is worth noting that the majority of patients with neurodegenerative diseases are elderly, hence such double effects make them more susceptible to COVID-19.

Although thousands of studies regarding to COVID-19 and SARS-CoV-2 have been published in the past year, the data of the impact of COVID-19 on neurodegenerative diseases is still limited. In this report, we analyzed and reviewed the current status and possible influencing factors

of the patients with neurodegenerative diseases from different countries during the COVID-19 pandemic based on data from multiple channels, hoping to propose the potential direction of further research and concern.

COVID-19 AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a common neurodegenerative disease mainly affecting the population of elderly. Clinically, it is mainly manifested as severe cognitive function and memory decline (Joe and Ringman, 2019). Pathologically, it is mainly caused by amyloid β (Aβ) deposition and neurofibrillary tangles (NFTs) in the brain (van der Kant et al., 2020). There are also neuron loss and inflammatory response observed in the relevant brain regions (Wilcock et al., 2011; Guo et al., 2014). About half of AD patients require home or professional long-term care (Perry, 2020). During the COVID-19 pandemic, the patients with AD appeared to be disproportionately affected. The New York Times reported that as many as 80% of COVID-19 deaths are in long-term care, meaning that more than a third of deaths are those affected with AD (Perry, 2020). Analyses revealed that certain characteristics of AD patients may increase the risk of SARS-CoV-2 infection. Patients with AD may not be able to follow the recommendations issued by public health authorities to reduce the transmission of SARS-CoV-2, including hand hygiene, covering mouth and nose when coughing, monitoring and reporting symptoms of COVID-19, maintaining physical distance from others, and self-isolation at home alone (Brown et al., 2020).

Another impact that cannot be ignored is that the COVID-19 pandemic is putting more stress on the mental and psychological health of AD patients. The investigation from Boutoleau's group proposed for the first time that home confinement had a great effect on neuropsychiatric symptoms in the AD patients with lower baseline cognitive function during COVID-19 epidemic (Boutoleau-Bretonniere et al., 2020). They found that the increase of psychological stress would further accelerate the deterioration of cognitive function. The longer the confinement, the worse the symptoms. Such phenomenon may associate with the reduction of social contact and stimulation of physical activity during home confinement. In addition, the study found that the duration of confinement was significantly correlated not only with symptom severity, but also with their caregiver's distress. They recommended that during the crisis such as COVID-19 pandemic, social services authorities should provide more supports to caregivers in order to help them to cope with their own social isolation and the neuropsychiatric changes of the patients they cared for.

Apolipoprotein E4 (APOE4), the most important susceptibility gene for AD, is genetically associated with the common late onset familial and sporadic AD (Rao et al., 1996). In European ancestral populations, the APOE4 homozygous genotype is associated with a significant risk of AD (Mayeux, 2003; Kuo et al., 2020). A recent observation found that the population with APOE4 homozygotes had a 2.2-fold higher COVID-19 infection rate and a 4.3-fold higher fatal rate than those of ApoE3 homozygous, with a high prevalence of APOE4 in the patients with severe COVID-19. Among the recruited population, about 2.36% of the participants with European ancestry were APOE4 homozygous, while among those of SARS-CoV-2 positive 5.13% were APOE4 homozygous, highlighting that the risk of SARS-CoV-2 infection was doubled for APOE4 homozygous individuals. But the study also suggested that APOE4 variants may not be an independent risk factor for severe COVID-19 infection. The weakness in AD patients themselves make them be vulnerable to SARS-CoV-2 infection and more likely be severe phenotype. Furthermore, since respiratory problems are common in most patients with advanced AD (Perry, 2020) and SARS-CoV-2 infection mainly affects the respiratory system, symptoms become more severe once AD patients are infected with SARS-CoV-2. However, it needs to be clarified that AD patients are at increased risk of SARS-CoV-2 infection, but that AD itself is not the direct cause for COVID-19 susceptibility. Preliminary studies have also showed that the variations in angiotensin-converting enzyme 2 (ACE2) gene, HLA gene, and ABO blood group gene on hosts and cells were also associated with susceptibility or severity of COVID-19 (Bourgonje et al., 2020; Kaiser, 2020; Ovsyannikova et al., 2020; Severe Covid et al., 2020).

Numerous studies have showed that virus invasion of brain tissue is associated with COVID-19 (Alquisiras-Burgos et al., 2020; Baig and Sanders, 2020; Lechien et al., 2020). The penetration of SARS-CoV-2 into cells is mediated by binding to ACE2, a cell surface receptor distributing mainly in the respiratory epithelium, vascular endothelium, kidney, small intestine, and brain (Donoghue et al., 2000; Hamming et al., 2004; Yan et al., 2020). Increasing evidence shows that SARS-CoV-2 may firstly invade peripheral nerve terminals, and then enter the CNS via a synaptic connection pathway (Fenrich et al., 2020). In mild and moderate COVID-19 cases, olfactory (85.6%) and gustatory (88.0%) dysfunctions were recorded frequently. About 11% of those patients developed anosmia prior to any other clinical symptoms (Lechien et al., 2020). ACE2 has been found to be highly expressed in nasal goblet and ciliated cells, which strongly indicates the possibility that SARS-CoV-2 may enter the human brain through olfactory nerves (Klingenstein et al., 2021). Another potential invading route for SARS-CoV-2 is probably via ventricular choroid plexus into cerebrospinal fluid (CSF) and brain (Abate et al., 2020). The high expression of ACE2 in lateral ventricular choroid plexus further increases the possibility of SARS-CoV-2 invading the CNS (Abate et al., 2020; Moriguchi et al., 2020). Recently, the SARS-CoV-2 was also detected by genomic sequencing in CSF sample from a 24-year-old male COVID-19 patient in Japan (Moriguchi et al., 2020). The invitation and infection of SARS-CoV-2 in the CNS may produce unpredictable effect on neurodegenerative diseases.

Recently, it has been hypothesized that SARS-CoV-2 infection may silently initiate or accelerate neurodegeneration. ACE2 expressing cells, such as neurons and glial cells, can be used as susceptible targets for SARS-CoV-2 infection (Zhou et al., 2020). SARS-CoV-2 can activate glial cells, induce pro-inflammatory state, and even cause severe innate immune response and sustained increase in cytokine levels. In addition, persistent

SARS-CoV-2 infection can also induce neuroimmune responses (Ur and Verma, 2020). Retrospective studies have showed that corticosteroids were frequently used in the treatment of hospitalized COVID-19 patients, while it's worth noting that inappropriate corticosteroid therapy produced adverse neuropsychiatric symptoms, affecting about 35% of COVID-19 patients, including cognitive and sleep disorders, delirium, hypomania, mania, depression, and psychosis (Troyer et al., 2020). As AD usually has long term of clinical course, the impact of COVID-19 on AD progression, either by direct virus infection or by inappropriate therapeutic deserves long term observation.

COVID-19 AND PARKINSON'S DISEASE

Parkinson's disease (PD) is the second largest neurodegenerative disease in the world. The main pathological features are the absence of dopaminergic neurons in the dense area of substantia nigra, and the presences of the inclusion bodies in residual neurons namely Lewy bodies (Homayoun, 2018). The main clinical manifestations are tremor, myotonia, tardiness and abnormal gait. However, some non-motor symptoms, including sleep disorder, hypoxia, anxiety, depression and cognitive disorders, are also important factors affecting the life quality of PD patients (Armstrong and Okun, 2020). During the COVID-19 pandemic, social measures of containment or mitigation significantly affected the lifestyle of PD individuals (Helmich and Bloem, 2020). This is because increased stress levels in COVID-19 outbreaks directly increase psychological stress, which can temporarily aggravate various motor symptoms, such as tremor, gait freezing or movement disorders (Macht et al., 2007; Zach et al., 2017a,b; Ehgoetz Martens et al., 2018; Helmich and Bloem, 2020). Increased stress induces an underlying low kinetic energy stiffness syndrome that causes dopaminergic cells to lose their energy rapidly in response to toxin. Meanwhile, reduction of physical exercise during COVID-19 pandemic may lead to an increased psychological stress, while lack of aerobic exercise is likely to worsen motor symptoms in PD patients (Helmich and Bloem, 2020). In addition, the neurophilic property of SARS-CoV-2 can cause inflammatory responses in CNS, and further worsen the pathology of PD.

Angiotensin-converting enzyme 2 is also highly expressed in dopaminergic neurons. Although the expression levels of ACE2 in the brain of PD patients is decreased due to degeneration and loss of dopaminergic neurons, there are still evidences that SARS-CoV-2 can invade CNS of PD patients and further aggravate the CNS injury and clinical situations (Achbani et al., 2020; Pavel et al., 2020; Victorino et al., 2020). Recently, the first case of encephalopathic complications in a 74-year-old PD patient infected with SARS-CoV-2 was reported (Filatov et al., 2020). Study showed that PD patients with older age (mean, 78.3 years) and longer disease duration (mean, 12.7 years) were particularly susceptible to COVID-19, with a case fatality rate as high as 40% (Antonini et al., 2020). However, the sample size of the study was small, and the conclusion needed further clarification of lager sample size. Nevertheless, older PD patients infected with SARS-CoV-2 have a significantly higher risk of death than the age-matched individuals who do not infected with PD. Whether the incidence of SARS-CoV-2 infection in PD patients increases or not remains unclear. A recent large cohort study of a relatively unselected patients with homogeneous PD has found that the risk, morbidity and mortality of COVID-19 in patients with mild to moderate PD do not differ from those in the general population (Fasano et al., 2020). Hainque et al. believed that the rapid recognition of COVID-19 in PD patients was quite challenged, because the common clinical manifestations of COVID-19, such as fatigue, anosmia, flushing or limb pain, were also non-motor PD signs. In addition, the exact severity of SARS-CoV-2 infection in PD patients remains to be further observed (Hainque and Grabli, 2020). Although it is unlikely that the SARS-CoV-2 can cause or aggravate PD, it has been reported that SARS-CoV-2 can aggravate certain motor and non-motor symptoms (Sulzer et al., 2020).

COVID-19 AND PRION DISEASE

Prion diseases are a group of rare transmissible neurodegenerative diseases usually have a long incubation period and short clinical duration (Saa et al., 2016). Pathologically, it can cause the loss of neurons in infected areas of the brain, formation of vacuoles and sponge-like lesions, and activation of astrocytes and microglia (Prusiner et al., 1998). Approximately 85% of the patients were sporadic Creutzfeldt-Jakob disease (CJD). Recently, a patient with suspected diagnosis of CJD was reported to be infected with SARS-CoV-2. The patient was a man in his 60s who was infected during family gathering. Soon, he developed neurodegenerative symptoms, including mutism, right hemiplegia, spontaneous multifocal myoclonus, lethargy, and restlessness. He died 2 months after onset. Examinations of EEG, MRI, CSF RT-QuIC, CSF 14-3-3, and tau protein highly indicated the diagnosis of sporadic CJD (sCJD) (Young et al., 2020). He displayed a fast progression and a short duration compared with majority of sCJD patients (Young et al., 2020). It has been noticed that COVID-19 can sometimes trigger unspecific inflammatory in CNS (Ellul et al., 2020; Pan et al., 2020; Paterson et al., 2020). Coincidentally, increased inflammatory response is also commonly documented in the brains of sCJD patients and numerous prion infected experimental animals at preclinical and terminal stage, including activate microglia and astrocytes with the release of proinflammatory cytokines, such as IL-1, IL-6, IL-12, and TNF-a (Xie et al., 2013; Aguzzi and Zhu, 2017; Ma et al., 2019; Chen C. et al., 2020; Chen J. et al., 2020). Whether the infection of COVID-19 can aggravate the brain inflammatory reactions and eventually accelerate the progression of human prion diseases needs further observation.

COVID-19 AND AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS, also known as motor neuron disease, MND) is a progressive and fatal neurodegenerative disease characterized with the degeneration of the motor neurons

in brain and spinal cord (Hardiman et al., 2017; Owens, 2017). Clinically, ALS displays muscle weakness, spasm, respiratory failure, and communication disorders (Kiernan et al., 2011; Brown and Al-Chalabi, 2017). The incidence rate of ALS is about 2.76 per 100,000 people, with a prevalence of 9.62 cases in every 100,000 people worldwide (Xu et al., 2020). Similar to other neurodegenerative conditions, ALS is thought to be caused by a combination of genetic factors, environmental factors and aging-related dysfunction (Masrori and Van Damme, 2020). The diagnosis of ALS is mainly based on medical history, physical examination, electrodiagnostic testing (with needle-EMG) and neuroimaging (Masrori and Van Damme, 2020). COVID-19 has presented challenges to clinical care for ALS patients. COVID-19 pandemic also showed impact on ALS diagnosis and relevant studies, e.g., many clinical trials, as the diagnostic process and monitor safety and efficacy outcomes in clinical trials relied largely on face-to-face visits (Andrews et al., 2020). The COVID-19 pandemic has increased the need to telemedicine and technological devices, making it difficult to provide the best care for patients (De Marchi et al., 2020; Pinto et al., 2020). Recently, results of an internet-based questionnaires including self-perceived anxiety, depression, motor worsening, and changes in clinical care indicates that COVID-19 emergency and its management exert a significant impact on health status of ALS patients, particularly those in the early stages and more aggressive course of the disease (Cabona et al., 2021). Three patients without previous neurologic or autoimmune disorders who were diagnosed with myasthenia gravis after COVID-19 infection, indicating that COVID-19 infection may break immunologic self-tolerance (Restivo et al., 2020). So far, accurate data on SARS-CoV-2 infection in ALS patients are not available. Thereby, based on the impact of COVID-19 on clinical care, diagnosis and related experimental studies of ALS, the indirect impact of COVID-19 on ALS patients seems to be significant.

CONCLUDING REMARK

Up to now, several routes through which COVID-19 affects central nerve system have been proposed, such as the direct infection of SARS-CoV-2 upon neuronal cells, vast inflammatory agents induced by severe systemic inflammation flooding into brains, respiratory failure associated brain ischemia, thrombosis and stroke, etc. (Verkhratsky et al., 2020). Psychological stress is frequently noticed in COVID-19 patients, medical staffs and general population (Fiest et al., 2021; Osimo et al., 2021; Saita et al., 2021). The global impact of the COVID-19 pandemic is unprecedented, with the entire population vulnerable possibly until COVID-19 vaccines are developed and widely available. Patients with neurodegenerative diseases need special attention as a special group. Although the size and data of current studies for the impacts of COVID-19 on neurodegenerative diseases are still limited, several potential impacts have been already proposed. First, as the elderly population with underlying diseases, the patients with some neurodegenerative diseases, such as AD, have already revealed significantly higher case fatality rate and more susceptible to SARS-CoV-2. Second, COVID-19 pandemic has already showed the great influences on the routine processes of diagnosis, treatment and daily care of the patients of neurodegenerative diseases, such as amyotrophic lateral sclerosis, which may have even more significant impacts in the future. Third, the immune storm and inflammatory response induced by SARS-CoV-2 infection seems to be able to increase the risk having more severe COVID-19 cases in the patients of neurodegenerative diseases, such as prion disease. Fourth, COVID-19 may accelerate the progression of neurodegenerative diseases, though the mechanisms remain unclear and may vary among different neurodegenerative diseases, such as AD and PD. Although different types of vaccines for COVID-19 are being vaccinated globally, when COVID-19 pandemic will slowdown, even stop, is still questionable. Therefore, the exact impacts of COVID-19 on neurodegenerative diseases need further long-term observation and investigation in order to propose appropriate interventions.

AUTHOR CONTRIBUTIONS

CH and CC designed the study and drafted the manuscript. CC and X-PD conceived the study, participated in its design, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

National Key Research and Development Program of China (2018YFC1200305 and 2021YFC0863000), National Natural Science Foundation of China (81772197, 81401670, and 81630062), National Science and Technology Major Project of China (2018ZX10102001), SKLID Development Grant (2019SKLID401 and 2019SKLID603), and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2018RC330004).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 20 April 2021
doi: 10.3389/fnagi.2021.653533

Being the Family Caregiver of a Patient With Dementia During the Coronavirus Disease 2019 Lockdown

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Received: 14 January 2021
Accepted: 03 March 2021
Published: 20 April 2021

Citation:
Zucca M, Isella V, Di Lorenzo R, Marra C, Cagnin A, Cupidi C, Bonanni L, Laganà V, Rubino E, Vanacore N, Agosta F, Caffarra P, Sambati R, Quaranta D, Guglielmi V, Appollonio IM, Logroscino G, Filippi M, Tedeschi G, Ferrarese C, Rainero I, Bruni AC and the SINdem COVID-19 Study Group (2021) Being the Family Caregiver of a Patient With Dementia During the Coronavirus Disease 2019 Lockdown. Front. Aging Neurosci. 13:653533. doi: 10.3389/fnagi.2021.653533

Background: Family caregivers of patients with dementia are at high risk of stress and burden, and quarantine due to the coronavirus disease 2019 (COVID-19) pandemic may have increased the risk of psychological disturbances in this population. The current study was carried out during the national lockdown declared in March 2020 by the Italian government as a containment measure of the first wave of the coronavirus pandemic and is the first nationwide survey on the impact of COVID-19 lockdown on the mental health of dementia informal caregivers.

Methods: Eighty-seven dementia centers evenly distributed on the Italian territory enrolled 4,710 caregiver–patient pairs. Caregivers underwent a telephone interview assessing classical symptoms of caregiver stress and concern for the consequences of COVID-19 infection on patient's health. We calculated prevalence of symptoms and regressed them on various potential stress risk factors: caregivers' sociodemographic characteristics and lifestyle, patients' clinical features, and lockdown-related elements, like discontinuity in medical care.

Results: Approximately 90% of caregivers reported at least one symptom of stress, and nearly 30% reported four or more symptoms. The most prevalent symptoms were concern for consequences of COVID-19 on patient's health (75%) and anxiety (46%). The main risk factors for stress were identified as a conflicting relationship with the patient and discontinuity in assistance, but caregiver's female sex, younger age, lower education, and cohabitation with the patient also had an impact. Availability of

help from institutions or private individuals showed a protective effect against sense of abandonment but a detrimental effect on concern about the risk for the patient to contract COVID-19. The only protective factor was mild dementia severity, which was associated with a lower risk of feeling isolated and abandoned; type of dementia, on the other hand, did not affect stress risk.

Conclusion: Our results demonstrate the large prevalence of stress in family caregivers of patients with dementia during the COVID-19 pandemic and have identified both caregivers and situations at a higher risk of stress, which should be taken into account in the planning of interventions in support of quarantined families and patients.

Keywords: caregiver, dementia, COVID-19, stress, burden

INTRODUCTION

Caregiver stress and burden, often described as an "enduring stress and frustration" phenomenon (Butcher et al., 2001), may have an extremely heavy impact on lives of family members who take care of relatives with dementia. Caregiver stress is mainly characterized by psychological symptoms such as anxiety, depression, irritability, feelings of being overwhelmed or abandonment, and tendency toward social isolation; but it is also associated with physical morbidity, disruption of family and professional life, and financial hardship (Faison et al., 1999; Chiao et al., 2015). Multiple factors have been shown to increase the risk of caregiver stress. Type of dementia, e.g., frontotemporal dementia (FTD) (Riedijk et al., 2006; Mioshi et al., 2013; D'Onofrio et al., 2015; Pilon et al., 2016; Liu et al., 2018), greater severity of cognitive and functional impairment (Wolfs et al., 2012; Mioshi et al., 2013; Liu et al., 2017; Riffin et al., 2019), and, most of all, worse behavioral disturbances (Wolfs et al., 2012; Papastavrou et al., 2007; Poon, 2019), have all been associated with higher levels of caregiver burden. Among carers' characteristics, younger age, lower education, female gender, and some type of kinship, namely, being patient's child, have also been linked with more severe anxiety and depression (Etters et al., 2008; Hughes et al., 2014). Finally, poor quality of the relationship between carer and care recipient (Faison et al., 1999; Steadman et al., 2007; Mioshi et al., 2013) and unavailability of social support and territorial resources (Upton and Reed, 2006) have also been shown to increase caregiver's perceived burden.

In late 2019, a new infectious disease [coronavirus disease 2019 (COVID-19)] caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and subsequently spread in most countries and territories around the world. COVID-19 causes severe pneumonia and acute respiratory distress and may progress to multiple organ failure and death (Guan et al., 2020), especially in older adults and in patients with comorbidities (Shahid et al., 2020). In the absence of an antiviral treatment, anti-COVID interventions are now based on symptomatic therapy and on the prevention of contagion, which takes place through close contact with an infected person. In the majority of affected countries, national health institutions have therefore imposed periods of lockdown and mass quarantines, with extremely strict limitations on activities and movements, generally only allowed for work or emergencies. These measures have proved efficacious for the containment of the infection (Nussbaumer-Streit et al., 2020; Sebastiani et al., 2020), but requested restrictions are likely to have augmented the difficulties that family caregivers of patients with dementia have to deal with daily. Social isolation, limitation, and difficulties in accessing health and social support services, worsening of patient's cognitive and motor deficits (Rainero et al., 2020), and behavioral and psychological symptoms (Cagnin et al., 2020) during the quarantine, in addition to dementia patients' vulnerability to the viral infection, may all have increased the stress and burden perceived by dementia caregivers. Evidence in support of this hypothesis has in fact been provided by a few studies on pandemic-related caregiver stress performed in Italy (Carpinelli Mazzi et al., 2020; Altieri and Santangelo, 2021), the first epicenter of COVID-19 epidemic outside China, in two other European countries, Greece (Tsapanou et al., 2020) and Portugal (Borges-Machado et al., 2020), in Argentina (Cohen et al., 2020), and in India (Vaitheswaran et al., 2020). However, available data are scarce, and additional data are warranted. The current study was aimed at contributing to this literature and expanding knowledge on the impact of the coronavirus pandemic on caregiver stress. Published studies used telephone or online scales of caregiver burden, quality of life, or depression and anxiety and included a maximum of 239 participants. In our study, we relied on a nationwide survey carried out during the lockdown declared in Italy in the first COVID-19 wave, and we investigated an extensive array of stress symptoms and a comprehensive set of potential risk factors of higher caregiver stress due to the quarantine.

Northern Italy hosted the first European case of the coronavirus disease, in late February 2020; and Italy was the first country in the world to declare a national lockdown, on March 9, 2020. The Italian Neurological Society for Dementia (SINdem), a scientific society involved in dementia care and research, devised a nationwide survey on the effects of the quarantine on patients with dementia and their informal caregivers, which was carried out in April 2020 and involved nearly 5,000 caregiver–patient pairs. The survey was based on a telephone interview with family caregivers, which included a questionnaire on the worsening of patients' motor, cognitive, and behavioral symptoms during the lockdown (Cagnin et al., 2020; Rainero et al., 2020), and a brief caregiver stress inventory. This paper reports on analysis of responses to the stress inventory, providing unique data on

caregiver burden and related risk factors in such exceptional circumstances and in a particularly large cohort.

MATERIALS AND METHODS

Eighty-seven Italian Centers for Dementia and Cognitive Disorders (CDCD) were involved in the study and enrolled a total of 4,913 caregivers who participated on a voluntary basis. The only inclusion criterion was being the informal carer of a patient with dementia. Patients were included if they met criteria for one of the four most common forms of dementia (in regard to mixed dementia, patients were characterized according to predominant type of dementia): Alzheimer's disease (AD), dementia with Lewy body disease (DLB), FTD, and vascular dementia (VaD). Moreover, for the present study, we only included caregivers of community-dwelling patients; hence, 203 caregivers of institutionalized patients who presented a different starting condition from other participants were excluded, leading to a final sample size of 4,710 cases. Their distribution on the Italian territory was homogeneous: 1,654 participants (35.0%) were from the north of Italy, 1,491 (32.0%) from the center of Italy, and 1,565 (33.0%) from the south. The total number of Italian regions involved was 16 out of 20.

Caregiver Stress Questionnaire and Risk Profiling

Caregivers were contacted by telephone by a neurologist, a geriatrician, or a psychologist from patients' referring CDCD and underwent a semi-structured interview after being informed about the study purpose and procedures and after giving oral consent to participate. All interviews were carried out from April 14 to April 24, 2020, i.e., from day 38 to day 48 from the start of the national lockdown (44.7 $\pm$ 1.2 days on average).

The survey protocol comprised a section reporting general information about the patient and the caregiver, an informant interview assessing changes in patient's clinical conditions during the lockdown, and the caregiver stress questionnaire.

The caregiver stress questionnaire was composed of six binary present/absent questions tapping the following stress symptoms: (1) depression, (2) anxiety, (3) anguish, (4) irritability, (5) overwhelmed/helplessness (OH), and (6) isolation/abandonment (IA). In addition, a seventh question dealt with a caregiver's concern for the consequences of COVID-19 infection on patient's health. Caregivers were explicitly asked to respond focusing (1) on *changes* that occurred in their psychological status *since the beginning of the lockdown* and (2) on feelings related to *caregiving*, rather than to the pandemic or quarantine *per se*. Identification of risk factors for caregiver stress took into account caregivers' and patients' sociodemographic features, dementia characteristics, and factors related to the lockdown. Information about patient's age and sex, disease stage, as defined by Clinical Dementia Rating (CDR) scale, and diagnosis of dementia were derived from CDCD's clinical records, while the following data were collected during the phone interview: caregiver's sex, age, and educational level; type of kinship (spouse, child, and other); cohabitation with the patient during the lockdown; presence of other family members at home; and temporary interruption of work activity (for professionally active caregivers). During the interview, the caregiver was also asked about presence of conflicts with the patient, availability of in-person help from other carers (relatives, friends, social services, or associations), and discontinuity in medical care during the quarantine.

Ethical Standards

The study was initially approved by the Ethics Committee of the Coordinating Centre (University of Torino on April 7, 2020, no. 00150/2020) and then by the local ethics boards.

Statistical Analysis

We conducted a descriptive analysis on the general characteristics of the study, prevalence of symptoms of caregiver stress, and frequency of risk factors. Mean, median, and standard deviation were produced for continuous variables, and frequencies and proportions for categorical variables. Rate of missing data was <2%; hence, no imputation was made. We performed logistic regression analyses in order to identify risk factors for caregiver stress. Each of the seven stress symptoms were first entered, as a dependent variable, in a series of *preliminary* uni- or multivariable regressions, with the following predictors or groups of predictors: caregiver's and patient's sex and age (<70 or $\geq$70 years), caregiver's education ($\leq$8 or >8 years of schooling), kinship (spouse, child, and other), cohabitation with the patient (yes/no), presence of other family members (yes/no), and interruption of work during lockdown (yes/no); type of dementia (AD/DLB/FTD/VaD) and disease stage (mild/moderate/severe or bedridden—the last two stages were pooled due to the low number of bedridden cases); presence of conflicts with the patient (present/absent); and availability of help from others (present/absent) and discontinuity in medical care or assistance for the patient (yes/no). Significant predictors were then entered in a *global* multivariable regression, one for each stress symptom as a dependent variable. Significance threshold was set at $p < 0.05$ for all analyses. All analyses were carried out with SPSS, version 26 (IBM Corp., 2019, Armonk, NY).

RESULTS

General Characteristics of the Study Cohort

Study participants' main features are shown in **Table 1**. The majority of caregivers were women (59.6%) and were patients' children (53.6%). Their mean age was 59.5 $\pm$ 13.0 years, and mean education was 12.0 $\pm$ 4.3 years. In most cases (61.3%), caregivers lived with the patient and also with other family members (63.0%) and were not working during the quarantine (59.5%).

Most patients had a diagnosis of AD (68.5%), and half were in a moderate disease stage (49.5%).

Only 22.8% of caregivers had experienced conflicts with the care-recipient.

Help from others was available for 51.4% of caregivers, while discontinuity in care and assistance during the lockdown was reported by 23.4%.

TABLE 1 | General characteristics of the study cohort.

Caregivers' features		
	Mean	**Standard deviation**
Age (years)	59.5	13.0
Education (years)	12.0	4.3
	N.	**Valid%**
Sex (women)	2,809	59.6
Kinship:		
Spouse	1,731	37.3
Child	2,488	53.6
Others	425	9.2
Cohabitant with the patient (yes)	2,884	61.3
Other family members (yes)	2,958	63.0
Caregiver not working during lockdown	2,191/3,682*	59.5
Conflicts with the patient (yes)	1,072	22.8
Help from others (yes)	2,423	51.4
Discontinuity in care/assistance (yes)	1,094	23.4
*Number of professionally active caregivers.		
Patients' features		
	Mean	**Standard deviation**
Age (years)	78.2	8.1
	N.	**Valid%**
Sex (women)	2,784	59.1
Type of dementia:		
Alzheimer's disease	3,227	68.5
Dementia with Lewy bodies	339	7.2
Frontotemporal dementia	404	8.6
Vascular dementia	740	15.7
Disease stage by CDR: Mild	1,197	25.5
Moderate	2,317	49.5
Severe/bedridden	1,169	25.0

CDR, Clinical Dementia Rating.

Prevalence of Stress Symptoms

The vast majority of caregivers (4,116 subjects, 87.4%) reported at least one symptom of stress. Sixty percent (2,827 subjects) reported one to three symptoms, and 27.4% (1289 subjects) reported four or more symptoms. Concern about COVID-19 infection on health of patients with dementia was the most prevalent complaint, reported by 74.5% of participants, followed by anxiety and OH, reported, respectively, by 45.9 and 34.0% of participants; the other symptoms had a frequency ranging from 18.7 to 29.2% (**Figure 1**).

Distribution of Stress Symptoms After Stratification of Caregiver Cohort by Various Characteristics of Interest

A higher prevalence of all symptoms, and especially anxiety (**Figure 2**), OH (**Figure 3**), IA, and anguish (**Supplementary Materials**), was found for female caregivers, carers of patients with more severe dementia, and caregivers experiencing conflicts with the patient or discontinuity in medical assistance.

Anxiety (**Figure 2**) was more frequent also among carers who, due to lockdown restrictions, temporarily suspended work and who had contacts with people or institutions, which helped them in assisting the patient.

Depression was found to be more prevalent in older, less educated caregivers and in spouses, than in other categories of relatives; in carers who lived with the care recipient, who did not live with other family members, and who had to interrupt work during lockdown; and in caregivers of patients with a diagnosis of FTD (**Supplementary Materials**). Only another stress symptom was affected by type of diagnosis: irritability was slightly more frequent in caregivers of patients with DLB (**Supplementary Materials**). Finally, concern about COVID (**Figure 4**) was more frequent in younger caregivers, in patient's children, and in carers who were not cohabitant with the patient, and also in those who had contacts with helpers.

Identification of Risk Factors of Stress Symptoms Through Regression Analyses

Results of Preliminary Univariate Regressions

Significant predictors of stress symptoms that emerged from preliminary logistic regressions are displayed in **Table 2**, while the **Supplementary Table** shows non-significant predictors (patient's age and sex, presence of other family members at home, interruption of work activity, and type of dementia).

Female caregivers were more prone to develop stress symptoms of all types, but especially anxiety (OR 1.78) and anguish (OR 1.85); younger caregivers were more likely to show anxiety and anguish (ORs 1.30 and 1.33, respectively); and caregivers with a lower educational level tended to be at major risk of depression (OR 1.27), anxiety (OR 1.27), and concern about COVID infection (OR 1.29). Unlike other relatives, patients' children were more likely to feel anxious (OR 1.86) and, above all, irritable (OR 2.03). Irritability was also more probable in caregivers who lived with the patient, together with depression and IA (with ORs ranging from 1.37 to 1.40).

Conflicts with the patient had a heavy negative impact on all stress symptoms. In particular, they caused a nearly threefold rise in the risk of IA (OR 2.96), depression (OR 2.83), and irritability (2.78).

Discontinuity in assistance was also strongly associated with a higher risk of stress, especially IA (OR 3.58), but also OH and irritability (ORs 2.57 and 2.34, respectively). On the other hand, availability of help increased anxiety (OR 1.15) and concern about COVID infection (OR 1.28), in spite of a protective effect against sense of abandonment (OR 0.81).

The only other protective factor was a mild dementia stage, which was associated with a minor risk of IA (OR 0.34).

Results of Multivariable Regressions

Almost all predictors that were significant at preliminary regressions were confirmed by global regressions (**Figure 5**). The only exceptions were the associations between caregivers'

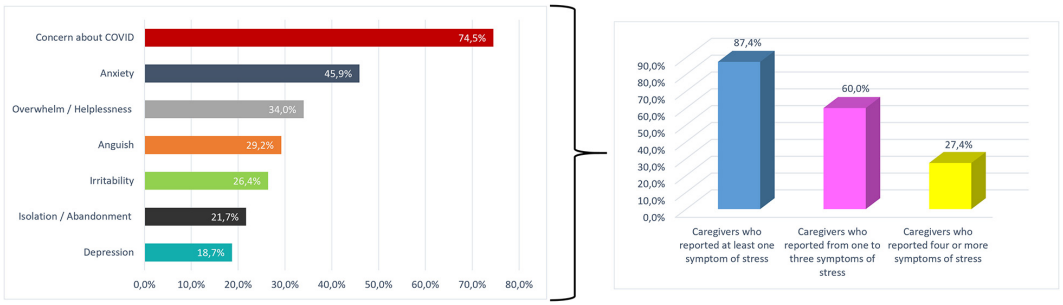

FIGURE 1 | Overall prevalence of stress symptoms in the study cohort.

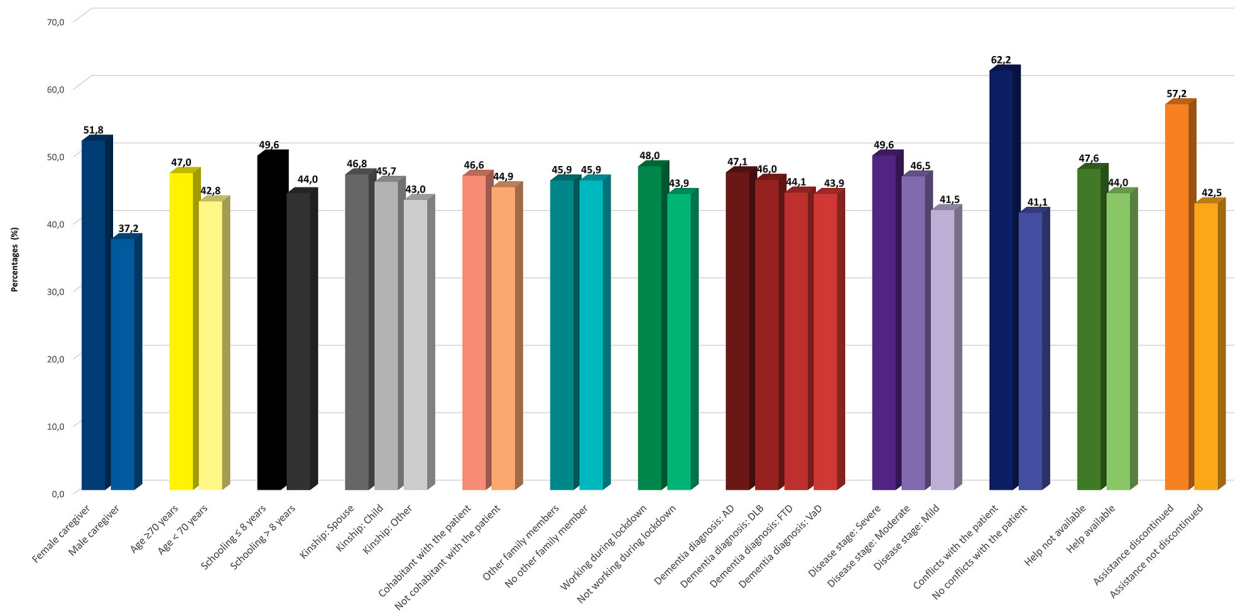

FIGURE 2 | Prevalence of anxiety according to caregiver and patient features. Legend: AD, Alzheimer's disease; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VaD, vascular dementia.

age and education and concern about COVID, and type of kinship (child) and help from others and anxiety, which were no longer significant.

Female sex, presence of conflicts with the patient, and discontinuity in medical assistance were confirmed to increase the risk of all stress symptoms. In particular, female caregivers were more likely to feel anguished (OR 1.96) and anxious (OR 1.78); caregivers with a conflicting relationship with the patient were more likely to feel isolated/abandoned (OR 2.52), irritated (OR 2.49), and depressed (OR 2.40); and those experiencing discontinuation in assistance were more likely to develop sense of IA (OR 3.27) and OH (OR 2.43).

Global regressions also confirmed a higher risk of anxiety (OR 1.20) and anguish (OR 1.22) for younger caregivers, of anxiety (OR 1.30) and depression (OR 1.40) for caregivers with a lower educational level, and of irritability for patients' children than for other relatives (OR 1.36).

Cohabitation with the patient was still a significant risk factor for depression (OR 1.48), irritability (OR 1.19), and IA (OR 1.26); and receiving help from others was confirmed to have a protective effect against IA (OR 0.75) but a detrimental effect on concern about COVID (OR 1.27).

Finally, carers of patients with mild dementia were confirmed to be at a lower risk of IA (OR 0.68).

DISCUSSION

To date, few studies have investigated the impact of the COVID-19 pandemic on the mental health of family caregivers of patients with dementia (Borges-Machado et al., 2020; Carpinelli Mazzi et al., 2020; Cohen et al., 2020; Tsapanou et al., 2020; Altieri and Santangelo, 2021), but this is the first nationwide multicenter survey, performed in Italy during the first wave of the coronavirus

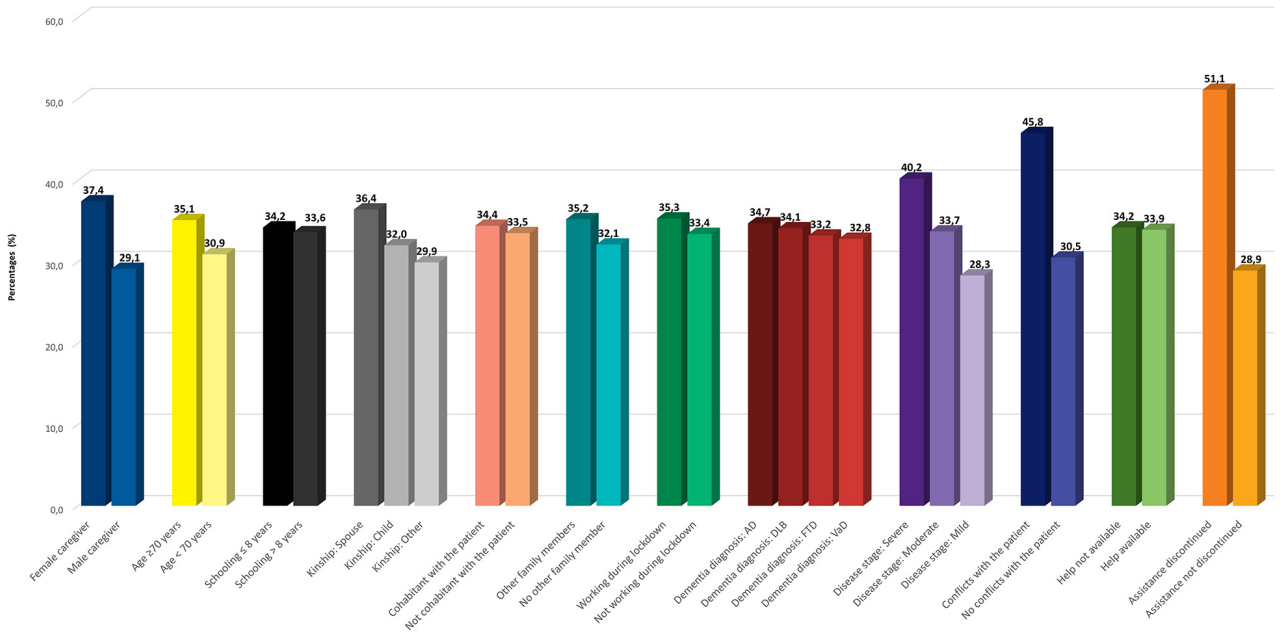

FIGURE 3 | Prevalence of sense of being overwhelmed and helpless according to caregiver and patient features. Legend: AD, Alzheimer's disease; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VaD, vascular dementia.

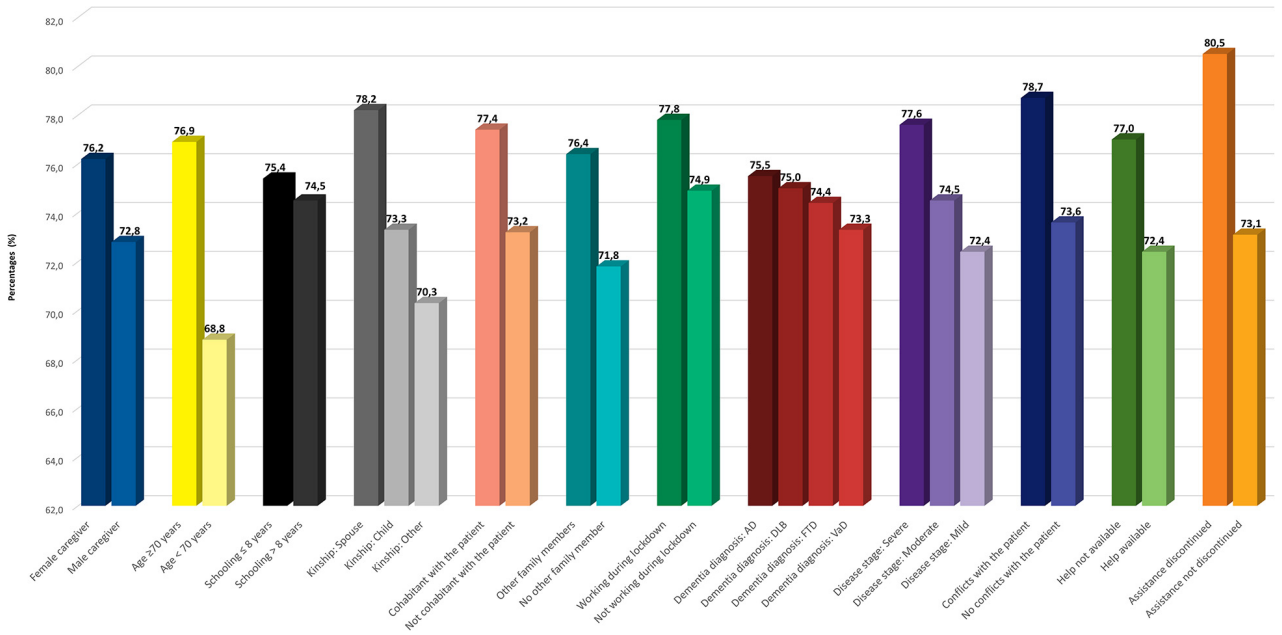

FIGURE 4 | Prevalence of concern about consequences of COVID-19 on patient's health according to caregiver and patient features. Legend: AD, Alzheimer's disease; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; VaD, vascular dementia; COVID-19, coronavirus disease 2019.

pandemic, that took into consideration a very large sample, a wide spectrum of symptoms of caregiver stress, and a comprehensive array of potential risk factors for higher stress levels.

Nearly 90% of our participants reported at least one symptom of stress, and nearly 20% reported four or more symptoms. In particular, anxiety and sense of being overwhelmed and helplessness were present in one in two and one in three caregivers, respectively, and were second only to concern about the consequences of COVID-19 infection on patient's health, reported by three quarters of participants. Depression, anguish, irritability, and sense of isolation and abandonment

TABLE 2 | Results (odds ratios and 95% confidence intervals) of preliminary regression analyses carried out for each stress symptom.

	Depression	Anxiety	Anguish	Irritability	Overwhelmed/helplessness	Isolation/abandonment	Concern for consequences of COVID on patient's health
Female caregiver	1.59*** (1.32–1.90)	1.78*** (1.56–2.02)	1.85*** (1.59–2.14)	1.37*** (1.18–1.59)	1.47*** (1.28–1.68)	1.29** (1.10–1.52)	1.17* (1.01–1.36)
Caregiver's age < 70 years	0.85 (0.64–1.14)	1.30* (1.02–1.64)	1.33* (1.02–1.72)	1.12 (0.86–1.47)	1.07 (0.83–1.37)	0.95 (0.71–1.25)	1.13 (0.87–1.46)
Caregiver's education ≤ 8 years	1.27** (1.07–1.51)	1.27*** (1.11–1.46)	1.13 (0.98–1.32)	1.01 (0.86–1.17)	0.99 (0.86–1.15)	1.08 (0.92–1.27)	1.29** (1.11–1.52)
Kinship: child	1.49 (0.70–3.18)	1.86* (1.08–3.19)	1.39 (0.77–2.52)	2.05* (1.03–4.08)	1.74 (0.98–3.11)	1.23 (0.64–2.34)	1.63 (0.94–2.83)
Cohabitation with the patient	1.38** (1.13–1.69)	1.04 (0.90–1.22)	1.14 (0.97–1.35)	1.37*** (1.16–1.62)	1.17 (1.0–1.36)	1.40*** (1.16–1.67)	1.00 (0.84–1.20)
Dementia severity: mild	0.43 (0.19–1.01)	1.42 (0.63–3.18)	0.93 (0.39–2.22)	0.57 (0.25–1.29)	0.49 (0.23–1.07)	0.34** (0.15–0.76)	0.74 (0.30–1.86)
Conflicts with the patient	2.83*** (2.41–3.31)	2.36*** (2.05–2.72)	2.00*** (1.73–2.31)	2.78*** (2.40–3.21)	1.92*** (1.67–2.21)	2.96*** (2.54–3.44)	1.33*** (1.12–1.56)
Help from others	0.98 (0.84–1.13)	1.15* (1.02–1.29)	0.99 (0.87–1.13)	0.91 (0.80–1.04)	0.98 (0.86–1.10)	0.81* (0.70–0.93)	1.28*** (1.12–1.47)
Discontinuity in assistance	1.94*** (1.65–2.28)	1.81*** (1.58–2.07)	1.94*** (1.68–2.24)	2.34*** (2.03–2.71)	2.57*** (2.24–2.95)	3.58*** (3.08–4.16)	1.52*** (1.29–1.80)

*Only predictors that were significant for at least one symptom are displayed. COVID, coronavirus disease. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.*

were less common but were still the complaints of 20 to 30% of respondents.

Analysis of stress symptoms across subgroups of participants, stratified by various characteristics of interest (caregivers' demographics, dementia features, and life conditions during the quarantine), and regression analyses assessing the relationship between these characteristics and stress symptoms outlined several risk factors for higher stress levels: caregiver's female gender, younger age, and lower educational level, parent–child kinship, cohabitation with the care recipient, conflicts with the patient, and discontinuity in medical assistance due to lockdown were associated with a twofold or even threefold increase in the risk of developing symptoms within the anxiety or depression spectrum. Only two factors seemed to exert a protective effect against stress: carers of patients in a milder disease stage and those receiving help from institutions, associations, or individuals were at a lower risk of feeling isolated.

Old Risk Factors for Caregiver Stress in a New Scenario

Most of the stressors identified by our survey are known determinants of caregiver stress in several prior studies (Pearlin et al., 1990; Faison et al., 1999; Rabinowitz et al., 2006; Campbell et al., 2008; Etters et al., 2008; Prince et al., 2012; Chiao et al., 2015; Liu et al., 2017; Carpinelli Mazzi et al., 2020). Cohabitation with the patient, conflicts between carer and care recipient, caregiver female sex, younger age, lower educational level, and close kinship tie with the patient have all been associated with increased caregiver perceived burden, depressed mood, feelings of isolation, anxiety, and also major physical and health problems (Faison et al., 1999; Campbell et al., 2008; Etters et al., 2008; Prince et al., 2012; Chiao et al., 2015).

In addition to confirming the association between stress and these well-known risk factors in our caregivers, we showed how a novel situation like the pandemic modulated such factors and their impact on caregiver burden. As an example, if we accept the use of schooling as a proxy measure for socioeconomic status (Hughes et al., 2014), we assume that less educated caregivers were more heavily affected by the economic consequences of the pandemic and that this contributed to raising their levels of perceived distress. Along the same line, carer–patient relationship was certainly hard-tested by the extremely strict limitations in movements, activities, and social contacts imposed by the quarantine, magnifying its impact on caregiver burden. A final example of how the quarantine modulated risk and protective factors of caregiver stress was the ambivalent reaction of our carers to availability of help from others. Our results confirmed the known effect of formal and informal social support in reducing burden of caregiving and feelings of isolation, as the risk of sense of abandonment was lower in the 50% of our participants who received support from acquaintances or services and associations. However, we also revealed the other side of the coin, since caregivers who took advantage of help during the lockdown were also more prone to be concerned about the risk, for their demented relative, to contract SARS-CoV-2 infection,

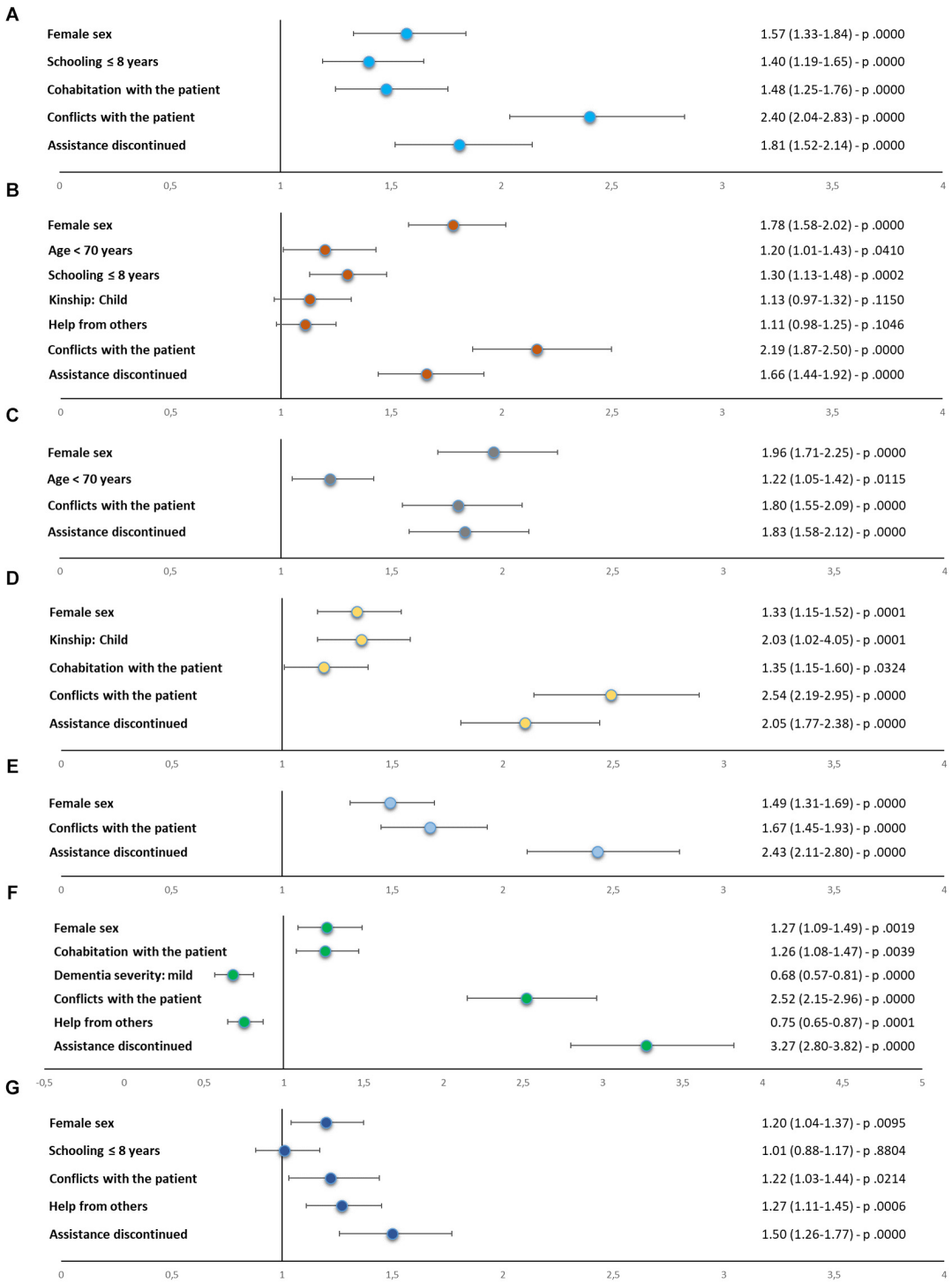

FIGURE 5 | Results (odds ratios, 95% confidence intervals, and p values) of global regression analyses for identification of risk factors for each stress symptom: **(A)** depression, **(B)** anxiety, **(C)** anguish, **(D)** irritability, **(E)** sense of being overwhelmed/helplessness, **(F)** sense of isolation/abandonment, and **(G)** concern about consequences of COVID-19 on patient's health. COVID-19, coronavirus disease 2019.

probably through contact with helpers. Fear of spreading the disease while assisting patients had also been pointed out in another study on caregiver stress related to COVID-19 (Cohen et al., 2020) and will necessarily have to be taken into account in the planning of interventions in favor of quarantined patients and caregivers.

The Pandemic and the Lockdown as a Novel Burden for the Caregiver

One of the strongest stressors that emerged from our survey, but also from similar studies (Carpinelli Mazzi et al., 2020; Cohen et al., 2020; Tsapanou et al., 2020), was discontinuation in medical care. This situation was reported only by 23% of our participants, probably due to the fact that the interview was performed a few weeks since the beginning of the lockdown, but its impact was quite heavy. Specifically, it put caregivers at a much higher risk of feeling isolated, abandoned, overwhelmed, and helpless. Interestingly, all these symptoms are typically associated with perception of an increased burden of care. As already suggested previously (Borges-Machado et al., 2020), caregivers in our cohort might have felt the responsibility to handle alone situations normally managed by, or in collaboration with, specialists or might have felt the load of having to find alternative ways to guarantee assistance to their loved ones.

The need for continuative medical care is known to be particularly intense in informal caregivers of dementia patients, and, when unmet, it is one of the main determinants of distress (Hughes et al., 2014). Importantly, specialist assistance has been shown to be relevant to caregivers not only for its medical content but also for its ability to boost caregivers' confidence in their own competence and efficacy as carers, improving their mood, and also their capacity to deal with patients' behavioral disturbances (Rabinowitz et al., 2006; Campbell et al., 2008).

Pandemic-Related Stress: Confounder or Secondary Stressor?

Our caregiver stress questionnaire was aimed at detecting specifically carers' psychological reactions to the strains of taking care of their relatives in a quarantine situation and was thus structured to induce responders to focus on changes in their mood and feelings, related to caregiving, rather than to the pandemic scenario itself. Nevertheless, this scenario has surely had an impact on responses to the questionnaire. Rather than being seen as a pure confounder, however, reactions of caregivers to the pandemic may be considered as a fundamental contributor of caregiver stress. One of the most influential and comprehensive models of stress process of dementia caregiving (Pearlin et al., 1990) distinguishes separate but highly interacting determinants of caregiver stress: "background/context" features, such as demographic, socioeconomic, and relational characteristics of the caregiver; "primary" stressors, anchored directly in caregiving, e.g., patient cognitive and functional deficits or behavioral disturbances; and "secondary" stressors, related to situations outside of the caregiver role. We suggest that the pandemic acted as a secondary stressor for our caregivers and that the influence of its psychological consequences (Luo et al., 2020) on responses to our interview added accuracy and completeness to the survey, rather than interfering with the data collection.

The Role of Dementia Characteristics

In disagreement with past literature evidence, in our survey, we only found a minor impact of severity of dementia on stress levels and no impact of type of dementia. Patients with FTD or DLB present more severe neuropsychiatric symptoms than patients with AD, and those with AD present more severe cognitive deficits than those with VaD, and these clinical characteristics have been associated with higher burden for caregivers (Riedijk et al., 2006; Mioshi et al., 2013; D'Onofrio et al., 2015; Pilon et al., 2016; Liu et al., 2018). In our study, descriptive analysis showed a higher prevalence of depression in carers of patients with FTD and a slightly higher prevalence of irritability in carers of patients with DLB, but regression analysis did not identify dementia diagnosis as a significant, independent predictor. Within the framework of the model of Pearlin et al. (1990), this result may be seen as an interesting overturn in the relative impact of context and primary and secondary stressors on caregiver burden induced by the pandemic.

A possible account for this finding is suggested by the results of analyses of two subsets of data collected through the current survey and recently reported by Cagnin et al. (2020) and Rainero et al. (2020). These two studies investigated modifications of our patients' cognitive, motor, and neuropsychiatric symptoms during the quarantine and reported a worsening in all forms of dementia, even if in different domains for different diagnoses (e.g., cognitive changes were major in AD and behavioral changes in DLB and FTD). The quarantine seems to have levelled out the differential impact of the various forms of dementia on caregiver burden.

Study Limitations

Our study has some of the limitations of large multicenter studies. In particular, although items of caregiver stress questionnaire were straightforward, yes/no, questions, and interviewers followed a common procedure of assessment, there may have been variability in how questions were delivered and how responses were interpreted. Second, we did not use a standardized and validated scale for measuring caregiver stress. However, symptoms assessed in our interview are core symptoms included in the most used caregiver burden questionnaires (Zarit et al., 1980; Cohen et al., 1983; Hoefman et al., 2013). Third, all data were collected through a telephone interview because a face-to-face assessment was not possible due to the quarantine, and this may have increased the risks of misunderstandings, especially with older caregivers.

Finally, unlike other similar studies that were able to compare pre-lockdown and during-lockdown data (Borges-Machado et al., 2020; Altieri and Santangelo, 2021), we did not acquire information about caregivers' mental state before the pandemic outbreak and the lockdown. Participants were asked expressly to focus on changes occurred during the quarantine, but their prior psychological conditions may have influenced their responses. This probably made our data less specific but added a naturalistic tenor, since caregiver stress related to the lockdown surely was the result of interaction of multiple, complex factors, including a caregiver's baseline mood. Finally, even if we believe that our study cohort is representative of Italian family caregivers of patients with dementia, in virtue of the large sample size and of the homogeneous distribution of participating CDCD on the Italian territory, generalizability of our findings to other settings may be limited. Differences in caregivers' sociodemographic

characteristics and lifestyle, in organization of health and social systems, and also in the course of COVID-19 pandemic restrain applicability of our results to other populations. Also, our data cannot be generalized to caregivers of institutionalized patients, who were excluded from the current analyses.

Implications for Interventions in Support of Caregivers

Despite the limitations discussed above, we believe that our survey has given a contribution to the knowledge of the consequences of the COVID-19 pandemic and quarantine on dementia caregivers and might have important psychosocial implications. First of all, we drew attention on the issue of the impact of the coronavirus disease on the mental health of informal carers of patients with dementia, and we provided a measure of the dimensions of this phenomenon with an exceptionally timely and large-scale study. Moreover, results of our risk profiling analysis identified a series of red flags that should be carefully scrutinized to detect situations and caregivers at greater risk of breakdown, hence in greater need of support. Finally, potentially useful indications have emerged for the planning of interventions targeted at the prevention of caregiver stress and relief of caregiver burden in quarantine situations. For instance, a conflicting patient–caregiver relationship might benefit from specific counseling, risks associated with contacts with support services might be contained through a reorganization of dispensation of social care, and interruptions in medical assistance might be overcome through potentiation of telemedicine. An increase of online services such as remote diagnosing and monitoring of patients, tele-consultation, online caregivers support, and patient tele-rehabilitation are potential promising solutions for counterbalancing the forced interruption imposed by the COVID-19 pandemic. Encouraging results were recently reported in reference to the efficacy of telehealth interventions to increase the psychological well-being of people with different types of dementia and their caregivers (Costanzo et al., 2020). However, although telemedicine can be a potential solution for the difficulties found in access to conventional health-care services, it is important to note that subjects with major neurocognitive disorders and/or with severe neurosensory deficits have greater difficulty in the management of online interventions especially if they are performed via audio-visual devices (Sekhon et al., 2021). In line with these suggestions, clinicians should consider adopting more often a combination of different and flexible telemedicine approaches to try and overcome these problems, making the use of telehealth services more effective and generalizable.

Such indications might even be transferred to "quarantine-like" scenarios unrelated with a pandemic, e.g., in cases of forced and prolonged cohabitation, problematic access to services, or restriction of social contacts.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of University of Torino, Turin, Italy. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IR, AB, CM, AC, LB, CC, and VL designed the study and planned center recruitment. MZ and VI wrote the report. RDL did the statistical analyses. ER, VI, NV, FA, IA, PC, RS, DQ, VG, GL, MF, GT, and CF contributed to the interpretation and discussion of results and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica (MIUR) under the project "Dipartimenti di Eccellenza 2018-2022."

ACKNOWLEDGMENTS

We thank all patients and caregivers involved in the study for their kind collaboration. We are also thank Gabriele Bartalini, Laura Franci, and Barbara Frati for the technical assistance in collecting the data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.653533/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 30 April 2021
doi: 10.3389/fnagi.2021.653591

Hepcidin Increases Cytokines in Alzheimer's Disease and Down's Syndrome Dementia: Implication of Impaired Iron Homeostasis in Neuroinflammation

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The liver-derived hormone hepcidin, a member of the defensin family of antimicrobial peptides, plays an important role in host defense and innate immunity due to its broad antibacterial and antiviral properties. Ferritin, an iron storage protein is often associated with iron deficiency, hypoferritinemia, hypoxia, and immune complications, which are all significant concerns for systemic infection in Alzheimer's disease (AD) and Down's syndrome (DS) dementia. Serum and post-mortem brain samples were collected from AD, DS and age-matched control subjects. Serum samples were analyzed with ELISA for ferritin, hepcidin and IL-6. Additionally, post-mortem brain sections were assessed by immunohistochemistry for iron-related and inflammatory proteins. A significant increase in serum hepcidin levels was found in DS, compared to controls and AD subjects ($p < 0.0001$). Hepcidin protein was visible in the epithelial cells of choroid plexus, meningeal macrophages and in the astrocytes close to the endothelium of blood vessels. Hepcidin co-localized with IL-6, indicating its anti-inflammatory properties. We found significant correlation between hypoferritinemia and elevated levels of serum hepcidin in AD and DS. Hepcidin can be transported *via* macrophages and the majority of the vesicular hepcidin enters the brain *via* a compromised blood brain barrier (BBB). Our findings provide further insight into the molecular implications of the altered iron metabolism in acute inflammation, and can aid towards the development of preventive strategies and novel treatments in the fight against neuroinflammation.

Keywords: Alzheimer's disease, Down's syndrome dementia, ferritin, hepcidin, choroid plexus, macrophage activation syndrome, neuroinflammation

OPEN ACCESS

Edited by:
Thomas Wisniewski, New York University, United States

Reviewed by:
Paolo Arosio, University of Brescia, Italy
Masafumi Ihara, National Cerebral and Cardiovascular Center (Japan), Japan

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Received: *14 January 2021*
Accepted: *23 March 2021*
Published: *30 April 2021*

Citation:
Raha AA, Ghaffari SD, Henderson J, Chakraborty S, Allinson K, Friedland RP, Holland A, Zaman SH, Mukaetova-Ladinska EB and Raha-Chowdhury R (2021) Hepcidin Increases Cytokines in Alzheimer's Disease and Down's Syndrome Dementia: Implication of Impaired Iron Homeostasis in Neuroinflammation. Front. Aging Neurosci. 13:653591. doi: 10.3389/fnagi.2021.653591

INTRODUCTION

Dementia is a global public health challenge for this generation, and the most prevalent cause of dementia is late onset of Alzheimer's disease (LOAD), a fatal neurodegenerative disorder characterized by progressive cognitive and functional impairment associated with memory loss (Hardy et al., 1998). The two primary pathological hallmarks of AD are senile plaques (SP), which are extracellular deposits of Aβ derived from the β-amyloid precursor protein (APP), and neurofibrillary tangles (NFTs), primarily composed of hyper-phosphorylated tau (Goedert et al., 1995; Hardy and Selkoe, 2002). Down's syndrome (DS) is an aneuploidy due to triplication of all or part of chromosome 21, where the amyloid precursor protein (APP) gene is encoded, and plays a key role in the pathogenesis of AD dementia in DS (Wisniewski et al., 1985; Mann, 1988; Raha et al., 2013). Although dysfunction of APP processing is believed to be the key upstream factor in the pathogenesis of AD (Wilcock, 2012a), neuroinflammation and activation of innate immunity are considered early events in the genesis of AD and in DS dementia (Wilcock, 2012b). In DS and in LOAD, neuroinflammation has been linked to both the exacerbation of SP and NFT pathology, as well as the clearance of Aβ from amyloid plaques (Bell et al., 2007; Mawuenyega et al., 2010; Wildsmith et al., 2013).

The main cell types involved in the brain neuroinflammatory responses are microglia, astrocytes and to a lesser extent, the peripheral and meningeal macrophages (Xue and Streit, 2011; Walsh et al., 2014; Mammana et al., 2018). Microglia in the vicinity of the pathological hallmarks of AD become activated and release a cocktail of inflammatory cytokines and chemokines (Jorda et al., 2020). The systemic infections and its ability to contaminate macrophages, microglia and astrocytes in the central nervous system (CNS) have a particular role (Merad and Martin, 2020). The viruses and bacteria can activate glial cells and induce a pro-inflammatory state in the brain (Kanberg et al., 2020).

Acute infection initiates complex systemic inflammatory responses as part of the innate immunity (Chen et al., 2020). An extensive interaction between the brain and the immune system is present in neurodegenerative diseases (Manson et al., 2020). These are often triggered in a subcellular compartment known as the inflammasome, where IL-6 and IL-1 are the main pathological mediators causing cytokine storm during acute infection (Mehta et al., 2020). These cytokine-mediated multisystem inflammatory responses are common in AD, DS, and other age-related dementia and associated with an increased risk of severe infection (Kox et al., 2020).

Inflammation is often accompanied by abnormal iron homeostasis that leads to systemic hypoferritinemia and low iron levels (Raha et al., 2020). The hypoferritinemia can likely be due, at least in part, to inflammation-driven increases in hepcidin concentrations (Litton and Lim, 2019; Hippchen et al., 2020). How iron homeostasis is maintaining in the whole-body as well as inside the brain is crucial, yet the mechanism remain poorly understood.

Ferritin is an iron storage protein. Excess iron stored, in the form of ferritin protein, is found in many neurodegenerative diseases, including AD (Smith et al., 1998; Raha et al., 2013). The age-associated increase in iron stores in the brain tissue appears to be linked to neuroinflammation (Todorich and Connor, 2004). Aβ and ferritin co-localize within the vascular amyloid deposits in the post-mortem AD brain, with iron accumulation being a ready source of redox generated free radicals that promote neuronal cell death (Smith et al., 1997; Atamna and Boyle, 2006; Raha et al., 2013). The understanding of how iron homeostasis is maintained both at cellular and whole-body level has exponentially increased following the identification of a number of iron related proteins, such as the divalent metal transporter 1 (DMT1), ferroportin (FPN) and hepcidin (McKie et al., 2001; Ganz, 2003; Hentze et al., 2010). The liver-derived hormone hepcidin plays a significant role in host defense and innate immunity due to its broad antibacterial and antiviral properties (Ganz, 2003). Hepcidin regulates systemic iron homeostasis by controlling iron flux into the plasma from the duodenum, as well as through iron recycling macrophages binding to its receptor, the iron exporter FPN (Krause et al., 2000; Pigeon et al., 2001; Nemeth et al., 2004b). Low hepcidin levels cause iron overload, whereas high hepcidin levels cause anemia of inflammation by restricting intestinal iron absorption and macrophage associated iron release (Cheng et al., 2011).

Besides the circulating iron levels, inflammation is another factor regulating hepcidin transcription in hepatocytes. Inflammatory cytokines, mainly in the form of IL-6, are released during inflammation and induce hepcidin expression in the hepatocytes *via* the JAK/STAT3 signaling pathway, leading to phosphorylation of STAT3, its translocation to the nucleus and the hepcidin gene activation (Pietrangelo et al., 2007; Eikelenboom et al., 2012b). The inflammation in AD and DS can therefore be an additional reason for the increase in hepcidin levels, like that seen in the systemic environment.

To evaluate hepcidin and ferritin expression in controls, AD and DS subjects, serum and post-mortem brain samples were analyzed to determine the crosstalk between inflammation and iron dysregulation in normal ageing, AD and DS pathology.

MATERIALS AND METHODS

Ethics and Participants

Ethics plus research and development (R&D) and approvals were granted by the National Research Ethics Committee of the East of England—Norfolk and Cambridgeshire and Peterborough NHS Foundation Trust, respectively. Cambridge Health Authorities Joint Ethics Committee granted ethical approval for the use of human brain tissue and serum samples (Project ref no.: REC:15/WM/0379). Written consents were obtained from controls, adult DS participants and subjects with AD with the capacity to consent. Verbal assent was obtained from participants with AD and DS, who lacked the capacity to provide written assent, and this was provided instead by an appointed consultee, in accordance with the Mental Capacity Act of the

UK (2005). Information on older controls (n = 50), younger controls (n = 50), DS (n = 47) and AD (n = 50) has already been disclosed in a previous publication (Raha-Chowdhury et al., 2018).

Assessment of Dementia Status

This was undertaken as described previously using the CAMDEX-DS informant interview and the CAMCOG-DS neuropsychological assessment (Annus et al., 2017).

Blood and Serum-Collection

Whole blood and serum samples were collected from younger human controls (n = 50, aged between 30 and 55 years), and older controls (n = 50, aged between 56 and 85 years, with intact cognitive functioning and devoid of neurological and mental health disease), 47 DS cases (aged between 32 and 70 years) and assessed at our Research Centre. A cohort of AD cases (n = 50, aged between 56 and 85 years) was provided by collaborator (co-author, RF) for DNA and protein analysis. All blood samples were collected for serum in BD vacutainer SST advance tubes (containing inert gel barrier and clot activator coating). Serum and plasma were separated immediately by centrifugation at 2,465 g for 6 min at 4°C, aliquoted, and stored at −80°C until analysis. Biochemical and hematological profiles including serum iron were analyzed by pathology laboratories at Addenbrooke's Hospital, Cambridge University NHS Foundation Trust, Cambridge, UK.

Human Post-Mortem Brain Sections

Human post-mortem brain tissues from controls (mean age 60 ± 15 years), DS (mean age 60 ± 15 years) and AD (mean age 82.0 ± 8.0 years; n = 10 in each group) were provided by the Cambridge Brain Bank (**Table 1**). Cambridge Health Authorities Joint Ethics Committee granted ethical approval for use of human brain tissue and serum samples (Project ref no.: REC:15/WM/0379).

Solid-Phase Enzyme Linked Immunosorbent Assay (ELISA)

The human serum ferritin level was measured with the human ferritin kit ELISA (Abcam, cat number Ab108698) and serum hepcidin (human hepcidin Quantikine ELISA kit, cat number DHP250) and IL-6 (human IL-6 Quantikine ELISA kit, cat number S6050, R&D) according to the manufacturer's instructions. Briefly, for the detection of hepcidin, samples in 96-wells culture plates were incubated overnight with monoclonal antibody (R&D, MAB83071) or anti-hepcidin capture antibody (1 μg/ml; R&D system, cat number 842127). The following day, the plates were washed three times with washing buffer [0.05% Tween 20 in 0.1 M phosphate buffer saline (PBS) pH7.4] and blocked in blocking solution (1% BSA and 0.05% Tween 20 in 0.1 M PBS) for 2 h at room temperature (RT). After blocking, the plates were washed three times with washing buffer and loaded with 10 μl plasma into 90 μl blocking solution and incubated 4 h at RT. All experiments were performed in quadruplicate unless otherwise specified. A recombinant human protein (R&D, cat number 842129) was diluted in assay buffer in a 2-fold serial dilution and used for the standard curve with a concentration range of 1,000, 500, 250, 125, 62, 31, 15, and 0 pg/ml. After 4 h of incubation, the samples were removed and the plates were washed three times for 5 min with washing buffer before incubation for 2 hs at RT for detection with a biotinylated rabbit polyclonal anti-human hepcidin (Abcam, cat number ab30760) antibody (1 μg/ml) diluted in blocking buffer. After three further washing steps, the plates were incubated with anti-rabbit HRP-conjugated secondary antibody (1:4,000) for 1 h followed by three washes. One-hundred microliter of 1-Step ULTRA tetramethylbenzidine (TMB-ELISA, Thermo Fisher Scientific) was added for ∼30 min at RT. Finally, 100 μl of 2 M H_2SO_4 was added to quench the reaction. Colorimetric quantification was performed with an Infinite M200 plate reader (Tecan) at 450/540 nm.

Antibodies

A polyclonal rabbit anti-hepcidin 25 (Abcam ab30760) recognising a 2.8 kDa protein (Raha-Chowdhury et al., 2015), human anti-ferritin light chain (Abcam ab69090), human anti-ferritin heavy chain (Abcam ab65080), Anti-FPN (Abcam ab85370), anti-GFAP (Abcam ab48050), anti-CD68 (Sigma–Aldrich, MAB98073), and monoclonal anti-Iba1 (Thermo Fisher Scientific, MAB M1/70), Polyclonal anti-Iba1(Wako cat number 019-19741), monoclonal anti-IL-6 (Thermo Fisher, cat number M620), monoclonal anti-IL-1β (Thermo Fisher Scientific, cat number ILB1-H67), Anti-β amyloid (Covance cat number SIG 39320), Anti-Phospho-Tau (AT8, Thermo Fisher Scientific, cat number MN1020), was used for IHC. The following secondary antibodies were used: biotinylated goat anti-rabbit-Ig and biotinylated horse anti-mouse (both from Vector Laboratories, 1:250 for IHC); Alexa Fluor 568-labeled donkey anti-mouse-Ig, Alexa Fluor 488-labeled donkey anti-rabbit-Ig, and Alexa Fluor 568-labeled donkey anti-goat-Ig (all from Invitrogen, 1:1,000 for immunofluorescence).

Perls Staining Methods for Brain Iron

Perls Prussian blue method was followed for staining ferric iron: The ferric iron combines with potassium ferrocyanide to form the insoluble Prussian blue precipitate as follows:

$$\underset{\text{(ferric iron)}}{4FeCl_3} + \underset{\text{ferrocyanide)}}{\underset{\text{(potassium}}{3K_4Fe(CN)_6}} = \underset{\text{(ferric ferrocyanide)}}{Fe_4[Fe(CN)_6]_3 + 12KCl}$$

Paraffin fixed brain sections (n = 6, in glass slides) were deparaffinized and hydrated with iron free distilled water. The sections were then transferred to a mixture of equal parts of 2% potassium ferrocyanide for Perls staining at pH6 and 2% HCL in distilled water for 20–30 min. The brain sections were then washed in distilled water. All sections were counterstained in eosin, dehydrated, and mounted with a synthetic resin medium (Meguro et al., 2005).

Congo Red Staining for Amyloid Plaques

Congo red stain applied to the tissue gives the amyloid protein a salmon-pink color and when placed under polarized light,

TABLE 1 | Characteristics of post-mortem brain samples of Alzheimer's disease (AD), Down's syndrome (DS) and age-matched control study population, showing age, gender, post-mortem time delay, Braak stage and cause of death.

Case number	Category	Age	Gender	PM delay (h)	Braak stage	Cause of death
Down's syndrome (DS)						
DS1	DS	56	F	6	6	Not known
DS2	DS	76	F	18	6	Septicaemia
DS3	DS	46	F	8	2	Not known
DS4	DS	52	M	24	6	Bronchopneumonia
DS5	DS	64	M	31	6	Not known
DS6	DS	66	F	26	5	Not known
DS7	DS	67	M	8	5/6	Alzheimer's disease (AD), Cerebrovascular disease (CVD)
DS8	DS	52	F	–	6	AD, Lewy body dementia
DS9	DS	52	M	–	5	Traumatic brain injury (TBI)
DS10	DS	76	F	18	6	Dementia
Alzheimer's disease (AD)						
AD1	AD	86	F	86	6	Urinary tract infection/Advanced dementia
AD2	AD	88	M	81	6	Urinary tract infection/Addison's disease and poor immunity/Vascular and Alzheimer's dementia
AD3	AD	83	M	46	6	Bowel ischaemia/Hypothyroid/ Hypertension/Alzheimer's/Atrial fibrillation/Chronic kidney disease/Vascular dementia
AD4	AD	88	M	22.3	5	Pneumonia/Aortic stenosis/Mixed dementia/Left cerebellar hemisphere haemorrhage
AD5	AD	70	M	71	6	Pneumonia/Alzheimer's disease
AD6	AD	79	F	45.3	6	Cerebrovascular accident/Dementia
AD7	AD	78	M	62	6	Alzheimer's disease
AD8	AD	89	M	44	5	Alzheimer's disease
AD9	AD	78	M	24	4	Alzheimer's disease
AD10	AD	95	M	61	1	Alzheimer's disease
Controls						
C1	Normal	66	M	10.3	5	Cerebrovascular disease/Dementia
C2	Normal	45	F	43.3	0	End stage renal failure/diabetic nephropathy
C3	Normal	54	F	10.3	0	Metastatic myxoid liposacroma/Bronchopneumonia
C4	Normal	52	F	30.3	1	Bronchogenic cancer
C5	Normal	75	F	24	2	Cancer of the ovary
C6	Normal	66	F	29.3	2	Metastatic breast cancer
C7	Normal	83	M	45	0	Not known
C8	Normal	68	M	48	0	Not known
C9	Normal	60	F	60	0	Not known
C10	Normal	66	M	74	0	Not known

the amyloid proteins have an apple-green birefringence. This apple-green birefringence is considered pathognomonic for amyloid fibril deposits (Howie et al., 2008). Congo red was purchased from Sigma–Aldrich (cat number C6277). It is an organic compound, a sodium salt of 3,3′-[(1,1′-biphenyl)-4,4′-diyl]bis(4-aminonaphthalene-1-sulfonic acid) and is an azo dye. Congo red is water-soluble, yielding a red colloidal solution. Paraffin fixed human brain sections (n = 6, in glass slides) were deparaffinized and hydrated with iron free distilled water. The brain sections were then immersed in Congo red dye for 10 min and rinsed thereafter in distilled water. The sections were differentiated quickly (5–10 dips) in alkaline alcohol solution and rinsed in tap water. Slides were counterstained in Gill's hematoxylin for 30 s and mounted with a synthetic resin medium.

Immunohistochemistry (IHC)

Paraformaldehyde (PFA) fixed tissues were first quenched with 5% hydrogen peroxide and 20% methanol in 0.01 M PBS for 30 min at RT followed by three rinses for 10 min in 0.01 M phosphate buffer saline (PBS). Non-specific binding sites were blocked using blocking buffer (0.1 M PBS, 0.3% Triton-X 100, and 10% normal goat serum for polyclonal antibodies or 10% normal horse serum for monoclonal antibodies) for 1 h at RT. Tissue sections were incubated overnight with the primary antibody diluted in blocking buffer. Binding of the primary

antibody was detected using a biotinylated secondary antibody followed by an avidin-biotin complex conjugated to peroxidase (Elite standard kit SK6100, Vector Laboratories) and DAB substrate (ABC substrate SK-4200, Vector Laboratories).

Immunofluorescence (IF)

Brain and other sections were blocked using blocking buffer (0.1 M PBS, 0.3% Triton X 100, 10% normal donkey serum) for 1 h at RT, then incubated overnight at 4°C with primary antibody diluted in blocking buffer. Alexa Fluor-conjugated secondary antibodies were used for detection and samples counterstained with 4′6-diamidino-2-phenylindole (DAPI, Sigma). The sections were then mounted on glass slides with coverslips using Fluoro Save (Calbiochem).

Microscopy

Bright field images were taken and quantified using Lucia imaging software and a Leica FW4000 upright microscope equipped with a SPOT digital camera. Fluorescence images were obtained using a Leica DM6000 wide field fluorescence microscope equipped with a Leica FX350 camera with 20× and 40× objectives. Images were taken through several z-sections and de-convolved using Leica software. A Leica TCS SP2 confocal laser-scanning microscope was used with 40× and 63× objectives to acquire high-resolution images.

Image and Statistical Analysis

Data were analyzed by paired Student's *t*-test (two-tailed) for two group comparison, or by ANOVA test for multiple comparison testing. Values in the figures are expressed as mean ± SEM. A one–way ANOVA was used for comparison of data among control, AD and DS and conducted with IBM-SPSS statistic 19 software. Significance was analyzed using GraphPad and *p*-values ≤0.001 were considered significant and are indicated in the corresponding figures and figure legends.

RESULTS

Significant Elevation of Serum Hepcidin in DS Subjects

We investigated serum iron, ferritin and hepcidin levels in AD, DS and age-matched control subjects with sandwich ELISA. Serum iron was measured by clinical biochemistry, at the Addenbrooke's Hospital of Cambridge University NHS Foundation Trust located in Cambridge, UK. All samples were analyzed on the same day, using same standardized protocol to reduce the day-to-day variation.

Serum iron levels were significantly higher ($p < 0.0001$) in control subjects (25.07 ± 5.06 μmol/L) compared to AD (16.2 ± 9.2 μmol/L) and DS (15.42 ± 10.1 μmol/L; **Table 2**, **Figure 1A**). Similarly, serum ferritin levels were significantly higher ($p < 0.0001$) in controls (216.9 ± 171.1 μg/L), compared to AD (149.4 ± 199.5 μg/L) and DS (133.82 ± 85.7 μg/L; **Figure 1B**). In contrast, hepcidin levels were substantially higher ($p < 0.0001$) in DS (mean ± SD: 188.32 ± 430.5 μg/L) compared to AD (36.3 ± 18.2 μg/L) and controls (25.38 ± 22.1 μg/L; **Figure 1C**). The iron and ferritin level in control subjects indicated that iron and ferritin stored were within normal range as expected (**Figure 1D**). To evaluate that ferritin and hepcidin levels were not reflecting the age, we analyzed age matched controls (ages between 65–85 years) and AD subjects. We found that serum ferritin was significantly higher in aged controls compared to AD ($p < 0.0001$), whereas hepcidin levels were lower in AD (**Figure 1E**). However, hepcidin levels were high in DS compared to controls and AD individuals suggesting inflammatory changes or impaired dis-erythropoiesis affecting the DS subjects (**Figures 1D,E**).

Iron Accumulation Is Visible in DS Senile Plaques

DS brain sections from superior frontal gyrus (SFG), mid temporal gyrus (MTG), and hippocampus (HP) were then analyzed by immunohistochemistry (IHC) using antibodies specific to Aβ42 (6E10), Phospho-tau (AT8), hepcidin and ferritin heavy chain (FTH) using DAB stain. In the SFG from DS brain, abundant Aβ42 positive plaques were observed in the neocortex (**Figures 1F,G**, black arrows highlight the selected area of plaques formed) and very close to and even inside the blood vessels (**Figure 1I**). To confirm neurofibrillary (neuritic) plaque formation, a representative section from DS brain was stained with Congo red (**Figure 1H**). Congo red stain recognized the amyloid protein appearing as salmon-pink color and when placed under polarized light, the amyloid proteins had an apple-green birefringence. This apple-green birefringence is considered pathognomonic for amyloid fibril

TABLE 2 | Characteristics of AD, DS and age matched control study population used to measure serum iron, ferritin, hepcidin, and IL-6.

Characteristic	Controls *N* = 50	AD *N* = 50	DS *N* = 47	Significant *p*-value
Males, *n* (%) 25 (50%)	25 (50%)	30 (60%)	25 (53%)	
Females *n* (%)	25 (50%)	20 (4%)	22 (47%)	
Age	50 ± 27	72 ± 23	47 ± 22	
Older controls	*N* = 50, 65± 20			
Iron parameters				
Serum iron (μmol/L)	20.18 ± 5.1	15.4 ± 10.1	16.6 ± 9.9	
Serum Ferritin (μg/L)	212.67 ± 72.6	140.5 ± 231.1	133.82 ± 331.5	<0.0001
Serum Hepcidin (μg/L)	25.35 ± 26.6	36.3 ± 51.2	188.32 ± 430.9	<0.0001
Serum IL-6 (pg/ml)	66.23 ± 70.5	378.51 ± 201.89	304.03 ± 330	<0.0001

Data are expressed as number of patients (percent), mean ± SD. Probability value (p) denote difference among control, AD and DS patient groups. One-way analysis of variance (ANOVA) was used to compare age between groups and statistical analysis was measured with Mann–Whitney U test.

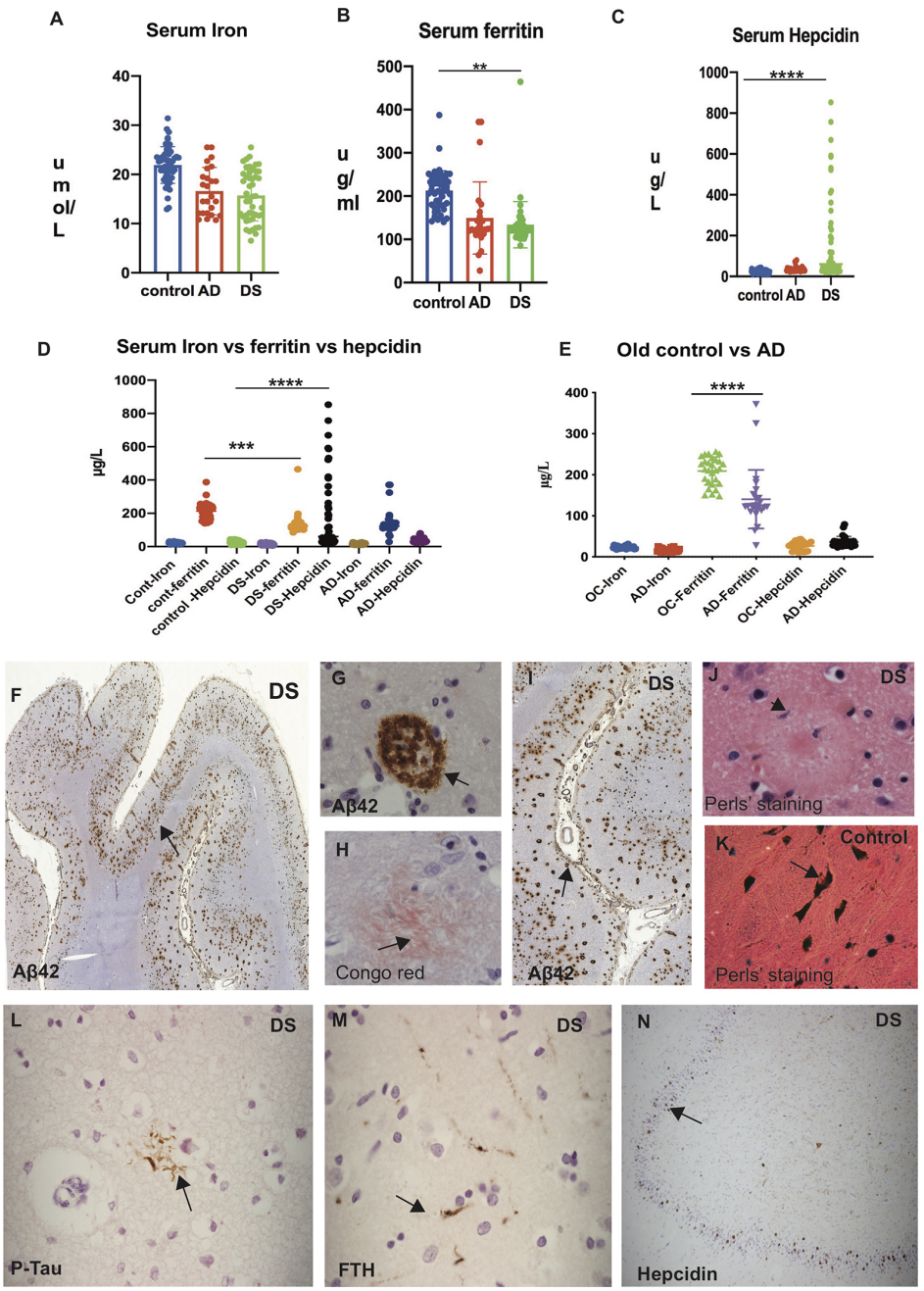

FIGURE 1 | Significant elevation of serum hepcidin in Down's syndrome (DS) subjects and iron accumulation visible in DS senile plaques. Human serum from Alzheimer's disease (AD), DS and age-matched control subjects showing iron **(A)**, ferritin **(B)**, and hepcidin (**C**; "Materials and Methods" section described in main text). Scattered plot showing levels of serum iron **(A)** and serum ferritin **(B)** significantly higher in control subjects compared to AD and DS ($p < 0.0001$). In contrast, hepcidin levels were substantially higher in DS compared to AD and controls ($p < 0.0001$; **C**). Comparison of iron, ferritin and hepcidin level showing highest hepcidin levels in DS when compared to controls and AD individuals **(D)**. Serum samples from AD and age matched older controls (OC) on comparison showed the highest ferritin levels in OC compared to AD, whereas there were no significant differences in hepcidin levels **(E)**. Statistical differences were calculated by Mann–Whitney *U* test. $^{**}p < 0.001$, $^{***}p < 0.0001$ and $^{****}p < 0.00001$. DS brain sections from superior frontal gyrus (SFG) stained with DAB and anti-Aβ42 antibody revealed strong signal of SPs positive for Aβ42 and visible throughout the cortex (**F**, black arrows highlighting the selected area of plaques formation, **(G)** in higher magnification inside the plaque formation and **(I)** close to the blood vessels. To confirm neurofibrillary (neuritic) plaque formation, a representative section was stained with Congo red **(H)** showing the amyloid proteins having apple-green birefringence under polarized light in senile plaques (SP). Perls' stain identifies the ferric (Fe3+) form of iron, showing limited ferric iron was visible albeit only in the glial cells periphery of senile plaques **(J)**, and in controls particularly seen in neuromelanin cells of substantia nigra pars compacta (SNPC) in controls **(K)**. Similarly, a section from mid temporal gyrus (MTG) was stained with phospho-tau (AT8) showing neurofibrillary tangle close to glial cells **(L)**, and some of those neuro-filaments were ferritin (FTH) positive **(M)**. In the hippocampus of DS brain section, granule cells were positive for hepcidin **(N)**. Scale bar: **(F** and **I)** = 200 µm, **(L–N)** = 50 µm, **(G,H,J,K)** = 25 µm.

deposits (**Figure 1H**). Similarly, a section from MTG was stained with phospho-tau (AT8) showing neurofibrillary tangle (NFT), close to glial cells (**Figure 1L**), and some of those neurofilaments were ferritin (FTH) positive (**Figure 1M**). In the DS hippocampus, some granule cells were positive for hepcidin (**Figure 1N**).

To confirm if iron accumulation in the brain tissues were stained with Perls stain to identify ferric form (Fe3+), we followed the procedures described in previous publications (Morris et al., 1992; Meguro et al., 2007), and compared the iron accumulation in aged normal and DS subjects (brain sections from cortex and substantia nigra pars compacta (SNPC) stained with Perls stain). In DS brain, presence of very faint ferric iron was seen around the SP (**Figure 1J**), whereas strong iron accumulation was seen in the SNPC (in neuromelanin cells; **Figure 1K**) as reported before (Morris et al., 1992; Meguro et al., 2007).

Hepcidin Protein Accumulates Around the Senile Plaques in AD and DS Brains

Brain sections from the hippocampus, entorhinal cortex and SFG were then analyzed by IF and imaged with confocal microscopy, using antibodies specific to Aβ42 (6E10) and hepcidin. Sections of AD SFG when stained for hepcidin (green) and Aβ42 (red), showed senile plaques recognized by Aβ42 and hepcidin staining was seen in the neuropil and fibrillary structures (**Figures 2A–C**). In DS brain, abundant Aβ42 positive cotton wool appearance of senile plaques (SP), close to the blood vessels were observed. In DS SFG, very limited hepcidin positive glial cells were seen in the periphery of plaques (**Figures 2D–F**). Contrastingly, in control brains (i.e., SFG), abundant hepcidin positive cells were present (**Figures 2G,H**) wherein the two proteins Aβ42 and hepcidin showed co-localization near the blood vessels, while hepcidin filaments were predominantly located in the astrocytes (**Figure 2H**).

Hepcidin and Ferritin Expression in Astrocytes Close to the Blood Vessels

As described above, hepcidin was observed in the astrocytes in the disease affected brains. We, therefore, evaluated the expression of hepcidin in sections from the MTG, sub ventricular zone (SVZ) and close to the blood vessels of cortex (SFG). In DS brain, GFAP positive activated astrocytes were present around the SP and surrounding the blood vessels (**Figures 3A,B**, indicated with an arrow or filled circle).

Hepcidin expression was visible in the periphery of blood vessels (in the endothelial cells) and co-localized with the GFAP positive astrocytes in the DS and AD brains (**Figures 3C,E,F**). In the DS and AD brain, particularly in the SVZ and near the blood vessels, a large number of small vesicles carrying hepcidin were present and co-localized with GFAP positive astrocytes (**Figures 3D,E**). Similarly, in the AD brain, astrocytes were present surrounding the blood vessels and co-localized with the ferritin light chain (FTL; **Figure 3F**). Furthermore, from the SFG section of controls, it appeared that soluble hepcidin entering from blood vessels may have been delivered *via* the red blood cells (**Figure 3G**), whereas ferritin (FTL) may have entered through the macrophages/microglia but did not co-localize with hepcidin close to the blood vessels (**Figure 3G**). In contrast, hepcidin was present in the pyramidal neurons in the hippocampus of a normal control brain and showed limited co-localization with FTL in the periphery of the neurons (**Figure 3H**).

Selective Population of Microglia and Meningeal Macrophages Are Involved in Brain Iron Homeostasis in DS

Hepcidin and ferritin could be involved in microglial activity and in the amyloid clearance process (Raha et al., 2013; Raha-Chowdhury et al., 2015). To assess this aspect, we extended our investigation of hepcidin expression in microglia and macrophages in control, AD and DS brain samples (n = 10 from each group, **Table 1**) with a particular focus on identifying hepcidin expression in the Iba1 positive microglia. The brain sections from AD, DS and controls were stained with microglial marker (Iba1) and hepcidin. In control brains, Iba1 positive ramified microglia were visible in the cortex and in the blood vessels. There was a limited co-localization with hepcidin in some cells but not with Iba1 positive microglia (**Figures 4A–C**). In the AD brain, sections from the dentate gyrus (DG), where most of the granule cells were damaged, Iba1 positive activated microglia were present close to the neurons, whereas hepcidin expression was visible only in the damaged granule cells with limited co-localization (**Figures 4D–F**). These findings indicate that there are different populations of microglia sub-types present in the human brain. To evaluate the effects of inflammatory changes in different microglia, another brain section from AD (MTG) was stained with Iba1 and pro-inflammatory marker IL-1β. Both proteins co-localized in the small plaques and activated microglia (**Figure 4G**). Similarly, a DS brain section, when stained with Iba1 and hepcidin, Iba1 positive microglia was visible close to blood vessels but there was no co-localization with hepcidin (**Figures 4H,I**).

As previously reported, the choroid plexus (CP) is damaged in AD brain and as CP is a conduit between the peripheral circulation and central nervous system *via* the cerebrospinal fluid (Raha-Chowdhury et al., 2019). We extended our investigation to CP sections from DS brain, and stained with hepcidin and CD68 (a phagocytotic macrophages/microglia marker). Hepcidin protein was present in the lateral ventricles in a monolayer of epithelial cells of the choroid plexus and CD68 was found in the macrophages close to CP and their co-localization was observed (**Figure 4J**). These findings suggest that hepcidin might be transported through exosomes or other small vesicles and *via* macrophages to the brain parenchyma. To investigate this phenomenon, another section from AD brain close to the lateral ventricle was stained with CD68 and hepcidin. A large number of CD68 positive peri-vascular macrophages were visible around the lateral wall of the 4th ventricles that co-localized with hepcidin, at the endothelial margin (**Figure 4K**).

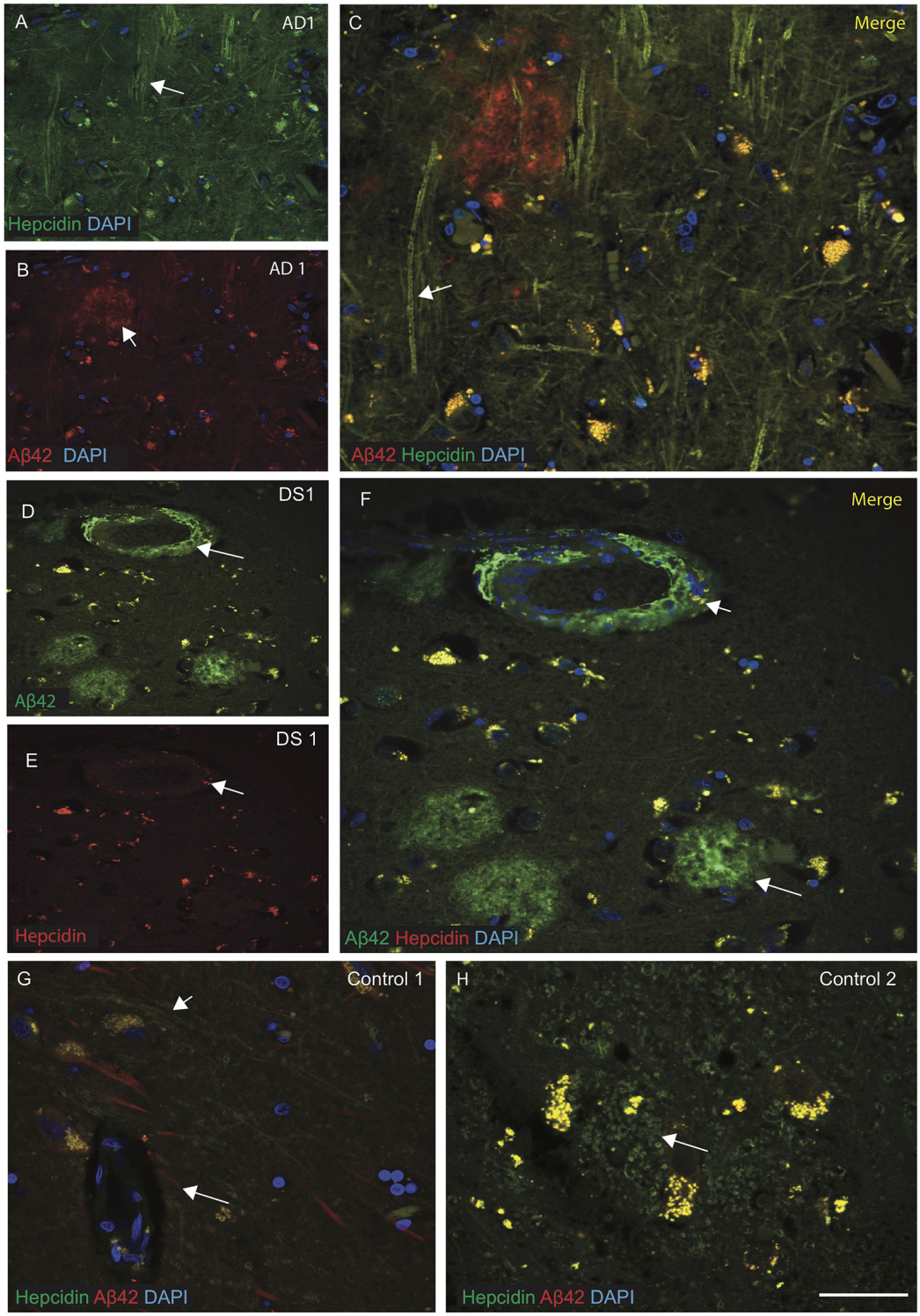

FIGURE 2 | Hepcidin protein accumulates around the senile plaques in AD and DS brains. AD and DS brain sections from the SFG were labeled with double immunofluorescence using anti-Aβ42, anti-hepcidin and counterstained with 4′6-diamidino-2-phenylindole (DAPI) for nuclei (blue) and imaged with confocal microscopy. In AD brain, hepcidin staining was visible in the neuropil and fibrillary structures close to the Aβ42 positive senile plaques (SP) **(A–C)**, white arrows highlighting the selected areas with hepcidin in neuropil and Aβ42 staining in the SP). In DS brain, abundant Aβ42 positive cotton wool appearance of SP, close to the blood vessels were observed, while very limited hepcidin positive glial cells were present in the periphery of plaques **(D–F)**. In contrast, control brains showed co-localization of Aβ42 and hepcidin near the blood vessels **(G)**, while hepcidin predominated in the astrocytes located in the periphery of the glial cells **(H)**. Scale bar: **(A–H)** = 25 μm.

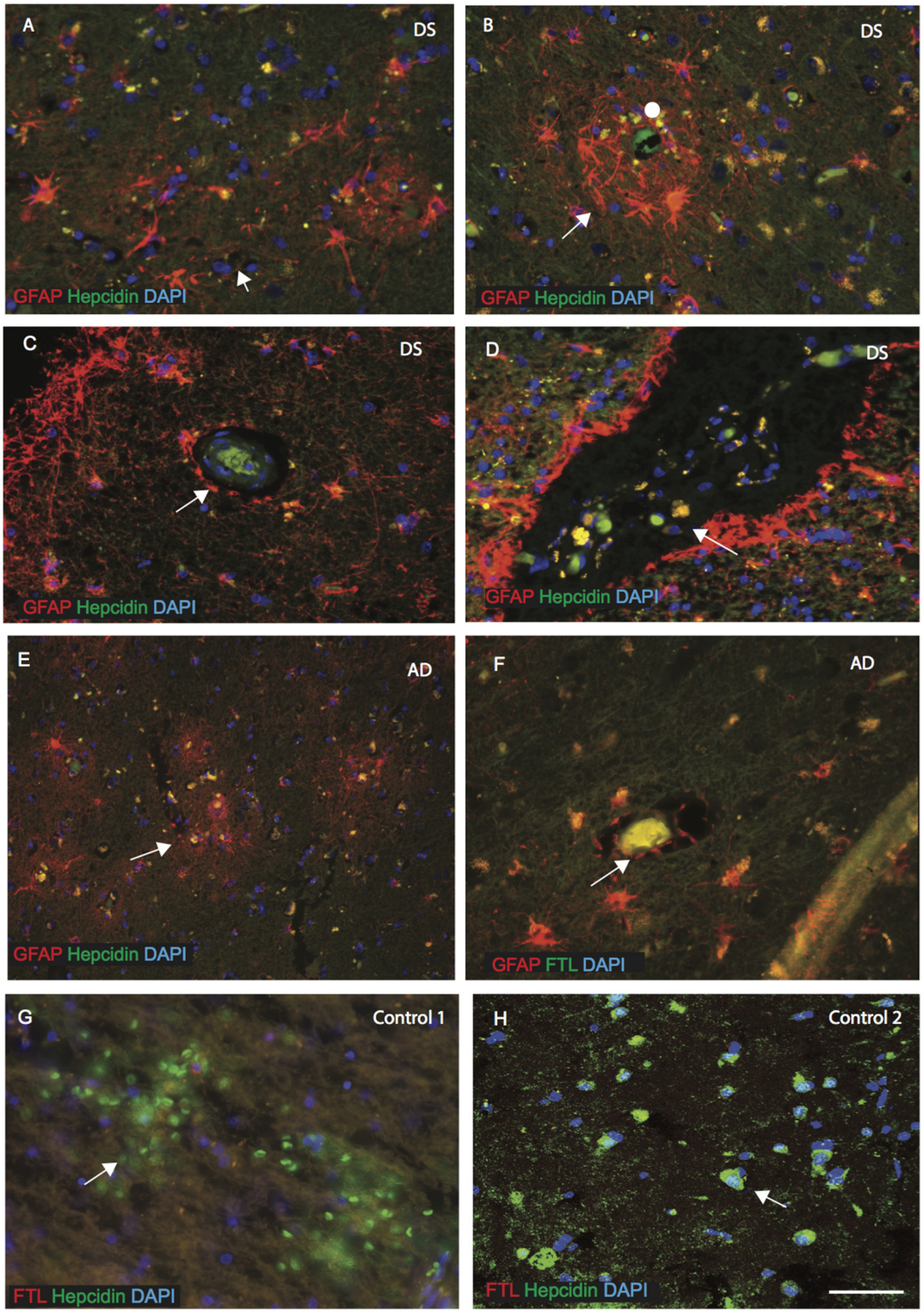

FIGURE 3 | Hepcidin and ferritin expression in astrocytes close to the blood vessels. AD and DS brain sections from the MTG, sub ventricular zone (SVZ) and close to the blood vessels of cortex (SFG) were labeled with double immunofluorescence using anti-hepcidin (green), anti-GFAP or ferritin light chain (FTL; red) and counterstained with DAPI for nuclei (blue) and imaged with confocal microscopy. In DS brain, GFAP positive activated astrocytes were present around the SP and surrounding the blood vessels (**A–B**, indicated with an arrow). Hepcidin expression was visible in the periphery of blood vessels (in the endothelial cells) **(C)**, and co-localized with the GFAP positive astrocytes in the DS and AD brains (**D,E,F**). In the DS brain, particularly in the SVZ, large numbers of small vesicles

(*Continued*)

FIGURE 3 | Continued
carrying hepcidin were present and co-localized with GFAP positive astrocytes **(D)**, and near the blood vessels in AD brain **(E)**. The end-feets of astrocytes were surrounding the blood vessels and co-localization with the FTL (green) was visible in the blood vessels **(F)**. In controls, brain section from SFG when labeled with hepcidin and FTL, both proteins were visible in different cells close to the blood vessels, hepcidin most probably in the red blood cells and FTL in the macrophages/microglia **(G)**. In contrast, control brain (in the hippocampus) showed hepcidin to be present in the pyramidal neurons, showing limited co-localization with FTL **(H)**. Scale bar: **(A–H)** = 25 μm.

Previously, we have shown in the mouse brain that macrophages are present on the pial surface (Raha et al., 2017). We further analyzed a cortical section from DS brain and stained with CD68 and hepcidin. The granular hepcidin protein was visible in the glial cells inside cortical layers I and II and CD68 was visible in the meningeal macrophages (**Figure 4L**). These data support the notion that soluble and vesicular hepcidin could be transported *via* macrophages and blood vessels into the brain parenchyma.

IL-6 Could be Involved in Host Defense in AD and DS-Brain

As we have seen, macrophages play a significant role in enabling iron to enter the plasma compartment. During infection and inflammation, IL-6 and other cytokines aid to increase the synthesis of hepcidin leading to sequestration of iron in the macrophages (Ganz, 2012). The increased levels of hepcidin in the serum described above (in **Figure 1C**), led us to measure serum IL-6 in AD, DS and controls and compare these results with serum hepcidin (**Figures 5A,B**). Serum IL-6 levels were significantly increased in AD compared to old-age-matched controls (**Figure 1B**) and in DS participants (**Figure 1A**, $p < 0.0001$). In controls, however, serum IL-6 level was lower than AD and DS subjects, suggesting that serum IL-6 could be involved in host defense mechanism in neuroinflammation (**Figures 5A,B**). We have also shown that expression levels of iron proteins (ferritin, hepcidin) are very different in the brain parenchyma compared to the periphery (in serum; Raha et al., 2013). DS brain sections were stained for Aβ42 and ferritin heavy chain (FTH). Both proteins were found to be co-localized close to the blood vessels, but FTH positive glia was only visible in the SP and did not co-localize with Aβ42 positive cells (**Figure 5C**). We had previously reported that in the rat brain, hepcidin and FPN expressed in the white matter tract (WMT) of corpus callosum (CC) and was involved in myelination (Raha-Chowdhury et al., 2015). In control brain, hepcidin protein expression was visible in the WMT (in the oligodendrocytes), whereas IL-1β was present in the microglia with minimal co-localization (**Figures 5D–F**). Brain sections from AD hippocampus (HP) and DS (SFG) when stained for hepcidin and IL-1β, revealed similarly the presence of hepcidin (punctate, vesicular appearance) in the hippocampal neurons, whereas IL-1β was visible only in the microglia with minimum co-localization (**Figures 5G,H**). Similarly, when control and DS brain sections of HP and SFG were stained for hepcidin and IL-6, there was less IL-6 visible in the control brain (**Figure 5I**), whereas there was a higher co-localization in the granule cells of HP in DS subjects (**Figures 5J–L**) suggestive of hepcidin and proinflammatory cytokines (IL-1β and IL-6) being involved in host defense during neuroinflammation.

DISCUSSION

Alzheimer's disease, Down's syndrome and age associated dementia leads to a variety of inflammatory symptoms, and disproportionately endangers people with pre-existing chronic conditions including cardiovascular disease, diabetes mellitus, hypertension, and age-related frailty (Friedland and Haribabu, 2020; Raha et al., 2020; Mukaetova-Ladinska et al., 2021). These populations are not only at a high risk for chronic infection, but also of prevalent SARS-COV-2 infection (Wright et al., 2008). Iron metabolism and anemia may additionally play an important role in multiple organ dysfunction syndrome such as that seen in SARS-COV-2 (Gómez-Pastora et al., 2020; Taneri et al., 2020).

Iron is an essential nutrient for almost all living organisms but when in excess, it is toxic and regulatory mechanisms have evolved to ensure that iron homeostasis is maintained at both the whole-body and cellular levels (Hentze et al., 2010). Ferritin, a highly conserved iron-binding protein and storage for iron, has emerged as a key molecule in the immune system, playing an important role in cellular defense against inflammation (Raha-Chowdhury et al., 1996). Iron is required for synthesis of many key enzymes, including myelin and neurotransmitter production. There are extensive interactions between the brain iron accumulation and the innate immune system in AD and other neurodegenerative diseases (Wright et al., 2008).

Hepcidin has emerged as the key regulatory molecule that controls systemic iron homeostasis in mammals (Krause et al., 2000; Park et al., 2001; Pigeon et al., 2001). Hepcidin is synthesized by the liver and regulates the delivery of iron into the circulation from macrophages, duodenal enterocytes and hepatocytes (Ganz and Nemeth, 2011). Hepcidin achieves this level of control by binding to FPN which is the only known iron exporter expressed by mammalian cells (Nemeth et al., 2004b). On binding with FPN at the cell surface, hepcidin triggers the internalization, ubiquitinoylation and lysosomal degradation of the complex thus limiting cellular iron export (Rivera et al., 2005).

Macrophages also play a key role both in iron homeostasis and in a vast range of biological activities, such as cellular development, scavenging and recycling, tissue repair and host defense (Pollard, 2009). The release of iron from macrophages into plasma, in response to systemic iron requirements, is managed *via* the interaction of hepcidin with its exporter FPN. In humans, macrophages contribute to most of the iron entering the plasma compartment. During infection and inflammation, cytokines, including IL-6, increase the hepcidin synthesis and cause iron sequestration in macrophages (Nemeth et al., 2004a). The resulting decrease in iron availability in

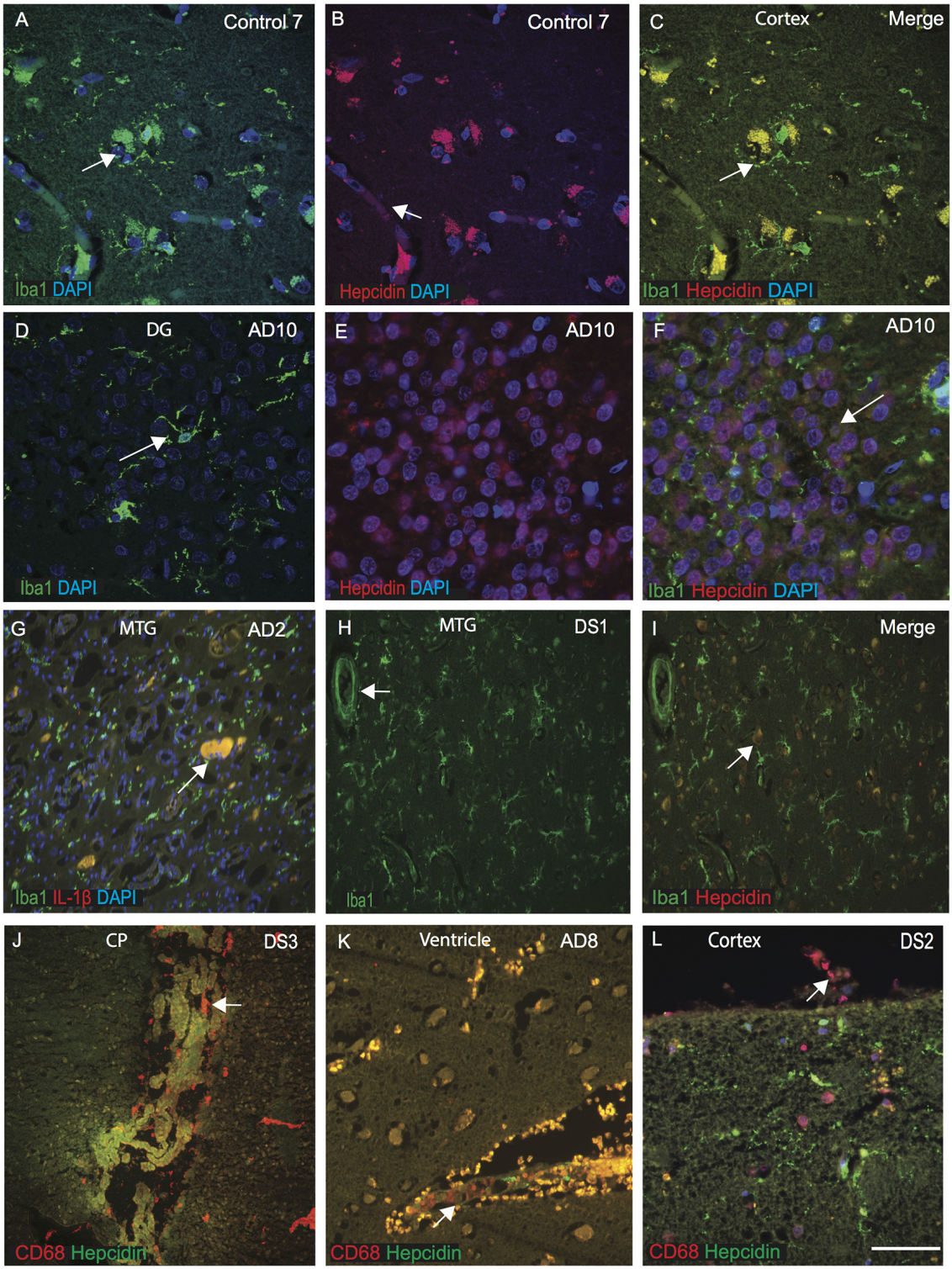

FIGURE 4 | Selective population of microglia and meningeal macrophages are involved in brain iron homeostasis in DS. The brain sections from controls, AD, and DS subjects were labeled with hepcidin and microglial marker (Iba1) or macrophages marker CD68, and counterstained with DAPI for nuclei (blue). Hepcidin was seen in the vesicles, most probably entering from blood vessels and Ibal positive ramified microglia, colocalized in the control cortex **(A–C)**. In AD brain dentate gyrus (DG), showing Ibal positive activated microglia **(D)**, whereas hepcidin was present in the DG granule cells not in the damaged microglia **(E)** with no visible co-localization **(F)**. Iba1 positive microglia may be involved in pruning and clearance of damage cells, where hepcidin protect the granule cells from further damage **(F)**. Brain section from AD (MTG) stained with Iba1 and pro-inflammatory marker IL-1β showing both proteins to be co-localized in the small plaques and activated

(*Continued*)

FIGURE 4 | Continued
microglia **(G)**. Cellular damage in this brain section was substantial **(G)**. Similarly, in DS brain section from MTG, Iba1 positive activated microglias being present close to the blood vessels **(H)**, but without any co-localization with hepcidin **(I)**. In DS brain, hepcidin protein was visible in the lateral ventricles in a monolayer of epithelial cells of the choroid plexus (CP) and CD68 was found in the macrophages close to epithelial cells of CP suggestive of involvement in transport of serum proteins from macrophages to the brain parenchyma **(J)**. AD brain tissue sections when stained with CD68 and hepcidin show a large number of CD68 positive peri-vascular macrophages visible around the lateral wall of the 4th ventricles co-localizing with hepcidin at the endothelial margin **(K)**. Similarly, a cortical section from DS labeled with CD68 and hepcidin, show granular hepcidin protein visible in the glial cells inside the cortical layers I and II and CD68 visible in the meningeal macrophages in the meninges **(L)**. These finding support the notion that soluble and vesicular hepcidin could be transport *via* macrophages and blood vessels into the brain parenchyma **(J–L)**. Scale bar: **(A–I)** = 50 μm, **(J–K)** = 70 μm, **(L)** = 20 μm.

tissues can limit the growth and pathogenic impact of invading extracellular microbes, providing an important means of host defense (Ganz, 2012).

The aim of this study was to investigate the expression of iron proteins ferritin and hepcidin, in AD and DS serum and compare these protein levels in brain parenchyma in normal and dementiarelated diseased brain and discuss these findings in relation to the reported hyperferremia in SARS-COV-2 infected patients (Dahan et al., 2020; Gómez-Pastora et al., 2020; Hippchen et al., 2020; Zhou et al., 2020). These findings may explain why people with AD and DS are at a higher risk for SARS-COV-2 infection.

We reported that serum iron and ferritin levels were significantly higher in normal controls compared to AD and DS participants. In contrast, the hepcidin levels were 20 times higher in DS than those detected in AD and controls suggesting the presence of inflammatory changes or dis-erythropoiesis affecting especially the DS subjects.

Using IHC, we analyzed brain iron and other proteins (i.e., ferritin and hepcidin) from AD subjects, and compared with our previously published work on AD brain and transgenic mouse model of AD (APP-PS1; Raha et al., 2013). In the DS brain, abundant Aβ42 positive plaques were present in the neocortex, similar to those seen in AD brain, and additionally when stained with Congo red showed the existence of fibrillary birefringence in SP, and Perls stains in glial cells, indicating the presence of iron in the SP of DS brain as previously reported (Morris et al., 1992; Howie et al., 2008). We have noted amyloid deposition within blood vessels signifying presence of cerebral amyloid angiopathy which is widely reported in almost all DS brains. We noted several meningeal vessels were positive for Aβ42 (**Figure 1I**). In **Figures 2D–F**, DS brain section stained with Aβ42 and analyzed by confocal microscope, showed amyloid expression in the blood vessel walls too. Similarly, in **Figure 3C** (hepcidin in the blood vessels) and 3F (FTL within blood vessel walls), and **Figure 1I** showed Aβ42 deposit in the blood vessels.

All DS subjects had aneuploidy, i.e., carried an extra copy of chromosomes 21, where APP gene is encoded. DS subjects do produce a much higher amount of amyloid β protein due to carrying an extra copy of APP gene, that subsequently produce excess amount of Aβ affecting its clearance from the blood vessels (Raha et al., 2013; Raha-Chowdhury et al., 2018). Our IHC analysis indicated that amyloid plaques were carrying ferritin in the core of SP, and consequently the iron accumulation could lead to increase in oxidative stress in DS subjects.

In the neocortex of AD and DS subjects, Aβ42 positive SPs were visible close to the blood vessels, while hepcidin predominated in the GFAP positive astrocytes in granular form and in the endothelial cells of blood vessels. Similarly, in AD brain, astrocytes were present surrounding the blood vessels and co-localized with FTL. These findings support the notion that astrocytes have a task in iron transport in the brain parenchyma. FTL and hepcidin may enter the brain from the periphery *via* blood vessels or could even export proteins from the brain parenchyma to the peripheral circulation.

Hepcidin and ferritin are also involved in microglial activity and the amyloid clearance process (Raha et al., 2013; Raha-Chowdhury et al., 2015). In AD brain section, Iba1 (a microglial marker) positive activated microglia were present close to the SP, whereas hepcidin expression was visible in the damaged granule cells of dentate gyrus (DG) but did not co-localize with Iba1. These findings indicate that there are different population of microglial sub-types present in the human brain and some of the Iba1 positive activated microglia are involved in pruning and clearance of dead cells, and co-localize with pro-inflammatory marker IL-1β but not with hepcidin. Our observations support previously reported notion that hepcidin also has a special role in repair and regeneration of glial cells and neural plasticity (Forostyak et al., 2020).

Previously, we have reported that the choroid plexus (CP) is damaged in AD brain, and CP is a conduit between the peripheral circulation and the central nervous system *via* the cerebrospinal fluid (Raha-Chowdhury et al., 2019). Our findings of hepcidin (present in a monolayer of cuboidal epithelial cells of the CP) and CD68 (present in the macrophages close to CP) and their colocalization, as well as their ventricular and cortical localization, support the notion that soluble and vesicular hepcidin could be transported both *via* different population of macrophages (CP, perivascular and meningeal macrophages) and *via* the blood vessels in to the brain parenchyma (Kalaria et al., 1996).

The hyperinflammatory response induced by SARS-CoV-2 through peripheral macrophages is a major cause of disease severity (Cohen et al., 2010). This population of innate immune cells sense and respond to microbial threats by producing inflammatory molecules that eliminate pathogens and promote tissue repair. A dysregulated macrophage response, however, can be damaging to the host, as seen in the macrophage activation syndrome induced by severe infections, including SARS-CoV-2 (Otsuka and Seino, 2020).

Microglia in the vicinity of the SP and NFT in AD/DS become activated and release a cocktail of inflammatory cytokines and chemokines (Akiyama et al., 2000). The persistence of infection and its impact on macrophages, microglia and astrocytes in the CNS are particularly important since a neurotropic virus can

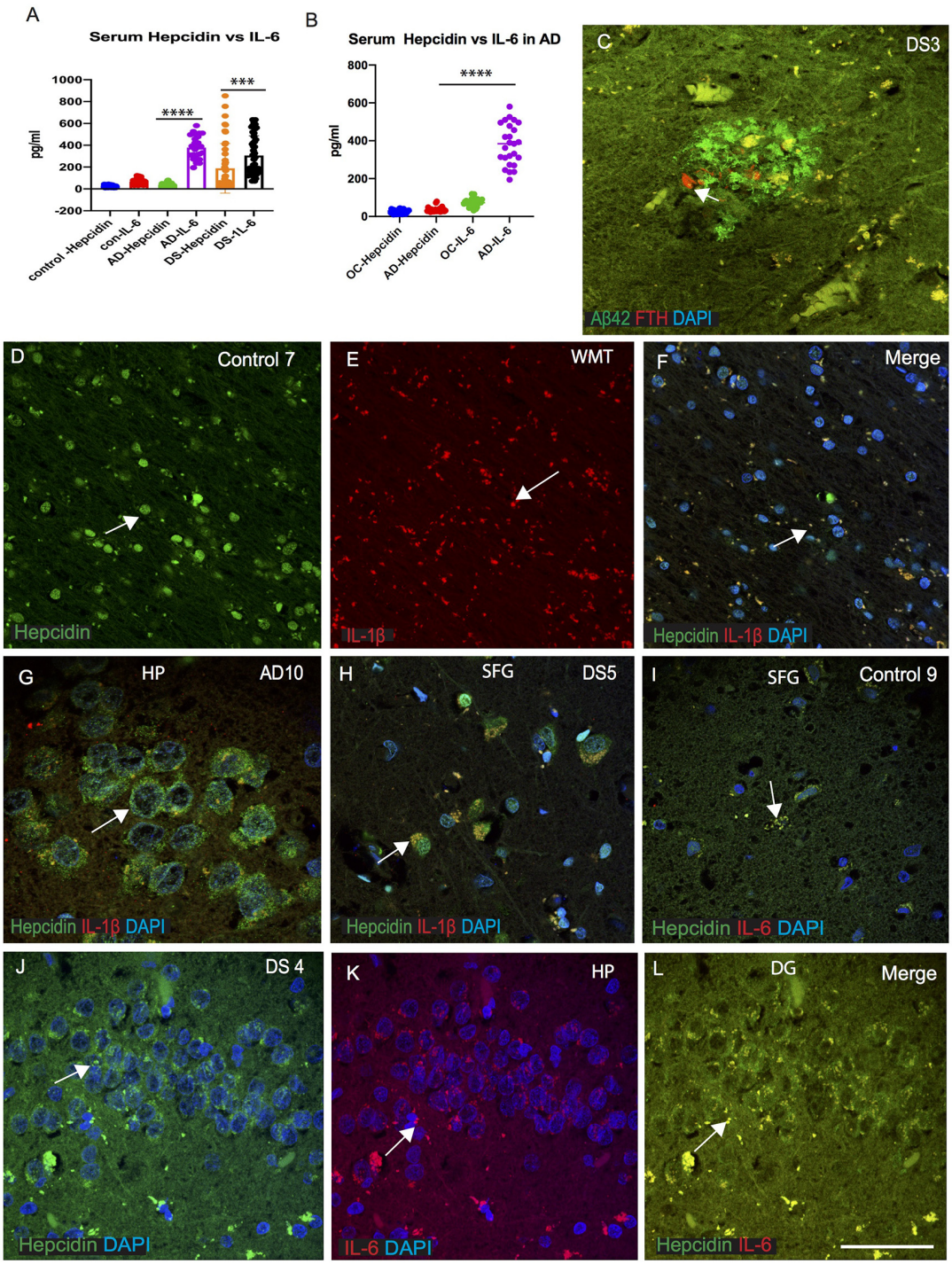

FIGURE 5 | IL-6 could be involved in host defense in AD and DS brain. ELISA based analysis of IL-6 in serum samples showing increased levels in AD and highest level in DS when compared with hepcidin ($p < 0.0001$; **A**). Samples were analyzed from AD and age matched older controls (OC), IL-6 levels were significantly higher in AD serum (**B**; $p < 0.0001$). Ferritin (FTH) was present close to a SP in DS brain analyzed by double immunofluorescence, and did not co-localize with Aβ42 positive plaques **(C)**. Another control brain section from white matter tract (WMT) of corpus callosum (CC), labeled with hepcidin, expression being visible in the WMT (in the oligodendrocytes), whereas IL-1β being present in the microglia with minimal co-localization **(D–F)**. Brain sections from AD (HP, hippocampus) and DS (SFG) when stained with hepcidin and IL-1β, revealed similarly the presence of hepcidin (punctuate, vesicular appearance) in the hippocampal neurons, whereas IL-1β was visible only in the microglia with minimum co-localization **(G,H)**. When control and DS brain sections of HP and SFG were stained for hepcidin and IL-6, there was less IL-6 visible in the control brain **(I)**, whereas there was a higher co-localization seen in the granule cells of hippocampus of DS subjects **(J–L)**. Scale bar: **(C** and **G)** = 20 μm, **(D–F)** = 50 μm, **(H–L)** = 25 μm. ***$p < 0.001$, ****$p < 0.0001$.

activate glial cells and induce a pro-inflammatory state (Kanberg et al., 2020).

Inflammation in AD and DS could further be a reason for the increase in hepcidin levels as noticed in the systemic environment. Besides the iron levels present in the circulation, inflammation is yet another factor regulating hepcidin transcription in the hepatocytes. Inflammatory cytokines, mainly in the form of IL-6, are released during inflammation and induce hepcidin expression in the hepatocytes (Pietrangelo et al., 2007; Eikelenboom et al., 2012a). IL-6, a major highly inducible pro-inflammatory cytokine, is secreted by many different cell types including monocytes, lymphocytes, fibroblasts, and endothelial cells (Zegeye et al., 2018).

Not surprisingly, we confirmed increased serum IL-6 levels in AD and DS subjects, while controls had IL-6 levels lower than that of ferritin suggesting that serum IL-6 could be involved in host defense in AD and DS. An increased serum level of IL-6 is linked to severity (Ulhaq and Soraya, 2020a) and increased fatality in SARS-COV-2 (Chan et al., 2020), as well as respiratory dysfunction (Ulhaq and Soraya, 2020b). Similar findings have now been reported using profiling plasma proteomics that not only identified IL-6 to be among the most perturbed proteins in SARS-COV-2 patients but also confirmed it as an indicator of disease severity. In addition, the rapid replication of SARS-CoV-2 triggers elevated IL-6 production that can lead to heightened respiratory distress. Therefore, IL-6 stands as a possible common biomarker for AD/DS and SARS-COV-2 (Hüll et al., 1996).

Levels of IL-1 have also been reported to have increased in AD and DS patients (Griffin et al., 1989). IL-1 has been noticed to be significantly higher in the SARS-COV-2 patients too during the disease onset as well as throughout the duration of disease progression (Cavalli et al., 2020).

Apolipoprotein E is the main carrier of cholesterol in the central nervous system (CNS) and an important constituent of very low–density lipoproteins (VLDL). Among its three alleles (ε2, ε3, and ε4), the individuals carrying the ε4 allele are at a higher risk of developing AD since the ApoE ε4/ε4 genotype increases fibrinogenesis in the brain of Alzheimer's disease patients (Hultman et al., 2013; Raha-Chowdhury et al., 2018). In our DS cohort, more than 25% subjects were carrying heterozygous ApoE ε4 allele and interestingly all such subjects had higher serum IL-6 levels (average 465.85 pg/ml) compared to the DS subjects carrying ApoE ε2/ε3 allele (average 129.93 pg/ml; Henderson et al., manuscript is in progress). Recently, ApoE ε4 has been regarded as a marker that could be indicative of increasing severity risk in SARS-COV-2 (Kuo et al., 2020). Our findings of higher inflammatory markers in ApoE ε4 carriers provide further evidence to suggest that AD and DS patients carrying the ApoE4 allele are at a heightened risk of developing SARS-COV-2 infection.

Older people are at a higher risk of falling victim to both AD dementia and SARS-COV-2 infection. Although DS subjects are usually younger than AD subjects, they suffer from accelerated ageing and neuroinflammation that itself are additional risk factors for SARS-COV-2 infection. Heightened production of reactive oxygen species (ROS), iron accumulation, exacerbated production of amyloidβ, its aggregation and consequent neurodegeneration, perturbed lifestyle modification have all been implicated in the pathogenesis of AD, and all such comorbidities also place them at a higher risk for SARS-COV-2 infection.

CONCLUSION

AD and DS subjects are likely to be both at a higher risk for SARS-COV-2 infection due to dis-balance in iron homeostasis and failure of amyloid protein clearance leading to neuro-inflammation. Macrophages plays a key role in iron homeostasis, regulating passage of iron proteins between the brain parenchyma and the peripheral circulation. Macrophages are a population of innate immune cells that sense and respond to microbial threats by producing inflammatory molecules that eliminate pathogens and promote tissue repair. DS, AD and SARS-COV-2 share common links with respect to iron proteins, hepcidin, ferritin and pro-inflammatory markers such as interleukin-1 (IL-1β), IL-6, and ApoE ε4 allele. Hepcidin, ferritin and IL-6 participate significantly towards host defense mechanism associated with neuroinflammation. Such mechanisms could well be implicated in SARS-CoV-2 infection and objective evaluation of perturbed iron homeostasis may be indicative of how severely someone may be infected by SARS-CoV-2.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics plus research and development (R&D) and approvals were granted by the National Research Ethics Committee of the East of England—Norfolk and Cambridgeshire and Peterborough NHS Foundation Trust, respectively. Cambridge Health Authorities Joint Ethics Committee granted ethical approval for the use of human brain tissue and serum samples (Project ref no.: REC:15/WM/0379). Written consents were obtained from controls, adults DS participants and subjects with Alzheimer's disease (AD) with the capacity to consent. Verbal assent was obtained from participants with AD and DS, who lacking capacity to provide written assent, and this was provided instead by an appointed consolutee, in accordance with the Mental Capacity Act of the UK (2005). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR and JH performed biochemical analysis. SC critically evaluated the results and edited the manuscript. AR and SG performed tissue analysis and confocal microscopy. SZ,

AH and RF evaluated clinical findings. EM-L evaluated clinical samples and edited the manuscript. KA selected the brain samples and preliminary assessment of disease status. RR-C and AR contributed to the hypothesis development, analyzed the results and edited the manuscript. RR-C performed study design, supervised the project, critically evaluated the results and wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by Medical Research Council (MRC grant number RNAG/254), National Institute of Health Research (NIHR), Alzheimer's Research UK (ARUK), the Down's Syndrome Association, The John Van Geest Foundation, the Health Foundation and Cambridgeshire and Peterborough Foundation NHS Trust, Cambridge, UK.

ACKNOWLEDGMENTS

AR and RR-C would like to thank to Dr. Adrian Bomford for his encouragement and critically discussing brain iron homeostasis, to Professor Rajesh N. Kalaria for his support and critically discussing cerebral amyloid angiopathy in DS subjects, to Dr. Michael Hollinshead for help and support for confocal microscopy, Cambridge Brain Bank [which is supported by the National Institute for Health Research (NIHR) and Cambridge Biomedical Research Centre] for providing human brain sections. We are very grateful for the support of people with DS, AD and that of their family members.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

REVIEW
published: 03 June 2021
doi: 10.3389/fnagi.2021.662786

COVID-19, Neuropathology, and Aging: SARS-CoV-2 Neurological Infection, Mechanism, and Associated Complications

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Received: *01 February 2021*
Accepted: *05 May 2021*
Published: *03 June 2021*

Citation:
Kalra RS, Dhanjal JK, Meena AS, Kalel VC, Dahiya S, Singh B, Dewanjee S and Kandimalla R (2021) COVID-19, Neuropathology, and Aging: SARS-CoV-2 Neurological Infection, Mechanism, and Associated Complications. Front. Aging Neurosci. 13:662786. doi: 10.3389/fnagi.2021.662786

The spectrum of health complications instigated by coronavirus disease 2019 (COVID-19, caused by the novel severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) pandemic has been diverse and complex. Besides the evident pulmonary and cardiovascular threats, accumulating clinical data points to several neurological complications, which are more common in elderly COVID-19 patients. Recent pieces of evidence have marked events of neuro infection and neuroinvasion, producing several neurological complications in COVID-19 patients; however, a systematic understanding of neuro-pathophysiology and manifested neurological complications, more specifically in elderly COVID-19 patients is largely elusive. Since the elderly population gradually develops neurological disorders with aging, COVID-19 inevitably poses a higher risk of neurological manifestations to the aged patients. In this report, we reviewed SARS-CoV-2 infection and its role in neurological manifestations with an emphasis on the elderly population. We reviewed neuropathological events including neuroinfection, neuroinvasion, and their underlying mechanisms affecting neuromuscular, central- and peripheral- nervous systems. We further assessed the imminent neurological challenges in the COVID-19 exposed population, post-SARS-CoV-2-infection. Given the present state of clinical preparedness, the emerging role of AI and machine learning was also discussed concerning COVID-19 diagnostics and its management. Taken together, the present review summarizes neurological outcomes of SARS-CoV-2 infection and associated complications, specifically in elderly patients, and underlines the need for their clinical management in advance.

Keywords: COVID-19, SARS-CoV-2, neuropathology, aging, neuroinvasion, neuroinfection, pandemic, neurodegenerative disease

INTRODUCTION

Primary physio-pathological evidence of Coronavirus Disease 2019 (COVID-19) exhibited severe respiratory and cardiovascular complications in the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients. Emerging reports lately revealed that SARS-CoV-2 infection develops a range of neurological complications (COVIDview, 2020). These complications are produced either by the direct contact of SARS-CoV-2 with the nervous system or by an indirect impact of immune-response during- or post-infection (Ellul et al., 2020). As an estimate, ∼35.6% of total COVID-19 cases were found to exhibit multiple neurologic manifestations (Tsai et al., 2020). Although neurological consequences of these events are evident across all age groups, yet, elderly COVID-19 patients remain at remarkably high risk (COVIDview, 2020). An acute phase of direct SARS-CoV-2 infection could produce immediate neurological complications, however, a secondary phase might take months to surface after the infection (Beghi et al., 2020). Multiple nervous tissue/cell types including macrophages, microglia, or astrocytes are invaded by coronaviruses that can cause direct damage to the nerves (Beghi et al., 2020; Wu et al., 2020). Recent reports also underlined evidence of neurotoxicity primarily caused by immune injury, hypoxia-induced injury, and angiotensin-converting enzyme 2 (ACE2, a SARS-CoV-2 host receptor) binding (Beghi et al., 2020; Wu et al., 2020). A recent systematic review analyzed the neuropathological features in patients who have died post-SARS-CoV-2 infection and it revealed that the majority of these patients were elderly (n = 66, 45%) and males (n = 79, 54%; Pajo et al., 2021). The striking neuropathological features they exhibited include diffuse edema (17%), gliosis (having diffuse microglia and astrocytes activation, 35.6%), cortical and subcortical regional infarctions in the brain (2.7%), intracranial (subarachnoid and punctate) hemorrhage (12.4%), arteriosclerosis (29.5%), hypoxic-ischemic injury (28.1%), and inflammation (35.6%). These observed features were suggested to be caused by direct cytopathic and indirect effects derived from host-specific inflammatory response post-SARS-CoV-2 infection (Pajo et al., 2021). These events greatly contribute to the development of neuro-pathophysiological symptoms in elderly COVID-19 patients. Although the long–term neurological complications in individuals who had COVID-19 are still unknown, similar viral infections were shown to exhibit neurological complications after months or years of infection by developing neuropsychiatric and cognitive impairment (Troyer et al., 2020).

The olfactory tract is a preferred route of coronavirus infection to the brain at an early stage, whereas evidence of brain invasion through systemic circulation is scarce (Wu et al., 2020). The common neurological complications resulting from direct infection are found to be encephalitis, myelitis, meningitis, and inflammatory central nervous system (CNS) vasculitis; whereas, immune-related CNS, peripheral nervous system (PNS) diseases, and the Guillain-Barré syndrome (GBS) emerged as the major post-infection complications (Beghi et al., 2020; Ellul et al., 2020). By an estimate, 20% of the COVID-19 patients with ICU admittance had neurological complications and faced a high risk of mortality (Fotuhi et al., 2020). Of note, in elderly patients, SARS-CoV-2 instigated neurologic and immunologic complications that have produced severe consequences leading to neurodegenerative diseases (Lennon, 2020; Pavel et al., 2020). Taken together, in the present report we comprehensively reviewed the SARS-CoV-2 routes, neuro-infection or -invasion mechanism(s), their emergent and post-infection neurological manifestations, with a special focus on the elderly patients. We have also shed light on the emerging artificial intelligence (AI) and machine learning diagnostic applications for COVID-19 patients.

SARS-COV-2 MANIFESTED NEUROLOGICAL COMPLICATIONS

An early clinical case series from Wuhan, China revealed a significant relevance of SARS-CoV-2 infection with developing neurologic complications (Mao et al., 2020). It was estimated that out of 214 COVID-19 patients, 36.4% developed neurologic complications including CNS manifestations (dizziness, headache, acute cerebrovascular disease, diminished consciousness, ataxia, and seizures), PNS manifestations (sensory ailments and neuralgia), and neuromuscular injury (Mao et al., 2020; **Figure 1**). A retrospective report from Wuhan showed that 5% of a total of 221 COVID-19 patients had incidences of acute ischemic stroke (Guan et al., 2020). A similar retrospective report from Wuhan revealed that 20% of 113 COVID-19 patients suffered from hypoxic encephalopathy (Chen et al., 2020a).

To assess neurological complications in elderly COVID-19 patients, a cross-hospital nationwide investigation in the UK comprising 125 COVID-19 patients (avg. age 71 years) analyzed clinical data for neurological and psychiatric manifestations and revealed that 62% of the patients suffered from cerebrovascular events, among which 74% were reported with ischemic stroke, 23% developed unspecified encephalopathy and 1% acquired CNS vasculitis (Varatharaj et al., 2020). Noticeably, among the total patients, 31% developed altered mental complications—encephalitis (18%) and intracerebral hemorrhage (12%; Varatharaj et al., 2020). The remaining 59% of the patients met the clinical case definitions of psychiatric diagnoses, among which 43% possessed new-onset psychosis, 26% acquired neurocognitive syndrome, and 17% exhibited an affective disorder (Varatharaj et al., 2020). Of note, 82% of total enrolled COVID-19 patients having cerebrovascular events were aged more than 60 years, which is suggesting that elderly patients are at high risk for COVID-19 associated neurological complications advancing to greater lethality. A retrospective meta-analysis enrolling 1,558 COVID-19 patients from a total of six studies revealed that cerebrovascular disease is a potential risk factor (Wang et al., 2020a). A multi-centric report involving 184 COVID-19 patients admitted to ICU in three Dutch hospitals showed a considerably high (31%) risk of thrombotic complications, while the death of 23 patients among these underlined the severity of such complications (Klok et al., 2020). A multi-centric retrospective study from Chicago, USA, further corroborated the fact that neurological

manifestation is a major risk factor in hospitalized COVID-19 patients (Liotta et al., 2020). In this study, among the 509 COVID-19 patients, neurological manifestations were revealed at onset (42.2%), hospitalization (62.7%), and other stages of COVID-19 disease (82.3%; Liotta et al., 2020). Another multi-centric retrospective study of SARS-CoV-2 infected hospitalized patients in New York City assessed the prevalence of neurologic disorders, also it analyzed in-hospital mortality and compared manifested features between COVID-19 patients with and without neurologic disorders (Frontera et al., 2021). It strikingly revealed that 13.5% of patients developed a new neurologic disorder in 2 days median time from the onset of COVID-19 symptoms. It included toxic/metabolic encephalopathy (6.8%), stroke (1.9%), seizure (1.6%), and hypoxic/ischemic injuries (1.4%), though no patient had meningitis/encephalitis or myelopathy/myelitis due to SARS-CoV-2 infection (Frontera et al., 2021). Of note, neurologic disorders were more common in aged patients, wherein the male, white, diabetic, hypertensive, intubated population was vulnerable (all $p < 0.05$) and faced an increased risk of in-hospital mortality and lesser recovery. This survey suggested that observed neurologic features may be sequelae of severe systemic illness (Frontera et al., 2021).

The neurologic manifestations i.e., myalgias, headaches, dizziness, dysgeusia, and anosmia, of all encephalopathies were found to be associated with poor health outcomes in admitted patients, irrespective of COVID-19 severity (Liotta et al., 2020; **Figure 1**). In the line, a 2-centric retrospective study from Spain also affirmed that neurological manifestations were frequent in admitted 841 COVID-19 patients (Romero-Sanchez et al., 2020). Montalvan et al. (2020) confirmed it further by systematically reviewing a total of 67 studies, wherein they found that risk of encephalitis, neuropathy, demyelination, and stroke are associated with COVID-19 (Montalvan et al., 2020). Providing insights on the SARS-CoV-2 infection route to the nerve tissue, it was revealed that the virus invasion occurs through the lamina cribrosa or olfactory tract and disperses through the trans-synaptic transfer (Montalvan et al., 2020). Furthermore, another systematic review assessed a greater risk of secondary neurologic complications in hospitalized COVID-19 patients (Herman et al., 2020); while, another estimate claimed that 1 out of 3 COVID-19 patients could acquire an altered mental state (Belluck, 2020).

SARS-CoV-2 manifested complications that include the CNS, PNS, and neuromuscular system, range from mild to severe, and can also appear in patients with asymptomatic SARS-CoV-2 infection. SARS-CoV-2 infects the host by establishing the binding of its spike (S) glycoproteins to the host ACE2 receptor that expresses in the brain, gastrointestinal tract (GI), respiratory tract, lung parenchyma, and endothelial cells, and therefore it serves as a potential target for the direct COVID-19 inhibitory regimens (Kalra et al., 2021) or indirect suppressive strategies including miRNAs (Li et al., 2018). The most common symptoms associated with SARS-CoV-2 are dry cough, fever, and lethargy; however, aged adults are more susceptible to severe infection involving shortness of breath, pneumonia, and acute respiratory distress syndrome (ARDS) leading to higher mortality incidence (**Table 1**). A natural decline in ACE2 levels, elevated angiotensin signaling, and subsequently chronic low-grade inflammation that develops with advanced age, termed inflammaging, might contribute to the severity and comorbid diabetic and cardiovascular complications in aged individuals (Alghatrif et al., 2020; Kalra et al., 2020). SARS-CoV-2 is a neuro-invasive and neurotrophic virus. Studies implicated that neurological manifestations are primarily associated with the severity of SARS-CoV-2 infection, which involves loss of taste, smell, consciousness, vision, seizures, neuralgia, and lack of coordination (Mao et al., 2020). SARS-CoV-2 can enter the CNS through the olfactory lobe and hematogenous route (**Figure 2**). A gradual decline of the blood-brain barrier (BBB) is associated with normal aging, which may enhance the effect of SARS-CoV-2 in aged individuals (Montagne et al., 2015). SARS-CoV-2 causes neurodegeneration, demyelination, and cellular senescence upon entry; all of these potentiate brain aging and aggravate the underlying pathophysiology of neurodegeneration (Lennon, 2020; Montalvan et al., 2020; Palao et al., 2020; Pavel et al., 2020).

At the beginning stage of infection, patients with the COVID-19 focus on managing cough, dyspnea, fever, and breathing complications. However, it is evident from studies that it gradually led to an increase in neurological complications, such as stroke, seizures, anosmia, encephalopathy, and paralysis (Li et al., 2020b; Mao et al., 2020). In 2002 and 2013, during the epidemics of SARS-CoV-1 and Middle East Respiratory Virus (MERS) respectively, the virus caused a detrimental effect in multiple organs, including the brains, nerves, and neuromuscular tissues. SARS-CoV-2, shares homology with SARS-CoV-1 and MERS and therefore emerges as an essential player in causing CNS and PNS injury, either direct or indirect (Nath, 2020; Wu et al., 2020). Neurological abnormalities have been documented in the patients who required hospitalization for COVID-19, respiratory illness, and acute respiratory distress syndrome (ARDS; Helms et al., 2020; Mao et al., 2020). In a clinical case series, neurological symptoms are restricted to general conditions such as headache, loss of smell and taste, dizziness, and malaise in mild conditions, which are routinely observed with viral infection (Mao et al., 2020). Among 1,420 mild-to-moderately infected COVID-19 patients, 70% of the patients experienced headache, which is a prominent neurological manifestation. Noticeably, severe neurological complications can be seen in mild-infected COVID-19 patients in the multiple clinical reports, while patients with pre-existing comorbidities had severe complications resulting in significantly high mortality (Iadecola et al., 2020; Merkler et al., 2020; Oxley et al., 2020; Yaghi et al., 2020; **Table 1**).

Central Nervous System (CNS) Manifestations

Symptoms related to mental status such as confusion, tiredness, and agitation, collectively known as encephalopathy, have been described in the COVID-19 in few clinical reports (**Table 1**). Diagnostic criteria for detecting encephalitis have been established and include fever, seizures, focal brain abnormalities, disturbed mental status, and white blood cells in the lymphatic-cerebrospinal fluid (CSF; Venkatesan et al., 2013). In the clinical

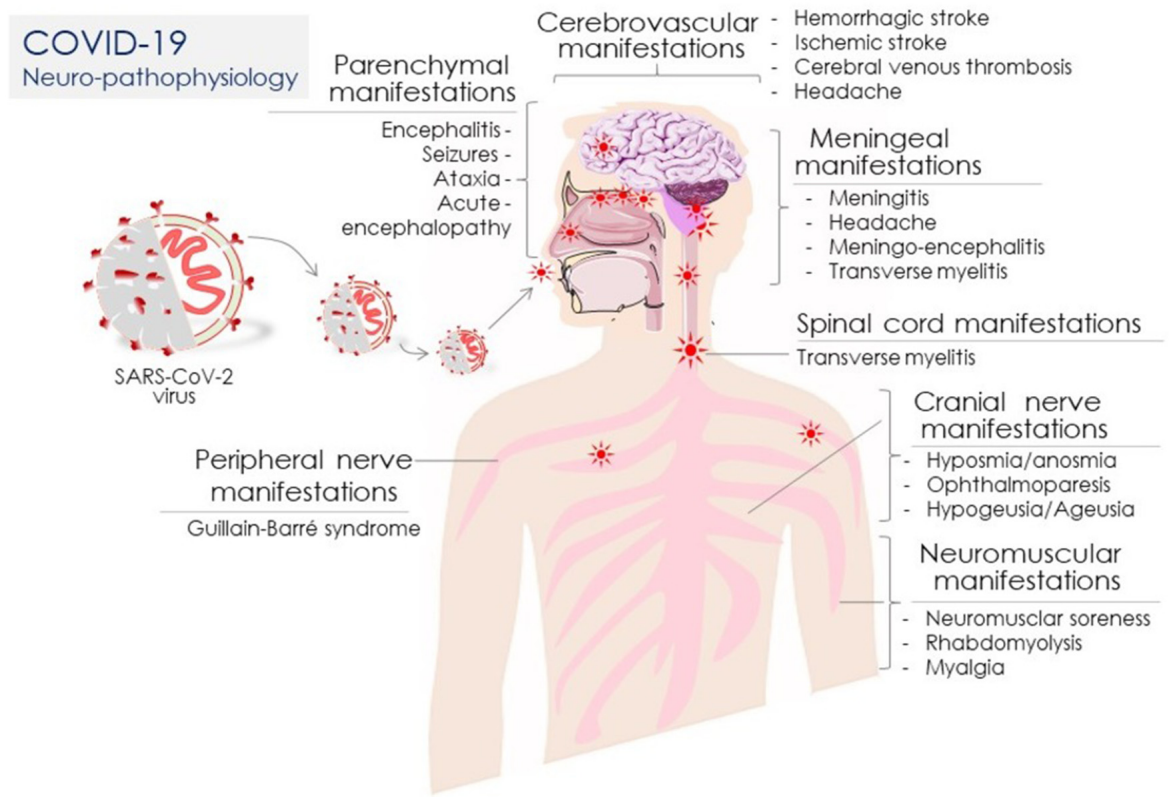

FIGURE 1 | Coronavirus disease 2019 (COVID-19) neuro-pathophysiology: COVID-19 clinical manifestations associated with diverse neuronal systems/organs including the peripheral nerve, parenchymal, cerebrovascular, meningeal, spinal cord, neuromuscular, and cranial nerve in SARS-CoV-2-infected patients.

case series, the cognitive level was primarily affected in most critically ill COVID-19 patients with ARDS (Helms et al., 2020) compared to COVID-19 patients with only respiratory illness (Mao et al., 2020). It is unclear whether the alteration in mental status is due to encephalitis caused by systemic disease or directly caused by SARS-CoV-2 infection. However, several reports suggest that COVID-19 patients exhibited well-established diagnostic markers for encephalitis (Efe et al., 2020; Farhadian et al., 2020; Huang et al., 2020a; Pilotto et al., 2021). In the very first reported case of meningitis/encephalitis associated with COVID-19, Moriguchi et al. (2020) observed SARS-CoV-2 level in the CSF but found only a modest amount of viral RNA load. In another case study, a biopsy from COVID-19 patient showed neuronal loss due to hypoxia and perivascular lymphocyte infiltration confirming temporal lobe encephalitis (Efe et al., 2020). However, Efe et al. (2020) did not detect SARS-CoV-2 in the brain or CSF. Brain tissue samples from autopsies of COVID-19 patients negative for evidence of encephalitis and CSF samples from COVID-19 patients with neurological abnormalities have not revealed evidence of SARS-CoV-2 (Kandemirli et al., 2020). Other significant mental status indicators such as confusion, delirium, and coma may be common symptoms in COVID-19 patients. These indicators are frequently associated with hypotension, kidney disease, usage of sedatives, hypoxia, and prolonged bedridden and isolation conditions—all these factors are significant contributors to the progression of encephalopathy (Helms et al., 2020; Mao et al., 2020; Martin-Jimenez et al., 2020; Maas et al., 2021; Rogers et al., 2021). Although SARS-CoV-2 affects all ages, adults aged 65 and older are at higher risk of severe disease, hospitalization, ICU use, and death. Geriatric age patients are prone to loss of consciousness, disorientation, and other cognitive disturbances. Delirium is a common symptom of older people with COVID-19 during hospitalization. Despite the lack of clinical data and histopathological evidence of encephalitis and occurrence of other alternative events impacting mental status, these data so far hint that the potential invasion of SARS-CoV-2 in the brain may be the sporadic cause of encephalopathy.

In retrospective clinical studies, 11 patients out of 221 showed acute ischemic stroke, along with one patient who developed cerebral venous thrombosis and cerebral hemorrhage. The majority of these patients were elderly and were suffering from severe COVID-19 along with common comorbidities (Li et al., 2020b). A small clinical case study from the UK, comprising six severely affected patients showed cerebral infarcts and elevated D-dimer levels, suggesting a coagulopathy (Beyrouti et al., 2020). In another small case study of five young patients, COVID-19

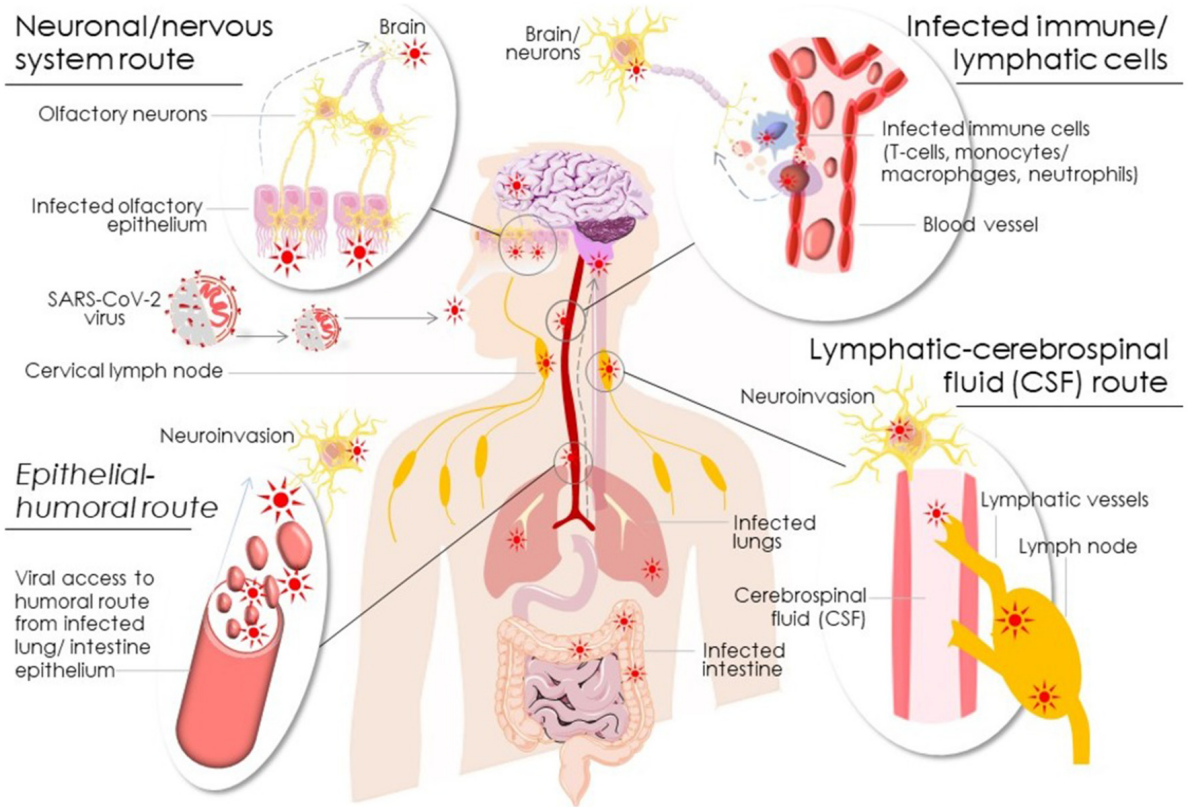

FIGURE 2 | Schematic diagram showing potential modes of SARS-CoV-2 neuroinfection *via* neuronal/nervous, epithelial-humoral, infected immune/lymphatic, and lymphatic-cerebrospinal fluid routes.

related strokes were shown to cause large-vessel infarct (Oxley et al., 2020). Al Saiegh et al. (2020) in a small case report, could not demonstrate the presence of SARS-CoV-2 in the CSF of aged patients that had an ischaemic stroke. Hypoxia, produced by lack of oxygen, increases stroke incidence due to impairment in sleep structure, increases blood pressure, atherosclerosis, promotes micro thrombosis, and decreases the blood flow (Lee et al., 2019). In a case series, Mao et al. (2020) showed that six hospitalized COVID-19 patients exhibited acute cerebrovascular disease, among these, five had a severe infection (5/88) and one was in non-severe condition (1/125). The symptoms of hypoxia are coupled with COVID-19, and it was predicted to be a consequence of S-protein's interaction with hemoglobin (Agrawal et al., 2021); therefore, it was believed to potentiate the patient's necessity for ventilator support. Of note, in a single-centric case series, the COVID-19 patients admitted to ICU were relatively old, and they had a more significant number of comorbid conditions, such as diabetes, cardiovascular complication, hypertension, and cerebrovascular disease, in comparison to those who did not require ICU (Wang et al., 2020b). The findings of this clinical case series imply that aging and comorbidities may be risk factors for poor neurological and survival outcomes (Wang et al., 2020a; **Table 1**). Seizure is a rare symptom in the COVID-19 setting. Reports involving a retrospective multi-centric study and a case series could not observe stroke in COVID-19 patients despite metabolic alteration (Lu et al., 2020; Mao et al., 2020).

Peripheral Nervous System (PNS) Manifestations

Moein et al. (2020) in the earliest analysis derived from a cohort of 100 COVID-19 patients showed that loss of smell sensation (anosmia) and taste sensation (ageusia) is the most common neurological manifestation of COVID-19, even in mild to moderate cases. Smell sensation is more affected compared to the taste sensation. Emerging evidence suggests that SARS-CoV-2 can enter the neuronal cells through the olfactory nerve and spreads to the olfactory bulb (**Figure 2**). Lechien and colleagues in a multi-centric European study and a case report showed that 86% and 88% of COVID-19 patients respectively, reported the loss of smell and taste (Lechien et al., 2020a,b). Cranial neuropathy is an erratic event in the setting of COVID-19; however, one case study involving a 40-year-old female COVID-19 patient showed isolated oculomotor nerve palsy in severely ill patients, which could be due to inflammatory reaction against SARS-CoV-2 (Wei et al., 2020). COVID-19 can cause detrimental effects

TABLE 1 | Summary of common peripheral nervous system (PNS), central nervous system (CNS), cerebrovascular, and intracerebral neurological complications in elderly Coronavirus disease 2019 (COVID-19) patients.

Neurological complications	Manifestations	Investigation/Region/ Study type	Clinical features/Symptoms	COVID-19 Diagnostics	Neurological investigation (CSF scans, neuroimaging, neurophysiology)
CNS disease	Encephalitis	Sohal and Mansur (2020); 1 case, USA, Case report.	72-year-old male patient. Weakness and lightheadedness. Altered mental status; Seizures (On day 2 post-hospitalization).	RT-PCR + ve	Head CT: no acute changes. 24-h EEG: six left temporal seizures and left temporal sharp waves that were epileptogenic.
		Paniz-Mondolfi et al. (2020); 1 case, USA, Case report.	74-year-old male patient. History of Parkinson's disease. Fever, confusion, and agitation.	RT-PCR + ve (nasopharyngeal)	Head CT: no acute changes.
		Zhou et al. (2020b); 1 case, China, Case report.	56-year-old patient. SARS-CoV-2 infection and pneumonia.	SARS-CoV2 + ve (CSF sequencing)	NR
	Acute disseminated encephalomyelitis	Zanin et al. (2020); 1 case, Italy, Case report.	54-year-old female patient. Agitation, decreased consciousness, and seizures after many days of ageusia and anosmia.	RT-PCR + ve	CSF: normal; Brain and spine MRI: periventricular confluent white matter lesions. Numerous cord lesions from (bulbomedullary junction to T6 level).
	Myelitis	Zhao et al. (2020b); 1 case, China, Case report.	66-year-old male patient. Fever, dyspnoea, and asthma. Developed acute flaccid paralysis of lower limbs (5 days after the beginning of respiratory symptom). Urinary and fecal incontinence. Sensory level at T10.	RT-PCR + ve (nasopharyngeal)	Brain CT: lacunar infarcts; spinal imaging not done
PNS disease	Guillain-Barré syndrome	Camdessanche et al. (2020); 1 case, France, Case report.	64-year-old male patient. Developed paraesthesia and progressive weakness in all limbs. Areflexia and loss of vibration sense. Later developed dysphagia and respiratory insufficiency.	RT-PCR + ve (nasopharyngeal)	CSF: normal. Nerve conduction and electromyography: acute inflammatory demyelinating polyneuropathy.
		Zhao et al. (2020b); 1 case, China, Case report.	61-year-old female patient. Progressive weakness of limbs and severe fatigue. Areflexia in lower limbs and reduced sensation distally. Dry cough and fever (after 7 days).	RT-PCR + ve (oropharyngeal)	CSF: normal. Nerve conduction study: acute inflammatory demyelinating polyneuropathy.
GBS variants and other neuropathies	Miller-Fisher Syndrome	Gutierrez-Ortiz et al. (2020); 1 case, Spain, Case report.	64-year-old male patient. Cough, fever, malaise, anosmia, headache, and ageusia. Developed right inter-nuclear opthalmoparesis with right fascicular oculomotor palsy, ataxia, and areflexia.	RT-PCR + ve(oropharyngeal)	CSF: normal. Brain CT with contrast: normal.
	Ophthalmoplegia	Dinkin et al. (2020); 1 in USA, Case report.	71-year-old female patient. Had isolated ophthalmoplegia (post-few days of cough and fever; right abducens palsy).	RT-PCR + ve (nasal)	CSF: normal opening pressure; brain MRI: enhancement of the optic nerve sheaths and posterior Tenon capsules.

(Continued)

TABLE 1 | Continued

Neurological complications	Manifestations	Investigation/Region/ Study type	Clinical features/Symptoms	COVID-19 Diagnostics	Neurological investigation (CSF scans, neuroimaging, neurophysiology)
	Rhabdomyolysis	Jin and Tong (2020); 1 case of rhabdomyolysis, China, Case report.	60-year-old male patient. Weakness and tenderness in lower limbs (15 days after beginning of fever and cough).	RT-PCR + ve (throat swab)	NR
Cerebrovascular disease	Ischaemic stroke	Avula et al. (2020); 4cases, USA, Case series.	4 patients (73–88 years old). Had hypertension; 3 had dyslipidaemia, 1 diabetes and neuropathy. 3 patients exhibited acute new focal neurological deficit and 1 showed altered mental status.	All RT-PCR + ve	All 4 had unifocal infarcts: 3 on CT, 1 on brain MRI.
		Beyrouti et al. (2020); 6 cases, UK, Case report.	6 patients (53–83 years old. 5 male and 1 female). 3 had hypertension, 2 ischemic heart disease, 2 atrial fibrillations, 1 had previous stroke, and 1 was a heavy smoker and alcohol drinker. All had respiratory symptoms (at avg. 13 days) before or after neurological symptom onset.	All RT-PCR + ve	Scans (CT and brain MRI) showed unifocal infarcts in 4 patients. 1 had bilateral infarcts on a follow-up brain MRI; 2 had bilateral infarcts on initial scans.
		Li et al. (2020a); 11 cases, China, Single-center, retrospective study.	11 patients (57–91 years old; 6 female and 5 male). 9 had hypertension, 6 diabetes, 3 cardiovascular disease. All had respiratory symptoms (at avg. 11 days) before neurological symptoms onset.	All RT-PCR + ve	NR
		Morassi et al. (2020); 4 cases, Italy, Case series.	4 patients (64–82 years old). 3 had hypertension, 2 had a previous stroke or transient ischemic condition and aortic valve disease, and 1 was a smoker with a previous myocardial infarction. 3 developed neurological manifestations during hospitalization, 1 exhibited episodes of transient loss of consciousness.	All RT-PCR + ve (nasopharyngeal)	1 patient had CSF: normal leukocyte count, protein, and IgG index. All had multifocal infarcts on brain CT or MRI; the patient presenting with transient loss of consciousness and ensuing confusion.
	Intracerebral hemorrhage	Morassi et al. (2020); 2 cases, Italy, Case series.	2 patients (57 years old). Admitted to hospital with critical COVID-19 condition; (at 14 and 17 days after onset of cough and fever), they had bilaterally fixed dilated pupils and coma (GCS 3/15).	Both RT-PCR + ve (nasopharyngeal)	1 patient had bilateral cerebellar hemorrhages on brain CT with hydrocephalus; the other had a large frontal hemorrhage with displaced ventricles and multiple smaller hemorrhages.

to the peripheral nerves, cranial nerve, and neuromuscular tissue. Dyspnea, facial weakness, inability to stand or walk, or struggling with weaning off respiratory ventilators might be partially due to GBS expedited by COVID-19. GBS is frequently observed neurological complications in COVID-19 (Zhao et al., 2020a). Miller-Fisher syndrome is measured by the acute onset of external loss of tendon reflexes, ataxia, and ophthalmoplegia. In a clinical case report in Spain, involving a hospitalized 64-year old male COVID-19 patient, clinical features and eye movement abnormalities were found to be consistent with the diagnosis of Miller-Fisher Syndrome and polyneuritis cranialis. The symptoms consisted of ataxia, fascicular palsy, areflexia, anosmia, and ageusia (**Table 1**). This patient received Intravenous immunoglobulin (IVIg) and showed rapid recovery (Gutierrez-Ortiz et al., 2020). In a case report from three hospitals in northern Italy, comprising five patients who had GBS syndrome, one patient diagnosed with COVID-19 exhibited sensory ataxia, facial weakness, and facial nerve, though this patient responded positively to the treatment with IVIg and improved within a week (Toscano et al., 2020). The other four patients showed more GBS and a variable degree of COVID-19 symptoms. The severity and mortality of COVID-19 patients depend on age and pre-existing comorbidities, and ongoing treatment regimen. Multiple sclerosis (MS) is particularly prevalent in young adults; however, a substantial number of individuals with MS are older than 60 years (Minden et al., 2004). Managing MS during the COVID-19 pandemic is critical for patient's health management as there are no evidence-based guidelines and published literature yet available. In general, elderly patients (≥65 years) are susceptible to COVID-19 severity and mortality. Analyses from a Sonya Slifka Longitudinal MS study indicated that 10–20% of MS patients are more than 65 years old (Minden et al., 2004). However, whether it could impact the COVID-19 mortality in older patients given their impaired immune regulation, yet need to be elucidated (Berger et al., 2020). Besides the age, other comorbidities are correlated in the MS population cohorts as well with increased risk of severity and mortality (reviewed by Marrie et al., 2015a,b).

In one cross-sectional study in Europe, 1,931 MS patients were engaged to determine the mortality associated with COVID-19 (Bsteh et al., 2020). Out of 1,931 patients, 63% showed a low risk of COVID-19 mortality, 26% had mild risk, 8.8% had moderate risk, while 0.9% exhibited a high risk of COVID-19 mortality. Only one patient received disease-modifying treatment (DMT) in the high-risk category, and none had any immunosuppressive therapy. The increased risk of COVID-19 mortality is below 1% in the population-based MS cohort (Bsteh et al., 2020). At the beginning of the COVID-19 pandemic, clinicians recommended delaying treatment with DMT in MS patients (Giovannoni et al., 2020). Recent data has suggested that COVID-19 positive MS patients are not different from the general MS population (Parrotta et al., 2020). However, clinicians and physicians need to be vigilant for prescribing the drugs and recommendations regarding MS to guide their patients during the COVID-19 pandemic.

Neuromuscular Dysfunction/Injury

As per a clinical case series analysis of 214 COVID-19 patients, 11% of patients were reported to have evidence of neuromuscular injury (Mao et al., 2020). The damage was more prominent in severely affected (19%) than non-severely affected individuals (5%); however, these results do not indicate whether the damage is due to the COVID-19 neuromuscular infection. Such injuries were suggested to be due to SARS-CoV-2 infection-mediated release of pro-inflammatory cytokines. However, no clinical details are yet available beyond the presence of neuromuscular pain. Lately, two reports suggested it to be rhabdomyolysis as its clinical features were manifested in COVID-19 infected patients (Jin and Tong, 2020; Suwanwongse and Shabarek, 2020). Rhabdomyolysis is skeletal/neuromuscular damage that can be a manifestation of COVID-19. In a case report, a 35-year-old female was found to have rhabdomyolysis correlated with COVID-19 (Alrubaye and Choudhury, 2020). Clinical data from the report suggests that clinicians should examine the level of liver enzyme and myalgia, which could serve as clinical features of rhabdomyolysis in COVID-19 patients. Detailed analysis of the CSF pro-inflammatory and T-cell response to SARS-CoV-2 is urgently warranted to comprehensively understand the neuromuscular manifestation in COVID-19 patients.

Although we presently lack a distinct and detailed analysis of SARS-CoV-2 -manifested neurological complications including CNS, PNS, and neuromuscular injuries in the aged population, we summarize the key clinical reports/case studies involving elderly COVID-19 patients in **Table 1**.

POST COVID-19-INFECTION NEUROLOGICAL COMPLICATIONS: WHAT IS KNOWN SO FAR

Like COVID-19, other coronaviruses *viz*. SARS-CoV-1 and Middle East respiratory syndrome (MERS-CoV) have also been associated with various prolonged neurological complications (Chan et al., 2003; Lee et al., 2018). As discussed earlier, the most common neurological difficulties in COVID-19 include anosmia, ageusia, and headache, moreover, more serious complications, such as stroke, impaired consciousness, seizures, and encephalopathy have also been reported. Reports on these neurological and neuropsychological complications during and after the course of COVID-19 infection are growing rapidly. Focusing on the aging population, we have here limited our discussion about post-COVID-19 neurological and neuropsychological complications reported only in elderly patients.

Acute disseminated encephalomyelitis (ADEM), an autoimmune disease of the CNS, that mainly affects children has been observed in SARS-CoV-2 infected patients. However, most of the cases reported to be diagnosed with ADEM post-COVID-19 have been aged 50 years or above. But this might be biased given the higher prevalence of COVID-19 in adults. Amongst these reported cases was a 51-year-old female who developed clinical coma and an impaired oculocephalic

response to one side post-COVID-19 infection, which was later diagnosed to be acute multifocal demyelinating lesions (Parsons et al., 2020). Another case study reported a 64-year-old woman with ADEM, who was hospitalized with mild behavioral abnormalities, headache, bilateral relative afferent pupillary defect, ageusia and anosmia, severe visual loss, right abdominal sensory level, and left-sided lower limb hyperreflexia with the Babinski sign (Novi et al., 2020). Both these patients recovered with the administration of high-dose steroids and intravenous immunoglobulins. ADEM was also diagnosed in the post-mortem biopsy of a 71-year-old male (Reichard et al., 2020). In another case study, similar immune-mediated brain damage was also detected in a 58-year-old male patient. The patient was hospitalized with low consciousness and loss of ability to walk. The patient was tested positive for SARS-CoV-2 infection even though pulmonary symptoms like cough or dyspnea were not observed. Though the patient initially responded to steroids but then died of status epilepticus (Abdi et al., 2020). Another case study of a likewise neurological syndrome that commonly called as acute myelitis has also been reported in a 69-year-old female (Sotoca and Rodriguez-Alvarez, 2020). The first clinical case of COVID-19 associated acute necrotizing hemorrhagic encephalopathy was reported by Poyiadji et al. (2020) in a 58-year-old female airline worker. This rare neurological condition was attributed to intracranial cytokine storm and disruption of the BBB without the direct viral invasion (Serrano-Castro et al., 2020). Investigating the case study of a 75-year-old man, Hayashi et al. (2020) have suggested that mild encephalitis/encephalopathy with reversible splenial lesion can also be considered as a neurological symptom in patients developing transient cerebellar ataxia or disorientations. To add to this list of neurological complications, vasculitis of CNS has also been reported to occur in a 65-year-old man (Hanafi et al., 2020). Along with CNS, the PNS has also been affected in COVID-19 patients. Pascual-Goni et al. (2020) reported a 60-year-old female patient who after 10 days of fever, hyposmia, nausea, and coughing experienced diplopia and right hemicranial headache that was later diagnosed as right abducens nerve palsy.

In terms of post-COVID-19 neuropsychological impact, a study concerning 700 clinically stable COVID-19 patients (mean age 50.2 $\pm$ 12.9 years) were examined for post-traumatic stress symptoms, and nearly 96% of the patient were found to be suffering from significant post-traumatic stress (Bo et al., 2020). A much larger cohort study involving 112 hospitalized patients and 2,001 non-hospitalized patients from Belgium and Netherland has revealed that symptoms like neuromuscular pain, dizziness, headaches, fatigue, and anosmia prevail also in asymptomatic or very mildly symptomatic patients even after months of contracting the disease (Goertz et al., 2020). Some patients treated for severe COVID-19 have been reported with disabling fatigue and impaired cognitive abilities after being discharged from the hospitals (Zhou et al., 2020a; Halpin et al., 2021). Also, the detection of delirium, the most common acute neuropsychiatric syndrome, has been significantly linked to COVID-19 in older adults and those with dementia (Poloni et al., 2020).

UNDERSTANDING THE SARS-COV-2 INFECTION AND ITS ROUTES

Considering these features of neuropathological manifestations discussed above, here we shed light on the SARS-CoV-2 infection, its diverse routes, the mechanism(s), and associated neurological complications.

POTENTIAL SARS-COV-2 INFECTION ROUTES

The neurotropic, neuroinvasive, and neurovirulent characteristics of SARS-CoV-2 were recognized in both humans and animals (Lima et al., 2020). Recent evidence suggested that coronaviruses can infect primary human neural cells, microglia, astrocytes, and oligodendrocytes (Lima et al., 2020). SARS-CoV-2 interacts with the host ACE2 receptor through the receptor-binding domain (RBD) of its Spike (S) protein. ACE2 receptor ubiquitously expresses in all human tissues including CNS and the endothelial cells. Emerging evidence reveals that SARS-CoV-2 binds to the ACE2 receptor to invade neurons in CNS *via* distinct routes as discussed here (**Figure 2**).

Epithelial-Humoral Route

Coronaviruses can efficiently invade the epithelial-humoral route and disrupt the primary epithelial barrier to attain access into the bloodstream. ACE2 abundantly expresses on the alveolar epithelial cells (Type II) that makes these cells a preferred target for SARS-CoV-2 infection (Lima et al., 2020). Also, an abundant expression of ACE2 on the epithelial cells of the gastrointestinal tract raises their vulnerability for SARS-CoV-2 infection and access to the bloodstream (Li et al., 2020b; **Figure 2**). On ensuring access to the systemic circulation, SARS-CoV-2 disrupts the endothelial barrier of the BBB or the blood-cerebrospinal fluid barrier (BCSFB) *via* its interaction with ACE2 receptors at the endothelial cells and subsequent CNS contact (Li et al., 2020b). The presence of SARS-CoV-2 like particles in the neural and frontal lobe capillary endothelial cells of the patient who died with COVID-19 affirmed the hematogenous-endothelial route of SARS-CoV-2 neuroinvasion (Paniz-Mondolfi et al., 2020). Moreover, SARS-CoV-2 was also suggested to cross BBB by inducing inflammation or hypoxemia by stimulating the release of pro-inflammatory cytokines and chemokines (Li et al., 2020b; Lima et al., 2020). The pro-inflammatory cytokines *viz*. interferon-gamma (IFN-γ), interleukin (IL)-2, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) were suggested to play a part in SARS-CoV-2 cellular invasion (Achar and Ghosh, 2020). However, it is unclear if induction of these pro-inflammatory cytokines is a result of SARS-CoV-2 cellular invasion activity or it reflects an elicited antiviral immune response for its neutralization/clearance. Multiple clinical reports exhibited a surge in IL-6, IL-10, IL-2, and IFN-γ levels in COVID-19 patients that was attributed to an activated neutrophils and leucocytes immune function, but the decline in lymphocyte/T Cell response (Gong et al.,

2020; Huang et al., 2020b; Liu et al., 2020). Therefore, further studies are warranted to elucidate the nature and cause of these elicited pro-inflammatory cytokines in COVID-19 patients and if it has a relation to SARS-CoV-2 immuno-invasive activity.

Neuronal/Nervous System Route

SARS-CoV-2 particles were primarily suggested to enter the nerve termini and undergo replication before transportation to the soma and ensuring CNS invasion (Li et al., 2020b). Among the potential SARS-CoV-2 neuroinvasion routes, the olfactory tract serves as an important route for respiratory viruses (Meinhardt et al., 2020; **Figure 2**). Also, the peripheral nerves namely trigeminal and vagus nerves that innervate distinct parts of the respiratory tract were suggested to be the target of SARS-CoV-2 neuroinvasion (Yavarpour-Bali and Ghasemi-Kasman, 2020). SARS-CoV-2 invades the neural-mucosal interface *via* its transmucosal entry across the nervous assemblies followed by their access to the olfactory tract of the CNS (Meinhardt et al., 2020). Coronaviruses can also invade CNS *via* a synapse-connected route by infecting the peripheral nerve terminals (Dube et al., 2018; Lima et al., 2020). Dube et al. (2018) earlier claimed that human coronavirus (HCoV OC43) might also actively transport through axonal transport by axoplasmic flow and/or may passively diffuse across this channel. SARS-CoV-2 is believed to enter CNS *via* trigeminal nerves that innervate nociceptor cells in the nasal fossa; while the sensory terminal of the trigeminal nerves exits in the conjunctiva (Lima et al., 2020). The finding of SARS-CoV-2 RNA fragment in the ocular discharge of a patient with conjunctivitis (Zhang et al., 2020) further suggested trigeminal nerve-mediated entry of SARS-CoV-2 to CNS.

Lymphatic-Cerebrospinal Fluid (CSF) Route

The bronchus and trachea tissues comprise a rich and intricate lymphatic network. The olfactory nerve perineural and nasal lymphatic tissue space is suggested to facilitate the CSF drainage by communicating with the channels constituted by ensheathing cells (**Figure 2**). Of note, endothelial cells in lymphatic networks express CD209L receptor that was claimed to be another receptor facilitating coronavirus invasion (Li et al., 2007). The presence of SARS-CoV-2 nucleocapsid protein in the cells of lymphoid organs affirmed the functioning of the CSF route in the SARS-CoV-2 neuroinvasion (Chen et al., 2020b). These pieces of evidence postulating invasion of CNS by SARS-CoV-2 involve perivascular or lymphatic path as an alternative route (Ylikoski et al., 2020).

Infected Immune/Lymphatic Cells

Coronaviruses-infected lymphatic/immune cells i.e., T cells, monocytes, and neutrophils were suggested to serve as reservoirs for the virus and were capable to enter and infect the CNS (Iadecola et al., 2020; **Figure 2**). These immune cells travel to the brain through the meninges and the choroid plexus vasculature (Engelhardt et al., 2017), which could serve as the entry sites for SARS-CoV-2 infected immune cells. As discussed earlier, immune cells also express ACE2 that serves as the molecular receptor for coronaviruses (Lima et al., 2020). Although presently we lack any direct clinical evidence of SARS-CoV-2 invasion of immune cells (Merad and Martin, 2020), immunoreactivity of CD169+ cells for SARS-CoV-2 nucleocapsid protein was seen in the lymph node splenic marginal zone and marginal sinuses (Chen et al., 2020b). Given the fact that CD169+ macrophages amply express ACE-2, makes them a potential target of SARS-CoV-2 neuroinvasion that may further facilitate the entry of infected immune cells to CNS (Park, 2020). Consistent with this, the presence of viral RNA in the macrophages of broncho-alveolar lavage in the COVID-19 patient further highlights the role of infected lymphatic/immune cells in SARS-CoV-2 neuroinvasion (Bost et al., 2020). This evidence postulates that SARS-CoV-2 may infect circulating immune cells and could potentially exploit them to disseminate/invade through the CNS (**Figure 2**). However, it is still unclear if such presence of SARS-CoV-2 virions/single strand RNA is due to its macrophage invasion or was a result of active phagocytic uptake of the infected cell or SARS-CoV-2 virion (Bost et al., 2020; Merad and Martin, 2020). In contrast, few clinical autopsy reports from COVID-19 patients showed a lack of any infected immune cell infiltration to CNS (Kantonen et al., 2020; Solomon et al., 2020).

The secretion of interferons is the foremost antiviral defense acquired by the immune cells that also stimulate the neighboring immune cells. Coronaviruses can evade the host immune response by producing severe leukopenia and lymphopenia (Wong et al., 2003; Zaki et al., 2012). Earlier investigations on SARS-CoV and MERS-CoV revealed that coronaviruses encode proteins that modulate downstream regulation of TLRs and the JAK-STAT signaling pathway by interacting with their effectors in immune cells. For instance, SARS-CoV and MERS-CoV encoded protein PLpro, inhibits the NF-κB from IκBα dissociation, while, SARSCoV's PLpro and ORF3b proteins block IRF3 phosphorylation and its nuclear translocation (Devaraj et al., 2007; Signaling et al., 2009). The role of these viral proteins was also implicated in the inhibition of the JAK-STAT pathway (Menachery et al., 2014). In the case of SARS-CoV-2 infection of immune cells, an overall decline in the transcription of antiviral genes was reported due to decreased Type I and III interferons production and an elevated chemokine secretion (Blanco-Melo et al., 2020). Of note, results from *in vivo* and *ex vivo* SARS-CoV-2 experiments affirmed *in vitro* findings and thereby suggested that a decline in the innate antiviral response with instigated hyper-inflammation, could be a potential mechanism of SARS-CoV-2 invasion of immune cells and may contribute to COVID-19 severity (Blanco-Melo et al., 2020). Apart from reducing the T cell number, SARS-CoV-2 also causes effector T cell exhaustion as another mechanism to compromise immune cell function (Diao et al., 2020; Zheng et al., 2020). SARS-CoV-2 exhausted effector T cells as a result show elevated levels of inhibitory receptors *viz*. PD-1, TIM-3, and TIGIT at its surface given the IL-6, IL-10, and TNF-α exposure and declined regulatory T cell function (Chiappelli et al., 2020; Qin et al., 2020).

POTENTIAL MECHANISMS OF SARS-COV-2 INDUCED NEUROLOGICAL INJURY

As mentioned, SARS-CoV-2 invasion requires ACE2 for S-protein binding followed by its priming by cell proteases TRMPSS2 (Hoffmann et al., 2020). Recent studies also implicated the role of heparan sulfate at the host cell membrane in facilitating the S-protein and ACE2 binding and viral invasion (Clausen et al., 2020; Kalra and Kandimalla, 2021). Co-expression analysis of ACE2 and TMPRSS2 revealed that nasal goblet, ciliated epithelial cells, and oligodendrocytes ubiquitously express both the proteins (Sardu et al., 2020). More specifically, ACE2-TMPRSS2 co-expression in oligodendrocytes could potentiate CNS infiltration as clinical features of acute encephalitis as observed in COVID-19 patients (Hung et al., 2003; Ding et al., 2004). As discussed in the earlier section, coronaviruses can invade the CNS either by a neuronal or humoral/hematogenous route (**Figure 2**). Therein, early anosmia, i.e., a primary feature of SARS-CoV-2 neuroinvasion that occurs through the olfactory bulb, whereas a retrograde migration of human coronaviruses to olfactory nerve and the CNS *via* nasal epithelium was studied in the murine model (Netland et al., 2008). An earlier study reported an eight-fold increase in the frequency of human coronaviruses infected cells in the CNS that was specifically noticeable in the hippocampus post 1–2 weeks of infection (Chan et al., 2020).

An alternative route of CNS entry for coronaviruses is through the BBB that comprises conditions/factors including endothelins, inflammatory mediators, infected macrophages shipping the virus, or directly infected endothelial cells (Edwards et al., 2000; Paniz-Mondolfi et al., 2020; Sardu et al., 2020). Once the virus reaches the CNS, it starts swift trans-neuronal spread and produces neurotoxicity in infected ACE2-positive neutrons, as validated in transgenic mice models (Netland et al., 2008). Although both SARS-CoV-1 and SARS-CoV-2 bind to ACE2 receptor for host cell entry, recent phylogenetic and virus–receptor binding structural data suggested that SARS-CoV-2 recognizes ACE2 more effectively (Wan et al., 2020; Xu et al., 2020). Therefore, high expression of ACE2 in brain endothelial cells, neurons, and glial cells, makes these neurological cells more prone to SARS-CoV-2 neuroinvasion (Hamming et al., 2004). SARS-CoV-2 recognition of ACE2 may disrupt the delicate balance of ACE-ACE2 cerebrovascular control that could result in incessantly activated ACE signal, severe vasoconstriction, or interrupted cerebral autoregulation. Moreover, SARS-CoV-2 pathogenicity in these tissues was found to elicit IL-1β, -2, -6, -7, -8, -10, -17, INFγ, G-CSF, TNFα, MCP1, and macrophage inflammatory protein 1α (Pedersen and Ho, 2020). The triggered levels of these pro-inflammatory factors produce a "cytokine storm" and are known to be associated with poor clinical outcomes. Besides ARDS, cytokine storm produces severe neurotoxicity by compromising the integrity of the BBB, in absence of direct viral transport or neuroinvasion. These features speculated that acute necrotizing encephalopathy (ANE), may essentially be produced by cytokine-induced neurotoxicity (Ouattara et al., 2011). Therefore, cytokine-induced neurotoxicity in SARS-CoV-2 infected patients may upset neurologic outcomes (Allan and Rothwell, 2001).

Among the different age groups of COVID-19 patients admitted to the hospital, the aforementioned neurological mechanisms were severely deregulated in the elderly population and have exposed their vulnerability (reviewed by COVIDview, 2020; Lekamwasam and Lekamwasam, 2020). These mechanisms of neurological complications underlined the role of disrupted immune function or cytokine-induced neurotoxicity in elderly COVID-19 patients. Koff and Williams (2020) reviewed the consequence of diminished immunity in the aging population and how COVID-19 took advantage of it to exploit it further (Koff and Williams, 2020).

EMERGING ROLE OF ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN COVID-19 DIAGNOSTICS

During this COVID-19 pandemic, hospitals and other healthcare services have experienced severe crises and are opening up to technologies that can be used in clinical settings as a support system for the frontline healthcare workers in the detection and containment of such diseases. AI is one of those technologies with long–term value. Not only diagnostics but AI is also being employed in hospitals to handle the rapidly increasing load of patients. To manage a similar situation in Boston, Partners HealthCare came up with a hotline service for patients, clinicians, and others with concerns related to COVID-19. The main aim of this initiative was: (i) to identify the class of people with mild symptoms who did not need additional care, to provide them with relevant information and direct them to relevant virtual care options; (ii) to manage the small high-risk patients by linking them to testing sites, newly created respiratory illness clinics, or emergency department of hospitals in case necessary. This initiative was further expanded in collaboration with St. Joseph Health system in Seattle and Microsoft, which served more than 40,000 patients in the 1st week itself. In line with this, smart AI bots are also being developed as chatbots to manage the increasing needs of patients and clinicians. Moving a step ahead, a group of researchers at MIT has trained an AI model that can distinguish asymptomatic people from healthy individuals through their forced-cough recordings. The model was able to accurately detect 98.5% of COVID-19 positive people, which included 100% cases of coughs submitted by asymptomatic patients (Laguarta et al., 2020). Though still in its infancy, such technology can be used as a pre-screening tool in various situations. Another group has reported an AI-based screening model for early detection of COVID-19 using the routinely collected healthcare data (laboratory tests, blood gas measurements, and vital signs) that typically become available within the first hour of presentation to any hospital with regular laboratory infrastructure (Soltan et al., 2020). During the 2 weeks of testing phase at the John Radcliffe Hospital in Oxford and

the Horton General Hospital in Banbury, this AI model could correctly predict the COVID-19 status of 92.3% of patients admitted to the emergency departments. So, as an alternative to the swab test that takes typically a day's time for results, this AI screening maintained the flow through the hospital by confidently predicting the negative COVID-19 cases. Several governments and hospitals across the globe are also using AI-powered sensors to identify suspected patients. Of note, physician-researchers at Brigham and Women's Hospital and Massachusetts General Hospital are trying to make use of intelligent robots (developed at Boston Dynamics and MIT) to monitor vital signs in COVID-19 patients and deliver their medications (Wittbold et al., 2020). This will assure the least human contact with infected patients and thus control disease transmission.

Scaling AI for better explainability and transparency of imaging for diagnostics is another major direction to improve upon. An AI algorithm has also been constituted that integrates a spectrum of chest CT imaging features with clinical symptoms, exposure history, and laboratory testing to rapidly diagnose COVID-19 positive patients. The trained model was able to achieve an Area under the ROC Curve (AUC) of 0.92, indicating a sensitivity comparable to that of a senior thoracic radiologist. It was also able to detect 17 out of 25 COVID-19 positive patients, who were reported as negative by the radiologists (Mei et al., 2020). Jin et al. (2020) have also reported a similar model that makes use of chest CTs for COVID-19 detection. In China, an AI-driven CT scan interpreter has been installed in Zhongnan Hospital that helps in the diagnosis of COVID-19 when radiologists are not available (Wittbold et al., 2020). Furthermore, this technology can have direct implications in the detection of post-COVID-19 neurological complications as well. For example, AI could have been efficiently used in the study to systematically characterize neurological symptoms in COVID-19 infected people that involved neuroimaging of about 108 patients from multiple institutions in Italy (Mahammedi et al., 2020). AI thus holds the promising potential to develop into a mainstream diagnostic for fast and efficient detection of various diseases.

Although AI seems to be a promising solution to our growing healthcare needs, it needs to be executed with human clinical expert decision-making at appropriate levels to ensure high quality and safe delivery of AI outcomes. AI can only be an aid but cannot be a replacement for human clinical reasoning and decision making.

CONCLUSION

Emerging clinical data revealed that neurologic manifestations are frequent in elderly and severely sick COVID-19 patients that significantly raised their mortality. Also, existing comorbidities in COVID-19 patients can further contribute to the neurological complications and impact the clinical outcome. Existing neurological conditions, neurodegenerative ailments, and inflammation in the elderly population were found to worsen the clinical outcome in COVID-19 patients. Although emerging clinical evidence underlined the role of neuroinvasion, neuroinflammation, immunopathogenesis, and hypoxemia in the development of CNS manifestations, the molecular mechanism of COVID-19 neurotoxicity is not yet completely known. Therefore, direct involvement of the above events during or post-SARS-CoV-2 infection is unclear to assess their exact clinical outcomes in elderly COVID-19 patients. Given the diverse and complex clinical signatures of COVID-19 affecting multiple cross-histological functions, it warrants more concerted efforts to distinctly characterize the molecular events involved in its pathogenesis, more importantly in elderly patients. Clinical data revealing SARS-CoV-2 presence in the brain postulated neuroinvasion theory, therefore, direct contact of SARS-CoV-2 with the nervous system is clinically relevant. However, the lack of SARS-CoV-2 virion/mRNA in CSF in the majority of the COVID-19 cases hinted at an alternative viral gateway. Also, in COVID-19 patients, SARS-CoV-2-induced inflammation and immune response appeared to further exacerbate the neurologic complications. Given the fact that COVID-19 infection severity has a direct link with the extent of inflammation, the possibility of deregulated immune function in neurotoxicity cannot be excluded. Incidences of "cytokine storm" in SARS-CoV-2 infected patients are seen to greatly contribute to neurological complications, more often in elderly patients. Therefore, in the COVID-19 patients, virus-induced inflammation is suggested to play a key role in potentiating neurological complications. However, it requires further investigation at the molecular and systemic level to precisely define the pathophysiological relevance of these events in neurological complications.

SARS-CoV-2 infected elderly patients are at higher risk of neurological complications. These complications beyond producing acute illness can also exert prolong impact on the functioning of the nervous system. These facts made aged COVID-19 patient's health management more complex, even greater for those having preexisting comorbidities. Careful assessment of these features in admitted elderly COVID-19 patients with the help of advanced AI and machine learning can make COVID-19 diagnostics more efficient and could also save lives. Conclusively, COVID-19 associated neurological complications are a serious health concern and require more concerted investigative efforts to understand and intervene in their progression in elderly patients.

AUTHOR CONTRIBUTIONS

RSK, JKD, and RK conceived the idea. RSK, JKD, AM, VK, BS, SDa, SDe, and RK wrote the manuscript. RSK drafted the manuscript figures. RSK, JKD, BS, and RK supervised and critically revised the study. All authors contributed to the article and approved the submitted version.

FUNDING

RK acknowledges DBT for Ramalingaswami Re-entry Fellowship (No. BT/RLF/Re-entry/22/2016 and SAN.No. 102/IFD/SAN/1117/2018–19) and CSIR IICT, Hyderabad, India.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

SYSTEMATIC REVIEW
published: 03 June 2021
doi: 10.3389/fnagi.2021.646908

Heterogeneity in Regional Damage Detected by Neuroimaging and Neuropathological Studies in Older Adults With COVID-19: A Cognitive-Neuroscience Systematic Review to Inform the Long-Term Impact of the Virus on Neurocognitive Trajectories

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OPEN ACCESS

Edited by:
Thomas Wisniewski,
New York University, United States

Reviewed by:
Mitchell Elkind,
Columbia University, United States
Steven Galetta,
New York University, United States

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Received: *28 December 2020*
Accepted: *28 April 2021*
Published: *03 June 2021*

Citation:
Manca R, De Marco M, Ince PG and Venneri A (2021) Heterogeneity in Regional Damage Detected by Neuroimaging and Neuropathological Studies in Older Adults With COVID-19: A Cognitive-Neuroscience Systematic Review to Inform the Long-Term Impact of the Virus on Neurocognitive Trajectories. Front. Aging Neurosci. 13:646908. doi: 10.3389/fnagi.2021.646908

Background: Other than its direct impact on cardiopulmonary health, Coronavirus Disease 2019 (COVID-19) infection affects additional body systems, especially in older adults. Several studies have reported acute neurological symptoms that present at onset or develop during hospitalisation, with associated neural injuries. Whilst the acute neurological phase is widely documented, the long-term consequences of COVID-19 infection on neurocognitive functioning remain unknown. Although an evidence-based framework describing the disease chronic phase is premature, it is important to lay the foundations for future data-driven models. This systematic review aimed at summarising the literature on neuroimaging and neuropathological findings in older over-60 patients with COVID-19 following a cognitive neuroscientific perspective, to clarify the most vulnerable brain areas and speculate on the possible cognitive consequences.

Methods: PubMed and Web of Science databases were searched to identify relevant manuscripts published between 1st March 2020 and 31th December 2020. Outputs were screened and selected by two assessors. Relevant studies not detected by literature search were added manually.

Results: Ninety studies, mainly single cases and case series, were included. Several neuroimaging and neuropathological findings in older patients with COVID-19 emerged from these studies, with cerebrovascular damage having a prominent role. Abnormalities (hyperintensities, hypoperfusion, inflammation, and cellular damage) were reported in most brain areas. The most consistent cross-aetiology findings were in white matter, brainstem and fronto-temporal areas. Viral DNA was detected mainly in olfactory, orbitofrontal and brainstem areas.

Conclusion: Studies on COVID-19 related neural damage are rich and diverse, but limited to description of hospitalised patients with fatal outcome (i.e., in neuropathological studies) or severe symptoms (i.e., in neuroimaging studies). The damage seen in this population indicates acute and largely irreversible dysfunction to neural regions involved in major functional networks that support normal cognitive and behavioural functioning. It is still unknown whether the long-term impact of the virus will be limited to chronic evolution of acute events, whether sub-clinical pathological processes will be exacerbated or whether novel mechanisms will emerge. Based on current literature, future theoretical frameworks describing the long-term impact of COVID-19 infection on mental abilities will have to factor in major trends of aetiological and topographic heterogeneity.

Keywords: neuroimaging, neuropathology, COVID-19, ageing, stroke, encephalopathy, encephalitis

INTRODUCTION

At the end of 2020, the global pandemic of Coronavirus Disease 2019 (COVID-19) has already affected more than 77 million people and caused over 1.8 million deaths worldwide. Although COVID-19 manifests primarily with respiratory problems, the detrimental consequences of this infection may be much wider. A fast-growing body of recent publications has been showing that infection due to COVID-19 may attack multiple organ systems to a variable extent, especially in vulnerable people with prior medical conditions. In particular, older adults are among those most severely affected by the current pandemic and mortality rates have been reported to be particularly high in older populations (Shahid et al., 2020). Possible causes of such increase in vulnerability to the COVID-19 infections include ageing-related changes occurring naturally in the immune system, associated with a reduction in the effectiveness of the immune response (Oh et al., 2019). As a consequence, older adults appear to be more vulnerable than younger adults and children to the cytokine storm activated as a response to the infection (Nidadavolu and Walston, 2020). This older population is also the cohort at greatest risk of neurodegenerative diseases.

The first pathological examinations carried out on patients deceased because of complications associated with COVID-19 showed that signs of this infection extend beyond body tissues directly associated with the respiratory system (Xu et al., 2020). These findings have raised several concerns about the consequences COVID-19 may have on extra-respiratory body systems in older patients, in particular the nervous system. In fact, a variety of neurological complications has been reported in about 25% of patients in some reports (e.g. Romagnolo et al., 2020), even though high variability in symptom prevalence and incidence has been observed across studies (Herman et al., 2020). At present, no evidence-based link exists between COVID-19 and risk of neurodegeneration; however, at this stage it is particularly important to outline a data-driven framework that could inform the study of the long-term neurological consequences of this infectious disease. Since COVID-19 was identified only in December 2019 and declared a pandemic in March 2020, thorough and incessant efforts have been made to prioritise the characterisation of its acute effects on the nervous system. Although studies of the acute effects of COVID-19 are, undoubtedly, a priority, it remains unknown whether the infection and its acute neurological effects play a role as part of long-term neurological trajectories. Acquired neural damage may increase the risk of initiating or worsening neurodegenerative processes (Heneka et al., 2020), possibly in a differential manner depending on the type of neurodegenerative condition (Ferini-Strambi and Salsone, 2020). The study of the effects of COVID-19 on cognitive decline is an area of interest that might become central in the study of the pathophysiological mechanisms of neurodegeneration and in the future management of neurological patients.

Multiple sources of evidence have already been accumulating on the impact of the current pandemic on mental health of older adults both with and without cognitive decline (Manca et al., 2020). A systematic examination of the literature reporting findings on neural damage observed as a consequence of COVID-19 infection in older adults will provide an understanding of its impact on cognitive (and neuropsychiatric) symptoms in this population. In particular, this systematic review focusses on neuroimaging and neuropathology findings from the viewpoint of cognitive neuroscience, in order to inform a theoretical framework that could be used to predict the long-term consequences on cognitive functioning triggered by the virus and its acute neurological manifestation. To do so, we were particularly interested in articles describing the consequences of COVID-related acute neurological events on the brain, and that included details on the regions affected. This was done to elucidate whether some brain regions may show variable degrees of vulnerability to the infection in older adults. Such consideration may provide new insights that could inform prognosis and treatment of the possible consequences of COVID-19 on brain health of older patients.

METHODS

A systematic literature search was carried out in PubMed and Web of Science to identify studies that included neuroimaging

and neuropathological examinations of older adults who tested positive for COVID-19. The keywords used to carry out this search were: (1) "COVID-19," "COVID19," and "SARS-CoV-2" for the COVID-19 infection; (2) "dementia," "mild cognitive impairment," "MCI," "neurodegeneration," "neurodegenerative," "Alzheimer's disease," "AD," "FTD," "frontotemporal dementia," "older adults," "ageing," and "aging" for the populations of interest; (3) "neuropathology," "autopsy," "post-mortem," "neuropathological," "neuroimaging," "brain," "MRI," "magnetic resonance imaging," "PET," "positron emission tomography," "SPECT," "Single-photon emission computed tomography," "neuroradiology," "neuroradiological," "nuclear medicine," "stroke," "ischaemia," "ischaemic," "ischemia," "ischemic," "vascular," "encephalitis," "meningitis," "vasculitis," and "encephalopathy" for the neuroimaging/neuropathological variables of interest. Papers published between March 2020 and 31st December 2020 (last day of literature search) were included. All publication entries resulting from the initial search were screened to identify papers reporting original data, with no restrictions on the type of article.

Inclusion criteria were defined as follows: original data describing changes to the nervous tissue associated with COVID-19 infection. The intent was to focus on studies mentioning or illustrating the regional properties of neural abnormalities in order to inform the theoretical basis of a model of cognitive dysfunction due to brain damage or increased vulnerability associated with the virus. Two partially distinct sets of exclusion criteria were then defined to identify eligible studies based on neuroimaging and neuropathology, respectively. Due to the "*intra-vitam*" and routine nature of neuroimaging procedures, exclusion criteria for neuroimaging evidence were defined according to the following four principles: (1) manuscripts not in English or not having completed a peer-review process; (2) manuscripts based on study participants whose inclusion was not associated with COVID-19 infection; (3) studies not distinctively focussing on adults older than 59; (4) studies not including adequate information on how regional properties of brain tissue were affected. Exclusion criterion 2 served to discard all studies run "in the era/at the time of COVID-19" not directly focussing on the physiological effects of the virus, or studies exploring the indirect effects of COVID-19-related factors, e.g., those triggered by lockdown or social-limitation policies. Exclusion criterion 3 was introduced to limit the remit of the review to adults typically defined as "older adults" by neurological studies. By doing so, single-cases of adults aged 59 or less were excluded and case-series were filtered to retain only patients meeting inclusion criteria. Similarly, cohort studies were discarded when no clear age group meeting criteria was identifiable or when the central-tendency and dispersion measures for the "age" variable were suggestive of a sample excessively skewed towards a younger age or excessively heterogeneous. Finally, exclusion criterion 4 was set to discard manuscripts not exploring or investigating the brain, as well as manuscripts describing cerebrovascular abnormalities (e.g., as informed by angiographic scans) without a specific focus on damage of the nervous tissue. Exclusion criteria for neuropathology studies were the same as above with the exception of criterion 3. Given the unique nature of neuropathological studies, no age-based exclusion was applied.

Two independent assessors (MDM and RM) reviewed the search output to process each entry and either exclude or retain it. A third assessor (AV) helped resolving any disagreement on publications to be included. Additional papers relevant to this review identified through other sources (i.e., references and key journals) were also screened and manually added.

RESULTS

A flow diagram illustrating the process of manuscript inclusion is reported in **Figure 1**. The above search strings resulted in a total of 1,972 articles. After removal of duplicates and objects with no digital object identifier (DOI), 1,621 elements were retained, 50 of which were immediately discarded. These included manuscripts not in English ($n = 30$), manuscripts deposited in pre-print servers and not having yet completed a process of peer review ($n = 3$) and non-article objects (i.e., figures, tables, and data sheets) that had their own DOI ($n = 17$). The remaining manuscripts were screened and separated according to the central medical specialty of reference (reported in **Figure 1**). Following this classification, 527 manuscripts on neurological or neurology-related themes (e.g., cardiological studies including reference to the cerebrovascular system or articles of mixed neurological-psychiatric interest) were retained and assessed for study eligibility. In addition, all pathology-related studies were also included in the list shortlisted for study eligibility since in this first year of COVID-19, pathological studies have investigated a wide-range of *post-mortem* tissues (including the brain) in a more general rather than specialised way. Following the procedures of assessment, 437 of the 527 manuscripts were excluded. These were categorised based on the reason behind failed suitability (see **Figure 1** for a complete list). In particular, 16 studies were excluded because, although describing patients with stroke, they limited their description to the cerebrovascular accidents without focussing on the damage to the neural tissue. Based on the same principle, 20 studies of pathology were discarded because they did not describe properties of the neural tissue, but instead limited the investigation to other organs or to aspects relevant to the nervous system other than tissue involvement (e.g., analysis of cerebrospinal fluid). Similarly, pathological studies that solely investigated the presence of the virus were not considered. As a result, 90 articles met study eligibility criteria and were thus included in this systematic review. These mainly included single-case reports and case series plus a small number of group studies (a summary for each article is reported in **Table 1**).

Neuroimaging Examinations

A total of 77 manuscripts reported neuroimaging examinations of older adults aged 60 or older who tested positive for COVID-19. Studies investigated a variety of neural abnormalities associated with viral infection that fall into three main categories: encephalopathy, encephalitis and cerebrovascular injuries. Three radiological/nuclear-medicine techniques were most commonly used to monitor brain damage, especially in hospitalised patients with severe symptoms: computerised tomography (CT),

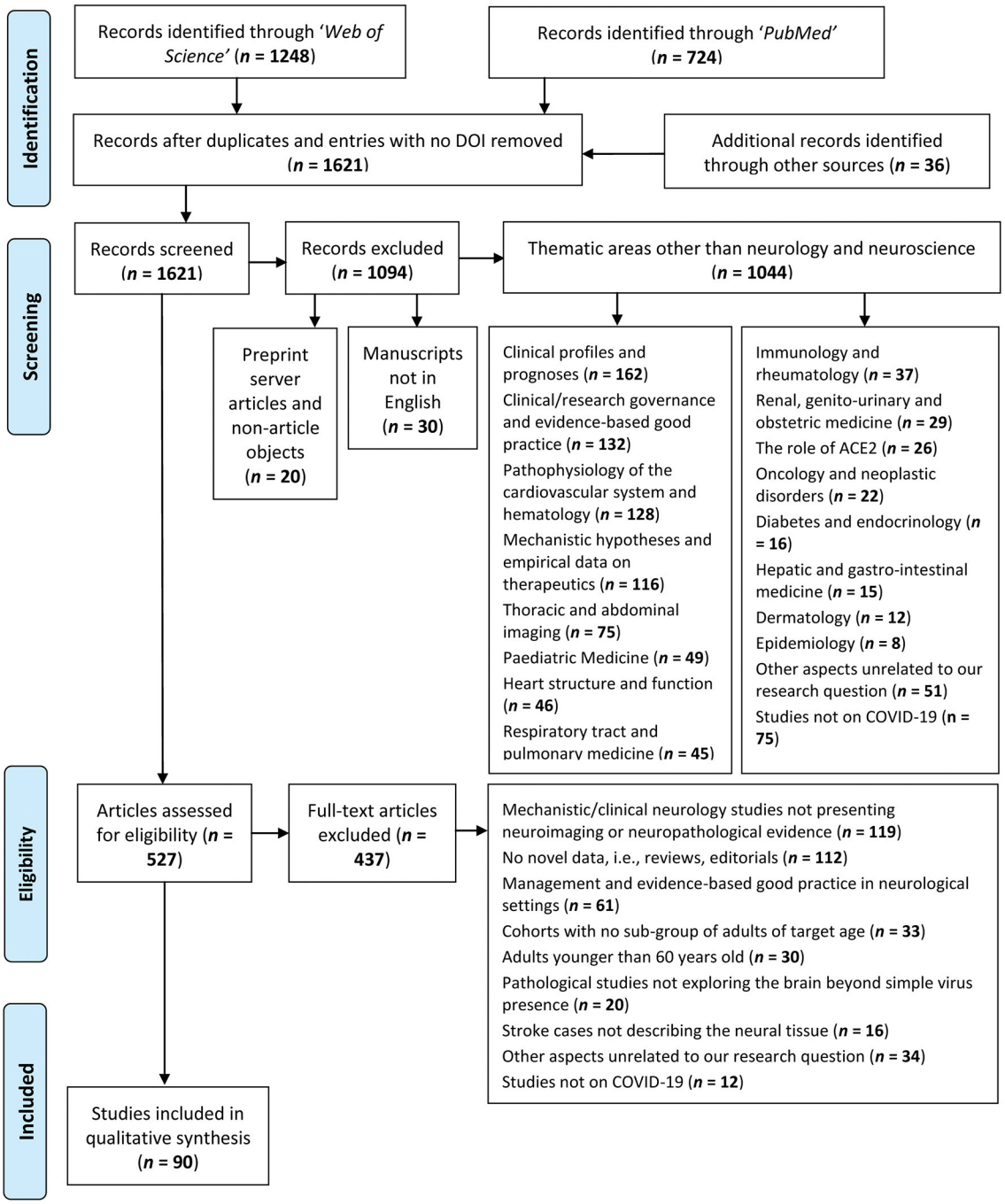

FIGURE 1 | Flow chart outlining the study selection process according to the PRISMA framework.

magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET).

Encephalopathy

Thirteen studies reported exclusively encephalopathy in either single cases or small case series of older patients with COVID-19. Comorbidities were not reported by all studies and were highly variable across cases, with hypertension being the most common. Other comorbidities included: history of cardiac arrest, history of lymphoma, Parkinson's disease, anorexia, depression, schizophrenia, neuropathic pain, atrial fibrillation, and epilepsy due to prior Herpes Simplex Virus-1 encephalitis.

In a case series of five patients with epileptic seizures, CT abnormalities were observed in three cases, with seizures mainly left-lateralised in frontal, parietal and temporal cortices while

TABLE 1 | Summary of the characteristics and findings of the studies included in the review.

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Neuroimaging findings									
Anand et al. (2020)	Case series	5	61, 75, 81, 88, 88	4/1	Encephalopathy - seizures	TBI, remote left MCA infarct, PD, history of cardiac arrest, end-stage renal disease, intellectual disability	CT	USA	CT abnormalities in left frontal, parietal, and temporal lobes (and in left MCA territory, due to a prior infarct); right frontal and bilateral cerebellar leukoencephalopathy and gyral diffusion alterations; no abnormalities in two cases.
Delorme et al. (2020)	Case series	4	60, 66, 69, 72	2/2	Encephalopathy	None reported	MRI and FDG-PET	France	Hypometabolism in bilateral frontal cortices in all cases (prefrontal in three and orbitofrontal in one case) and in posterior associative cortices in two cases (only left parieto-temporal in one case); hypermetabolism in the cerebellar vermis in all, bilateral striatum in two cases. In one case, right orbitofrontal hyperintensities,
Fernández-Domínguez et al. (2020)	Single case	1	74	1/0	Encephalopathy—Miller-Fisher-like syndrome	Hypertension and follicular lymphoma treated from 2014 to 2015	MRI	Spain	No abnormalities.
Guedj et al. (2020)	Single case (#2 from a case series)	1	62	0/1	Encephalopathy	No significant prior conditions	FDG-PET (whole body)	France	Hypometabolism in: bilateral medial temporal lobe, cerebellum, hypothalamus, left thalamus, right gyrus rectus, medulla oblongata, pons, left cingulate gyrus and right precentral, postcentral and superior temporal gyri.
Jang et al. (2020)	Single case	1	67	0/1	Encephalopathy	Anorexia and depression	CT and MRI	USA	No abnormalities on CT; mild scattered deep periventricular and subcortical WM ischaemic lesions on MRI, but no evidence of encephalitis, posterior reversible encephalopathy, or leukoencephalopathy.
Logmin et al. (2020)	Single case	1	70	1/0	Encephalopathy - recurrent non-epileptic seizures/convulsive syncope	Syncope, neuropathic pain, paroxysmal atrial fibrillation	MRI	Germany	No abnormalities, apart from three hyperintensities due to minimal prior ischaemic events.
Manganelli et al. (2020)	Case series	2	66, 67	1/1	Encephalopathy	None reported	CT and MRI	Italy	No MRI abnormalities in male patient; scattered gliosis in right pons on CT in one case.
Palomar-Ciria et al. (2020)	Single case	1	65	0/1	Encephalopathy	Schizophrenia	CT and MRI	Spain	Deep WM leukoencephalopathy due to small vessel pathology on CT (unclear relation to COVID-19); dilatation of ventricles and subarachnoid spaces in line with the patient's age on MRI.
Vollono et al. (2020)	Single case	1	78	1/0	Encephalopathy—non-convulsive status epilepticus	Hypertension, epilepsy due to prior Herpes Simplex Virus-1 encephalitis	CT and MRI	Italy	No abnormalities on CT; old gliosis and atrophy involving the left temporal/parietal lobes on MRI, but no recent acute lesions.
Young et al. (2020)	Single case	1	≥ 60	0/1	Encephalopathy—Creutzfeldt-Jakob disease	None reported	MRI and FDG-PET	USA	Hyperintensities and hypometabolism diffuse throughout the left hemisphere cortex, the left caudate nucleus and thalamus and the right cerebellum.
Muccioli et al. (2020)	Case series	4 (out of 5)	75, 69, 69, 67	1/3	Encephalopathy	Type 2 diabetes, hypertension, ischaemic heart disease, previous stroke, MCI, bipolar disorder, iatrogenic parkinsonism, hypertensive cardiopathy	MRI	Italy	Encephalopathy developed after sedation in two patients who showed chronic cerebral small vessel disease; cerebral atrophy and non-specific diffuse parietal WM hyperintensity in one case; old right fronto-parietal stroke in one case.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Parauda et al. (2020)	Case series	4	64, 73, 65, 74	2/2	Encephalopathy	Hypertension, diabetes, hypothyroidism, hyperlipidaemia	CT and MRI	USA	#1: CT at admission was unremarkable, but new bilateral occipital confluent WM hypodensities and lucencies in fronto-parietal WM and in left posterior limb of the internal capsule after 6 days; MRI-confirmed hyperintensities in same locations after 32 days. #2, #3, #4: hypoattenuation in bilateral parietal-occipital WM on CT and hyperintensities in same areas on MRI.
Pugin et al. (2020)	Case series	5	75 (69-78)[a]	2/3	Encephalopathy	Hypertension, diabetes, smoking, immunodepression, COPD, chronic kidney disease, cerebrovascular disease	MRI	Switzerland	All patients under mechanical ventilation. Abnormal contrast enhancement, consistent with inflammation of endothelial cells, in vascular walls of: vertebral artery (all cases), internal carotid (three cases), basilar artery (two cases) and both PCAs (one case); bilateral small watershed ischaemia in one case; no other brain abnormalities or enhancements in leptomeningeal spaces.
Chaumont et al. (2020)	Single case	1	69	0/1	Encephalitis—meningoencephalitis	None reported	MRI	France - Guadeloupe	No abnormalities.
Hosseini et al. (2020)	Single case (#2 from a case series)	1	79	1/0	Encephalitis—limbic encephalitis	None reported	CT and MRI	UK	Chronic small vessel ischaemic damage on first MRI; diffusion alterations in mediotemporal and limbic areas on subsequent CT and MRI.
Khoo et al. (2020)	Single case	1	65	1/0	Encephalitis—brainstem encephalitis	Osteoarthritis and gastro-oesophageal reflex disease, suspected AD	MRI	UK	No abnormalities.
Le Guennec et al. (2020)	Single case	1	69	0/1	Encephalitis—orbitofrontal encephalitis	Diabetes, hypertension, one previous seizure	CT and MRI	France	No abnormalities on CT; hyperintensity in the right orbitofrontal cortex, mesial prefrontal cortex and caudate nucleus. The hyperintensity persisted in the right caudate after 15 days, but completely resolved after 30 days.
Novi et al. (2020)	Single case	1	64	1/0	Encephalitis—ADEM	Vitiligo, hypertension, and monoclonal gammopathy	MRI	Italy	ADEM characterised by gadolinium-enhancing lesions in spinal cord, optic tract and in temporal/ occipital and frontal areas.
McCuddy et al. (2020)	Single case (#3 from a case series)	1	70	1/0	Encephalitis—ADEM	Obesity, peripheral neuropathy, glaucoma, type 2 diabetes, hypertension, chronic kidney disease, hyperlipidaemia	MRI	USA	Hyperintense lesions, mostly with restricted diffusion, in deep WM, corpus callosum and left brachium pontis. Slight improvement after 8 days.
Pilotto et al. (2020)	Single case	1	60	0/1	Encephalitis	None reported	CT and MRI	Italy	No abnormalities.
Avula et al. (2020)	Case series	4	73, 83, 80, 88	3/1	Cerebrovascular—ischaemia	Hypertension, dyslipidaemia, carotid stenosis, frequent urinary tract infections, type 2 diabetes and neuropathy	CT and MRI	USA	#1: Left parieto-occipital territory; #2: Right posterior frontal lobe; #3: Right middle-cerebral-artery stroke with hypoperfusion extending to almost the entire hemisphere; #4: Left mediotemporal lobe.
Basi et al. (2020)	Single case	1	66	0/1	Cerebrovascular—ischaemia	COPD, atrial fibrillation and previous ischaemic stroke	CT	UK	Right inferior medial prefrontal lobe with suspected infarction in the right cerebellum.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Katz et al. (2020)	Single case (from a case series)	1 (with neuroimaging details out of 86 cases)	62	1/0	Cerebrovascular—ischaemia	None reported	CT	USA	Bilateral middle cerebral artery infarction with anterior frontal involvement.
Morassi et al. (2020)	Case series	4 from a series of 6 cases	64, 75, 82, 76	1/3	Cerebrovascular—ischaemia	History of smoking, history of myocardial infarction, hypertension, diabetes mellitus, previous TIA, previous stroke, aortic valve replacement	CT	Italy	#1: Various cortical and subcortical regions of both hemispheres (including left occipital and right precentral territory); #2: Right cingulate gyrus, right fronto-parietal, left pericentral, bilateral occipital and vermian/left cerebellar areas; #3: Right thalamus and right temporal centrum semiovale; #4: Right caudate, left prerolandic and superior frontal areas.
Zayet et al. (2020)	Case series	2	84, 74	0/2	Cerebrovascular—ischaemia	Diabetes mellitus, arterial hypertension, coronary heart disease, peripheral arterial disease and atrial fibrillation, multiple cardiovascular diseases (including atrial fibrillation)	MRI	France	#1: Multiple regions including bilateral cerebellum, right occipital cortex, bilateral parieto-occipital cortical territory and fronto-parietal subcortical regions; #2: Large left frontal ischaemia and additional ischaemic areas in the cerebellum and in the parieto-occipital cortex, bilaterally.
Barrios-López et al. (2020)	Case series	3 from a series of 4 cases (#2, #3, #4)	64, 85, 87	2/1	Cerebrovascular—ischaemia	Hypertension, type 2 diabetes, hypertensive heart disease, asthma, atrial fibrillation and ischaemic heart disease	CT	Spain	#2: Left cerebellar and occipito-temporal regions; #3: Right fronto-temporal regions; #4: Right middle cerebral artery territory.
Mohamud et al. (2020)	Case series	4 from a series of 6 cases (#2, #3, #4, #6)	78, 62, 74, 67	1/3	Cerebrovascular—ischaemia	Diabetes, hypertension, chronic kidney disease and hyperlipidaemia	CT	USA	#2: Left caudate, putamen, and left fronto-parietal and paracentral cortices; #3: Right frontal and temporal lobes; #4 and #6: No abnormalities.
Papi et al. (2020)	Single case	1	79	1/0	Cerebrovascular—ischaemia	Hypertension, ischaemic heart disease, type 2 diabetes and atrial fibrillation	CT	Italy	Left frontal, parietal, insular and temporal areas of penumbra.
Bolaji et al. (2020)	Single case	1	63	0/1	Cerebrovascular—ischaemia	Diabetes and asthma	CT	UK	Right parietal cortex.
Goldberg et al. (2020)	Single case	1	64	0/1	Cerebrovascular—ischaemia	Hypertension, aplastic anaemia and splenectomy	CT	USA	Bilateral fronto-parietal regions.
Tunç et al. (2020)	Case series	3 from a series of 4 cases (#2, #3, #4)	67, 72, 77	1/2	Cerebrovascular—ischaemia	Hypertension	MRI	Turkey	#2: In proximity to the caudate body; #3: Left fronto-parietal regions; #4: Right pons.
Viguier et al. (2020)	Single case	1	73	0/1	Cerebrovascular—ischaemia	None reported	CT and MRI	France	Left fronto-parietal regions.
Zhang et al. (2020)	Case series	3	69, 65, 70	1/2	Cerebrovascular—ischaemia	Hypertension, diabetes and stroke, coronary artery disease, emphysema and nasopharyngeal carcinoma	CT	China	#1: Frontal, parietal and occipital lobe, basal ganglia, brainstem and cerebellum (bilaterally); #2: Right frontal and bilateral parietal lobe; #3: Bilateral frontal, right parietal, temporal and occipital lobe, and bilateral cerebellar hemispheres.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Diaz-Segarra et al. (2020)	Case series	2 from a series of 4 cases (#3 and #4)	65, 68	1/1	Cerebrovascular—ischaemia	Hypertension and type 2 diabetes	MRI	USA	#3: Scattered punctuated foci in both cerebral hemispheres; #4: Right medial occipital lobe.
Janjua and Moscote-Salazar (2020)	Single case	1	65	1/0	Cerebrovascular—ischaemia	Diabetes and mild dementia	CT	Colombia	Bilateral basal ganglia, occipital lobes and cerebellar hemispheres.
Co et al. (2020)	Single case	1	62	1/0	Cerebrovascular—ischaemia	Hypertension, prediabetes, dyslipidaemia and history of TIA	CT	Philippines	Left centrum semiovale and corona radiata.
Zhai et al. (2020)	Single case	1	79	0/1	Cerebrovascular—ischaemia	Atrial fibrillation	CT	China	Lacunar infarctions at the level of the insula, bilaterally, hippocampus and anterior temporal lobe, bilaterally.
Sparr and Bieri (2020)	Case series	2 from a series of 4 cases (#1 and #3)	84, 62	2/0	Cerebrovascular—ischaemia	Hypertension and diabetes mellitus	CT and MRI	USA	#1: Splenium of the corpus callosum; #3: Multiple bilateral cerebral and cerebellar infarctions and the right side of the splenium of the corpus callosum.
Jillella et al. (2020)	Case series	10 from a sample of 13 (#2, #3, #5, #6, #7, #8, #9, #11, #12, #13)	8 in their 60's, 2 in their 70's	1/9	Cerebrovascular—ischaemia	Atrial fibrillation or flutter, hypertension, hyperlipidaemia, diabetes, deep venous thrombosis/pulmonary embolism	CT and MRI	USA	#2: Left parietal, right frontal and occipital lobe, bilaterally; #3: Right insula; #5: Left frontal and temporal lobe, bilaterally; #6: Left parieto-occipital; #7: Left temporo-parietal; #8: Right frontal, temporal and parietal; #9: Right thalamus, left cerebellum and left capsula; #11: Left frontal; #12: Basal ganglia, cerebellum and parieto-occipital lobe, bilaterally; #13: fronto-parietal regions.
Kananeh et al. (2020)	Single case (from a case series)	1 from a sample of 4 (#2)	70	1/0	Cerebrovascular—ischaemia	Atrial fibrillation (new onset)	CT	USA	The majority of the right hemisphere.
Tiwari et al. (2020)	Case series	8 from a sample of 16 (#8, #9, #11, #12, #13, #14, #15, #16)	73, 82, 80, 74, 60, 62, 64, 67	4/4	Cerebrovascular—ischaemia	Hypertension, previous cerebrovascular accident, diabetes mellitus, chronic kidney disease, coronary artery disease, congestive heart failure	CT and MRI	USA	#8: Left parieto-occipital; #9: Left frontal; #11: Basal ganglia and capsula; #12: Thalamus and capsula; #13: Capsula; #14: Left putamen; #15: Unspecified right territory; #16: Left parieto-occipital.
Ghani et al. (2020)	Single case (from a case series)	1 out of 3 cases	61	0/1	Cerebrovascular—haemorrhage	Diabetes	CT	USA	Scattered subarachnoid haemorrhages and a subdural hematoma involving the cerebellum.
Benger et al. (2020)	Single case (from a case series)	1 out of 5 cases	54	1/0	Cerebrovascular—haemorrhage	None reported	CT and MRI	UK	Posterior division of the right capsule.
Keaney and Mumtaz (2020)	Single case (from a case series)	1 out of 2 cases	72	1/0	Cerebrovascular—haemorrhage	Hypertension, type 2 diabetes, mild asthma	CT	UK	Extensive damage to the right hemisphere including frontal, temporal and parietal lobes.
Sharifi-Razavi et al. (2020)	Single case	1	79	0/1	Cerebrovascular—haemorrhage	None reported	CT	Iran	Extensive damage in the right temporal lobe.
Roy-Gash et al. (2020)	Single case	1	63	1/0	Cerebrovascular—haemorrhage	None reported	CT and MRI	France	Bilateral temporal.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Al-Dalahmah et al. (2020)	Single case	1	73	0/1	Cerebrovascular—haemorrhage	Hypertension, type 2 diabetes	CT	USA	Large portion of the cerebellum.
Muhammad et al. (2020)	Single case	1	60	1/0	Cerebrovascular—haemorrhage	None reported	CT	Germany	Ruptured aneurysm with damage of left ventromedial prefrontal cortex.
Fitsiori et al. (2020)	Case series	7 out of 9 cases (#A, #C, #D, #F, #G, #I, #J)	66, 76, 78, 79, 65, 72, 62	1/6	Cerebrovascular—haemorrhage	COPD, human immunodeficiency virus, Waldenstrom macroglobulinemia, coronary artery disease, cardiac valvulopathy, hypertension, hypercholesterolemia, prostate cancer, diabetes, dyslipidaemia, sleep apnoea, MCI, vitiligo and obesity	MRI	Switzerland	#A: Microbleeds in subcortical white matter, corpus callosum, basal ganglia, right anterior limb of the anterior capsule and left middle cerebellar peduncle; #C: Microbleeds in the corpus callosum, subcortical white matter and left parietal lobe; #D: Microbleeds in subcortical white matter, corpus callosum, left middle cerebellar peduncle and lacunar infarct in the external capsule; #F: Microbleeds in subcortical white matter and corpus callosum; #G: Lacunar infarcts in subcortical white matter, microbleeds in corpus callosum, middle cerebellar peduncle, posterior limb of the internal capsule, subcortical white matter and pontine myelinolysis; #I: Infarct in the centrum semiovale, microbleeds in the corpus callosum, subcortical white matter, posterior limb of the internal capsule, left middle cerebellar peduncle and cerebellum; #J: Microbleeds in corpus callosum and posterior limb of the internal capsule.
Pavlov et al. (2020)	Case series	2 from a sample of 3 (#2, #3)	64, 60	0/2	Cerebrovascular—haemorrhage	Hypertension, smoking history, type 2 diabetes, type 1 diabetes, hyperlipidaemia	CT	Russia	#2: Right basal ganglia, capsula; #3: Right ganglia, capsula, posterior temporal.
Sabayan et al. (2021)	Single case (from a case series)	1 out of 15 cases (#9)	60	0/1	Cerebrovascular—haemorrhage	Hypertension	CT	Iran	Parietal lobe, bilaterally.
Radmanesh et al. (2020a)	Retrospective database analysis	242 (n = 6 with neuroimaging description: #1, #2, #3, #4, #5, #6)	68.7 (16.7)[b] (74, 61, 62, 77, 63, 78)	92/150 (2/4)	Cerebrovascular—haemorrhage (#1, #2), ischaemia (#3, #4, #5, #6)	Not systematically described (#1: stented carotid artery, #2: hepatic cirrhosis)	CT and MRI	USA	#1: Right temporal lobe; #2: Left superior parietal regions; #3: Left inferior frontal regions; #4: Right-sided damage extending to the frontal and temporal lobe, capsula and basal ganglia; #5: Left lateral cerebellum; #6: Cingulate gyrus and body of the corpus callosum.
Hernández-Fernández et al. (2020)	Retrospective database analysis	12 from a sample of 23 (#2, #4, #5, #8, #10, #11, #12, #19, #20, #21, #22, #23)	83, 65, 75, 76, 62, 86, 65, 69, 61, 64, 68, 66	1/11	Cerebrovascular—ischaemia (#2, #4, #5, #8, #10, #11, #12), ischaemia and haemorrhage (#19, #21), haemorrhage (#20, #22), encephalopathy and haemorrhage (#23)	Hypertension, dyslipidaemia, ischaemic cardiopathy, rheumatic valve disease and atrial fibrillation, smoking, schizophrenia, type 2 diabetes, COPD, vitamin B12 deficiency, stable angina, sleep apnoea	CT and MRI	Spain	#2: Bilateral cerebellum, left thalamus and occipital regions; #4: Right fronto-temporal regions; #5: Right parietal regions, thalamus and left frontal lobe; #8: Right insula; #10: Cerebellum; #11: Left insula; #12: Right parietal lobe; #19: Extensive left frontal and small right frontal haemorrhages; Bilateral parieto-occipital FLAIR hyperintensities; #20: Left lateral temporal extending to the Sylvian fissure; #21: Multiple foci of cortical-subcortical and subarachnoid haemorrhage in temporal and occipital regions; Bilateral parieto-occipital and cerebellar hyperintensities; #22: Left ventrolateral prefrontal regions and right parieto-occipital white matter; #23: Leukoencephalopathy in the right posterior frontal lobe and in parietal-occipital regions bilaterally (with microbleeding).

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Beyrouti et al. (2020)	Case series	5 from a series of 6 cases (#1, #3, #4, #5, #6)	64, 85, 61, 83, 73	0/5	Cerebrovascular—Ischaemia and haemorrhage (#1), ischaemia (#3, #4, #5 and #6)	Hypertension, hypercholesterolaemia, atrial fibrillation, ischaemic heart disease, prostate cancer, stroke, chronic leg ulcers, diabetes, smoking and alcohol consumption, Gastric carcinoma and benign essential tremor	CT and MRI	UK	#1: Left inferior posterior cerebellar petechial haemorrhage and ischaemia in posteromedial temporal, occipital and thalamic territory; #3: Left temporal stem and cerebral peduncle; #4: Right striatum; #5: Right anterior-temporal and lateral temporal/perisylvian; #6: Ischaemia in the left haemi-pons and right parieto-occipital patchy pattern.
Fan et al. (2020)	Case series (from a cohort)	7 from a cohort of 86 cases with AIS	All in the age range 65-70 y.o.	2/5	Cerebrovascular—ischaemia (#1, #2, #3, #4, #5, #6) and haemorrhage (#7)	Hypertension, diabetes mellitus, coronary artery disease, ischaemic stroke, hyperlipidaemia, ischaemic stroke in the cerebellum, nasopharyngeal carcinoma, myocardial infarction developed after COVID-19 onset and COPD	CT	China	#1: Right occipital lobe and bilateral frontal and parietal lobes; #2: Left hemisphere and bilateral occipito-temporal regions; #3: Parieto-frontal regions, bilaterally; #4: Right hemisphere; #5: Left midbrain; #6: In proximity of the right periventricular tissue; #7: Sub-arachnoid space and lateral ventricles.
Saggese et al. (2020)	Single case	1	62	1/0	Cerebrovascular—ischaemia and haemorrhage	Hypertension, diabetes, previous smoker, and previous myocardial infarction	CT	Italy	Bilateral basal fronto-temporal area of ischaemia with left haemorrhagic transformation.
Chougar et al. (2020)	Single case	1	72	0/1	Cerebrovascular—ischaemia and haemorrhage	None reported	CT and MRI	France	Bilateral hypo/hyperdensities in various areas, including thalamus, basal ganglia, internal capsule, splenium of the corpus callosum, deep white matter, cerebral peduncle and pons.
Jaunmuktane et al. (2020)	Single case (from a case series)	1 out of 2 cases	#2 in her 60's	1/0	Cerebrovascular—ischaemia and haemorrhage	Hypertension	MRI	UK	Involvement of multiple brain regions, including the right thalamus, the right intraparietal sulcus, and bilateral cerebellum.
Mohamed et al. (2020)	Single case	1	Patient in her 70's	1/0	Cerebrovascular—ischaemia and haemorrhage	Severe obesity, asthma and diabetes	CT	UK	Left ischaemic infarction with areas of haemorrhage involving frontal-to-occipital territory.
Hanafi et al. (2020)	Single case	1	65	0/1	Cerebrovascular—ischaemia and haemorrhage	None reported	CT and MRI	France	Ischaemic foci in deep white matter and centrum semiovale, basal ganglia, middle cerebellar peduncle and cerebellum; haemorrhage in the globus pallidus, bilaterally.
Chen et al. (2020)	Case series	5 from a sample of 11 (#2, #3, #5, #6, #8)	81, 68, 87, 70, 89	4/1	Cerebrovascular—ischaemia (#2, #5, #6, #8) and haemorrhage (#3)	Hypertension and diabetes (none in 3 cases)	CT	China	#2: Left fronto-temporal; #3: Brainstem; #5: Pons; #6: Left parietal; #8: Basal ganglia.
Sierra-Hidalgo et al. (2020)	Case series	6 from a sample of 8 (#1, #2, #3, #4, #5, #7)	78, 83, 77, 60, 76, 61	1/5	Cerebrovascular—ischaemia (#1, #2, #3, #5) and ischaemia and haemorrhage (#4, #7)	Hypertension, diabetes, dyslipidaemia, atrial fibrillation, coronary heart disease	CT	Spain	#1: Left temporo-occipital; #2: Left fronto-temporal; #3: Left basal ganglia and fronto-temporal cortex; #4: Frontal and parietal regions, bilaterally, with right frontal haemorrhagic transformation; #5: Right posterior parietal; #7: Right cerebellum and mediotemporal, bilaterally, with haemorrhagic transformation in right mediotemporal and bilateral frontal, temporal and occipital regions.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Oliveira et al. (2020)	Single case	1	69	0/1	Cerebrovascular—vasculitis	Hypertension	MRI	Brazil	Regional vasculitis (at the level of the brainstem) with no nervous tissue involvement.
Franceschi et al. (2020)	Single case (from a case series)	1 out of 2 cases	67	0/1	Cerebrovascular—encephalopathy and haemorrhage	Hypertension, diabetes, coronary artery disease, gout and asthma	CT and MRI	USA	Oedemas in the right frontal lobe, basal ganglia, cerebellum and parieto-occipital regions, with superimposed haemorrhage in the right parieto-occipital territory.
Benameur et al. (2020)	Single case (#3 from a case series)	1	64	0/1	Encephalopathy and encephalitis	None reported	MRI	USA	Non-enhancing abnormality in the right anterior-medial temporal lobe.
Farhadian et al. (2020)	Single case	1	78	1/0	Encephalopathy and encephalitis	History of kidney transplant, on immunosuppression	MRI	USA	Atrophy and widespread periventricular and subcortical WM hyperintensities due to small vessel ischaemic disease across all lobes.
Hayashi et al. (2020)	Single case	1	75	0/1	Encephalopathy and encephalitis	Mild AD	MRI	Japan	One reversible hyperintense area in the splenium of the corpus callosum.
Abdelnour et al. (2020)	Single case	1	69	0/1	Encephalopathy, encephalitis, cerebrovascular	Hypertension, type 2 diabetes and mild chronic obstructive pulmonary disease	MRI	UK	No abnormalities apart from old infarcts in the left frontal, parietal and occipital lobes.
Mahammedi et al. (2020)	Case series	108	71 (60.5-79)[a]	39/69	Encephalopathy, encephalitis, cerebrovascular	Hypertension, diabetes, coronary artery disease, cerebrovascular disease, malignancy, MS, HIV, Behçet disease, haemoglobinopathy	CT and MRI	Italy	Neuroimaging abnormalities in 51 out of 108 cases: mostly acute ischaemic infarcts (34 out of 51), especially in the MCA territory, but in the basal ganglia in seven cases; six intracranial haemorrhages (location not specified); WM lesions in subcortical WM and the basal ganglia; rare encephalopathies in three cases and PRES in 1 case.
Paterson et al. (2020)	Case series	15 (out of 43)	60-85	3/12	Encephalopathy (#1, #2, #8), encephalitis (#12, #14, #19), cerebrovascular (#23, #24, #25, #28, #29) and PNS signs (#31, #33, #35, #38)	CADASIL, previous right occipital stroke, TIA, bladder cancer, nephrectomy, hypercholesterolemia, hypothyroidism, hysterectomy, osteoarthritis, degenerative spine disease, diabetes, hypertension, cellulitis, increased BMI, Conn Syndrome, recurrent DVT, atrial fibrillation, ischaemic heart disease, prostate cancer (Gleason Score 4+5), gastric carcinoma, benign essential tremor, cluster headache, cervical myelopathy, arrhythmia, depression, myeloma, cerebellar stroke	CT and MRI	UK	*Encephalopathies*: no abnormalities. *Encephalitis*: hyperintensities in upper pons, limbic lobes, medial thalami and subcortical cerebral WM in one case; multifocal and confluent lesions in the cerebral hemispheric WM and several microhaemorrhages in the subcortical regions in one case; multifocal lesions in periventricular WM and corpus callosum in one case. *Cerebrovascular:* Acute infarct in the right striatum and multiple cortical and subcortical microhaemorrhages in one case; acute left cerebellar and bilateral PCA infarctions in one case; subacute infarcts in frontal WM and arterial border-zones bilaterally in one case; hyperdensity due to thrombus in the left PCA and acute infarction in the left temporal stem and cerebral peduncle in one case; infarction in the right thalamus, left pons, right occipital lobe and right cerebellum in one case. *PNS signs:* no abnormalities.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Pons-Escoda et al. (2020)	Cohort	103	74 (50-90)[c]	40/63	Encephalopathy, encephalitis, cerebrovascular	Only patients with cerebrovascular accidents: hypertension, hypercholesterolemia, diabetes, smoker, atrial fibrillation	CT and MRI	Spain	No abnormalities due to COVID-19 infection in 80 patients; 23 with mainly vascular damages: one basilar strip aneurysm, one cerebellar aneurysm, three basal ganglia haematomas, one left parietal haematoma, three lobar haematomas (location not specified), one cerebellar small vessel infarction, two left prefrontal infarctions, three small vessel and eight large vessel occlusions (location not specified), one left parietal haemorrhage due to TBI.
Helms et al. (2020a)	Case series	58	63[d]	Not reported	Encephalopathy, cerebrovascular	TIA, epilepsy, MCI (in seven out of 58)	MRI (only in 13 cases)	France	Leptomeningeal enhancements in eight cases (occipito-parietal and right frontal in one case and left parietal in another case); bilateral fronto-temporal hypoperfusion in 11 cases; cerebral ischaemic stroke in three cases (right cerebellar in one case).
Helms et al. (2020b)	Cohort	140 (118 with delirium)	62 (52–70)[a]; with delirium: 62 (52–71)[a]	40/100; with delirium: 29/89	Encephalopathy, cerebrovascular	Stroke, TIA; epilepsy, MCI, migraine, TBI, aneurysm, cardiovascular diseases, haemopathies, immune diseases, diabetes, chronic liver disease, chronic renal disease, COPD, asthma, OSA	MRI (only in 32 cases with severe delirium)	France	WM microhaemorrhages across all lobes and cerebellum in seven cases and one left frontal intraparenchymal haematoma; WM hyperintensities in four cases (location not specified); subarachnoid enhancements in 17 cases (location not specified); cerebral ischaemic stroke in three cases (location not specified); hypoperfusion in 17 cases, especially in medial temporal and right frontal areas.
Krett et al. (2020)	Single case	1	69	0/1	Encephalopathy, cerebrovascular	Hypertension, diabetes, coronary artery disease	CT and MRI	Canada	CT assessment at hospital admission and after 13 days showed no abnormalities and no vasculopathy. MRI at day 13 showed diffuse multicompartmental haemorrhages (location not specified), including subarachnoid, with surrounding oedema.
Lin et al. (2020)	Cohort	278 (with CT/MRI)	71.8 (15.4)[b]	113/165	Encephalopathy, cerebrovascular	Atrial fibrillation, hypertension, hyperlipidaemia, diabetes, coronary artery disease, chronic kidney disease, COPD	CT and MRI	USA	*Encephalopathy:* PRES in three cases; Enhancements in the optic nerve in two cases and in the olfactory bulb, in the absence of volume changes, in four cases. No evidence of cortical hyperintensities, haemorrhagic encephalitis and leptomeningeal enhancements. *Cerebrovascular:* Acute and subacute cerebral infarctions in 31 cases: mainly multiterritory, but without a consistent pattern; Intracranial haematomas in 10 cases (no location specified); Microhaemorrhages in 26 cases: mainly mild and without a consistent pattern (cortical, WM, basal ganglia, cerebellum), apart from three cases with predominant damage in the corpus callosum, internal capsules, and juxtacortical WM.
Nicholson et al. (2020)	Single case (#3 from a case series)	1	62	0/1	Encephalopathy, cerebrovascular	None reported	CT and MRI	Canada	No abnormalities on CT. On MRI: enhancements in the subarachnoid and subpial spaces (no location specified); widespread hyperintensities along small cortical veins (no location specified); abnormal signal in subcortical areas, especially the corpus callosum.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Radmanesh et al. (2020b)	Case series	5 from a series of 11 cases (#3, #5, #6, #10 and #11)	60, 64, 63, 64, 62	2/3	Encephalopathy, cerebrovascular	Hypertension, diabetes, coronary artery disease, hyperlipidaemia, atrial fibrillation, obesity	MRI	USA	All cases: leukoencephalopathy in bilateral deep and subcortical WM, especially in posterior regions of temporal and occipital horns; abnormalities in precentral gyrus juxtacortical WM, centrum semiovale and corona radiata; no abnormalities in deep GM nuclei. In four cases: microhaemorrhages, mostly acute, especially in juxtacortical WM and the splenium of the corpus callosum.
Neuropathology findings									
Al-Dalahmah et al. (2020)	Single case	1	73	0/1	Neuropathology examination (and CT)	Hypertension, type 2 diabetes	Macroscopic and microscopic examinations	USA	*Macroscopic:* Upward herniation of the midbrain; subarachnoid haemorrhage at the base of the brain; haematoma and oedema in the right deep cerebellar WM; bilateral tonsil herniation; intra-ventricular haemorrhage and dilatation of the lateral and third ventricles; alterations in brain stem structures; cortex and cerebral WM were spared. *Microscopic:* Severe hypoxic damage to neurons in the cerebral cortex, striatum, thalamus, amygdala, hippocampus, midbrain, pontine nuclei, medullary nuclei and Purkinje cells; red blood cells and neutrophilic infiltration in the cerebellar WM; no evidence of vasculitis; microglial activation in inferior olives and dentate nuclei; inflammatory infiltrates in corpus callosum, striatum, thalamus, hippocampus, midbrain and pons, but cortex and other subcortical structures were spared; astrogliosis in OFC and SFC; inflammation in olfactory epithelium. COVID-19 present in cerebellum (including clot) and olfactory bulb, but not in the medulla oblongata.
Hernández-Fernández et al. (2020)	Case series	2 (#19 and #20, out of 23 cases)	69, 61	0/2	Neuropathology examination (and CT)	Hypertension, dyslipidaemia	Macroscopic and microscopic examinations	Spain	*Macroscopic:* In both cases: large intraparenchymal haemorrhage (one left frontal and one left parieto-temporal) with diffuse fibrin microthrombi. *Microscopic:* Disappearance of endothelial cells in arterioles, capillaries and venules; degeneration of the neuropil in the capillary periphery; local inflammation; rare inflammation of blood vessel walls; no evidence of arteriolosclerosis and cerebral amyloid angiopathy.
Jaunmuktane et al. (2020)	Case series	2	F in her 60's, M in his 50's	1/1	Neuropathology examination (and MRI)	Hypertension	Macroscopic and microscopic examinations	UK	*Macroscopic:* Bilateral pallidal infarcts, widespread acute and subacute microinfarcts and microbleeds, especially in occipital lobe WM in one case; ischaemic lesions in watershed areas in the centrum semiovale and in the right lentiform nucleus, infarcts in bilateral occipital lobe and left hippocampus and thalamus in the other case. *Microscopic:* Axonal damage but no demyelination; no evidence of microglial nodules, neuronophagia, vascular injury and vasculitis (apart from infarct areas) in either cases; inflammation in the medulla was similar to patients with other neurological diseases; leptomeningeal inflammation in right intraparietal sulcus in one case.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Bradley et al. (2020)	Case series	5 (with brain examination out of 14 cases)	57, 76, 84, 81, 42	3/2	Neuropathology examination	End-stage renal disease, type 2 diabetes, hypertension, OSA, obesity, osteoporosis, hyperlipidemia, chronic kidney disease, COPD, mitral regurgitation, complete heart block, chronic pain, arthritis, breast cancer, demyelinating neuropathy, lacunar infarcts, pneumonia, AD, anaemia	Macroscopic and microscopic examinations	USA	*Macroscopic:* Scattered subarachnoid haemorrhages in one case in one case; no abnormalities in the other four cases. *Microscopic:* Scattered subarachnoid haemorrhages and microhaemorrhages in the brainstem in one case; no abnormalities in the other four cases.
Buja et al. (2020)	Case series	3 (with brain examination out of 23 cases)	77, 42, 48	0/3	Neuropathology examination	Obesity, hypertension, splenectomy, myotonic dystrophy	Macroscopic and microscopic examinations	USA	*Macroscopic:* No abnormalities in all cases. *Microscopic:* No histopathological changes in one case (no histopathology in the other two cases).
Bulfamante et al. (2020)	Single case	1	54	0/1	Neuropathology examination	None reported	Microscopic ultrastructural examinations of ON, GR and MO	Italy	Severe and widespread damage to neurons, glia, axons and myelin sheath (ON > GR > MO); detection of viral particles compatible with COVID-19; preservation of mitochondria.
Kantonen et al. (2020)	Case series	4	63, 82, 38, 90	1/3	Neuropathology examination	Hypertension, gout, chronic kidney disease, smoking, sick sinus syndrome, coronary artery disease, myocardial infarction, peripheral artery disease, stroke, PD, type 2 diabetes, COPD, colorectal cancer, obesity, retinopathy, polyneuropathy, cellulitis, asthma, AD, osteoporosis, spinal stenosis, lung infection	Macroscopic and microscopic examinations	Finland	*Macroscopic:* Mild swelling, depigmentation of substantia nigra and locus coeruleus, enlarged perivascular spaces, microhaemorrhages in cerebral and cerebellar WM in one case; no information for the other three cases. *Microscopic:* Hypoxic injury and perivascular degeneration in all cases; WM lesions and PD pathology in one case; AD, cerebral amyloid angiopathy and Lewy bodies in one case; no evidence of COVID-19 in the neural tissue.
Matschke et al. (2020)	Case series	43	76 (70–86)[a]	16/27	Neuropathology examination	COPD, dementia, ischaemic heart disease, renal insufficiency, atrial fibrillation, cardiac insufficiency, myelofibrosis, emphysema, hypertension, diabetes, stroke, aortic aneurysm, cardiac hypertrophy, acute myeloid leukaemia, cardiomyopathy, thyroid cancer, PD, trisomy 21, epilepsy, hypoxic brain damage, cardiac arrhythmia, OSA, ulcerative colitis, lung granuloma, aortic valve	Macroscopic and, for 23 out of 43, microscopic examinations of OB, SFC, basal ganglia (including the putamen), upper and lower medulla oblongata,	Germany	*Macroscopic:* No abnormalities in 13 cases; old infarctions in five cases; GM heterotopia in one case; one cerebellar metastasis from lung cancer; new infarctions in six cases (three in PCA, two in MCA, and one in ACA territories); oedema in 23, but none in 20 cases; atrophy in 20, but none in 23 cases; arteriosclerosis in all cases (mild in 12, moderate in 22, severe in 9). *Microscopic:* Astrogliosis in all cases, to variable extent, but severe in the olfactory bulb; microglia activation mainly in the olfactory bulb, medulla oblongata and cerebellum, but also in subpial and subependymal regions (sign of encephalitis); cytotoxic T cells in brain stem, frontal cortex, basal ganglia; evidence of COVID-19 in 21 patients, in the frontal lobe in nine cases (out of 23), medulla oblongata in four cases (out of eight), but also in cranial nerves.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
						replacement, hypothyroidism, lung cancer, colon cancer, paranoid schizophrenia, myelodysplastic syndrome, liver cirrhosis, dysphagia, multiple myeloma	cerebellar hemispheres		
Menter et al. (2020)	Case series	3 + 1[e] (with brain examination out of 21 cases)	68, 96, 71	1/2	Neuropathology examination	Hypertension, atherosclerosis, obesity, MS, PD, dementia, coronary artery disease, myocardial infarction, peripheral arterial disease, infrarenal aortic aneurysm, coronary heart disease, valvulopathy, double bypass	Microscopic examinations	Switzerland	No inflammatory infiltrates or neuronal necrosis in any of the cases; mild hypoxic injury in three of the cases; hydrocephalus internus in two cases; pathological changes consistent with neurological comorbidities (MS and PD); COVID-19 presence in the brain was less prominent than in other organs, higher presence in the olfactory bulb than in the brainstem.
Reichard et al. (2020)	Single case	1	71	0/1	Neuropathology examination	ischaemic heart disease, coronary artery atherosclerosis	Macroscopic and microscopic examinations	USA	*Macroscopic:* Widespread WM haemorrhagic lesions and mild general swelling. *Microscopic:* WM haemorrhagic lesions with macrophages, axonal injuries and myelin loss, but no reactive astrogliosis; general reactive gliosis and myelin loss in WM; additional WM lesions surrounding blood vessels with macrophages, myelin loss and axonal injuries; cortical infarcts with astrogliosis; preserved subpial myelin; scattered hypoxic damage to neurons in neocortex, hippocampus (CA1), cerebellum (Purkinje cells); no infarcts in rest of the brain, basal ganglia, brainstem and spinal cord; only age-related corpora amylacea in the olfactory bulb.
Remmelink et al. (2020)	Case series	11 (with brain examination out of 17 cases)	77, 68, 64, 56, 66, 49, 63, 75, 61, 70, 53	3/8	Neuropathology examination	Coronary artery disease, cerebrovascular disease, diabetes, COPD, cancer, hypertension, chronic renal failure, liver transplant	Macroscopic and microscopic examinations	Belgium	*Macroscopic:* Recently drained subdural haematoma in one case; cerebral haemorrhage in one case. *Microscopic:* Cerebral haemorrhage or haemorrhagic suffusion in eight cases; focal ischaemic necrosis in three cases; oedema and/or vascular congestion in five cases; diffuse or focal spongiosis in 10 cases; no evidence of viral encephalitis, vasculitis, neuronal necrosis, or perivascular lymphocytic infiltration.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Youd and Moore (2020)	Case series	9 (3 positive to COVID-19, 3 likely false negatives, 3 with other respiratory infections)	88, 86, 73, 67, 33, 70, 87, 77, 68	5/4	Neuropathology examination	Type 1 an type 2 diabetes, hypertension, COPD, asthma, heart diseases, dementia, DVT, alcoholism, PD, stroke, HIV	Macroscopic examinations	UK	No abnormalities in three cases; brain atrophy in case with COVID-19 and dementia; old infarct and head injury in one case; circle of Willis atheroma in four cases.
Hanley et al. (2020)	Case series	9 (with brain analysis out of 10)	61, 64, 69, 78, 22, 24, 79, 97, 79	2/7	Neuropathology examination	COPD, ischaemic heart disease, migraine, prostatic hyperplasia, OSA, hypertension, type 2 diabetes, peripheral neuropathy, dementia, osteoarthritis, hypercholesterolaemia, trigeminal neuralgia, past bladder cancer, anaemia, glaucoma, alcohol-related liver disease, hypothyroidism, cutaneous systemic lupus erythematosus, vitamin B12 deficiency	Macroscopic and microscopic examinations on eight regions (unnamed)	UK	No necrosis was noted in any of the cases, apart from a macroscopic infarction; microglia activation and mild T cell infiltrations were observed in all the cases where these pathological features were examined (five cases); no mention of brain findings in three cases. Viral genetic material was detected in brain samples, but with variable load across cases.
Lee et al. (2021)	Case series	19	50 (5–73)[f]	4/15	Neuropathology examination	Obesity, cardiovascular disease, hypertension, type 2 diabetes, old TBI, drug use disorders	Microscopic examinations and post-mortem 11.7T MRI of OB and brainstem (in 13 cases), but also frontal cortex, basal ganglia and cerebellum in some cases.	USA	On *post-mortem* MRI: punctuate hyperintensities in nine cases, with microvascular injuries and fibrinogen leakage; punctuate hypointensities in 10 cases, with blood vessel congestion and fibrinogen leakage, but preserved vasculature; microhaemorrhages. *Microscopic:* No vascular occlusion; minimal perivascular inflammation (activated microglia, macrophage infiltrates and hypertrophic astrocytes) in 13 patients; T cells adjacent to endothelial cells in eight cases; activated microglia adjacent to neurons in five cases, suggesting neuronophagia in OB, substantia nigra, dorsal motor nucleus of the vagal nerve and the pre-Bötzinger complex. Viral genetic material was not detected in any of the brain samples.
Schurink et al. (2020)	Case series	21	68 (41–78)[f]	5/16	Neuropathology examination	Diabetes, cardiovascular disease, COPD, asthma, active solid malignancy, active haematological malignancy	Macroscopic and microscopic examinations covering all brain, spinal cord and meninges. Analysis of viral presence only in 11 cases.	The Netherlands	*Macroscopic:* most brains and meninges were normal with no atrophy, infarctions and haemorrhages. One case of pre-existing necrotising encephalopathy and one case of medial temporal atrophy due to AD. *Microscopic:* Hypoxic changes in all cases; all cases had moderate to severe microglial activation and perivascular accumulation of T cells in the most severe cases; no loss of myelin or bleeding; mild to moderate isomorphic reactive astrogliosis. Alterations were most severe in OB and medulla oblongata, but they were observed in all brain areas. COVID-19 was not detected in brain tissue in any of the cases.

(Continued)

TABLE 1 | Continued

Study	Design	*N*	Age	Sex (F/M)	Aetiology	Comorbidities	Method	Country	Brain findings
Vaira et al. (2020)	Single case	1	63	1/0	Neuropathology examination	None	Biopsy of the left olfactory epithelium and MRI to investigate cause of anosmia due to COVID-19	Italy	MRI exam showed no macrostructural abnormalities in the OB. *Microscopic:* Loss of surface epithelium with no surface fibrin, inflammatory exudate, eosinophils or mast cells; minimal chronic lymphocytic inflammatory infiltrates; no abnormal neuronal infiltrates; no upregulation of the angiotensin-converting enzyme 2 receptors.

[a]*Median (Interquartile range).*
[b]*Mean (Standard deviation).*
[c]*Median (5–95th percentile).*
[d]*Median for the whole sample, but no data for the subgroup who underwent MRI assessments.*
[e]*Not possible to track one case with neuropathological examination from all the materials made available.*
[f]*Median (range).*
ACA, Anterior cerebral artery; AD, Alzheimer's disease; ADEM, Acute disseminated encephalomyelitis; AIS, Acute ischaemic stroke; BMI, Body mass index; CA1, Cornu Ammonis 1; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; COPD, Chronic obstructive pulmonary disease; CT, Computerised tomography; DVT, Deep-vein thrombosis; FDG-PET, Fluorodeoxyglucose-positron emission tomography; GR, Gyrus rectus; MCA, Middle cerebral artery; MCI, Mild cognitive impairment; MO, Medulla oblongata; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; OB, Olfactory bulb; ON, Olfactory nerve; OSA, Obstructive sleep apnoea; OFC, Orbitofrontal cortex; PCA, Posterior cerebral artery; PD, Parkinson's disease; PNS, Peripheral nervous system; PRES, posterior reversible encephalopathy syndrome; SFC, Superior frontal cortex; TBI, Traumatic brain injury; TIA, Transient ischaemic attack; WM, White matter.

leukoencephalopathy was detected in the right frontal lobe and in the cerebellum bilaterally (Anand et al., 2020). Delorme et al. (2020) also reported mainly frontal alterations using MRI and FDG-PET: hypometabolism in the frontal cortex bilaterally in all four reported cases (prefrontal in three and orbitofrontal in one) and in posterior associative parieto-temporal cortices in two cases, but also hypermetabolism in the cerebellar vermis in all cases and bilaterally in the striatum in two cases. Moreover, hyperintensities were evident in the right orbitofrontal cortex in one case. Similarly, widespread hypometabolism was found in a 62-year-old man particularly in mediotemporal, brainstem, thalamic/hypothalamic, and right inferior frontal areas (Guedj et al., 2020). Hyperintensities and hypometabolism were found throughout the left hemisphere cortex, the left caudate nucleus, the thalamus, and the right cerebellum in a case with concomitant Creutzfeldt-Jakob disease (Young et al., 2020). White matter (WM) damage was observed in multiple cases with encephalopathy: deep periventricular and subcortical WM ischaemic lesions in a patient with anorexia and depression (Jang et al., 2020), and widespread WM alterations, mainly in parietal and occipital areas, in two case series (Muccioli et al., 2020; Parauda et al., 2020). Manganelli et al. (2020) found signs of gliosis in the right pons of a woman with COVID-19 using CT, but no abnormalities were found on MRI examination. Additionally, signs of inflammation of endothelial cells were observed in several cerebral arteries in a small case series where only one patient had bilateral ischaemic damage detectable on MRI (Pugin et al., 2020).

A considerable proportion of studies found either no abnormalities or old/unrelated signs of neural damage on MRI including: four single cases, two of which also included CT examinations; a patient with Miller-Fisher-like syndrome (Fernández-Domínguez et al., 2020); one with schizophrenia (Palomar-Ciria et al., 2020); and two with non-epileptic seizures (Logmin et al., 2020; Vollono et al., 2020). Moreover, no evidence of abnormalities was also found by Anand et al. (2020) on the CT scans of two out of five patients with epilepsy and by Manganelli et al. (2020) in one of the two cases investigated.

Encephalitis

Signs of encephalitis were investigated specifically in seven patients with COVID-19: four men (Chaumont et al., 2020; Le Guennec et al., 2020; McCuddy et al., 2020; Pilotto et al., 2020), three women (Hosseini et al., 2020; Khoo et al., 2020; Novi et al., 2020), one of whom had suspected Alzheimer's disease (AD) (Khoo et al., 2020). The majority of these studies (Chaumont et al., 2020; Khoo et al., 2020; Pilotto et al., 2020) observed no abnormalities on either MRI (all cases) or CT examinations (Pilotto et al., 2020). Diagnosis of encephalitis was variable across studies, based mainly on MRI findings and confirmed by cerebrospinal fluid abnormalities only in three studies (Chaumont et al., 2020; Novi et al., 2020; Pilotto et al., 2020). In one case encephalitis was suspected on the basis of clinical presentation and response to corticosteroid treatment (Khoo et al., 2020). However, in the case investigated by Hosseini et al. (2020), alterations of diffusion in left mediotemporal and limbic areas were found over time, on both CT and MRI scans, and these

alterations were interpreted as limbic encephalitis. Le Guennec et al. (2020) found no abnormalities on CT examination, but a right-lateralised area of MRI hyperintense signal was found encompassing the orbitofrontal and medial prefrontal cortices and the caudate nucleus, that gradually resolved over one month. Similarly, hyperintensities with restricted diffusion were observed in deep WM, the corpus callosum and the left brachium pontis in a patient, with clinical improvement over a period of 8 days (McCuddy et al., 2020). Another case presented with multiple gadolinium-enhancing lesions affecting the spinal cord, the optic tract, temporal, occipital and frontal areas suggesting acute disseminated encephalomyelitis (Novi et al., 2020).

Cerebrovascular Events

Forty-five studies in total, mostly single-case or case-series reports, described the topological features of brain involvement due to acute cerebrovascular events occurring concomitantly with COVID-19 infection.

The only group study (Radmanesh et al., 2020a) included a total of 242 adults (68.7 ± 16.7 years old) and was based on recruitment carried out in a single academic clinical centre. The most common finding in this cohort was the presence of acute/sub-acute infarcts (∼19.4% of patients), followed by radiological evidence of abnormal microangiopathy (∼11%), intracranial COVID-19-related haemorrhage (∼3%), and in one patient there was an anoxic injury due to supra- and infra-tentorial haemorrhage. Additional details were provided for the following six patients: a 74-year-old man with a right inferior frontal haemorrhage, a 61-year-old woman with a left parietal haemorrhage, a 62-year-old man with a left frontal ischaemic stroke, a 77-year-old woman with a large right fronto-temporal ischaemia, a 63-year-old man with an acute infarct in the left cerebellum and a 78-year-old man with ischaemic involvement of the middle cingulate and the body of the corpus callosum. The map of neural damage for the remaining patients was not described.

When single cases and case series were assessed, a total of 120 patients met the demographic and methodological criteria set by this review study. These clinical reports included 84 cases of ischaemic stroke, 23 cases of haemorrhagic events, 10 patients with significant mixed ischaemic and haemorrhagic processes, two patients with a form of encephalopathy and microhaemorrhages and one case of vasculitis without any noticeable involvement of brain tissue.

Ischaemia

Various vascular findings (including coagulopathy and cardioembolism, with vessel occlusion, thrombosis, or stenosis) were responsible for the ischaemic events described in the literature, and the territory affected by the CT/MRI-informed changes involved multiple neural structures. All cerebral lobes have been reported to be affected by ischaemic events associated with COVID-19 including the frontal lobe (Avula et al., 2020; Basi et al., 2020; Fan et al., 2020; Hernández-Fernández et al., 2020; Jillella et al., 2020; Katz et al., 2020; Mohamud et al., 2020; Morassi et al., 2020; Papi et al., 2020; Tiwari et al., 2020; Zayet et al., 2020; Zhang et al., 2020) with additional involvement of pericentral areas (Mohamud et al., 2020; Morassi et al., 2020), the temporal lobe (Beyrouti et al., 2020; Jillella et al., 2020; Mohamud et al., 2020; Morassi et al., 2020; Papi et al., 2020; Tiwari et al., 2020; Zhai et al., 2020; Zhang et al., 2020), fronto-temporal regions (Barrios-López et al., 2020; Chen et al., 2020; Hernández-Fernández et al., 2020; Mohamud et al., 2020; Papi et al., 2020; Sierra-Hidalgo et al., 2020), the parietal lobe (Bolaji et al., 2020; Chen et al., 2020; Fan et al., 2020; Hernández-Fernández et al., 2020; Jillella et al., 2020; Papi et al., 2020; Sierra-Hidalgo et al., 2020; Zayet et al., 2020; Zhang et al., 2020), fronto-parietal regions (Fan et al., 2020; Goldberg et al., 2020; Jillella et al., 2020; Mohamud et al., 2020; Morassi et al., 2020; Tunç et al., 2020; Viguier et al., 2020; Zayet et al., 2020; Zhang et al., 2020), the occipital lobe (Diaz-Segarra et al., 2020; Fan et al., 2020; Hernández-Fernández et al., 2020; Janjua and Moscote-Salazar, 2020; Jillella et al., 2020; Morassi et al., 2020; Zhang et al., 2020), and the parieto-occipital (Avula et al., 2020; Beyrouti et al., 2020; Jillella et al., 2020; Tiwari et al., 2020; Zayet et al., 2020), temporo-parietal (Jillella et al., 2020), or temporo-occipital territory (Barrios-López et al., 2020; Fan et al., 2020; Sierra-Hidalgo et al., 2020). Seven of the 84 cases with cerebral ischaemia did show a cerebral involvement but no detailed description was provided to map brain damage with accuracy (Barrios-López et al., 2020; Co et al., 2020; Diaz-Segarra et al., 2020; Fan et al., 2020; Hanafi et al., 2020; Kananeh et al., 2020; Tiwari et al., 2020; Tunç et al., 2020; Zhang et al., 2020). Additionally, a number of studies have documented an involvement of the insular region (Hernández-Fernández et al., 2020; Jillella et al., 2020; Papi et al., 2020; Zhai et al., 2020), of limbic regions located in the mediotemporal lobe (Avula et al., 2020; Zhai et al., 2020) and in the cingulate gyrus (Morassi et al., 2020), and of the dorsal striatum (Beyrouti et al., 2020; Hanafi et al., 2020; Mohamud et al., 2020; Morassi et al., 2020; Tunç et al., 2020) or, more generally, of the basal-ganglia territory (Chen et al., 2020; Janjua and Moscote-Salazar, 2020; Jillella et al., 2020; Sierra-Hidalgo et al., 2020; Tiwari et al., 2020; Zhang et al., 2020). Two patients presented with an infarction affecting the corpus callosum (Sparr and Bieri, 2020). Other than the cerebrum, evidence of diencephalic ischaemia affecting the thalamus has been reported in six patients (Hernández-Fernández et al., 2020; Jillella et al., 2020; Morassi et al., 2020; Tiwari et al., 2020), and cerebellar involvement in 11 cases (Barrios-López et al., 2020; Basi et al., 2020; Hanafi et al., 2020; Hernández-Fernández et al., 2020; Janjua and Moscote-Salazar, 2020; Jillella et al., 2020; Morassi et al., 2020; Sierra-Hidalgo et al., 2020; Sparr and Bieri, 2020; Zayet et al., 2020). Brainstem infarction was described in six patients: three in the pons (Beyrouti et al., 2020; Chen et al., 2020; Tunç et al., 2020); one in the midbrain (Fan et al., 2020); one in the cerebral peduncle (Beyrouti et al., 2020); and one in an unspecified brainstem area (Zhang et al., 2020). Two cases of cerebrovascular occlusion with no acute neural damage were described by Mohamud et al. (2020).

Haemorrhage

A heterogeneous pattern was also observed in the case series with a pure haemorrhagic presentation (without any concurrent significant ischaemic or encephalopathic features). In the 11 cases

presenting with a large haemorrhage, the regions involved were the left temporal lobe (Ghani et al., 2020; Hernández-Fernández et al., 2020; Sharifi-Razavi et al., 2020), the right temporal/insular territory (Benger et al., 2020), the temporal lobe bilaterally (Roy-Gash et al., 2020), the left frontal lobe (Hernández-Fernández et al., 2020), the parietal lobe bilaterally (Sabayan et al., 2021), the cerebellum (Al-Dalahmah et al., 2020), the basal ganglia (Pavlov et al., 2020), and a large portion of the right hemisphere (Keaney and Mumtaz, 2020). In one case, the regions affected included the lateral ventricles and the subarachnoid space with no additional details reported (Fan et al., 2020). In the case of a patient, a frontal haemorrhage was due to the rupture of an aneurysm (Muhammad et al., 2020). Eight patients, finally, showed evidence of subcortical white-matter microbleeds with the involvement of the brainstem (Chen et al., 2020) and of the corpus callosum (Fitsiori et al., 2020), and of these latter, four also presented with a mixed pattern of widespread microbleeds and lacunar haemorrhagic infarcts.

Mixed Ischaemia and Haemorrhage Pattern

Of the cases with a mixed ischaemic-haemorrhagic presentation, one patient showed evidence of right frontal subarachnoid bleeding, left intraparenchymal hematoma, and a concurrent pattern of confluent hyperintensities affecting parieto-occipital regions bilaterally (Hernández-Fernández et al., 2020). A second patient presented with cortical/sub-cortical haemorrhage in the temporal and occipital lobe, multiple sub-arachnoid haemorrhages and bilateral parieto-occipital hyperintensities (Hernández-Fernández et al., 2020). A third patient suffered from ischaemia with haemorrhagic transformation in left temporo-parietal regions (Saggese et al., 2020). A fourth patient showed haemorrhage in proximity of the left cerebellar hemisphere and concurrent ischaemic changes in occipital, thalamic and posteromedial territories (Beyrouti et al., 2020). A fifth patient showed a subcortical ischaemic event affecting the thalamus, basal ganglia, internal capsule and the splenium, with concomitant haemorrhage in the right cerebral peduncle and pons (Chougar et al., 2020). A sixth patient showed numerous hyperintensities, leukoaraiosis in the right intraparietal sulcus and microhaemorrhages in the left centrum semiovale, thalamus, left cerebellum and left anterior temporal lobe (Jaunmuktane et al., 2020). A seventh patient presented with bilateral ischaemic-haemorrhagic infarctions affecting, above all, a large proportion of the left hemisphere from frontal to occipital regions (Mohamed et al., 2020). An eight patient had several ischaemic regions scattered across his white matter including the cerebellum, deep white matter and centri semiovale, with a concomitant lenticular haemorrhage (Hanafi et al., 2020). A ninth patient showed ischaemic changes affecting frontal and parietal regions, bilaterally, with haemorrhagic transformation in the right frontal lobe (Sierra-Hidalgo et al., 2020). A tenth patient presented with multiple infarctions in regions such as the medial temporal lobe and cerebellum, and showed concurrent bilateral haemorrhages in frontal, temporal and occipital territories, and also in the right medial temporal lobe (Sierra-Hidalgo et al., 2020).

Vasculitis

One patient presented with systemic vasculitis but no changes to the nervous tissue were reported (Oliveira et al., 2020).

Multiple Findings

Twelve studies used neuroimaging to investigate a multiplicity of different types of neural damage. Studies on five single cases reported a range of different findings, most consistently involving WM damage. A non-enhancing abnormality in the right anterior-medial temporal lobe was noted by Benameur et al. (2020). Atrophy and widespread periventricular and subcortical WM ischaemic lesions were found in a 78-year-old woman (Farhadian et al., 2020). Both studies investigated inflammatory changes compatible with encephalitis, by means of neuroimaging and cerebrospinal fluid (CSF) analysis, although the relationship with COVID-19 infection remained unclear. One reversible WM hyperintensity due to encephalopathy/encephalitis (diagnosed on the basis of MRI findings only) was found in the splenium of the corpus callosum in one patient with mild AD (Hayashi et al., 2020). One study (Nicholson et al., 2020), instead, found multiple abnormalities only on MRI, but not on CT scans, spreading from subarachnoid and subpial spaces (enhancements) to areas of hyperintense signal in perivascular regions and in subcortical WM, especially across the corpus callosum. Similarly, Krett et al. (2020) observed diffuse haemorrhages on MRI, in the absence of vasculopathy, across multiple brain compartments, including the subarachnoid space. Finally, two patients were reported having posterior reversible encephalopathy syndrome: the first one presented with hyperintensities (but no evidence of stenosis) in the right posterior frontal lobe, in the left centrum semiovale and in parieto-occipital regions bilaterally, accompanied by microbleeds in this latter territory (Hernández-Fernández et al., 2020); while the second one showed oedema extending to parieto-occipital regions bilaterally, cerebellum, right frontal lobe and basal ganglia, with evidence of an haemorrhagic process in left parieto-occipital areas (Franceschi et al., 2020).

Case series and cohort studies included patients with a variety of comorbidities, especially cardiovascular pathologies such as hypertension, history of stroke and transient ischaemic attack, atrial fibrillation and deep-vein thrombosis. However, multiple cases with diabetes, a history of cancer, mild cognitive impairment, chronic obstructive pulmonary disease and kidney pathologies were reported. Paterson et al. (2020) investigated patients falling into four main categories, depending on the predominant type of neural damage found: encephalopathy, encephalitis, cerebrovascular involvement, and peripheral nervous system signs. No brain abnormalities were reported in those with encephalopathy and peripheral nervous dysfunctions. Three patients with encephalitis, defined by means of both MRI and cerebrospinal fluid assessments, showed different pathological changes: hyperintense areas in the pons, limbic areas, medial thalamic nuclei, and subcortical cerebral WM were detected in one patient, while in the other two cases different types of subcortical WM lesions were mainly observed. Great variability in the type of cerebrovascular injuries and in the brain areas affected was also observed in five cases, since haemorrhages and infarcts were detected mainly in cerebellar/brainstem areas,

but also in cerebral WM (frontal and occipital) and in the basal ganglia. Thirteen out of 58 cases reviewed by Helms et al. (2020a) showed different cerebral abnormalities, yet almost all patients (11 out of 13) presented with bilateral fronto-temporal hypoperfusion detected with arterial spin labelling MRI. The same research group also found a similar pattern of hypoperfusion, mainly in mediotemporal and right frontal areas, in 17 out of 32 patients with COVID-19 who presented with severe delirium (Helms et al., 2020b). Moreover, WM microhaemorrhages were noted across all cerebral lobes and the cerebellum in seven cases and a left frontal intraparenchymal haematoma was detected in one case. Radmanesh et al. (2020b), instead, observed in five cases that WM damage, both as leukoencephalopathy and microhaemorrhages, was especially present in posterior occipital and temporal areas, in the corpus callosum, centrum semiovale, corona radiata, and in juxtacortical WM in the precentral gyrus, while deep grey matter nuclei were spared.

A cohort study (Pons-Escoda et al., 2020) found that only 23 out of 103 patients with COVID-19 presented with cerebrovascular accidents, mainly located in the basal ganglia (three cases), prefrontal (two cases), parietal, and cerebellar (one case each) regions. However, the location of some of the cerebrovascular injuries (three lobar haematomas) was not included. No cases of encephalitis were detected by neuroimaging examinations. Similarly, the largest cohort including 278 patients assessed with either CT or MRI (Lin et al., 2020) found little evidence of encephalopathy due to COVID-19: posterior reversible encephalopathy syndrome was present in three cases, while areas of signal enhancement in the optic nerve were present in two cases and in the olfactory bulb (with no evidence of volume changes) in four cases. However, cerebrovascular events were reported to be more common: infarctions were present in 31 cases, mainly in multiple vascular territories and without a consistent pattern across patients. Microhaemorrhages (26 cases) were mild and without a consistent pattern in the overall sample, but in three patients lesions were predominantly localised in the corpus callosum, in both internal capsules and in juxtacortical WM. Similarly, Mahammedi et al. (2020) observed neuroimaging abnormalities, especially of cardiovascular origin, in 47% of 108 hospitalised patients with COVID-19 presenting with neurological symptoms. Ischaemic infarcts represented the most common finding observed in various vascular territories, but also in the basal ganglia, with WM damage found in subcortical and basal ganglia areas. Encephalopathy was rare and only one case of posterior reversible encephalopathy was reported in this series.

A few more studies observed no recent and acute neural changes that could be ascribed to COVID-19 infection: Abdelnour et al. (2020) reported the case of a man who presented only with old infarcts and no signs of encephalitis on MRI, no brain abnormalities were found in 80 out of 103 patients by Pons-Escoda et al. (2020) and two studies detected either no signs of encephalopathy (Paterson et al., 2020) or no cortical hyperintensities, haemorrhagic encephalitis and leptomeningeal enhancement in all patients included (Lin et al., 2020).

Cognitive Correlates of Neuroimaging Findings

A subset of neuroimaging studies carried out in older patients also reported details of cognitive symptoms, although the relationship between neural damage and cognitive deficits was rarely discussed and not always transparent. For example, delirium was not associated with specific neuroimaging findings: Helms et al. (2020b) observed this symptom in people with WM damage, fronto-temporal hypoperfusion, stroke, and haematomas, while other patients with delirium had no MRI abnormalities at all (Paterson et al., 2020). Decline in, or loss of, consciousness was also reported in patients with right frontal ischaemia (Basi et al., 2020), right temporal haemorrhage (Sharifi-Razavi et al., 2020), lesions of the left midbrain (Fan et al., 2020) and of the left ventromedial prefrontal cortex (Muhammad et al., 2020), extensive right-sided (Fan et al., 2020) or left-sided lesions (Mohamed et al., 2020), diffuse WM lesions (McCuddy et al., 2020; Muccioli et al., 2020), diffuse cerebrovascular alterations (Pugin et al., 2020) and also in the absence of MRI abnormalities (Manganelli et al., 2020; Mohamud et al., 2020). Similarly, altered mental status was observed in patients with one lesion in the splenium (Sparr and Bieri, 2020), scattered WM lesions (Farhadian et al., 2020), and microbleeds (Fitsiori et al., 2020), in a case with haemorrhage in the right parieto-occipital territory (Franceschi et al., 2020), but in most cases alterations in mental state were not associated with any specific MRI finding (Radmanesh et al., 2020a,b).

A few cases were also described of patients presenting with some degree of unspecified cognitive decline, present either at hospital admission or developing during hospitalisation, that was associated with multiple haemorrhages in one case (Krett et al., 2020) and no structural neuroimaging findings in other two cases (Khoo et al., 2020; Pilotto et al., 2020). More specific cognitive symptoms were also observed: executive dysfunction in patients with frontal hypometabolism (Delorme et al., 2020), memory and attention deficits associated with persistent delirium in a patient with diffuse ischaemic damage mainly in temporal and limbic areas (Hosseini et al., 2020), left-sided neglect due to right frontal ischaemia (Avula et al., 2020) and aphasia in cases of diffuse left-sided (Beyrouti et al., 2020), left frontal (Jillella et al., 2020), and bilateral cerebrovascular injuries, mainly in temporal areas (Jillella et al., 2020; Roy-Gash et al., 2020; Saggese et al., 2020).

Neuropathological Examinations

Sixteen studies reported various macroscopic and microscopic results of neuropathological examinations: four single cases, three *post-mortem* examinations (Al-Dalahmah et al., 2020; Bulfamante et al., 2020; Reichard et al., 2020) and one *ante-mortem* biopsy of the olfactory epithelium (Vaira et al., 2020), and 12 case series (Bradley et al., 2020; Buja et al., 2020; Hanley et al., 2020; Hernández-Fernández et al., 2020; Jaunmuktane et al., 2020; Kantonen et al., 2020; Matschke et al., 2020; Menter et al., 2020; Remmelink et al., 2020; Schurink et al., 2020; Youd and Moore, 2020; Lee et al., 2021), for a total of 132 patients who died with COVID-19 (65 of whom aged 60 or older). Many comorbidities were reported in 14 out of the 16 studies, especially: hypertension, diabetes, kidney diseases and a range of cardiovascular pathologies. A few patients were also affected

by other neurodegenerative conditions, such as AD, Parkinson's disease and multiple sclerosis.

Macroscopic Findings

All but two studies (Bulfamante et al., 2020; Menter et al., 2020) reported the results of macroscopic inspections of patients' brains. The majority of the papers observed cerebrovascular damage of different type. Haemorrhages were found in seven patients and damage was located in: the right cerebellum (Al-Dalahmah et al., 2020), left frontal and left parieto-temporal lobes (Hernández-Fernández et al., 2020), subarachnoid space (Bradley et al., 2020), and both cerebral and cerebellar WM (Kantonen et al., 2020; Reichard et al., 2020). Cerebrovascular damage either without a specific localisation or widespread throughout the brain was reported by three studies (Hanley et al., 2020; Remmelink et al., 2020; Lee et al., 2021). New infarctions were found in eight cases in: bilateral globus pallidum, occipital lobe WM and left hippocampus and thalamus (Jaunmuktane et al., 2020); and in territories of the posterior (three cases), middle (two cases), and anterior (one case) cerebral arteries (Matschke et al., 2020). Ischaemic lesions were noted in the centrum semiovale and in the right lentiform nucleus in one case (Jaunmuktane et al., 2020). Matschke et al. (2020) reported non-specific oedema in 23 cases, atrophy in 20 cases and arteriosclerosis in all 43 cases. Additionally, tentorial and foramen magnum herniations were found in one case (Al-Dalahmah et al., 2020), while depigmentation of the substantia nigra and locus coeruleus, and enlarged perivascular spaces were noted in another case (Kantonen et al., 2020). However, no evidence of macroscopic brain abnormalities was observed in 50% of the neuropathological cases (Bradley et al., 2020; Buja et al., 2020; Hanley et al., 2020; Matschke et al., 2020; Remmelink et al., 2020; Schurink et al., 2020; Vaira et al., 2020; Youd and Moore, 2020) (**Figure 2**).

Microscopic Findings

All but one study (Youd and Moore, 2020) carried out microscopic pathological analyses on samples of neural tissue. Null findings were observed in the microscopic examination of only 11 cases of older adults deceased with COVID-19 included in three studies (Bradley et al., 2020; Buja et al., 2020; Hanley et al., 2020) (**Figure 2**).

Damage was observed in a wide variety of neural cells. Hypoxic damage was found in a single case in neurons across the cerebral cortex, striatum, thalamus, amygdala, hippocampus, midbrain, pontine nuclei, medullary nuclei, and Purkinje cells (Al-Dalahmah et al., 2020). Non-specific hypoxic damage was also reported by other studies (Kantonen et al., 2020; Menter et al., 2020; Schurink et al., 2020). WM axonal loss and demyelination were detected in sites of vascular damage in combination with scattered hypoxic damage to neurons in neocortex, hippocampus (CA1) and the cerebellum in one case (Reichard et al., 2020). Moreover, non-specific WM axonal damage in the absence of demyelination (Jaunmuktane et al., 2020) and WM lesions (Kantonen et al., 2020) were also reported. In one patient, severe damage to neurons, glia, axons and myelin sheath was found to be more prominent in the olfactory nerve, followed by the gyrus rectus and the medulla oblongata (Bulfamante et al., 2020).

Signs of inflammation were also found throughout the central nervous system (CNS) in the corpus callosum, striatum, thalamus, hippocampus, midbrain and pons, and olfactory epithelium of one patient (Al-Dalahmah et al., 2020), leptomeningeal inflammation in the right intraparietal sulcus in one case (Jaunmuktane et al., 2020), and widespread across the brainstem, the frontal cortex and the basal ganglia in a case series (Matschke et al., 2020). In particular, microglial activation was reported by several studies (Hanley et al., 2020; Schurink et al., 2020; Lee et al., 2021) and across different regions, namely: the inferior olives and dentate nuclei (Al-Dalahmah et al., 2020), the medulla oblongata, cerebellum, olfactory bulb, and subpial and subependymal regions (Matschke et al., 2020). Additionally, astrogliosis was found in all cases analysed by Matschke et al. (2020), especially in the olfactory bulb, and in the orbitofrontal and superior frontal cortices of a patient examined by Al-Dalahmah et al. (2020). A few studies, instead, found no traces of either increased microglia activation (Jaunmuktane et al., 2020), vasculitis (Al-Dalahmah et al., 2020; Jaunmuktane et al., 2020; Remmelink et al., 2020), which was reported to a mild extent only by one neuropathological study (Hernández-Fernández et al., 2020), or of any inflammatory processes (Menter et al., 2020; Remmelink et al., 2020).

A variety of cerebrovascular injuries, often reported as a general finding without brain localisation (Remmelink et al., 2020), was observed in endothelial cells in arterioles, capillaries, and venules and degeneration of the pericapillary neuropil (Hernández-Fernández et al., 2020). Subarachnoid haemorrhages and microhaemorrhages in the brainstem were reported in one patient (Bradley et al., 2020) and a haemorrhagic WM lesion in one case (Reichard et al., 2020). The absence of cerebrovascular damage was recorded by one neuropathological study (Jaunmuktane et al., 2020).

One study that investigated the olfactory epithelium of a patient with COVID-19 and anosmia found a reduction in surface with minimal levels of chronic lymphocytic inflammatory infiltrates (Vaira et al., 2020). MRI examination revealed no macrostructural abnormalities in the olfactory bulb.

Finally, a few studies also investigated the presence of COVID-19 in the CNS tissue samples. Although three studies (Kantonen et al., 2020; Schurink et al., 2020; Lee et al., 2021) found no evidence of viral infection in the CNS, this was observed repeatedly across different brain regions: the olfactory nerve (Al-Dalahmah et al., 2020; Bulfamante et al., 2020; Matschke et al., 2020; Menter et al., 2020), frontal lobe (Bulfamante et al., 2020; Matschke et al., 2020), and brainstem (Bulfamante et al., 2020; Matschke et al., 2020; Menter et al., 2020), especially in the medulla oblongata, and in the cerebellum of a patient with cerebellar haemorrhage (Al-Dalahmah et al., 2020) (**Figure 3**). Hanley et al. (2020) detected the presence of COVID-19 across the brain, but viral load was highly variable across cases.

Only a minority of the neuropathological investigations assessed whether microscopic alterations and viral presence in the neural tissue was associated with neuroimaging and clinical findings. Pervasive vascular damage due to haemorrhages,

as expected, was consistently detected by both macroscopic and microscopic examinations (Al-Dalahmah et al., 2020; Hernández-Fernández et al., 2020) and linked to the presence of viral genetic material in the brainstem in one patient, possibly due to blood contamination (Al-Dalahmah et al., 2020). Anosmic patients with COVID-19 presented with alterations in both the olfactory epithelium (Vaira et al., 2020) and bulb (Bulfamante et al., 2020); however, such microstructural alterations did not correlate with volumetric changes in the olfactory bulb as assessed by means of MRI (Vaira et al., 2020). Similarly, patients who presented with delirium and altered mental status before death showed no specific neuropathological signatures (Kantonen et al., 2020; Schurink et al., 2020; Lee et al., 2021) and some had no CNS tissue abnormalities at all (Bradley et al., 2020).

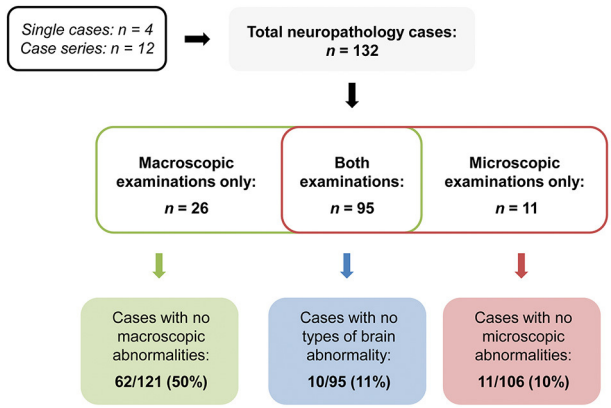

FIGURE 2 | Summary of the rates of null neuropathological findings.

DISCUSSION

As of December 2020, the COVID-19 pandemic has become established across the planet for at least 12 months. The medical community has promptly responded to the emergency to the best of their capabilities and has documented the mechanistic and clinical features of this viral infection, putting emphasis on the nervous system as one of its major targets. It is thus particularly important for cognitive and clinical neuroscientists to study the

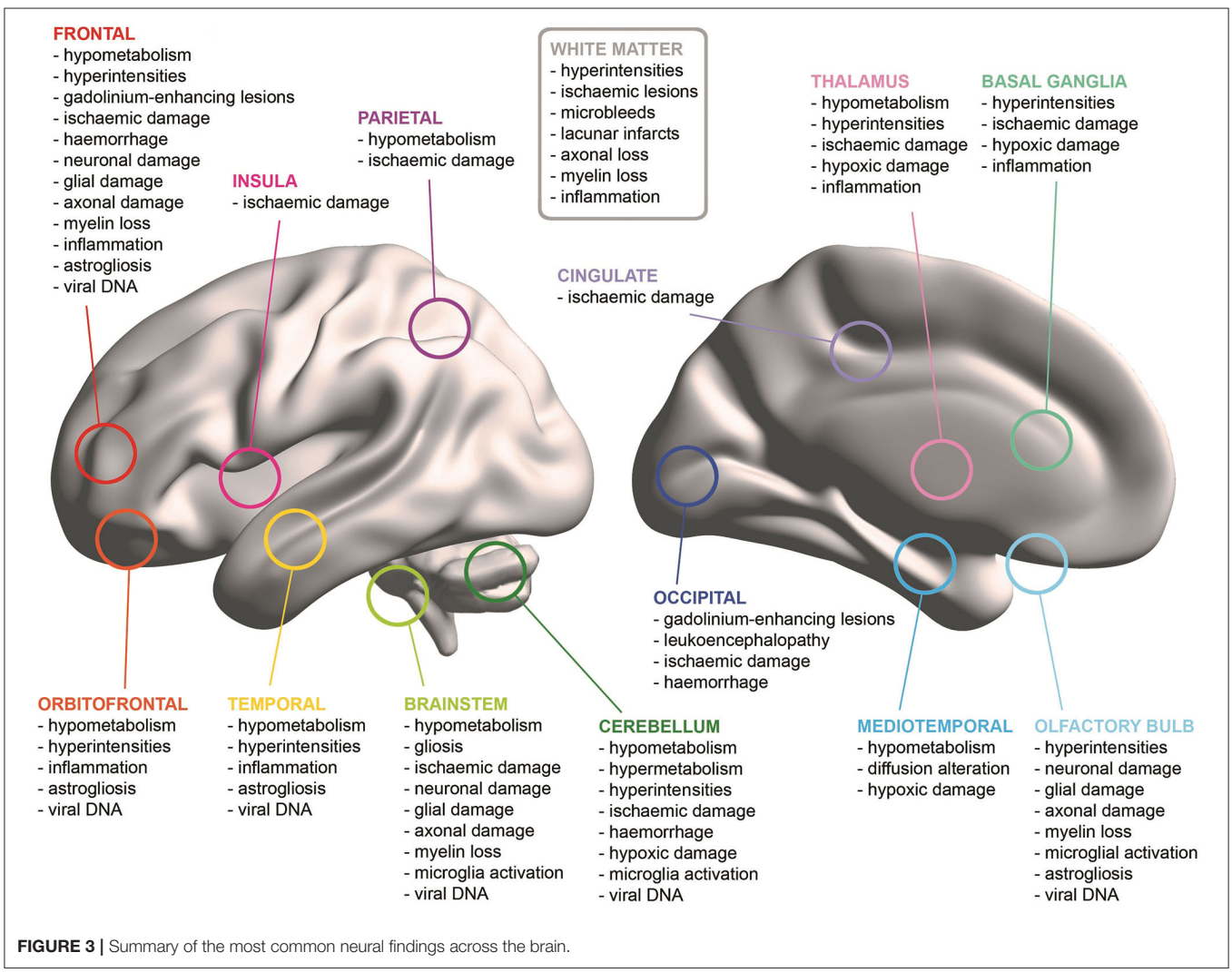

FIGURE 3 | Summary of the most common neural findings across the brain.

link between the neural effects of COVID-19 and changes in cognitive and psychiatric/behavioural functioning. At present, however, the evidence available in the literature is limited to (1) the acute effects of the virus and (2) patients who have contracted the infection and developed symptoms of sufficient concern to justify hospitalisation and radiological investigations. As a result, we have only partial knowledge of the link between COVID-19 infection and mental abilities. Although characterisation of the long-term neural effects of COVID-19 infection will be investigated in due course, and indeed there are several ongoing studies at present, it is of primary importance to review the current evidence in order to define a theoretical backbone in support of future experimental studies.

At first glance, the literature currently available on the neural changes observed in older adults with COVID-19 shows great variability of findings across studies. While variability is expected in any condition (in this case, especially when the damage route is *via* cerebrovascular and inflammatory mechanisms of typical patchy presentations), it is possible that a better defined pattern will be apparent in the long term. Many examples of brain damage of vascular aetiology associated with COVID-19 infection were noted, thus suggesting that the cerebrovascular system may be particular susceptible. In general, neuroimaging findings do not appear to be distinctly associated with a set of specific brain areas (Jang et al., 2020; Krett et al., 2020; Mahammedi et al., 2020) and a variety of neural changes have been observed everywhere in the brain, the meninges and the cerebrovascular system (Lin et al., 2020; Pons-Escoda et al., 2020) (**Figure 3**). However, some recurrent findings emerged from the studies focussing on encephalopathies. In particular, multiple papers reported WM lesions of variable aetiology, presentation, and location (Anand et al., 2020; Benameur et al., 2020; Farhadian et al., 2020; Hayashi et al., 2020; Jang et al., 2020; Nicholson et al., 2020) that have also been commonly observed in larger cohorts (Paterson et al., 2020; Radmanesh et al., 2020b). A considerable amount of older adults with COVID-19 examined with FDG-PET and arterial spin labelling MRI presented with hypoperfusion in bilateral frontal and temporal cortices (Delorme et al., 2020; Guedj et al., 2020; Helms et al., 2020a,b), while both hyperperfusion and hypoperfusion have been observed in the cerebellum (Delorme et al., 2020; Young et al., 2020). It must be noted, however, that, encephalopathy, is an umbrella term and that different pathophysiological changes, some primarily related to COVID-19 infection and some related to collateral events, might have contributed to such condition. While accounts of patients with encephalopathy responsive to corticosteroids suggest an immune-mediated pathogenesis (Pilotto et al., 2020; Pugin et al., 2020), intubation and mechanical ventilation might have also contributed to neural damage in a minority of patients (Delorme et al., 2020; Parauda et al., 2020). Indeed, a few patients with diffuse subcortical damage developed encephalopathy after sedation (Muccioli et al., 2020) and extubation (Lin et al., 2020). Therefore, it cannot be excluded that invasive medical procedures as well as several pre-existing comorbidities in older patients might have contributed to the heterogeneity of neuroimaging findings.

In several cases, brain abnormalities of any type were detected bilaterally across most cerebral and cerebellar regions. Cerebrovascular damage, instead, was most frequently lateralised to a single hemisphere at the individual level, although both brain sides appeared to be equally affected, overall. A trend for a higher rate of cerebrovascular findings on the right side of the brain was observed across all lobes, but, since no studies have investigated whether one of the two hemispheres may be more prone to COVID-19-related damage, any speculation on this issue appears premature. However, vascular injuries of any type appeared to be more often located in the frontal lobes, followed by parietal, temporal and occipital areas. This pattern appears to be similar to that detected in other critical illnesses, e.g., sepsis is associated with dysfunction in cerebrovascular regulation and, consequently, hypoperfusion, particularly in mediotemporal and frontal areas, is frequently observed (Tauber et al., 2021). Moreover, a case series of three patients with Middle East respiratory syndrome coronavirus showed similar widespread bilateral brain abnormalities in frontal, temporal as well as subcortical areas on MRI assessment (Arabi et al., 2015). A study that compared the clinical profiles of patients with COVID-19 and patients with Influenza virus revealed that the flu virus was associated with a lower risk of developing an ischaemic stroke (Merkler et al., 2020). No information on the anatomical localisation of these acute vascular events was provided in this study, however.

In a minority of cases, several cognitive alterations were reported. Delirium, loss of consciousness and altered mental status appeared not to be associated with specific pathological signatures, possibly because such symptoms are vaguely defined and, therefore, may arise in patients because of different medical and environmental conditions. However, they could also be caused mainly by functional, rather than structural, cerebral alterations that have not been investigated by the majority of the studies currently available. Indeed, hypoperfusion of medial temporal and right frontal areas was observed to be pronounced in patients who presented with severe delirium (Helms et al., 2020b). In contrast, more specific impairments were observed in cases with injuries of differing aetiologies to brain structures known to be involved in the functions affected: executive function decline in patients with frontal hypometabolism (Delorme et al., 2020), memory impairment due to limbic damage (Hosseini et al., 2020), neglect in a case with right frontal damage (Avula et al., 2020), and aphasia due to left-sided and temporal injuries (Beyrouti et al., 2020; Jillella et al., 2020; Roy-Gash et al., 2020; Saggese et al., 2020).

Although longitudinal investigations on neural and cognitive alterations are not available yet, these findings are particularly relevant for the long-term cognitive health of older patients. Indeed, signs of hypoperfusion in frontal and temporal lobes were consistently highlighted across studies; these brain regions mainly consist of associative cortex, implicated in memory, executive functions as well as complex behavioural control (Badre and Nee, 2018; Jackson et al., 2018). Such negative consequences of COVID-19 on the neural tissue in these areas may either be transient or a driver for long-lasting effects on mental and cognitive health of patients. The increased frequency of acute

ischaemic strokes following COVID-19 infections in comparison to other respiratory conditions might also reduce brain reserve in older individuals. These negative neural consequences, in turn, might increase the risk of developing a variety of neurodegenerative conditions leading to dementia, e.g., sporadic AD or fronto-temporal lobar degeneration (Maillet and Rajah, 2013; Mann and Snowden, 2017), or might accelerate the clinical manifestation of existing latent sub-clinical conditions. The possibility exists that significant CNS involvement in COVID-19 infection may join other vascular components of "brain-at-risk" for cognitive decline alongside mid-life hypertension, diabetes, smoking, and many other reported factors. This might be particularly evident in carriers of the ε4 variant of the apolipoprotein E (ApoE) gene, the most strongly established genetic risk for sporadic AD that also modulates cardiovascular diseases and cellular processes related to viral infections (Finch and Kulminski, 2020). ApoE ε4 appears to be a risk factor common to both AD and COVID-19-related outcomes, since symptom severity (Kuo et al., 2020a) and mortality rates (Kuo et al., 2020b) have been found to be significantly worse in ε4 homozygotes, independently of any common comorbidities (i.e., coronary heart disease, dementia, diabetes, and hypertension). Therefore, longitudinal monitoring of older adults who have recovered from COVID-19 infection, especially those with known genetic vulnerabilities, should be taken into consideration not only to ascertain the long-term impact of COVID-19 on the central nervous system, but also to detect any signs of cognitive decline early and arrange a prompt management plan. In fact, one study on young patients who have been assessed with MRI 3 months after recovery from COVID-19 found increased volumes in olfactory, cingulate and both medial and lateral temporal cortices that correlated negatively with loss of olfactory and memory functions (Lu et al., 2020), thus suggesting a compensatory role of these hypertrophic neurovolumetric changes to sustain functional recovery.

It must be noted that a considerable number of cases included in these studies reported null neuroimaging findings (Abdelnour et al., 2020; Anand et al., 2020; Fernández-Domínguez et al., 2020; Logmin et al., 2020; Manganelli et al., 2020; Palomar-Ciria et al., 2020; Vollono et al., 2020). This was especially the case for those that investigated COVID-19-related encephalitis (Chaumont et al., 2020; Khoo et al., 2020; Pilotto et al., 2020), a condition that was not always confirmed by abnormal cerebrospinal fluid findings and in some cases diagnosed only on the basis of clinical manifestations. Consistently, one of the largest studies here reviewed found no brain abnormalities in about 80% of the cases examined (Pons-Escoda et al., 2020). This may mean either that the majority of older patients does not experience neurological complications or that functional brain alterations, rather than structural ones, might represent the predominant neural consequences of COVID-19 infection as suggested by hypoperfusion detected by means of PET and functional MRI. However, it is also possible that COVID-19 infection may mainly cause microstructural damage, at least at the acute/early stage, as suggested by the fact that macroscopic alterations were less common than microscopic ones in neuropathological case descriptions. The detection of microstructural damage can be improved by the use of techniques such as diffusion MRI and by the use of 7T MRI scanners that enable greater image resolution. As of December 2020, however, brain imaging in COVID-19 cases has mainly served a clinical purpose and at present there are no studies that have explored microstructural brain features using a research-led approach.

Consistently, neuropathological examinations have also highlighted macroscopic brain injuries of predominantly vascular origin across all brain regions, with a heterogeneous pattern unable to clarify aetiology and tease apart new phenomena from pre-existent comorbidities. Indeed, in almost half of the cases reviewed no macroscopic abnormalities were reported (Bradley et al., 2020; Buja et al., 2020; Matschke et al., 2020; Remmelink et al., 2020; Youd and Moore, 2020). Microscopic examinations, instead, revealed a wide multiplicity of pathological processes found in the majority of cases. In particular, widespread WM damage has been observed as axonal loss, demyelination, and lesions (Jaunmuktane et al., 2020; Kantonen et al., 2020; Reichard et al., 2020) along with WM inflammation (Al-Dalahmah et al., 2020). Consistently, multiple scattered cerebrovascular injuries have been found especially in WM (Bradley et al., 2020; Hernández-Fernández et al., 2020; Reichard et al., 2020; Remmelink et al., 2020). Moreover, neuronal damage and microglial activation have been detected across several brain areas, but especially in the medial temporal lobe (Al-Dalahmah et al., 2020; Reichard et al., 2020), the brainstem, the olfactory bulb and the orbitofrontal cortex (Al-Dalahmah et al., 2020; Bulfamante et al., 2020; Matschke et al., 2020). Such neuropathological findings appear particularly interesting, since they seem to suggest that COVID-19 can induce neural damage particularly in a series of brain structures directly connected or proximal to the olfactory areas, also observed in some cases with neuroimaging assessment (Le Guennec et al., 2020; Lin et al., 2020). This scenario is in line with the hypothesis that infection may spread to the central nervous system through the olfactory epithelium, as for instance demonstrated in a mouse model exposed to Middle-East respiratory syndrome coronavirus (Li et al., 2016). In this respect, the olfactory bulb has already been proposed as the neural point of entry for toxic proteins at the basis of certain neurodegenerative conditions (Rey et al., 2018). Moreover, the structures specialised in the processing of olfactory stimuli are tightly coupled with the mediotemporal lobe. In fact, the piriform cortex projects to the hippocampus *via* the entorhinal and perirhinal cortices (Vismer et al., 2015). These connexions play a central role in the early stages of AD, because TAU pathology is known to spread from cell to cell (Vogels et al., 2020) and the olfactory bulb harbours neurofibrillary pathology already during the transentorhinal Braak stages of AD (Tsuboi et al., 2003). On similar grounds, the mediotemporal lobe would be a prime candidate as target of a COVID-19 axonal propagation originating from the olfactory bulb. Although as a speculation, this mechanism might be at the basis of the mediotemporal involvement described in the MRI and PET case series illustrated above (Delorme et al., 2020; Guedj et al., 2020; Helms et al., 2020a,b; Hosseini et al., 2020; Novi et al., 2020). Additionally, although not all the neuropathological studies detected the presence of COVID-19 in samples of neural

tissue, it appears that COVID-19 may be able to penetrate the brain. In fact, viral genetic material has been found mainly in the olfactory bulb (Al-Dalahmah et al., 2020; Bulfamante et al., 2020; Matschke et al., 2020; Menter et al., 2020) and, to a more limited extent, in the frontal lobe (Bulfamante et al., 2020; Matschke et al., 2020) and brainstem (Bulfamante et al., 2020; Matschke et al., 2020; Menter et al., 2020). Since both COVID-19 genetic material (Matschke et al., 2020) and signs of neuronophagia (Lee et al., 2021) were detected in nuclei of the cranial nerves, especially of the vagus nerve, this has been suggested as an alternative route enabling retrograde invasion of the CNS (Bulfamante et al., 2020). In fact, the vagus nerve innervates most abdominal organs, including the lungs. Through the vagal sensory innervation of the alveolar epithelium, the virus could reach the dorsal vagal complex in the brainstem and generate multiple autonomic dysfunctions (Rangon et al., 2020). However, it has also been hypothesised that viral detection in CNS tissue can be due to contamination with blood rich in viral material, especially in cases of cerebrovascular damage (Al-Dalahmah et al., 2020). In support of this hypothesis, the presence of COVID-19 in the CNS was not associated with severity of neuropathology in the study by Matschke et al. (2020), suggesting that the neural alterations observed in patients may be the result of a combination of both direct (i.e., damage to CNS tissue caused by the virus itself) and indirect processes triggered by COVID-19, e.g., neuroimmune stimulation, systemic infection and haematogenous dissemination (Riederer and Ter Meulen, 2020). Therefore, definite conclusions on the spatial distribution and the type of impact, either direct or indirect, of COVID-19 throughout the brain (especially in structures other than those reported by the few neuropathological studies available to date) cannot be yet drawn due to methodological limitations of the available studies.

A large number of publications has described the co-occurrence of COVID-19 and cerebrovascular events, documented by neuroimaging. Slightly less than 2/3 (about 64%) of the patients belonging to this category presented with evidence of ischaemic infarctions. This percentage is not dissimilar from the epidemiological proportion of ischaemic strokes, i.e., equal to ∼58% (Shiber et al., 2010), indicating that COVID-19 does not seem to alter this overall proportion. However, COVID-19 infection appears to pose a greater risk of ischaemic stroke to patients than infection by Influenza (1.6 vs. 0.2%) (Merkler et al., 2020). Although these studies appear to consolidate an association between viral infection and stroke, patients presenting with cerebrovascular damage were a small part of the hospitalised patients and an even smaller part of all symptomatic patients. The description of these 84 cases details an extremely heterogeneous picture, with all regions of the brain that appear to be susceptible to adverse acute events. Aetiological variability was also observed, with a number of cases presenting with mixed ischaemic-haemorrhagic or haemorrhagic-encephalopathic profiles. Although, to date, no definite framework has been formulated to account for a definite and established link between COVID-19 and cerebrovascular events, the evidence so far collected indicates that multiple mechanistic avenues are at play. Processes ascribable to a hypercoagulability state, encephalopathy, vasculitis, and cardiomyopathy seem to play a central role (Spence et al., 2020), including increased risk of thromboembolic complications (Lodigiani et al., 2020). It is important to remark that the evidence so far documented has been obtained in a period of acute crisis during which clinical work has taken priority over medical research. Under these circumstances the cause-effect and temporal relationships between viral infection and neurological dysfunction has been challenging to verify or investigate (Radmanesh et al., 2020a). As a consequence, it is not possible to draw a separating line between neuroimaging- and pathology-based consequences of the virus and other relevant variables that are premorbid or contingent.

Interpretations of the neuroimaging and neuropathological findings in older adults with COVID-19 must take into account a series of additional potential limiting factors. First, some of the patients included in the papers reviewed had prior neurological conditions (e.g., epilepsy), while other studies focussed only on individuals who presented with neurological signs and symptoms. Second, often neuroimaging examinations were carried out on the most severe cases only. Third, equivalence between MRI and CT examinations is unclear, since it appears highly likely that these techniques provide complementary information and are more suitable to detect different types of neural injuries. Fourth, location of neural injuries was not always fully documented by all studies, some of which were excluded due to the absence of precise topographical details about neurological damage. This selection approach might have potentially steered the results of this review mainly towards studies reporting topographical information. Fifth, an additional point on regional differences relates to 11 out of 16 neuropathological studies examining the whole brain. Some studies focussed their analyses on olfactory, frontal, and brainstem areas only (Bulfamante et al., 2020; Matschke et al., 2020; Lee et al., 2021), while Hanley et al. (2020) limited their analyses to eight non-specified areas, leading to a potential over-representation of such areas among the currently available results. In fact, the first neuropathological studies may have focused on a limited number of regions to generate knowledge on COVID-19 impact on the central nervous system more quickly (Glatzel, 2020) and may have been mainly led by the dominant hypothesis suggesting that viral spreading into the CNS might be mediated by olfactory neurons (Riederer and Ter Meulen, 2020). Sixth, the causal relationship between COVID-19 infection and some of the neural changes observed has not been addressed, since only some studies distinguished acute and prior neural findings. Finally, no paper focussed exclusively on the effects of COVID-19 on patients with neurological conditions, although some papers included people with conditions such as AD, Parkinson's disease and multiple sclerosis.

In conclusion, the evidence in support of a link between COVID-19 and acute neurological abnormalities is abundant but is characterised by wide heterogeneity. It is still undetermined whether the long-term effects of this infection will be limited to the sequelae of acute neural dysfunction or whether additional mechanisms will play a part in the long term. While it is possible to speculate about the long-term neurofunctional consequences

derived from the chronic evolution of acute events, it is still unknown whether other, sub-clinical events may be exacerbated by COVID-19 infection. It is thus possible that any long-term effect may be the result of a complex interplay of chronic alterations and subtle and insidious mechanistic changes that are clinically negligible *per se*, but that may contribute to increase neural vulnerability. It is also unknown whether any effect on the nervous system will be relevant to patients who have not undergone a serious disease phase (i.e., non-hospitalised and asymptomatic patients who may have been only subjected to silent changes, e.g., microscopic ischaemic events). We expect that the link between COVID-19 and neurologically-informed cognitive/psychiatric dysfunction will be better elucidated when concrete data are available and when these are collected and analysed based on the formulation of research-based hypotheses. In the meantime, however, a systematic review of the regions of the brain that are targeted in the acute phase suggests that multiple neural systems (e.g., brain networks) may be exposed to a virus-related vulnerability. These are large-scale functional patterns that sustain high-order mental abilities such as memory and attention/executive functioning, cognitive domains that are also negatively influenced by the ageing process and by major neurodegenerative conditions, suggesting that due their high susceptibility to viral-related additional pathological processes, long-term post-COVID cognitive/neuropsychiatric sequelae might manifest with potentially more severe/more rapidly progressing phenotypes in older adults. Indeed the findings of this review seem to parallel some preliminary findings indicating that older adults with reduced connectivity pre-infection (from scans acquired on average 3 years prior to infection) in regions within the networks supporting attention and executive functioning are at increased risk of COVID-19 infection (Abdallah, 2021), but at the same time indicating a potentially specific pre-existing neural vulnerability of older individuals that significantly lowers their brain resilience potential. Finally, it is also important to point out that, other than reporting preliminary findings, the conclusions of this systematic review are also exclusively based on single-case descriptions and case series. Although the large number of clinical cases linking COVID-19 and brain alterations is, *per se*, sufficient to discard the possibility of this association being anecdotal, the description of this link is still, to some extent, *anecdotal*, and is still conceptually distant from the gold standard of "evidence-based" clinical research. Evidence-based medicine is at the basis of modern healthcare policies, and for this reason, considerable progress is warranted in this field of research, in order to strengthen the nature of the data in support of the above link.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AV conceived this study, reviewed, and finalised the manuscript. RM and MDM designed this study, carried out the literature search, selected the papers for inclusion, summarised the literature findings, and wrote this manuscript. PGI critically reviewed this manuscript. All authors approved the final version of this manuscript.

FUNDING

This research is supported by the COVID-19 Clinical Neuroscience Study (COVID-CNS), a MRC/UKRI funded grant: MR/V03605X/1.

ACKNOWLEDGMENTS

This is a summary of independent research carried out at the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

REVIEW
published: 11 June 2021
doi: 10.3389/fnagi.2021.647875

Sleep in Older Adults and Its Possible Relations With COVID-19

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Since the beginning of the COVID-19 pandemic, older adults have been found to be a highly vulnerable group, with a higher prevalence of severe cases and negative outcomes. Research has focused on the reasons why older adults are at greater risk; Sleep-related factors have been suggested as one possible explanation for this. An individual's sleep pattern undergoes significant changes over the course of their life. In older adults a specific sleep profile can be observed, one characterized by advanced sleep timing, a morningness preference, longer sleep-onset latency, shorter overall sleep duration, increased sleep fragmentation, reduced slow-wave sleep and, increased wake time after sleep onset. Additionally, an increased prevalence of sleep disorders can be observed, such as obstructive sleep apnea and insomnia. Previous research has already linked sleep disorders (especially sleep apnea) with COVID-19, but few studies have focused specifically on the older population. We believe that the intrinsic sleep patterns of older adults, and the prevalence of sleep disorders in this population, may be important factors that could explain why they are at a greater risk of negative COVID-19 outcomes. In this review, we discuss the relationship between sleep and COVID-19 among older adults, focusing on three different aspects: (1) Sleep-related issues that might increase the likelihood of getting infected by SARS-COV-2; (2) Sleep disturbances that might increase the predisposition to worse COVID-19 prognosis and outcomes; and (3) COVID-19-related aspects affecting community-dwelling older adults, such as social isolation, quarantine, and home confinement, among others, that might impact sleep.

Keywords: sleep, 2019-nCoV, COVID-19, elderly, corona virus, novel corona virus, SARS-CoV-2, sleep deprivation

OPEN ACCESS

Edited by:
Agustín Ruiz Laza, Fundació ACE, Spain

Reviewed by:
Julie Suhr, Ohio University, United States
Shireen Sindi, Karolinska Institutet (KI), Sweden

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Received: *30 December 2020*
Accepted: *15 April 2021*
Published: *11 June 2021*

Citation:
Pires GN, Ishikura IA, Xavier SD, Petrella C, Piovezan RD, Xerfan EMS, Andersen ML and Tufik S (2021) Sleep in Older Adults and Its Possible Relations With COVID-19. Front. Aging Neurosci. 13:647875. doi: 10.3389/fnagi.2021.647875

INTRODUCTION

Since the beginning of the COVID-19 pandemic, older adults have been one of the most vulnerable groups, with a higher prevalence of severe cases and negative outcomes [such as intensive care unit (ICU) admissions and death; Guan et al., 2020; Zhou et al., 2020]. Due to this close and clear relationship, research has focused on the reasons why older adults are at greater risk.

Abbreviations: AHI, Apnea-Hypopnea Index; CBTi, Cognitive-Behavioral Therapy for Insomnia; COVID-19, Coronavirus Disease 2019; CPAP, Continuous Positive Air Pressure; GH, Growth Hormone; ICU, Intensive Care Unit; NREM, Non-Rapid Eye Movements; OSA, Obstructive Sleep Apnea; PLMD, Periodic Limb Movement Disorder; RBD, REM Behavior Disorder; REM, Rapid Eye Movement; RLS, Restless Legs Syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SDB, Sleep-Disordered Breathing; SWA, Slow Wave Activity; WASO, Wake After Sleep Onset.

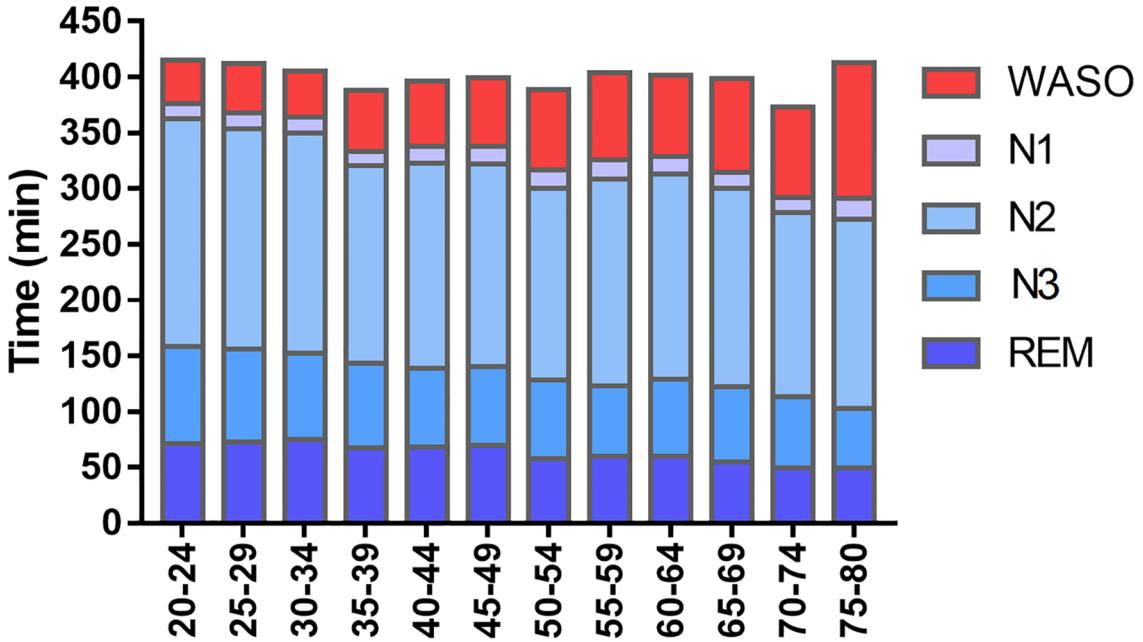

FIGURE 1 | Sleep structure throughout the lifespan. Values obtained in relation to prevalence obtained by the São Paulo Epidemiologic Sleep Study. Comparing the 20–24 to the 75–80 age strata, reductions in total sleep time (376–291 min), N3 sleep (87–53 min) and REM sleep duration (70–49 min), and an increase in time awake after sleep onset (WASO: 39–141 min) can be observed. A reduction in sleep efficiency (87–64%) and an increase in sleep latency (14–35 min) were also observed (data not shown). The reductions in N3 and REM sleep should be contextualized in respect of the global reduction in total sleep time. In terms of percentage, REM sleep proportion stays stable (18–17%) while slow-wave sleep is subjected to a small reduction (24–18%). Adapted from Moraes et al. (2014).

Among the age-related changes observed in multiple physiological functions and behaviors, sleep pattern across lifespan undergoes marked modifications and a specific sleep profile can be defined for each major life stage. Total sleep time, sleep efficiency, and the proportion of sleep changes from the first weeks of life until old age (Roffwarg et al., 1966; Moraes et al., 2014; Boulos et al., 2019; as shown in **Figure 1**). Changes can also be seen in other aspects of sleep, including sleep microarchitecture, circadian preferences, and the prevalence and clinical presentation of sleep disorders.

The relationship between sleep disorders and COVID-19 has already been discussed but has mostly focused on the general population (Agoramoorthy et al., 2020; Altena et al., 2020; De Mello et al., 2020; Jahrami et al., 2020; Meira E Cruz et al., 2020; Morin et al., 2020; Roitblat et al., 2021). There has been less discussion about the specific sleep patterns and prevalence of sleep disorders in older adults, which might mediate the increased severity of COVID-19 in this population.

In this review, we discuss the relationship between sleep and COVID-19 in older adults. We start with a brief overview of the sleep characteristics and sleep disorders in older adults, and how aging changes the relationship between sleep and immunity. We then examine how sleep and COVID-19 are associated in older adults, focusing on three different aspects: (1) sleep-related factors that increase the likelihood of being infected; (2) predisposing elements that worsen prognosis; and (3) COVID-19-related aspects, such as social isolation, home confinement, and quarantine, among others, and how they might impact sleep in older adults.

SLEEP IN OLDER ADULTS

Aging is characterized by significant physiological alterations in the human body. Studies with older adults and centenarians have revealed the essential role of sleep in respect of longevity (Mazzotti et al., 2014). Sleep is widely recognized to be an elementary physiological process for good health that supports vital restorative functions. More specifically, the maintenance of healthy sleep habits is associated with successful aging, a term used to describe older people who have no significant detriment in their physiological, physical, and social functioning, and no major disease (Rowe and Kahn, 1997). Conversely, sleep disturbances in older adults are associated with impairment in these domains.

The main alterations in sleep observed in older adults include altered sleep architecture, reduced total sleep time, a preference for morningness, and reduced slow-wave activity (**Figure 2**). Additionally, comorbidities associated with aging, such as chronic pain, nocturia, diabetes, anxiety, and depression provoke awakenings during sleep reducing the efficiency and the amount of sleep (Foley et al., 2007; Vitiello, 2009).

In young adults, the average total sleep time is 6.5–8.5 h per night, but this is reduced to 5–7 h per night in older adults (Ohayon et al., 2004; Mazzotti et al., 2014). At 60 years of age, a further decline in sleep efficiency can be observed

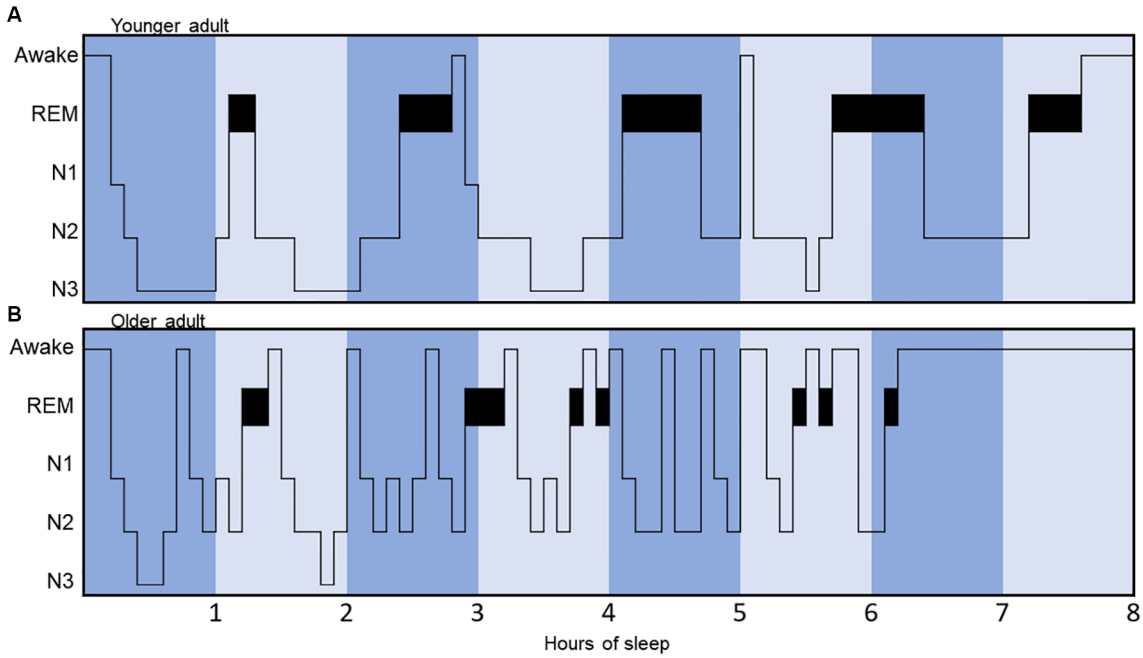

FIGURE 2 | Hypnograms illustrating and comparing sleep architecture between a younger and an older adult. The younger adult hypnogram **(A)** displays a regular cyclicity, with appropriate total sleep time (8 h), five sleep cycles, few arousals, more N3 sleep (slow-wave sleep) concentrated in the first half of the night and more REM sleep concentrated in the second half of the night. Conversely, the older adult hypnogram **(B)** displays a more fragmented sleep pattern, with less clearly identifiable sleep cycles, less N3 sleep, reduced total sleep time, and early awakening.

(Ohayon et al., 2004; Mazzotti et al., 2014). Studies have revealed a negative correlation between short sleep duration and successful aging (Liu et al., 2016; Foscolou et al., 2019). A recent Chinese study found a higher prevalence of successful aging in participants sleeping 7 h, and a lower prevalence in participants sleeping <6 h more than four times per week (Liu et al., 2016).

The high incidence of awakenings during aging may contribute significantly to reducing sleep efficiency and increasing daytime naps, as 25% of older adults reported daytime sleepiness severe enough to impair daytime functioning on a regular basis (Foley et al., 2007). A study with Mediterranean older adults observed that midday nappers were more physically active and presented a 20% higher successful aging index score (Foscolou et al., 2019). Midday napping has more pronounced effects in adults aged >80 years, with a nine-fold increase in the odds of having a high successful aging score (Foscolou et al., 2019). On the other hand, excessive diurnal sleepiness has been associated with an increased risk of adverse outcomes in older adults, including lower gait speed and disabilities (Nakakubo et al., 2016; Tyagi et al., 2017). These findings reveal the restorative function sleep may have in the older population.

A number of studies (Ohayon et al., 2004; Foley et al., 2007; Vitiello, 2009) showed that good sleep is an important factor in respect of functioning in a variety of domains that impact the quality of life of older adults. Sleep plays a critical role in cognitive function, as confirmed by impaired psychomotor vigilance, reaction time, memory and, learning following a sleep restriction protocol (Lim and Dinges, 2010). Poor sleep in adults >75 years old predicts future declines in mental and physical adaptation, fewer social activities, greater depressive symptoms, and more chronic medical burden (Dew et al., 2003). The risk of mortality increases 1.9-fold in older adults with a sleep efficiency of <80% (Dew et al., 2003), and short sleep duration has been shown to be a predictor for cardiovascular diseases (Gangwisch et al., 2006; Hoevenaar-Blom et al., 2011; Faraut et al., 2012), obesity, diabetes, and stress (Tufik et al., 2009; Grandner et al., 2016). Alongside behavioral factors, such as diet, physical exercise, smoking, and social life, sleep plays an important role in successful aging.

SLEEP DISORDERS AND COMPLAINTS IN OLDER ADULTS

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing (SDB) in the general population, and in the older population (Young et al., 2002; Tufik et al., 2010). It is characterized by the reduction (hypopneas) or complete cessation (apneas) of airflow in the upper airways during the night (Kimoff et al., 1994; Patil et al., 2007).

Different studies have estimated that OSA incidence ranges from 5.6% to 60% in people >65 years (Ahmad et al., 2014; Suzuki et al., 2017), with age being positively related with an increase in its prevalence (Morrell et al., 2012; McMillan and Morrell, 2016; Yaremchuk, 2018). A population-based survey

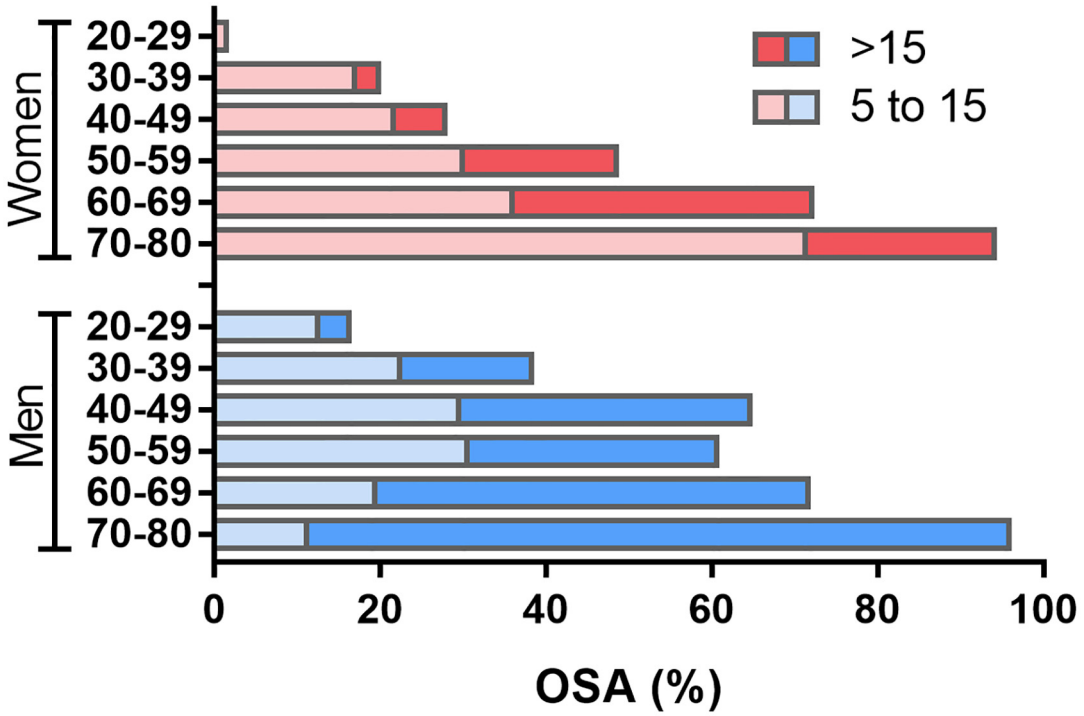

FIGURE 3 | Prevalence of obstructive sleep apnea (OSA) from 20–80 years old. Data are presented for each 20 years range, separately for men and women. Apnea-Hypopnea Index (AHI) ranging from 5–15 represents mild OSA, while an AHI>15 represents moderate to severe OSA. Considering the older adult population, the prevalence of OSA is remarkably high, but the proportion of moderate to severe OSA is higher among men, while mild OSA is more common among women. Values refer to the prevalence obtained in the São Paulo Epidemiologic Sleep Study. Adapted from Tufik et al. (2010).

(Tufik et al., 2010) showed a prevalence of OSA of 32.8% in the general population, with a progressive increase with aging, reaching 60.2% in those aged 60–69 years and 86.9% in those aged 70–80 years (**Figure 3**). Another population-based study comprising 5,615 men and women between 40–98 years of age found that OSA is most frequent in subjects aged 60 years or older—approximately 50% had an apnea and hypopnea index (AHI) of 5–14, and approximately 20% had an AHI $\geq$15 (Heinzer et al., 2015, 2018). The main cause of the high prevalence of OSA among older adults is increased pharyngeal collapsibility (Bixler et al., 1998, 2001; Vicini et al., 2018; Posadas et al., 2020).

OSA among older adults is not so closely related with excessive daytime sleepiness as it is among younger adults (Whitney et al., 1998; Bixler et al., 2005) and the harmful consequences of OSA are usually milder in older patients than in younger ones. It has been proposed that this protection against OSA cardiovascular consequences among older adults are due to mild cycles of hypoxia-reoxygenation leading to ischemic preconditioning, inducing favorable vascular remodeling (Lavie and Lavie, 2006). On the other hand, the presence of OSA in older adults is associated with clinical and neuropsychiatric manifestations not frequently observed in younger adults; such as dementia, depressive symptoms, epileptic crises, glaucoma, unexplained nocturia, frequent falls, and cardiovascular events (Lévy et al., 1996; Collop, 1997; Launois et al., 2007), as well as more recently described geriatric syndromes, such as frailty, sarcopenia, and sarcopenic obesity (Piovezan et al., 2015, 2019). SDB in older adults is associated with reduced quality of life (Stepnowsky et al., 2000; Baldwin et al., 2001; Kezirian et al., 2009), increased low-grade systemic inflammation (Chung et al., 2009) and cardiovascular alterations (McMillan and Morrell, 2016). Neurocognitive repercussions of OSA have also been observed, as Alzheimer's disease patients have a five times higher chance of having OSA than cognitively non-impaired individuals of similar age (Emamian et al., 2016). In addition, OSA treatment may decelerate dementia progression in early Alzheimer's (Ancoli-Israel et al., 2008; Cooke et al., 2009; Troussière et al., 2014).

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA (Nurwidya et al., 2016; Weiss and Kryger, 2016), and improves several OSA consequences (including daytime sleepiness, quality of life, and metabolic, cardiovascular, and neurocognitive parameters) and has proved to be an effective treatment among older adults (Troussière et al., 2014; Cao et al., 2017; Ponce et al., 2019; Richards et al., 2019).

Insomnia

Insomnia is characterized by complaints relating to: (1) initiating sleep; (2) maintaining sleep throughout the night; or (3) early awakenings and inability to return to sleep. To be diagnosed as insomnia, there need to be daytime symptoms and it must

happen even when sleep opportunity and the environment for sleeping is adequate (AASM, 2014).

A meta-analysis of the prevalence of insomnia in the general population estimated it to be 22.0% (Zeng et al., 2020). The actual prevalence in older adults is hard to estimate, as there are few population-based studies that have diagnosed insomnia in samples of older adults. The prevalence of insomnia is subjected to high variability among studies, due to methodological inconsistencies and different diagnostic criteria. A population-based study in the city of Sao Paulo found that the prevalence of clinical insomnia peaks between 30 and 39 years old, reaching 34.7%, but reducing to 16.8% in people 50–59 years old and to 9.1% in individuals above 60 years old (Castro et al., 2013). The same study showed that the prevalence of insomnia symptoms is reasonably stable throughout the whole lifespan, ranging from 18.4 to 21.5% in the general population and reaching 19.6% above 60 years old (Castro et al., 2013). Another population-based study, representing the population of South Korea, found the prevalence of clinical insomnia (based on national records of hypnotic drugs prescription and use of ICD-10 codes compatible with insomnia) to be 10.3% in people over 60 years old and increasing to 18.2% in people over 80 years old (Chung et al., 2020). In Canada, a nationwide representative survey estimated the prevalence of self-reported insomnia symptoms among people over 65 years old to be 22.2% (Chaput et al., 2018). Other studies, mainly based on clinical samples or on non-standard diagnostic methods, have observed a prevalence of insomnia as high as 60% overall (Kamel and Gammack, 2006), 51% in Denizli, Turkey (Korkmaz Aslan et al., 2020), 44.5% in Chongqing, China (Zou et al., 2019), 32.8% in Osan-Si, South Korea (Kim et al., 2017) and 30.7% in Cuenca, Spain (Redondo-Martínez et al., 2000).

The causes of insomnia in older adults are multifactorial, but usually include changes in daily routine, underlying medical conditions, behavioral aspects, and environmental conditions. Important factors are the incidence of acute medical illnesses, hospitalization, changes in the sleep environment, medications, and psychosocial stress (Kamel and Gammack, 2006).

Other Sleep Disorders

Other sleep disorders also have specific patterns in older adults. The prevalence of sleep-related movement disorders usually increases with age, including restless legs syndrome (RLS) and periodic limb movement disorder (PLMD; Yaremchuk, 2018). The prevalence of PLMD is of about 45% among older adults, compared to 6% in young individuals (Yaremchuk, 2018). Conversely, the prevalence of sleep bruxism (which is a movement disorder according to the International Classification of Sleep Disorders - 3rd Ed.) was reportedly reduced among older adults (Manfredini et al., 2013), although a population-based study in São Paulo, Brazil found it to be stable throughout life, ranging from 6.3% to 11.3% and reaching 9.2% in those older than 60 years old (Maluly et al., 2013).

REM sleep behavior disorder (RBD) is a REM parasomnia closely related to advanced age. It is more common in men, with initial symptoms being more likely to be observed in the 6th decade of life (Olson et al., 2000; Suzuki et al., 2017). It is characterized by the maintenance of muscle tonus during normal REM sleep (called REM without atonia) resulting in patients acting out their dreams, which are usually of an aggressive nature (Högl et al., 2018). This disorder has an increased prevalence in older individuals and can coexist or precede the diagnosis of neurogenerative diseases by many years, including Parkinson's disease and Lewy body dementia, is currently considered as an early or prodromal manifestation of the typical motor and cognitive symptoms of these conditions (Dauvilliers et al., 2018; Högl et al., 2018).

Sleep Deprivation

Sleep deprivation is a generic term that encompasses different types of sleep loss, including extended wakefulness (total absence of sleep for shorter periods), sleep restriction (chronic reductions in total sleep time per night) and sleep fragmentation (recurrent awakenings or arousals throughout the night). Sleep deprivation is one of the major problems of modern society and it has health, social, and economic implications (Foster and Wulff, 2005; Malik and Kaplan, 2005).

Although sleep deprivation and insufficient sleep syndrome are more commonly associated with adolescent and younger adults (AASM, 2014), often as a result of work- or lifestyle-related factors of modern societies (e.g., shift-work, excessive workload, parenthood, social jetlag, nighttime leisure activities, among others; Komada et al., 2008; Chattu et al., 2018), older adults are not fully protected from it. The normal sleep profile of older adults includes increased sleep fragmentation and more awakenings, consequently resulting in increased daytime sleepiness and daytime naps (Mander et al., 2017).

Older adults have been considered to be resistant to sleep deprivation, as they have less sleep rebound, subjective sleepiness, and attention deficit following sleep deprivation and restriction protocols (Münch et al., 2004; Adam et al., 2006; Dijk et al., 2010; Mander et al., 2017). That does not mean that the sleep need or sleep pressure in older adults is reduced, but rather that their sleep-generating capacity is impaired (Mander et al., 2017). Sleep deprivation in older adults should be contextualized to their age range. According to the Sleep Health Foundation, the recommended total sleep time for older adults is between 7 and 8 h; sleeping 5 and 6 h or around 9 h might be appropriate, and sleeping less than 5 h or more than 9 h is considered to be not appropriate (Hirshkowitz et al., 2015). In a sample of 3,576 older adults from Spain, 9.8% of them reported sleeping less than 5 h (López-García et al., 2008), while in a sample of 4,064 older adults from Taiwan, 26.2% reported sleeping 5 h or less (Chen et al., 2013).

SLEEP AND COVID-19 AMONG OLDER ADULTS

It is possible that the specific sleep patterns found among older adults may underlie their increased susceptibility to COVID-19 and the severity of the disease. Three general scenarios are possible in this context: (1) sleep-related issues might

increase the likelihood of getting infected by SARS-COV-2; (2) sleep disturbances might increase the predisposition to worse COVID-19 prognosis and outcomes; and (3) COVID-19-related aspects especially affecting community-dwelling older adults, such as social isolation, quarantine, and home confinement, among others, may impact sleep.

A selection of important sleep disorders and associated conditions among older adults is listed below, and their possible relationship with COVID-19 is detailed.

Obstructive Sleep Apnea

Many studies have related OSA with COVID-19, especially as severe cases of both conditions have similar profiles: they are worse among people who are obese, male, aged over 60, and with cardiometabolic dysfunction (Miller and Cappuccio, 2020; Tufik, 2020; Tufik et al., 2020). The fact that older adults have a significantly higher prevalence of OSA might contribute to the increased likelihood of negative outcomes in this population, mostly by predisposing patients to the incident and worsened hypoxemic states and cardiovascular events that increase the odds of negative respiratory and cardiac COVID-19 outcomes (De Mello et al., 2020).

This relationship has been confirmed by large observational studies with clinical samples. A study of 4,668 individuals with positive COVID-19 RNA PCR results has shown that the mortality rate is higher among OSA patients (11.7%) compared with controls (6.9%; Cade et al., 2020). Significant, but smaller associations with OSA were also observed with negative COVID-19 outcomes (ICU admission, mechanical ventilation, and death) and with inpatient admission (Cade et al., 2020). Another study with 9,405 COVID-19 patients found that a history of OSA was more common among those requiring hospitalization (15.3% vs. 3.4% among those who did not) and among those who presented respiratory failure (19.4% vs. 4.5% among those who did not; Maas et al., 2020). A recent meta-analysis has corroborated the fact that OSA increases the risk of hospitalization among COVID-19 cases (Strausz et al., 2021).

The possible mechanisms for this relationship are still under discussion. A provisional explanation involves the onset of cardiovascular events caused by OSA, mainly arrythmias, which have been related to COVID-19 complications. Tachycardia is a primary effect of the increased sympathetic tonus observed in OSA patients and intermittent hypoxia might be an underlying factor for both atrial and ventricular arrythmias (Di Fusco et al., 2020). An increased inflammatory pattern caused by OSA, particularly among obese patients, might also contribute to this relationship, as it might worsen hypoxemia in these patients (Miller and Cappuccio, 2020).

Information about other viral respiratory diseases reinforces the relationship between OSA and COVID-19. Untreated OSA patients have 4.7-fold higher odds of hospitalization from influenza infections (Mok et al., 2020). Sleep apnea (both obstructive and central) has been found to be an independent risk factor for ICU admission among influenza patients (Beumer et al., 2019). The prevalence of sleep apnea was 11% among influenza patients requiring ICU admissions, while among influenza patients in regular wards it was 3% (Beumer et al., 2019). OSA is also a risk factor for lower airway infections and pneumonia, mostly due to upper airway dysfunction (Chiner et al., 2016), which is more common among older adults.

Regarding the treatment of sleep apnea, it is possible that adherent CPAP users are at lower risk of severe cases (Mutti et al., 2020), although further investigation is warranted. It is not clear whether untreated OSA patients diagnosed with COVID-19 would benefit from CPAP, as the cardiovascular and inflammatory background caused by years of untreated OSA would hardly remit in the short term. It has been recommended that the initiation of CPAP therapy should be restricted to severe cases, as the risk of aerosolization and possible infection of people in the same area outweighs the benefits of the treatment in mild to moderate cases (De Mello et al., 2020). In these cases, myofunctional, physical and, respiratory therapies have been suggested, as some can be delivered via telemedicine (De Mello et al., 2020), being also more target-oriented to the pathophysiology of OSA in older adults.

Insomnia

The incidence of insomnia symptoms, insomnia disorders, and other subjective sleep complaints during the pandemic is likely to increase, probably in all age groups. A meta-analysis comprising 55 studies and a sample of 189,159 individuals indicated a 23.87% prevalence of insomnia during the pandemic (regardless of the diagnosis of COVID-19; Cénat et al., 2021). In another meta-analysis considering 31 studies and 5,153 individuals, the pooled prevalence of sleep disturbances was 34% among COVID-19 patients (Deng et al., 2021). A few studies have compared the prevalence of insomnia before and during the pandemic. Two studies have demonstrated that the prevalence of insomnia has increased by about 7% during the pandemic (Lin et al., 2021; Sun et al., 2021). However, the quality of the current evidence is low, as most studies are simple cross-sectional surveys on insomnia symptoms or retrospective studies subjected to recall bias (Morin and Carrier, 2021).

There is only limited data available regarding older adults. In a sample of 7,127 adults >50 years old from London, 37.1% reported having poor sleep at least once a week during the pandemic, while 17.0% reported having it at least three times a week (Robb et al., 2020). In a Swedish study that evaluated 1,854 individuals aged 70 and older, 23.5% reported having poor sleep due to the pandemic (Gustavsson and Beckman, 2020). In China, a study with a sample of 583 individuals >60 years old reported that the prevalence of moderate to severe insomnia had slightly increased, from 10.8% before the pandemic to 11.9% during it. A meta-analysis concluded that higher age is associated with a higher prevalence of sleep problems during the COVID-19 pandemic, both among the general population and among COVID-19 patients (Jahrami et al., 2020).

Several circumstances resulting from the COVID-19 pandemic might act as precipitating factors for insomnia, especially among older adults, including social isolation, home

confinement, anxiety, fear of getting infected, stress, and economic uncertainties (De Mello et al., 2020; Xue et al., 2020). Being alone is probably the most important factor, and some studies have already demonstrated that the subjective feeling of loneliness became more prevalent and more associated with insomnia during the pandemic (Parlapani et al., 2020; Wong et al., 2020; Grossman et al., 2021). Although living alone is an important determinant of the subjective feelings of loneliness in older adults, it is also impacted by related instances, such as poor family functioning and poor social support (Wong et al., 2020). In a sample of 583 older adults from China, the prevalence of moderate to severe loneliness increased from 40.6% to 70.4% (although only 14.3% of them were living alone; Wong et al., 2020). Coping strategies and resilience mediate this relationship, as the impact of loneliness on sleep problems tends to be higher among older adults with lower resilience scores or more COVID-19-related worries (Grossman et al., 2021).

The pandemic and all its related circumstances (home confinement, social distancing, feelings of loneliness, etc.) may act as insomnia precipitators and perpetuators, meaning that they can both trigger insomnia and make it chronic. Given the possible long-term effects of the pandemic on mental health (da Silva et al., 2020), it is possible that some individuals will present persistent insomnia even when the pandemic is over. This is especially true for the older population, due to the levels of loneliness and home confinement in these cases.

Telemedicine was becoming increasingly common in sleep medicine even before the pandemic (Zia and Fields, 2016), but due to the social isolation recommendations, telemedicine and different types of remote medical treatment have been preconized (Hollander and Carr, 2020). Cognitive behavioral therapy for insomnia (CBTi), which is the first line of insomnia treatment and can also improve other subjective sleep disturbance parameters (Morin et al., 2015), has been adapted to online delivery in three different methods: telemedicine (regular CBTi program with psychologists in a virtual environment), internet-based platforms and mobile phone applications. The last two options have been proven to be as effective as standard CBTi, with results sustained up to 1 year after finishing the program (Seyffert et al., 2016; Ye et al., 2016; Zachariae et al., 2016). However, older individuals may have problems to adhere to internet-delivered treatments. In a study about the feasibility of using sleep-related mobile applications (including a sleep diary and behavioral interventions) during the COVID-19 lockdown in France, older adults failed to complete the screening overview more often and found the app-based approach less credible than younger ones (Philip et al., 2020).

Sleep hygiene is an important set of guidance, practices, and behaviors that can help to promote healthy sleep habits and prevent the onset of insomnia symptoms. There is no standard list of recommendations, but the World Sleep Association has recently released what they have called "the Ten Commandments of Sleep Hygiene for Adults (available at https://worldsleepday.org/10-commandments-of-sleep-hygiene-for-adults). These items are valid for older adults and recommendations, such as keeping a regular sleep-wake schedule, being active during the daytime, having some sun exposure, practicing physical activity, and avoiding light-emitting devices close to bedtime are especially relevant (De Mello et al., 2020; Erren and Lewis, 2020). A broader list of sleep hygiene advice tailored to the older population and contextualized to the COVID-19 pandemic is presented in **Box 1**.

The prescription of psychotropic medication for insomnia should be cautiously considered during the pandemic (De Mello et al., 2020). The main risks from a pharmacological standpoint are the interactions of hypnotic medication with drugs used in the treatment of COVID-19, possible liver damage by these medications (given that SARS-CoV-2 already leads to impaired life function) and respiratory depression (Rismanbaf, 2020). Another concern is the possible perpetuation of insomnia or the development of dependence on an otherwise circumstantial insomnia, possibly better managed by cognitive-behavioral interventions.

BOX 1 | Advice for healthy sleep during the pandemic.

Below is some advice to prevent circadian misalignment, sleep deprivation, and insomnia symptoms due to lockdown, social isolation, or home confinement for the older population [based on Erren and Lewis (2020), Barone et al. (2020), and Morin et al. (2020)].

– *Regular sleep-wake schedule*: regular awake and bedtimes should be maintained, including at weekends.

– *Regular daytime activities*: daytime activities such as meals and housework should be part of a regular schedule and should ideally be kept at the same time every day, as a way to entrain the circadian rhythm based on social cues. If possible, meals and other activities should be done with the relatives who live together.

– *Regular physical activity*: ideally in the morning or early afternoon, and prescribed by a physical education professional to assure proper adaptations to the home environment and to avoid injury or accidents.

– *Regular online calls with family and friends*: when social isolation norms do not allow visits, scheduled online calls should be encouraged, ideally at a fixed time. This might help to entrain the circadian rhythm and to prevent feelings of loneliness.

– *Exposure to sunlight in the morning and throughout the day*: even when in home confinement, older adults should be exposed to sunlight as much as possible. Windows and curtains should be kept open whenever possible, especially in the morning.

– *Limited screen time in the evening*: screen light disrupts the physiological pattern of melatonin secretion and the whole circadian timing system. Screen exposure should be avoided at least 1 h before bedtime, especially cell phones and tablets.

– *Limited consumption of caffeinated beverages*: coffee, chocolate drinks, soft drinks, and caffeinated teas should be restricted to the morning or early afternoon.

– *Get out of bed if not able to sleep*: if sleep latency is higher than 15–20 min, get up and return to bed only when sleep is imminent.

– *Avoiding any activity in the bed or bedroom that promotes anxiety*: this includes problem-solving or planning for the next day and watching or reading the news.

However, these recommendations regarding drug therapy for insomnia are mainly based on opinion pieces and on available pharmacological information, have not been actually tested during the COVID-19 pandemic and are not specifically related to older adults.

Other Sleep Disorders

Other less prevalent sleep disorders have not received much attention in the still growing literature on sleep and COVID-19, especially in older adults. Yet, a few considerations and conjunctures can be drawn.

A possible increase in the prevalence of sleep bruxism during the pandemic has been suggested, although data are still scarce. This has been corroborated by a single online study conducted with adults in Israel and Poland, in which an aggravation of sleep bruxism symptoms was observed (Emodi-Perlman et al., 2020). The reasons for the increase in bruxism prevalence probably include increased anxiety levels, stress, and other psycho-emotional issues (Almeida-Leite et al., 2020; Emodi-Perlman et al., 2020). It is reasonable to speculate that the same might happen among older adults.

In a study conducted in India with 832 patients with Parkinson's disease (84% over 50 years old), 135 individuals reported RLS-compatible symptoms and 73% of them (24.7% of the total sample) reported that these symptoms worsened during the pandemic (Kumar et al., 2020). These results are in accordance with a hypothesis that proposed that the stresses and behavioral changes related to the COVID-19 pandemic (including home confinement and social distancing) might worsen or trigger symptoms of RLS (Franco et al., 2020).

In the same study, 147 individuals with Parkinson's disease indicated having RBD-compatible symptoms (Kumar et al., 2020). Among these, 67 (8% of the total sample) reported that these symptoms worsened during the pandemic. Such a high prevalence is explained by the intimate relationship between RBD and Parkinson's disease (Mahowald and Schenck, 2013; Högl et al., 2018) and the same should not be expected among non-Parkinsonian older adults.

Data regarding these three disorders should be cautiously analyzed, as they are either indirect evidence from other age groups (as for sleep bruxism) or data based on self-reported symptoms in a sample with a specific background disease (as for RBD and RLS). More studies regarding these disorders in older adults are needed, using better diagnostic criteria and unbiased sample characteristics.

Sleep Deprivation

Older adults seem to be at particular risk of reducing their total sleep time during the COVID-19 pandemic. In an online study with 843 participants carried out in the United Kingdom, sleep-restricted individuals (those sleeping <6 h per night) were on average older than those not sleep-restricted (Pérez-Carbonell et al., 2020).

Among all the effects of sleep deprivation, the most significant in relation to COVID-19 is the impairment of the immune response. Specific sleep parameters, such as slow-wave sleep intensity (which is reduced in older adults and in cases of OSA and sleep fragmentation), are predictive of the magnitude of antibody response and play a role in the adequate formation of an antigen-specific immune response (Lange et al., 2011). The effects of sleep deprivation on the immunological system are widely understood, and it is now recognized that lack of sleep affects the integrity of both innate and acquired immunity (Opp and Krueger, 2015; Irwin and Opp, 2017; Besedovsky et al., 2019) leading to immunosuppression and an increase in the risk of viral and opportunistic infections. Indeed, individuals sleeping less than 7 h per night are more susceptible to the common cold (Cohen et al., 2009; Prather et al., 2015). Sleep deprivation around the time of influenza, H1N1, and hepatitis A vaccination prevents or delays antibody production (Spiegel et al., 2002; Lange et al., 2003; Benedict et al., 2012). On average, the response to vaccination in groups with good sleep was double that in sleep-restricted groups (Spiegel et al., 2002; Lange et al., 2003, 2011; Benedict et al., 2012). This response seems to especially depend on proper amounts of N3 sleep, which is associated with high levels of growth hormone (GH), prolactin and aldosterone, and low levels of cortisol; although REM sleep might also have some role (Besedovsky et al., 2019).

These data allow us to speculate that the same could be true in respect of sleep deprivation and COVID-19, including an increased risk of becoming infected, a poorer prognosis, and reduced efficacy of vaccines. The theoretical immunological threats posed by sleep deprivation in the context of COVID-19 have already been discussed, both in general terms (Mônico-Neto et al., 2020; Silva et al., 2020b) and in relation to specific populations (such as shift workers; Silva et al., 2020a). Although no studies have yet been published that evaluate this relationship among older adults, the indirect evidence indicates that the same might be expected in the older population. Follow-up of vaccination cohorts for COVID-19 could provide definitive information regarding the relationship between sleep deprivation and immunization.

Regular sleep-wake schedules should be prioritized and sleep deprivation by any cause should be prevented. Daytime naps are usually not recommended to individuals with insomnia, but sleep-deprived older adults might benefit from napping for up to 20 min around noon, as a way to diminish the deleterious effects of nighttime sleep deprivation (Morin et al., 2020). Naps in the late afternoon should be avoided, as they can reduce sleep pressure and postpone bedtime, thus perpetuating insomnia symptoms and sleep deprivation.

Circadian Disruption

The pandemic represents an important challenge to the maintenance of regular sleep-wake schedules, a relationship that has already been discussed by some researchers (De Mello et al., 2020; Erren and Lewis, 2020; Morin et al., 2020). Some factors listed as chronodisruptors are mostly related to the adult, economically active population and are not totally applicable to older adults (such as working from home and altered commuting time). However, it does not mean that older adults are at lesser risk of circadian disorders in the current circumstances. The major challenges older adults face to keep a regular sleep-wake schedule during COVID-19 pandemic are described below:

- *Reduced exposure to sunlight*: home confinement and lockdown policies have reduced the opportunity for direct sunlight exposure for most people. This is especially true in respect of older adults, who might have increased their home confinement due to their high-risk condition, which further reduces their sunlight exposure. Natural light is the main driver of human circadian rhythmicity, and chronodisruption is the natural consequence of its lack. Even daylight illuminated rooms or artificial lights do not meet the needs of our circadian timing system, as the intensity and light exposure periods differ from that obtained by natural direct light exposure (Cardinali et al., 2020b).
- *Reduced effect of social zeitgebers*: these are social activities that support the entraining and synchronizing of our sleep-wake cycle. Since the circadian timing system and, more specifically, suprachiasmatic nuclei functionally deteriorates during the aging process (Cardinali et al., 2020b), the role of social zeitgebers is possibly more important among older adults. Outdoors activities at specific times (walking a pet or going to a supermarket/drugstore) and regular social interactions (receiving or visiting relatives, participating in social/religious group meetings) have been impacted by social isolation, resulting in disruptions to circadian rhythmicity and the sleep-wake cycle.
- *Increased screen time*: older adults might have increased their screen time due to social isolation and home confinement. This is more likely to be associated with television use, but older adults are getting increasingly used to computers, tablets and, mobile phones. In comparison with other sources of artificial light (such as incandescent or fluorescent light sources), portable handsets are an important source of blue light, a wavelength spectrum that is observed in regular daylight. Thus, exposure to these light sources effectively suppresses the production of melatonin similarly to the effects of sunlight exposure, potentially promoting circadian misalignment (Chellappa et al., 2011).

A multinational sample of 3,787 individuals from 18 to 60 years old, demonstrated a shift toward eveningness in 66% of the population, especially marked by later bedtimes of at least 1 h (Roitblat et al., 2021). This probably reflects a social jetlag condition that existed prior to the pandemic, but which working from or staying at home has allowed people to adjust their bedtime and awake times to match their personal preferences, rather than to work-related times. This tendency towards eveningness was not observed in older adults, probably because they were less subjected to social jetlag before the pandemic. Conversely, among the individuals classified as having a desynchronized sleep-wake cycle in this same sample (i.e., without a regular sleep-time and wake-up time), 67% were older adults. A link between circadian clock malfunctioning and SARS-CoV-2 infection has already been described (Meira E Cruz et al., 2020), and if true, would be a possible explanation for the higher likelihood of infection among older adults. In any case, this relationship is mostly based on theoretical assumptions, and more studies are needed regarding chronodisruption and COVID-19 in older adults.

Melatonin is a hormone synthesized mainly by the pineal gland and also by other nonendocrine organs, including the immune system (Cipolla-Neto and Amaral, 2018; Cardinali et al., 2020b). Melatonin has been discussed as a potential therapeutic agent for COVID-19 (Cardinali et al., 2020a,b; Miller and Cappuccio, 2020; Obeysekare et al., 2020; Ramlall et al., 2020), which would potentially benefit older adults due to their reduced melatonin secretion, as it has demonstrated antiapoptotic, antioxidative, and anti-inflammatory effects (Radogna et al., 2007; Jockers et al., 2016). However, clinical data in relation to this hypothesis is scarce and the available evidence to support the use of melatonin against SARS-CoV-2 has come from *in silico* studies (Artigas et al., 2020), a case series (Hardeland and Tan, 2020), and a preprint retrospective study (Ramlall et al., 2020). A few protocols for randomized controlled trials about melatonin administration for COVID-19 have been registered and their results will be essential in respect of knowledge about the effectiveness of melatonin (Cardinali et al., 2020b; Öztürk et al., 2020).

SUMMARIZING THE RELATIONSHIP

Given the current evidence and the issues discussed above, there are three possible relationships between sleep and COVID-19 in the older population. These are discussed below.

Sleep-Related Factors Increasing the Likelihood of Being Infected

Previous experience with other viral respiratory diseases indicates that sleep disturbances might cause immunological imbalances, increasing the likelihood of getting infected. Although this is indirect evidence, it is likely that the same may happen with COVID-19.

Sleep deprivation is the main factor that might impair the immune response, but any type of sleep disorder leading to reduced sleep time or sleep fragmentation might also have similar results. At least two sleep disorders that lead to some sort of sleep disruption might contribute to this relationship: Insomnia, which leads to sleep deprivation *per se*, as total sleep time and sleep efficiency can be considerably reduced, and OSA, which results in sleep fragmentation that might also impair the immunological response and increase the likelihood of becoming infected.

Health professionals dealing with older adults with sleep disorders should be aware of this relationship, in order to promote or increase social distancing and mask usage among their patients, thus reducing the risk of infection and negative outcomes.

Sleep Disorders Predisposing to a Worse Prognosis

Older adults with pre-existing sleep disorders, when infected, are more likely to present a worse prognosis, including a higher chance of ICU admission, mechanical ventilation, and death. The actual mechanisms responsible for this relationship are not clear, but two possible explanations have been suggested.

The first explanation proposes that there is a mechanistic relationship between OSA and COVID-19. This may happen because sleep disorders promote cardiometabolic and respiratory disturbances (e.g., arrythmias, diabetes, and hypoxia due to SDB), which increase the likelihood of negative COVID-19 outcomes. The inflammatory profile observed in patients with sleep disorders might also contribute to this. This seems particularly likely for older adults with OSA, while there is less evidence for other sleep disorders.

The second explanation proposes that both severe OSA and COVID-19 cases share the same characteristics, including obesity, hypertension and diabetes and are more prevalent among older adults. In this case, OSA does not causally increase the likelihood of a poor COVID-19 prognosis, but individuals with severe OSA are at higher risk due to their previously presented risk factors.

COVID-19-Related Aspects Impacting Sleep

Social isolation, home confinement, anxiety, fear of getting infected, stress, and economic uncertainties due to the current COVID-19 pandemic directly impact sleep, promoting circadian disruption and acting as precipitators or perpetuators of insomnia. Among older adults, loneliness seems to be an important additional factor. Social and emotional support for this population is important during the pandemic, in order to reduce the emotional burden and, consequently, insomnia and other sleep-related symptoms.

Reduced light exposure, reduced time outdoors, and increased exposure to light-emitting electronics might also contribute to poor sleep quality and alterations in the sleep-wakefulness cycle. Sleep hygiene measures might be a useful alternative to promote better sleep quality, to entrain the sleep-wakefulness cycle, and to prevent insomnia symptoms. For those already facing insomnia symptoms, CBTi is a good treatment option, although in-person appointments might be a challenge due to home confinement and social isolations norms.

LIMITATIONS AND RESEARCH AGENDA

Despite the fact that the relationship between sleep and COVID-19 has been widely discussed in the literature and also in general media outlets, original research on the subject is still scarce. Thus, the discussion of this subject and reviews about sleep and COVID-19 rely on theoretical reasoning and speculation. Indirect evidence is also frequently used, such as when data about other viral respiratory diseases are considered to predict what might happen regarding COVID-19. There are even fewer studies regarding this relationship specifically among older adults. Consequently, data acquired from studies of other age groups are frequently used to predict the possible results among older adults. The use of reasoning, generalizations, assumptions, and indirect evidence is valid, as long as the reader understands its risks. While indirectly predicting the prevalence of a sleep disorder is potentially harmless; suggesting new drugs or treatments that have not yet been tested might bring significant risks.

Even the limited number of original studies regarding sleep and COVID-19 have important limitations. Most are cross-sectional studies, which do not allow the establishment of causal relationships. Some are retrospective, either based on the participant reporting their symptoms during pre-pandemic times (thus being subject to reporting bias) or rely on medical records (which are frequently incomplete or inaccurate). Few longitudinal studies have been performed and even fewer randomized controlled trials. The assessment methods are frequently problematic, as most studies used online research tools, which leads to selection bias, as people with sleep complaints might feel more prone to participate. Very few studies have been performed with polysomnography (none of them specifically focused on older adults).

Thus, future research in this field should focus on longitudinal prospective studies, in order to properly assess the causal relationship between sleep disorders, SARS-CoV-2 infection, and COVID-19 outcomes; hopefully corroborating the current assumptions. Regarding treatment proposals, they should be based on randomized controlled trials.

CONCLUSIONS

The COVID-19 pandemic has been a challenge for the global population, and especially for older adults, who are at a greater risk of complications from this disease. Consequently, factors that might predispose or are somehow related to negative outcomes (such as hospitalization, ICU admission, mechanical ventilation, and death) need to be properly understood and warrant ongoing study. Sleep is potentially related to COVID-19 in many ways, and this relationship seems to be especially relevant in older adults.

It should be mentioned that most of the arguments presented above come from clinical observations, theoretical reasoning, and comparisons with other age groups. Studies about the relationship between sleep and COVID-19 in older adults are still scarce, but those published so far confirm this hypothesis. More studies on the subject are needed in order to confirm these points.

AUTHOR CONTRIBUTIONS

GP: project conceptualization, project administration, supervision, writing original draft, and review/editing. II, SX, CP, RP, and EX: project conceptualization, writing original draft, and review/editing. MA and ST: project conceptualization, supervision, and review/editing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the Associação Fundo de Incentivo à Pesquisa (AFIP), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). MA and ST are CNPq fellowship recipients.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 17 June 2021
doi: 10.3389/fnagi.2021.645611

Prognostic Factors in COVID-19 Patients With New Neurological Manifestations: A Retrospective Cohort Study in a Romanian Neurology Department

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Introduction: The emerging Coronavirus Disease (COVID-19) pandemic caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a serious public health issue due to its rapid spreading, high mortality rate and lack of specific treatment. Given its unpredictable clinical course, risk assessment, and stratification for severity of COVID-19 are required. Apart from serving as admission criteria, prognostic factors might guide future therapeutic strategies.

Aim: We aimed to compare clinical features and biological parameters between elderly (age $\geq$ 65 years) and non-elderly (age $<$ 65 years) patients with COVID-19 and new neurological symptoms/conditions. We also aimed to determine factors independently associated with all-cause in-hospital mortality.

Methods: All consecutive patients with COVID-19 and new neurological symptoms/conditions admitted in our Neurology Department between April 1 and August 23, 2020 were enrolled in this observational retrospective cohort study. Patient characteristics such as demographic data, comorbidities, biological parameters, imaging findings and clinical course were recorded. All-cause in-hospital mortality was the main outcome, whereas COVID-19 severity, hospitalization duration and the levels of supplemental oxygen were the secondary outcomes.

Results: One hundred forty-eight patients were included, out of which 54.1% were women. The average age was 59.84 $\pm$ 19.06 years and 47.3% were elderly, the majority having cardiovascular and metabolic comorbidities. In the elderly group, the most frequent neurological symptoms/manifestations responsible for hospitalization were stroke symptoms followed by confusion, whereas in the non-elderly, headache prevailed. The final neurological diagnosis significantly varied between the two groups, with acute cerebrovascular events and acute confusional state in dementia most commonly encountered in the elderly (65.71 and 14.28%, respectively) and secondary headache

OPEN ACCESS

Edited by:
Thomas Wisniewski, New York University, United States

Reviewed by:
Marina Emborg, University of Wisconsin-Madison, United States
David García-Azorín, Hospital Clínico Universitario de Valladolid, Spain

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Received: *23 December 2020*
Accepted: *26 April 2021*
Published: *17 June 2021*

Citation:
Davidescu EI, Odajiu I, Tulbă D, Sandu CD, Bunea T, Sandu G, Mureşanu DF, Bălănescu P and Popescu BO (2021) Prognostic Factors in COVID-19 Patients With New Neurological Manifestations: A Retrospective Cohort Study in a Romanian Neurology Department. Front. Aging Neurosci. 13:645611. doi: 10.3389/fnagi.2021.645611

attributed to SARS-CoV-2 infection often experienced by the non-elderly (38.46%). The elderly had statistically significant higher median values of white blood cell (8,060 vs. 6,090/μL) and neutrophil count (6,060 vs. 4,125/μL), C-reactive protein (29.2 vs. 5.72 mg/L), ferritin (482 vs. 187 mg/dL), fibrinogen (477 vs. 374 mg/dL), D-dimer (1.16 vs. 0.42), prothrombin time (151.15 vs. 13.8/s), aspartate transaminase (26.8 vs. 20.8 U/l), creatinine (0.96 vs. 0.77 mg/dL), and blood urea nitrogen level (51.1 vs. 27.65 mg/dL), as well as lower median value of hemoglobin (13.05 vs. 13.9 g/dL) and lymphocyte count (1,245 vs. 1,670/μL). Moreover, advanced age was significantly associated with more extensive lung involvement (25 vs. 10%) and higher fatality rate (40 vs. 9%). Overall, the mortality rate was 23.6%. Age as well as neutrophil count, C-reactive protein, fibrinogen, and activated partial thromboplastin time levels were independently associated with mortality.

Conclusions: Older age, higher neutrophil count, C-reactive protein, fibrinogen, and activated partial thromboplastin time levels are independent predictors of mortality in COVID-19 patients with new neurological manifestations/conditions at admission.

Keywords: COVID-19, elderly, neurological symptoms, risk factors, confusion, stroke, headache, mortality

INTRODUCTION

The current pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) responsible for Coronavirus Disease 2019 (COVID-19) has rapidly led to significant changes in all aspects of our existence, mainly due to its large-scale spreading, high mortality rate, and lack of specific treatment.

The elderly patients are the most affected by COVID-19, since the mortality rate gradually increases with age. Fatality rate differs between countries; in addition to the epidemiological evolution of the pandemic, it is related to different demographic and socio-economic aspects. Considering the higher life-expectancy in high-income countries, the mortality rate due to COVID-19 in people over 70 years reaches 87%, whereas in low-income countries it is around 37% (Demombynes, 2020). For instance, in the United States more than 80% of deaths amid adults occurred in patients aged ≥65 years (Centers for Disease Control Prevention., 2020) whereas in Romania a similar rate was registered in patients older than 60 years (Institutul National de Sănătate Publică, 2020). In Germany, it was estimated that the lifespan of patients with multiple comorbidities is reduced by 9 years due to SARS-CoV-2 infection (Deutsche Akademie der Naturforscher Leopoldina e.V., 2020). Another important indicator is the excess mortality that shows higher numbers for older subjects especially in the European population—more than 30,000 excessive deaths for people over 65 years during the first wave of the pandemic in comparison to around 2,500 deaths for subjects between 45 and 64 years old (Excess Mortality., 2020a). The situation in the United States is slightly different, since there is an excess mortality of 14.4% for adults aged 45–64, 24.1% for 65–74 years, 21.4% for 75–84 years, and 14.7% for ≥85 years old (Excess Mortality., 2020b). Gender differences were also noticed, with males experiencing more aggressive forms of SARS-CoV-2 infection as well as higher mortality rates with aging compared to females (Karlberg et al., 2004).

Neurologic manifestations seem to be encountered rather frequently in COVID-19 patients, ranging from 36.4% of hospitalized patients in China (Mao et al., 2020) to 57.4% in Europe (Romero-Sánchez et al., 2020). Among these, the following were described: headache, myalgias, confusion or agitation, impaired consciousness, stroke (Kremer et al., 2020), encephalopathy, dizziness, anosmia, dysgeusia, motor and sensory deficits, myopathy, movement disorders, ataxia, seizures (Mao et al., 2020; Romero-Sánchez et al., 2020), Guillain-Barré syndrome (Scheidl et al., 2020), acute necrotizing encephalitis (Poyiadji et al., 2020), and optic neuropathy (Romero-Sánchez et al., 2020). Altered mental status upon admission was even depicted as a predictor of in-hospital mortality (García-Azorín et al., 2021). Encephalopathy and delirium were observed more frequently in the elderly compared to younger patients and were associated with negative outcome (Kennedy et al., 2020; Liotta et al., 2020).

Considering that older patients who are more affected by neurological diseases commonly have an unpredictable clinical course, risk assessment and stratification for severity are required. Therefore, the aim of this study was to compare the clinical features and biological parameters between older (age ≥ 65 years) and younger (<65 years) patients with COVID-19 and new neurological symptoms/conditions. We also aimed to determine factors independently associated with all-cause in-hospital mortality that could serve as admission criteria and guide future therapeutic strategies.

MATERIALS AND METHODS

Patients

We performed an observational retrospective cohort study enrolling all consecutive patients admitted in the Neurology Department of Colentina Clinical Hospital from Bucharest, Romania between 01.04 and 23.08.2020. Starting from the

16th of May 2020, Colentina Clinical Hospital has been one of the first COVID-19 support hospitals in Romania (i.e., a second line hospital that admits patients with comorbidities and SARS-CoV-2 infection in order to support the first line hospitals—infectious disease and pulmonology hospitals). Adult patients with both new neurological manifestations (including worsening of pre-existing conditions and development of novel manifestations) and SARS-CoV-2 infection (contracted before or after the emergence of neurological symptoms and confirmed by RT-PCR test for SARS-CoV-2) hospitalized in COVID-19 first line hospitals or non-COVID-19 hospitals (including emergency outpatient departments) were directed to and admitted in the Neurology Department if the severity of neurological manifestations prevailed over the course of COVID-19. Patients with a poor baseline situation requiring ICU care were directed toward other departments. All of the consecutively admitted patients in the Neurology Department during the aforementioned period were included in our study, without any exclusion criteria.

Informed consent was either signed by the patients themselves or obtained from a legal representative over the telephone (due to biosafety reasons), this fact being specified in the patient's chart. According to our local ethical regulatory items, since our clinic is affiliated to "Carol Davila" University of Medicine and Pharmacy from Bucharest, patients specifically consent for research activities when signing the informed consent upon admission—this is specified in the operational procedure regarding the access to archived data for scientific interest—PO MED 01 Edition 1. Rev 0/09.09.2015 and the operational procedure regarding the access to patient data and the processing and protection of data—PO MED 02 Edition 1. Rev 0/01.07.2019. The study was approved by the local Ethics Committee (Nr.496/10.09.2020) and was completed in conformity with the World Medical Association Declaration of Helsinki from 1975.

Management

Management of the patients was carried out in accordance with the internal and the national treatment guidelines corresponding to the aforementioned period, which were timely updated (Ministerul Sănătăii – M. S., 2020). The patients were evaluated and monitored by the neurology team as well as an infectionist appointed to our clinic. The follow-up lasted for the period of hospitalization as it was intended to determine the prognostic factors related to in-hospital mortality.

The standard treatment included supplemental oxygen by non-invasive mechanical ventilation: nasal cannula, facial mask or high-flow ventilation according to patient's requirements; medication involved low-molecular-weight heparin in prophylactic or therapeutic dosage, dexamethasone, antibiotics (ceftriaxone, linezolid, meropenem, amoxicillin/clavulanic acid, vancomycin, azithromycin, and doxycycline), remdesivir, and tocilizumab. The scheme was adapted individually based on patient's clinical and paraclinical parameters. Some patients also received hydroxychloroquine and/or lopinavir/ritonavir at the beginning of the pandemic. Patients with severe forms and negative evolution were transferred to the ICU. During hospitalization, all patients underwent at least one lung CT scan upon admission—as an internal standard of care, or they had performed the CT in the hospital from where the patient was redirected to our institution. The severity of COVID-19 was ranked as follows: mild form for patients with blood oxygen saturation >95% who did not require oxygen supplementation and had <10% pulmonary involvement on CT scan, moderate form for patients who required oxygen supplementation by non-invasive mechanical devices and had between 10 and 50% pulmonary involvement on CT scan, and severe form for all other patients with >50% lung involvement and/or invasive mechanical ventilation.

Laboratory Results

Blood was extracted by venipuncture in clot activator vacutainer tubes for serum separation, afterwards it was processed in a COBAS 8000 Analyzer or in a VITROS 5.1 FS for biochemistry and in a SYSMEX XN 3000 Analyzer or in a DxH 900 High Volume Lab Hematology Analyzer for complete blood count. The extraction of SARS-CoV-2 was completed with the use of an automatic extractor and certified and validated by CE-IVD Real Time PCR Kits with the CFX 96 Analyzer (GRAL Medical Molecular Biology Laboratory, Bucharest), respecting the workflow and all necessary conditions with BSL-2 safety level.

Data Analysis

Patients were segregated into two study groups: non-elderly (including patients <65 years old) and elderly (involving subjects ≥65 years old). Patient characteristics such as demographic data, comorbidities, biological parameters, imaging findings, and clinical course were recorded. In-hospital mortality was the main outcome, while COVID-19 severity, hospitalization duration and the levels of supplemental oxygen were the secondary outcomes.

Database design and data analysis were performed using IBM SPSS Statistics 25. Categorical variables were reported as frequency and analyzed with Chi-square test. Continuous variables were reported as median (minimum, maximum). We considered parametric tests when distribution of the continuous variable was normal and non-parametric tests when distribution was not normal. We tested normality with Kolmogorov–Smirnov tests. Since all variables had non-normal distribution, Mann–Whitney *U*-tests were applied. In the logistic regression, we adjusted for all the variables that significantly correlated with the mortality ($p < 0.05$); we used age as a continuous variable. They were selected as covariates by the "enter" method, with mortality (yes/no) as a dependent variable. Hypothesis testing was two-tailed and statistical significance was defined as $p < 0.05$. A number of 140 patients were necessary to be included in order to develop a regression model with 12 predictors, at an estimated outcome proportion of 0.25 with a root mean square percentage error set at 0.14 (https://mvansmeden.shinyapps.io/BeyondEPV/). We report missing values in the following variables: comorbidity (two missing values), history of arterial hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, stroke, ischemic heart disease, chronic kidney disease and dementia (each with four missing values).

TABLE 1 | Demographic and clinical characteristics of patients.

Characteristics		Non-elderly, *N* (%) 78 (52.7%)	Elderly, *N* (%) 70 (47.3%)	*p*-value	OR	95% CI
Demographic factors	Age, years (mean, range)	47 (20–64)	76 (65–93)			
	Sex, females *N* (%)	40 (51.3%)	40 (57.1%)	0.475		
	Area, urban *N* (%)	64 (82.1%)	57 (81.4%)	0.922		
Comorbidities (risk factors for severe COVID-19 illness)	Dyslipidemia, *N* (%)	13 (16.9%)	40 (59.7%)	<0.001	7.293	[3.37, 15.76]
	Arterial hypertension					
	Grade 1, *N* (%)	3 (3.9%)	18 (26.9%)	<0.001	26.165*	[10.23, 66.89]
	Grade 2, *N* (%)	9 (11.7%)	22 (32.8%)			
	Grade 3, *N* (%)	7 (9.1%)	20 (29.9%)			
	Overweight/Obesity, *N* (%)	18 (25.4%)	22 (38.6%)	0.252		
	Diabetes mellitus, *N* (%)	7 (9.1%)	25 (37.3%)	<0.001	5.952	[2.36, 14.95]
	Atrial fibrillation, *N* (%)	4 (5.2%)	29 (43.3%)	<0.001	13.927	[4.56, 42.53]
	Ischemic heart disease, *N* (%)	5 (6.5%)	24 (35.8%)	<0.001	8.037	[2.85, 22.62]
	Chronic kidney disease, *N* (%)	2 (2.6%)	11 (16.4%)	0.004	7.366	[1.56, 34.56]
Neurological comorbidities	Prior stroke, *N* (%)	5 (6.49%)	27 (39.13%)	<0.001	8.037	[2.85, 22.62]
	Dementia, *N* (%)	0 (0%)	11 (15.94%)	0.004	19.214	[1.07, 343.13]
	Parkinson's disease, *N* (%)	1 (1.29%)	3 (4.34%)	–		
	Epilepsy, *N* (%)	9 (11.68%)	1 (1.44%)	0.232		
	Other**, *N* (%)	12 (15.58%)	0 (0%)	–		
Neurological symptoms/manifestations	Headache, *N* (%)	31 (39.7%)	5 (7.1%)	–		
	Dizziness, *N* (%)	8 (10.3%)	1 (1.4%)	–		
	Confusion, *N* (%)	0 (0%)	8 (11.4%)	–		
	Coma, *N* (%)	3 (3.8%)	6 (8.6%)	–		
	Epileptic seizure, *N* (%)	3 (10.3%)	1 (1.4%)	–		
	Motor deficit, *N* (%)	12 (15.4%)	14 (20%)	–		
	Sensory manifestations, *N* (%)	2 (2.6%)	1 (1.4%)	–		
	Ataxia, *N* (%)	1 (%)	1 (1%)	–		
	Language impairment, *N* (%)	0 (%)	4 (%)	–		
	Hyposmia, *N* (%)	2 (2.6%)	0 (%)	–		
	Combined***, *N* (%)	9 (11.5%)	19 (27.1%)	–		

*OR values and 95% confidence interval (CI) were presented only for significant associations; *OR is calculated for arterial hypertension presence (no/yes) within the two groups; **includes: multiple sclerosis, neurodevelopmental disorders, peripheral vestibular syndrome, myasthenia gravis, history of head trauma, etc.; *** includes: motor deficit+sensory manifestation, motor deficit+language impairment, etc.*

RESULTS

One hundred forty-eight patients were included, all Caucasians of Romanian descent. The mean age was 59.84 ± 19.06 and the majority were females (54.1%) and from urban areas (81.8%).

Demographic data, comorbidities (including risk factors for severe COVID-19 illness and neurological disorders), and neurological symptoms/manifestations upon admission are listed in **Table 1**. The elderly group consisted of 70 patients (47.3%), out of which 57.1% were women. Comorbidities were significantly more frequent in this group ($p < 0.001$), including neurological disorders. Apart from overweight/obesity, all other risk factors (i.e., cardiovascular and metabolic disorders) for severe COVID-19 illness significantly prevailed among the elderly.

The final neurological diagnosis is presented in **Table 2**, with significant differences between the two groups ($p < 0.001$). In the elderly group, stroke, acute confusional state in dementia, and worsening parkinsonism in Parkinson's disease were most frequently encountered (65.71, 14.28, and 4.28%, respectively), whereas the non-elderly commonly had secondary headache (attributed to SARS-CoV-2 infection), stroke, and peripheral vestibular syndrome (38.46, 8.97, and 7.69%, respectively).

Paraclinical characteristics (biological parameters and imaging findings) are listed in **Table 3**. The elderly had significantly higher median values of white blood cell ($p = 0.02$) and neutrophil count ($p = 0.003$), C-reactive protein (CRP), ferritin, fibrinogen, D-dimer ($p < 0.001$ for each), prothrombin time (PT), aspartate transaminase (AST) ($p = 0.001$ for each), creatinine, and blood urea nitrogen level (BUN) ($p < 0.001$) as well as lower median value of hemoglobin ($p = 0.007$) and lymphocyte count ($p = 0.001$). Moreover, advanced age

TABLE 2 | Neurological diagnosis.

Non-elderly, *N* (%) 78 (52.7%)	Elderly, *N* (%) (47.3%)
1. Secondary headache, 30 (38.46%) 2. Stroke, 15 (19.23%): - Ischemic stroke, 11 - Haemorrhagic stroke, 2 - Cerebral venous - thrombosis, 2 3. Peripheral vestibular syndrome, 7 (8.97%) 4. Multiple sclerosis relapse, 6 (7.69%) 5. Epilepsy, 5 (6.41%) 6. Encephalitis, 2 (2.56%) 7. Guillain-Barre syndrome, 1 (1.28%) 8. Worsening parkinsonism in Parkinson's disease, 1 (1.28%) 9. Myasthenic crisis, 1 (1.28%)	1. Stroke, 46 (65.71%): - Ischemic, 41 - Haemorrhagic, 4 - Cerebral venous thrombosis, 1 2. Acute confusional state in dementia, 10 (14.28%) 3. Worsening parkinsonism in Parkinson's disease, 3 (4.28%) 4. Secondary headache, 3 (4.28%) 5. Encephalitis, 1 (1.42%) 6. Hypercapnic encephalopathy, 1 (1.42%) 7. Epilepsy, 1 (1.42%)

TABLE 3 | Paraclinical characteristics of patients.

Characteristics	Non-elderly, *N* (%) 78 (52.7%)	Elderly, *N* (%) 70 (47.3%)	*p*-value
Hemoglobin, g/dL	13.9 (8, 17.4)	13.05 (5.7, 17.8)	0.007
Leukocytes, /μL	6,690 (2,700, 26,000)	8,060 (2,100, 20,500)	0.022
Neutrophils, /μL	4,125 (1,100, 23,400)	6,060 (1,400, 18,100)	0.003
Lymphocytes, /μL	1,670 (300, 4,000)	1,245 (400, 9,800)	0.001
Platelets, $\times 10^3$ /μL	244.5 (47, 462)	205.5 (63, 460)	0.06
CRP, mg/L	5.72 (0.2, 222.2)	29.27 (0.3, 343.1)	<0.001
Ferritin, μg/L	187 (12.9, 4,070)	482 (23, 10,538)	<0.001
Fibrinogen, mg/dL	374 (117, 675)	477 (115, 907)	<0.001
D-dimer	0.42 (0.2, 21)	1.16 (0, 21)	<0.001
PT, s	13.8 (11.3, 26.9)	15.15 (12.2, 50.9)	0.001
aPTT, s	28.9 (7.1, 38.4)	29.5 (22.7, 53.5)	0.109
IL-6, pg/mL	28.9 (1.5, 989.6)	48.96 (5.9, 603.9)	0.293
AST, U/L	20.8 (11.2, 145.9)	26.8 (8.7, 121.8)	0.001
ALT, U/L	20.3 (2.8, 106.6)	21 (6.2, 107.9)	0.908
GGT, U/L	43 (7, 1,626)	46.5 (8, 530)	0.309
Creatinine, mg/dL	0.77 (0.2, 8.9)	0.96 (0.2, 4)	<0.001
BUN, mg/dL	27.65 (0.6–104)	51.1 (13.7–139.1)	<0.001
Sodium, mmol/L	140 (132, 149)	140 (126, 151)	0.846
Potassium, mmol/L	4.05 (3, 6.6)	3.96 (2.8, 5.8)	0.781
Pulmonary involvement, %	10 (0, 60)	25 (0, 80)	<0.001
Viral positivity duration, days	15 (0, 51)	12 (0, 67)	0.575

was significantly associated with higher percentage of lung involvement ($p < 0.001$).

The clinical outcome of patients is presented in **Table 4**. Thirty-five patients (23.6%) died. The elderly had significantly more severe COVID-19 illness ($p < 0.001$), higher need for supplemental oxygen ($p < 0.001$), and higher mortality rate than the non-elderly ($p < 0.001$).

In the univariate analysis, apart from advanced aged, mortality was significantly associated with comorbidity presence, initial hemoglobin level, neutrophil and lymphocyte count, inflammatory markers, coagulation tests, AST, and BUN (**Table 5**).

After adjusting for all these possible confounders, advanced age remained associated with mortality. In addition to age, neutrophil count, CRP, fibrinogen, and aPTT levels also remained associated with fatality rate (**Table 6**). Interestingly, comorbidity presence did not reach statistical significance.

DISCUSSION

The results of this observational retrospective cohort study revealed that elderly patients (age ≥ 65 years) with new neurological symptoms have poorer outcomes than younger ones. A possible explanation is that older age was significantly associated with more extensive lung involvement, lower oxygen saturation levels, and higher need for oxygen supplementation. Consequently, these patients had more severe COVID-19 (17.47%) and required mechanical ventilation and ICU admission more often (8.97%) than younger patients, as it was stated in previous studies (Guo et al., 2020; Lian et al., 2020). In line with other publications, advanced age was significantly associated with: leucocytosis, neutrophilia, lymphocytopenia, anemia, a more severe inflammatory syndrome reflected by higher values of CRP, fibrinogen and ferritin, increased levels of D-dimers, as well as impaired renal and hepatic function (based on increased values of BUN, creatinine, AST and PT) (Kennedy et al., 2020). Therefore, the mortality rate (23.6%) was significantly associated with advanced age ($p < 0.001$), as it was stated in previous reports Centers for Disease Control and (ISS (Istituto Superiore di Sanità)., 2020; Salje et al., 2020; Wu and McGoogan, 2020). Mortality was 4.4 times more common in elderly patients than in non-elderly ones, an approximatively similar rate to another publication (Giangreco, 2020). Moreover, after adjusting for other possible confounders apart from age, mortality was significantly associated with higher neutrophil count, fibrinogen, and aPTT levels. However, in contrast to other results (Karlberg et al., 2004), mortality did not correlate with gender.

According to other studies, elderly patients tend to have slightly different symptoms upon admission; they often complain of fatigue, myalgia, digestive symptoms, headache (Guo et al., 2020), behavioral changes, confusion, delirium, balance problems or even falls before the onset of respiratory symptoms (Godaert et al., 2020; Lithander et al., 2020; Neerland et al., 2020; Tay and Harwood, 2020). None of our elderly patients had digestive symptoms at presentation, but confusion was the only initial symptom in 14.28% of them, mostly in patients with dementia. Since hypoxia could potentially complicate the presentation of dementia and promote delirium (Marcantonio, 2017) [which is associated with high risk for negative outcomes, such as ICU stay, the need to be discharged to a rehabilitation institution, and mortality (Kennedy et al., 2020)], we advocate

TABLE 4 | Clinical outcome of patients.

Characteristics	Non-elderly, *N* (%) 78 (52.7%)	Elderly, *N* (%) 70 (47.3%)	*p*-value	OR	95% CI
Hospitalization duration, days	14 (1, 70)	12.5 (1, 140)	0.897		
Supplemental	0 (0, 8)	0 (0, 10)	<0.001		
oxygen, L/min	2 MV	11 MV			
COVID-19 severity					
Mild, *N* (%)	43 (55.12%)	25 (35.71%)			
Moderate, *N* (%)	28 (35.89%)	33 (47.14%)	<0.001		
Severe, *N* (%)	7 (8.97%)	12 (17.14%)			
Mortality, *N* (%)	7 (9%)	28 (40%)	<0.001	6.761	[2.71, 16.83]

OR values and 95% confidence interval (CI) were presented only for significant associations; MV=mechanical ventilation.

TABLE 5 | Factors associated with mortality in the univariate analysis.

Characteristics	Survivor, *N* (%) 113 (76.4%)	Non-survivor, *N* (%) 35 (23.6%)	*p*-value	OR	95% CI
Age, years (mean, range)	55 (20, 85)	79 (39–93)	<0.001		
Comorbidity (no/yes), *N* (%)	33/79 (29.46/70.53%)	0/34 (0/100%)	<0.001	29.075	[1.73, 488.24]
Hemoglobin, g/dL	13.8 (7.9, 17.8)	12.6 (5.7, 16.6)	0.013		
Neutrophils, /μL	4.18 (1.1, 18.1)	8.13 (2.8, 23.4)	<0.001		
Lymphocytes, /μL	1.6 (0.4, 9.8)	1.05 (0.3, 2.8)	<0.001		
CRP, mg/L	7.53 (0.2, 343.1)	88.11 (0.4, 279.2)	<0.001		
Ferritin, μg/L	251.5 (12.9, 3,115)	703.5 (59.2, 10,538)	<0.001		
Fibrinogen, mg/dL	398 (115, 907)	490 (117, 807)	0.002		
D-dimer, μg/ml FEU	0.5 (0, 21)	1.81 (0.3, 21)	<0.001		
PT, s	14 (11.3, 50.9)	16.2 (12.6, 43.3)	<0.001		
aPTT, s	28.9 (7.1, 53.5)	32.1 (22.7, 48.9)	0.004		
AST, U/L	22.2 (11.2, 145.9)	33 (8.7, 107.8)	0.005		
BUN, mg/dL	32.3 (0.6, 102.9)	51.1 (18.1, 139.1)	<0.001		

OR values and 95% confidence interval (CI) were presented only for significant associations.

for hospitalizing elderly patients with confusion. Moreover, it was already ascertained that dementia is an independent risk factor for mortality (Li et al., 2020).

We emphasize the fact that the initial symptoms most commonly encountered in our patients were due to stroke in both groups, twice more frequent in the elderly. This could be explained by the fact that the elderly had at least two comorbidities in 90% of cases, out of which cardiovascular and metabolic disorders prevailed, which are predisposing risk factors for acute cerebrovascular events. In line with this, according to previous studies, the presence of such comorbidities in the elderly is linked to a higher risk of progression to a severe or even critical form of COVID-19 (Guo et al., 2020; Press et al., 2020; Sardu et al., 2020). Furthermore, according to a retrospective analysis, patients with COVID-19 and history of stroke seem to be more prone to develop ARDS, to require non-invasive and mechanical ventilation and to be transferred to the ICU; they have a poor outcome with decreased rates of discharge and increased mortality risk (Fu et al., 2020). This could be related to the anti-inflammatory responses that are generated after the occurrence of stroke, which promote infection (Emsley et al., 2008). Considering our results and previous publications (Zhai et al., 2020), it seems that severe neurological complications (e.g., stroke, acute functional decline, and delirium) are more frequent and more damaging in the elderly patients with COVID-19. Therefore, acute severe neurological conditions should be viewed as potential aggravating factors, as also stated in a previous publication (Salahuddin et al., 2020). Even in the absence of extensive pulmonary involvement, these patients require close monitoring.

Other Possible Risk Factors for Severe COVID-19 Course in the Elderly

Apart from the fact that elderly people are possibly less compliant than younger subjects to follow authorities' recommendations such as wearing a face mask or social distancing (Daoust, 2020), the risk of developing a severe form increases with the number of comorbidities (Fu et al., 2020). However, according to a study group analysis, frailty rather than age or comorbidities

TABLE 6 | Age as predictor of mortality, adjusted for blood cell count, biological inflammatory markers, coagulation tests, AST, and BUN (logistic regression).

Variables	B	OR	95% CI for OR		*p*-value
			Lower	Upper	
Age	0.107	1.113	1.039	1.191	0.002
Hemoglobin	0.142	1.153	0.803	1.654	0.440
Neutrophils	0.281	1.324	1.043	1.682	0.021
Lymphocytes	−0.422	0.656	0.147	2.920	0.580
CRP	0.015	1.015	1.000	1.030	0.049
Ferritin	0.001	1.001	1.000	1.002	0.064
Fibrinogen	−0.009	0.991	0.985	0.998	0.011
D-dimer	−0.055	1.008	0.811	1.104	0.484
PT	−0.034	0.946	0.858	1.071	0.452
aPTT	0.189	1.225	1.033	1.452	0.020
AST	−0.005	0.995	0.962	1.030	0.785
BUN	0.000	1.000	0.966	1.0366	0.987
Comorbidity	17.043	25,228,154.49			0.998

may be a better predictor of poor outcome (Hewitt et al., 2020). Due to frailty, a higher proportion of old patients develop more often adverse effects related to medication and the risk-benefit might not be justifiable in selected cases such as methylprednisolone/dexamethasone use (Rosenberg et al., 2020). In addition, other possible explanations for higher prevalence of SARS-CoV-2 infection and more severe course of disease among elderly might be: age-related deterioration in the clearance of inhaled particles especially in the territory of small airways (Svartengren et al., 2005) probably due to a progressive reduction in the number of cilia and ciliated cells (Levitzky, 1984), decrease in the upper airway size which tends to be more collapsible in men, gradual increase in the volume of the nasal cavity with subsequent reduced nasal resistance with age (Xu et al., 2019) as well as reduced levels of angiotensin-converting enzyme 2 (AlGhatrif et al., 2020).

Furthermore, in regard to immune changes in the elderly, a disruption of the innate and adaptive immune system was observed, resulting in an extensive production of cytokines and inflammatory mediators—the so-called inflammaging process (Aw et al., 2007)—as well as a more profound depletion of $CD4^+$ cells (Napoli et al., 2020a) that consequently lead to a disproportionate cytokine storm (Napoli et al., 2020b) and a reduced virus clearance. Also, elderly patients tend to have a vascular pro-inflammatory state, due to a reduced capacity of the senescent macrophages to phagocytose apoptotic cells (Napoli et al., 2020b). No less important is the fact that, apart from the cytokine storm and heart failure, brain injuries could also increase the mortality in older COVID-19 patients (Kremer et al., 2020).

Limitations

The main limitations of this study originate from the small number of participants, the absence of a control group of patients without neurological conditions (in order to establish if new neurological manifestations are independent predictors of outcome) and the insufficient data in patients' charts regarding some paraclinical parameters. Other issues arise from the demographically homogenous group of patients (which might lead to difficulties in extrapolating the results to other population) and the COVID-19 severity classification that we used, which was adjusted in compliance with the local protocol (that might limit the comparison of our results with other studies). Larger cohort studies focusing on the elderly patients with new neurological conditions are required in order to establish the best approach toward them.

CONCLUSIONS

According to our study, older age along with neutrophil count, CRP, fibrinogen, and aPTT levels are independent predictors of mortality in COVID-19 patients with new neurological manifestations at presentation. Consequently, the presence of a new neurological condition could be regarded as a risk factor for a negative outcome in the elderly patients infected with SARS-CoV-2. Inflammation markers and the extension of pulmonary involvement are important means of monitoring the severity of SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee—Colentina Clinical Hospital, Bucharest, Romania. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EID, DFM, and BOP: conceptualization. EID, IO, DT, PB, and BOP: methodology. IO, DT, CDS, TB, and GS: formal analysis. EID, IO, DT, CDS, TB, and GS: investigation. EID and BOP: resources. EID, IO, and DT: writing—original draft preparation. EID, IO, PB, and BOP: writing. EID, DFM and BOP: visualization. DFM and BOP: supervision. BOP: project administration. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

We would like to thank the entire medical staff from the Neurology Department of Colentina Clinical Hospital for watching over the COVID-19 patients.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 29 June 2021
doi: 10.3389/fnagi.2021.698184

Dementia as Risk Factor for Severe Coronavirus Disease 2019: A Case-Control Study

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Background: The aim of the present study was to investigate the outcome of patients with SARS-CoV-2 infection and dementia.

Patients and Methods: In a multicenter, observational, 1:2 matched case-control study all 23 patients with a history of dementia, hospitalized with a diagnosis of SARS-CoV-2 infection from February 28th 2020 to January 31st 2021 were enrolled. For each Case, 2 patients without dementia observed in the same period study, pair matched for gender, age (±5 years), PaO_2/FiO_2 (P/F) ratio at admission (<200, or >200), number of comorbidities (±1; excluding dementia) were chosen (Control group).

Results: The majority of patients were males (60.9% of Cases and Controls) and very elderly [median age 82 years (IQR: 75.5–85) in the Cases and 80 (IQR: 75.5–83.75) in the Controls]. The prevalence of co-pathologies was very high: all the Cases and 43 (93.5%) Controls showed a Charlson comorbidity index of at least 2. During hospitalization the patients in the Case group less frequently had a moderate disease of COVID-19 (35 vs. 67.4%, $p = 0.02$), more frequently a severe disease (48 vs. 22%, $p = 0.03$) and more frequently died (48 vs. 22%, $p = 0.03$). Moreover, during coronavirus disease 2019 (COVID-19), 14 (60.8%) patients in the Case group and 1 (2.1%; $p < 0.000$) in the Control group showed signs and symptoms of delirium.

Conclusion: Patients with dementia are vulnerable and have an increased risk of a severe disease and death when infected with COVID-19.

Keywords: dementia, SARS-CoV-2, death, severity, COVID-19

Edited by:
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Received: *20 April 2021*
Accepted: *02 June 2021*
Published: *29 June 2021*

Citation:
Pisaturo M, Calò F, Russo A, Camaioni C, Giaccone A, Pinchera B, Gentile I, Simeone F, Iodice A, Maggi P and Coppola N (2021) Dementia as Risk Factor for Severe Coronavirus Disease 2019: A Case-Control Study. Front. Aging Neurosci. 13:698184. doi: 10.3389/fnagi.2021.698184

INTRODUCTION

The novel coronavirus SARS-CoV-2, first identified in China on 31 December 2019, has rapidly spread around the world causing a global pandemic with over two million deaths.

The clinical presentation of the coronavirus disease 2019 (COVID-19) is variable, ranging from an asymptomatic infection to mild and more severe progressive respiratory failure (Macera et al., 2020; Cascella et al., 2021). Several risk factors for poor outcomes and mortality have been identified, such as age, hypertension, obesity, diabetes, and cancer (Gautret et al., 2020; Marfella et al., 2020; Onder et al., 2020; Zhou et al., 2020; Fedeli et al., 2021; Monari et al., 2021).

Older adults are particularly susceptible to COVID-19 infection due to the presence of multiple comorbidities and chronic diseases (Wynants et al., 2020). Moreover, the cognitive decline due to dementia, such as Alzheimer's disease, exposes elderly subjects to a greater risk of becoming infected with COVID-19 (Korczyn, 2020); in fact, the poor adherence to infection control measures (e.g., hand washing, social distancing, and wearing masks) and their close physical contact with caregivers are risk factors for SARS-CoV-2 infection (Canevelli et al., 2020a). Furthermore, they often show an atypical clinical presentation (Bianchetti et al., 2020; Isaia et al., 2020; Ward et al., 2020) that may delay diagnosis and appropriate treatment and consequently impact their prognosis and survival (Alonso-Lana et al., 2020). Moreover, in the case of respiratory failure, the compliance with oxygen (O_2) treatment with non-invasive or invasive ventilation is very low, with a possible poor prognosis.

Few data have been published on the impact of SARS-CoV-2 infection in patients with dementia (Canevelli et al., 2020b; Caratozzolo et al., 2020; Burns et al., 2021; Tsapanou et al., 2021; Wang et al., 2021; West et al., 2021). Although results are controversial, a worse outcome has been described among these patients (Hariyanto et al., 2020; Liu et al., 2020; McMichael et al., 2020). However, being older the patients with dementia had multiple comorbidities, so the nature of the association between dementia and poor prognosis of COVID-19 without the evaluation of age and co-pathologies associated has not yet been clearly evaluated.

The aim of the present pair-matched case-control study was to investigate the outcome of patients with SARS-CoV-2 infection and dementia, compared with patients without dementia but of the same age, presence of co-morbidities and clinical presentation at hospitalization, in order to assess its impact on the mortality and severity of the disease.

PATIENTS AND METHODS

Study Design and Setting

We performed a multicenter, observational, 1:2 matched case-control study involving three COVID-19 Units in two cities in the Campania region in southern Italy, Naples and Caserta.

The patients enrolled were adults (≥18 years), hospitalized with a diagnosis of SARS-CoV-2 infection confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) on a naso-oropharyngeal swab. Viral RNA was extracted by naso-oropharyngeal swab with QIAamp Viral RNA Kits (Qiagen GmbH, Hilden, Germany); the detection of SARS-CoV-2 was performed by RT-PCR test using Bosphore® Novel Coronavirus (Anatolia Diagnostics and Biotechnology Products Inc., İstanbul, Turkey) Detection Kit V3, by primers designed on three viral regions: E, ORF1ab, and N regions.

The study period was from February 28th 2020 to January 31st 2021. All the patients with a diagnosis of dementia observed in the study period in one of the three centers participating were enrolled as Cases (Case group). For each Case, two patients without dementia observed by the same centers in the same study period, pair matched for gender, age (±5 years), PaO_2/FiO_2 (P/F) ratio at admission (<200, or >200), number of comorbidities (±1; excluding dementia) were chosen (Control group).

All demographic, clinical and laboratory data of both Cases and Controls were collected in a database. From this database we extrapolated the data.

The study was approved by the Ethics Committee of the University of Campania L. Vanvitelli, Naples (*n*°10877/2020). All procedures performed in this study were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. Informed consent was obtained from all participants included in the study.

Variables and Definitions

The microbiological diagnosis of SARS-CoV-2 infection was defined as a positive RT-PCR test on a naso-oropharyngeal swab.

Dementia was diagnosed according to the clinical history of the patients.

The P/F ratio was considered as the arterial partial pressure of oxygen (aPP O_2) investigated through hemogas analysis divided by the fraction of inspired oxygen concentration (FiO_2) at the time of hospital admission.

The presence of underlying chronic diseases were defined according to the Charlson age-comorbidity index (Charlson et al., 1987), while medical conditions at risk of clinical deterioration were defined through a modified Early Warning Score (MEWS) (Subbe et al., 2001).

We defined patients with a mild, moderate or severe disease according to the clinical presentation of COVID-19. Precisely, patients with a mild infection did not need O_2 therapy and/or had a MEWS score below 3 points. Patients with a moderate infection required low flow O_2 therapy or non-invasive O_2 therapy and/or had a MEWS score equal to or above 3 points (≥3). Lastly, patients with a severe infection needed management in an intensive care unit (ICU) and/or mechanical ventilation; in this definition we also included patients who died because of respiratory failure, multi-organ failure or septic shock. Patients were followed until SARS-CoV-2-RNA negativity at naso-oropharyngeal swab or discharge from hospital.

Statistical Analysis

For the descriptive analysis, categorical variables were presented as absolute numbers and their relative frequencies. Continuous variables were summarized as mean and standard deviation if normally distributed or as median and interquartile range (IQR) if not normally distributed. We performed a comparison of patients with dementia and without dementia using Pearson chi-square or Fisher exact test for categorical variables and Student's *t*- or Mann-Whitney tests for continuous variables.

A *p*-value below 0.05 was considered statistically significant. Analyses were performed by STATA.

RESULTS

During the study period, overall 672 patients with SARS-CoV-2 infection were observed in the three centers participating in

the study. Of these 672 patients enrolled, 23 had a pre-existing diagnosis of dementia before the development of COVID-19 and were included in the Case group. Among the 649 patients observed without dementia, 46 were chosen as the Control group.

Of the 23 patients in the Case group, nine had a history of senile dementia, six of vascular dementia, five of Alzheimer's disease, one of frontotemporal dementia, one of Parkinson dementia, and one of human immunodeficiency virus (HIV)-related dementia. Twelve patients in the Case group were in chronic treatment (**Table 1**): memantine in two, dopaminergic drug in two, benzodiazepine in one, selective serotonin reuptake inhibitors in one, antiepileptic drug in one, antipsychotic drug and benzodiazepine in one, antipsychotic drug and NMDA receptor antagonist in one, antipsychotic drug and gabapentin in one, antipsychotic drug and lithium in one; antipsychotic drug and acetylcholinesterase inhibitors in one. Eight patients had a history of delirium before COVID-19 that required pharmacological treatment.

Table 2 shows the epidemiological and clinical characteristics of the Cases and Controls. There were no statistically significant differences in age, gender, and co-morbidities among COVID-19 patients with and without dementia. The majority of patients were males (60.9% of Cases and Controls) and very elderly [median age 82 years (IQR: 75.5–85) in the Cases and 80 (IQR: 75.5–83.75) in the Controls] (**Table 2**). The prevalence of co-pathologies was very high: all the Cases and 43 (93.5%) Controls showed a Charlson comorbidity index of at least 2; moreover, the median Charlson comorbidity index was similar in the two groups of patients [median 6 (IQR: 5–7) in Case group vs. 6 (IQR: 4–6) in the Control group] (**Table 2**). However, the patients in the Control group more frequently showed as underlying chronic diseases arterial hypertension (86.9 vs. 56.8%, $p = 0.004$).

Table 3 shows the data on the clinical presentation of COVID-19 in the Cases and Controls. No statistically significant differences were found at admission between $P0_2$ [median 69.5 mmHg (IQR: 56.3–79) in the Cases and 65 (IQR: 59.5–74. 5) in the Controls] and P/F [median 244.5 (IQR: 169.7–320.5) in the Cases and 245 (IQR: 205–290) in the Controls] (**Table 3**).

As regards the most serious respiratory support needed during hospitalization, a similar prevalence was found in high flow nasal cannulas (HFNC) [9 (39.1%) vs. 9 (19.6%; $p = 0.08$] in continuous positive airway pressure (CPAP) [1 (4.3%) vs. 8 (17.4%); $p = 0.25$] in non-invasive ventilation (NIV) [4 (17.4%) vs. 6 (13%); $p = 0.72$]. In the Case group, the prevalence of patients needing invasive ventilation was higher [10 (43.5) vs. 10 (21.7); $p = 0.06$], but with a difference not significant to the statistical analysis (**Table 2**). However, during hospitalization, with respect to the patients in the Control group, those in the Case group less frequently had a moderate disease of COVID-19 (35 vs. 67.4%, $p = 0.02$), more frequently a severe disease (48 vs. 22%, $p = 0.03$) and more frequently died (48 vs. 22%, $p = 0.03$) (**Table 2**). Moreover, although no difference between the two group of patients was observed in time from admission to discharge, the patients with dementia had a shorter period between admission and death [median and IQR of 12 (9–21) days vs. 19 (12.5–30) days], a difference without statistical significance (**Table 3**).

During COVID-19, 14 (60.8%) patients in the Case group and 1 (2.1%; $p < 0.000$) in the Control group showed signs and symptoms of delirium and required the addition of drugs to control these (**Table 1**): antipsychotic drug in three, benzodiazepine in seven and both in three patients in the Case group; the only patient in the Control group showing signs of delirium required the addition of an antipsychotic drug and benzodiazepine.

In the Case group, no difference in mortality was observed between the 14 patients with signs and symptoms of delirium during COVID-19 and the nine without (35.7 vs. 66.6%, $p = 0.21$).

DISCUSSION

In the present 1:2 case-control study performed in three COVID-19 Units in southern Italy we found that the patients with pre-existing dementia showed a worse prognosis of COVID-19. They more frequently showed a severe clinical outcome and more frequently died than those without dementia, but showed a similar age, number of pre-existing co-pathologies and respiratory failure at admission.

We know that globally more than 50 million people have dementia that has emerged as a pandemic in an aging society (Fox and Petersen, 2013; Alzheimer's Disease International, 2019). Thus, the double hit of dementia and COVID-19 pandemics has raised great concern.

A meta-analysis on 24 studies with 46,391 dementia patients showed that dementia was associated with severe COVID-19 [RR 2.63 (95% CI 1.41–4.90), $p = 0.002$] and mortality from COVID-19 infection [RR 2.62 (95% CI 2.04–3.36), $p < 0.00001$] (Hariyanto et al., 2020). However, the data available in the literature on this topic cannot be considered conclusive. In fact, since the patients with dementia were very elderly, they had a lot of co-pathologies. Thus, the impact of age and the presence of co-pathologies in the clinical presentation of patients with dementia have not been clearly analyzed. For example, Bianchetti et al. (2020) showed that the mortality rate was higher (62.2%) among 82 patients suffering from dementia than that (26.2%) observed in 545 without. Instead, the 82 patients with dementia were older (mean age of 82.6 $\pm$ standard deviation 5.3) than the 545 without (68.9 $\pm$ 12.7), with no analysis of the presence of co-pathologies.

Interestingly, the majority (69.5%) of patients with dementia in the present study during COVID-19 showed symptoms that required the addition of antipsychotic or benzodiazepine drugs. Thus, as already suggested by other authors (Kales et al., 2019), the SARS-CoV-2 patients with dementia who need hospital care represent a challenge for COVID-19 units and an increase in stress to manage non-compliant patients and with behavioral problems. In fact, delirium caused by hypoxia, a prominent clinical feature of COVID-19, can complicate the presentation of dementia (Marcantonio, 2017) and increase the suffering of people with dementia hospitalized

TABLE 1 | The therapies of the patients in case group.

Pts	Dementia drugs followed at home (previous hospitalization)	Need to increase therapy during hospitalization (0: not, 1: yes)	Need to add antipsychotic therapy during hospitalization (0: not, 1:yes)	Need to add benzodiazepine therapy during hospitalization (0: not, 1:yes)	Need to add opioids during hospitalization (0:not,1:yes)	Need to add other neuro/psychiatric drugs during hospitalization
1	//	0	0	0	0	No
2	Selective serotonin reuptake inhibitors	0	1	1	0	No
3	Antiepileptic drug	0	0	0	0	No
4	Benzodiazepine, antipsychotic drug	0	0	0	0	No
5	//	0	0	0	0	No
6	NMDA receptor antagonist, antipsychotic drug	0	0	0	0	No
7	Dopaminergic drug	0	0	0	0	No
8	Antipsychotic, gabapentin	0	0	0	0	No
9	Dopaminergic drug	1	1	0	0	No
10	Benzodiazepin	1	1	1	0	Antiepileptic drug (valproate)
11	//	0	0	1	0	No
12	//	0	1	0	0	Nr
13	//	1	0	0	0	No
14	Memantine	1	1	0	0	Nr
15	Lithium, antipsychotic drug	1	0	0	0	No
16	Antipsychotic drug, dopaminergic drug	0	0	1	0	No
17	//	1	0	1	0	No
18	//	1	0	1	0	No
19	//	1	0	1	0	No
20	//	0	0	1	0	No
21	//	0	0	1	0	Nr
22	Memantine	0	0	0	0	Nr
23	//	1	1	1	0	No

Pts, patients number; //, no treatment required at home; Nr, not reported; NMDA, N-Methyl-D-aspartate.

TABLE 2 | Demographic and clinical characteristics of the patients according to the presence or absence of dementia.

	With dementia	Without dementia	*p*-value
N° of patients	23	46	
Males, *N*° (%)	14 (60.9%)	28 (60.9%)	1
Age, years, median (IQR)	82 (75.5;85)	80 (75.5; 83.75)	0.62
N° (%) of patients in different age classes (years)			
40–49	0	1 (2,3%)	1
50–59	2 (8.7%)	3 (6.5%)	1
60–69	1 (4.3%)	3 (6.5%)	1
70–80	5 (21.7%)	17 (36.9%)	0.27
>80	15 (65.2%)	22 (47.8%)	0.17
Charlson comorbidity index, median (IQR)	6 (5;7)	6 (4;6)	0.06
N° (%) of patients with Charlson index ≥ 2	23 (100%)	43 (93.5%)	0.54
N° (%) of patients with an underlying chronic disease (dementia)	23	44	0.55
With hypertension	13 (56.8%)	40 (86.9%)	**0.004**
With cardio-vascular disease	11 (47.8%)	21/45.6%)	0.86
With diabetes	4 (17.4%)	17 (36.9%)	0.16
With chronic obstructive pulmonary disease	8 (34.8%)	15 (32.6%)	0.86
With liver cirrhosis	0	2 (4.3%)	0.55
With malignancy	2 (8.7%)	6 (13%)	0.71

Bold value indicate our way to highlight statistically significant p-value.

TABLE 3 | Clinical presentation of coronavirus disease 2019 (COVID-19) in case and control groups.

	With dementia	Without dementia	*p*-value
N° of patients	23	46	
PA02 (mmHg) at admission, median (IQR)	69.5 (79,563)	65 (74.5–59.5)	0.46
P/F at admission, median (IQR)	244.5 (320.5–169.75)	245 (290–205)	0.81
N° (%) of patients with the worst respiratory support:			
No respiratory support or need for nasal cannula	9 (39.13)	23(50)	0.39
With need for HFNC	9 (39.13)	9 (19.56)	0.08
With need for CPAP	1 (4.34)	8 (17.39)	0.25
With need for NIV	4 (17.4)	6 (13)	0.72
With need for invasive ventilation	10 (43.5)	10 (21.7)	0.06
N° (%) of patients with mild disease	4 (17.4)	7 (15.2)	1
N° (%) of patients with moderate disease	8 (34.8)	29 (63)	**0.02**
N° (%) of patients with severe disease	11 (47.8)	10 (21.7)	**0.03**
N° of deaths (%)	11 (47.8)	10 (21.7)	**0.03**
Days form admission to discharge, median (IQR)	20(12–45)	20(15–31)	0.63
Days from admission to death, median (IQR)	12(9–21)	19(12.5–30)	0.34

IQR, interquartile range; HFNC, high flow nasal cannulas; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation. Bold value indicate our way to highlight statistically significant p-value.

for COVID-19, as well as the cost of medical care and the need for dementia support.

Although without a difference in the statistical significance probably due to the small number of patients enrolled, it seems interesting that the patients with dementia had a shorter period between admission and death compared with those without. These data are in agreement with the observation of the Italian Institute of Health: considering the data on the 2,621 deaths due to COVID-19 in Italy, the patients with dementia showed a more rapid clinical worsening compared with individuals with intact cognition (Canevelli et al., 2020a).

The factors involved in the association between dementia and worse prognosis of COVID-19 could be many. Of course, the patient's lack of cooperation in performing the main therapy for SARS-CoV-2 pneumonia could be one of the reasons for the negative outcome of the disease in these patients. Then, the neurotropism of the virus and the presence of angiotensin-converting enzyme 2 (ACE-2) receptor, the cellular receptor for the SARS-CoV-2, on the brain and glial tissue makes the central nervous system a potential target for the virus (Yan et al., 2020; Barillari et al., 2021). The virus could infect the brain also through a disrupted blood-brain barrier that was often compromised in the aging brain and in neurodegenerative diseases, such as Alzheimer's disease (Hascup and Hascup, 2020). In view of this, it is likely that neurological manifestations caused by the virus worsen the already damaged neurological function of patients with dementia, making the prognosis worse. Furthermore, some studies had shown how the ACE receptor polymorphisms could influence the prognosis of patients with COVID 19 and are associated with Alzheimer's disease (Cao et al., 2020; Delanghe et al., 2020; Gómez et al., 2020). Finally, severe COVID-19 outcomes are often associated with a "cytokine storm" (Castelli et al., 2020); so elderly individuals affected by dementia could be at a higher risk due to a higher baseline of inflammation that steadily increases with age (Rea et al., 2018; Naughton et al., 2020).

Our study shows several limits; first, the retrospective nature of the study; second, we evaluated only in-hospital mortality; third, the number of patients enrolled with dementia was low. The strengths of the study are the multicenter and case-control nature of the design, which makes it possible to look at multiple risk factors at the same time, especially age and the presence of co-pathologies.

In conclusion, patients with dementia are vulnerable and have an increased risk of serious morbidity, admission to ICUs, and death when infected with COVID-19. Thus, it is necessary to carry out an early diagnosis of SARS-CoV-2 infection in this

population and to implement all measures to ensure proper management of the disease at home, with the use of telemedicine and digital technological devices, such as smart phones, which can be very useful in remote monitoring and care. Ideally, the use of monoclonal antibodies can be considered in these patients in an early phase to reduce the need of hospitalization and progression of the disease. In addition, it is necessary to establish a multidisciplinary team with an infectious disease specialist, a psychiatrist, a psychologist, social workers, nurses and volunteers to manage this difficult-to-treat-population. Finally, implementing the anti-COVID-19 vaccination in these patients is a priority.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by AOU Vanvitelli. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP, FC, and NC were involved in study concept and design, and drafting of the manuscript. PM and IG were involved in critical revision of the manuscript for important intellectual content. CC, AR, AG, and BP were involved in acquisition of data, analysis and interpretation of data, and in critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

POR Campania FESR 2014-2020-Avviso per l'acquisizione di manifestazioni di interesse per la realizzazione di servizi di ricerca e sviluppo per la lotta contro il Covid-19 (DGR n. 140 del 17 marzo 2020), Project: "Identificazione dei Fattori Demografici, Clinici, Virologici, Genetici, Immunologici e Sierologici Associati ad Outcome Sfavorevole Nei Soggetti Con COVID-19", Regione Campania, Italy.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 19 July 2021
doi: 10.3389/fnagi.2021.690383

Prevalence and Predictors of Prolonged Cognitive and Psychological Symptoms Following COVID-19 in the United States

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Background/Objectives: Little is known regarding the prevalence and predictors of prolonged cognitive and psychological symptoms of COVID-19 among community-dwellers. We aimed to quantitatively measure self-reported metrics of fatigue, cognitive dysfunction, anxiety, depression, and sleep and identify factors associated with these metrics among United States residents with or without COVID-19.

Methods: We solicited 1000 adult United States residents for an online survey conducted February 3–5, 2021 utilizing a commercial crowdsourcing community research platform. The platform curates eligible participants to approximate United States demographics by age, sex, and race proportions. COVID-19 was diagnosed by laboratory testing and/or by exposure to a known positive contact with subsequent typical symptoms. Prolonged COVID-19 was self-reported and coded for those with symptoms $\geq$ 1 month following initial diagnosis. The primary outcomes were NIH PROMIS/Neuro-QoL short-form T-scores for fatigue, cognitive dysfunction, anxiety, depression, and sleep compared among those with prolonged COVID-19 symptoms, COVID-19 without prolonged symptoms and COVID-19 negative subjects. Multivariable backwards step-wise logistic regression models were constructed to predict abnormal Neuro-QoL metrics.

Results: Among 999 respondents, the average age was 45 years (range 18–84), 49% were male, 76 (7.6%) had a history of COVID-19 and 19/76 (25%) COVID-19 positive participants reported prolonged symptoms lasting a median of 4 months (range 1–13). Prolonged COVID-19 participants were more often younger, female, Hispanic, and had a history of depression/mood/thought disorder (all $P < 0.05$). They experienced significantly higher rates of unemployment and financial insecurity, and their symptoms created greater interference with work and household activities compared to other COVID-19 status groups (all $P < 0.05$). After adjusting for demographics, past medical history and stressor covariates in multivariable logistic regression analysis, COVID-19

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Edited by:
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Reviewed by:
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Gabriel Natan Pires,
Santa Casa of São Paulo, Brazil

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Received: *02 April 2021*
Accepted: *02 June 2021*
Published: *19 July 2021*

Citation:
Frontera JA, Lewis A, Melmed K, Lin J, Kondziella D, Helbok R, Yaghi S, Meropol S, Wisniewski T, Balcer L and Galetta SL (2021) Prevalence and Predictors of Prolonged Cognitive and Psychological Symptoms Following COVID-19 in the United States. Front. Aging Neurosci. 13:690383. doi: 10.3389/fnagi.2021.690383

status was independently predictive of worse Neuro-QoL cognitive dysfunction scores (adjusted OR 11.52, 95% CI 1.01–2.28, P = 0.047), but there were no significant differences in quantitative measures of anxiety, depression, fatigue, or sleep.

Conclusion: Prolonged symptoms occurred in 25% of COVID-19 positive participants, and NeuroQoL cognitive dysfunction scores were significantly worse among COVID-19 positive subjects, even after accounting for demographic and stressor covariates. Fatigue, anxiety, depression, and sleep scores did not differ between COVID-19 positive and negative respondents.

Keywords: COVID-19, long-hauler, cognitive, stressors, Community Dwellers, post-acute sequelae of SARS-CoV-2 infection

INTRODUCTION

Prolonged symptoms of COVID-19 including fatigue, cognitive abnormalities and mood disorders have been reported (Carfì et al., 2020; Tenforde et al., 2020; Al-Aly et al., 2021; Huang et al., 2021; Nalbandian et al., 2021), however, the prevalence of these symptoms in the general population is not known. Furthermore, community members without COVID-19 may suffer similar symptoms related to social and economic stressors encountered during the global pandemic. Qualitative reports of COVID-19-related symptoms are limited in their ability to assess the severity of physical and psychological manifestations. Self-reported health status batteries that have been validated in clinical and reference populations provide quantitative measures of symptoms and may help parse the impact of SARS-CoV-2 infection from pandemic-related stressors.

We aimed to estimate the prevalence of symptoms of anxiety, depression, fatigue, sleep abnormalities, and subjective cognitive dysfunction among United States residents with or without the diagnosis of COVID-19 using quantitative NIH PROMIS/Neuro-QoL metrics.

MATERIALS AND METHODS

Design and Participants

We surveyed an unprimed sample of adult (≥18 years old) community-dwelling United States residents between February 3–5, 2021, utilizing the online platform Prolific.co[1]. Prolific.co, which is compliant with European Union General Data Protection Regulations (GDPR), is a crowdsourcing platform developed to recruit human subjects for research purposes (Kondziella et al., 2020). Data quality, participant diversity and honesty of responses compare favorably with other similar crowdsourcing/micro-jobbing platforms (Peer et al., 2017). Prolific has approximately 148,000 participants representing all 50 US states that routinely participate in community research surveys. The site has security checks to ensure that bots are not infiltrating the site. Potential survey participants were presented with a generic survey title ("Prevalence of Medical Conditions among Community Dwellers") to avoid influencing survey participation. Survey questions specifically pertaining to COVID-19 status and prolonged COVID-19 symptoms or "long-hauler" syndrome were placed at the end of the survey to avoid confounding of responses to Neuro-QoL metrics (**Supplementary Table 1**). All Neuro-QoL batteries inquired about self-reported health within the "past 7 days". A representative respondent sample reflecting age, sex and race proportions in the United States population was automatically curated by the survey platform utilizing United States Census Bureau data with a target of 1,000 responses (**Table 1**). Regions of the United States were defined according to United States Census Bureau standards (Northeast, Midwest, South, and West) (U.S. Census Bureau Map of the United States Showing Census Divisions and Regions, 2021), and population centers were characterized as rural, suburban, or urban.

Exposure

A diagnosis of COVID-19 was coded for subjects that had self-reported positive SARS-CoV-2 RT-PCR or antibody testing or for those that had exposure to a person with SARS-CoV-2 infection *and* subsequent symptoms of COVID-19 including fever > 99.5F, new onset cough, shortness of breath, muscle pain, headache, sore throat and/or loss of taste/smell (Centers for Disease Control and Prevention Covid-19, 2019). "Prolonged COVID-19" was self-reported among COVID-19 participants who continued to have symptoms ≥1 month after initial diagnosis (Datta et al., 2020; Lerner et al., 2021). COVID-19 status was trichotomized as negative, positive without prolonged symptoms and positive *with* prolonged symptoms. Symptom lists were developed from Centers for Disease Control and Prevention (CDC) (CDC, 2019; Centers for Disease Control and Prevention Covid-19, 2019) and World Health Organization (WHO) post-COVID questionnaires (World Health Organization, 2021).

Outcome Measures

The primary outcomes were the NIH/NINDS PROMIS Quality of Life in Neurological Disorders (Neuro-QoL, 0000; Cella et al., 2012; Gershon et al., 2012; NIH, 2015) (NeuroQoL) short form self-reported health measures of anxiety, depression, fatigue, cognition and sleep. Neuro-QoL raw scores were converted into T-scores with a mean of 50 and standard deviation of 10 in a reference population (United States general population or clinical

[1]https://www.prolific.co

TABLE 1 | Demographics of survey respondents (*N* = 999) compared to United States census data from 2020*.

	Survey respondents	United States census data
Age (years) – median, 95% CI	45 (95%*CI*44 – 46)	39
Sex (male),%, 95% CI	490/999 (49%, 95%*CI*46 – 52%)	162,478,564/328,239,523 (49.5%)
Race		
White, *N* (%, 95% CI)	765/999 (77%, 95%*CI*74 – 79%)	236,332,457/328,239,523 (72%)
Black, *N* (%, 95% CI)	130/999 (13%, 95%*CI*11 – 15%)	42,014,659/328,239,523 (12.8%)
Asian, *N* (%, 95% CI)	68/999 (7%, 95%*CI*5 – 9%)	18,709,653/328,239,523 (5.7%)
American Indian and Alaska Native, *N* (%, 95% CI)	4/999 (0.4%, 95%*CI*0.1 – 1%)	29,541,557/328,239,523 (0.9%)
Native Hawaiian/Pacific Islander, *N* (%, 95% CI)	2/999 (0.2%, 95%*CI*0.02 – 0.7%)	656,479/328,239,523 (0.2%)
Other or mixed race, *N* (%, 95% CI)	26/999 (3%, 95%*CI*2 – 4%)	27,572,120/328,239,523 (8.4%)
Hispanic ethnicity, *N* (%, 95% CI)	47/999 (5%, 95%*CI*4 – 6%)	60,396,072/328,239,523 (18.4%)
Population by United States Regions		
Northeast, *N* (%, 95% CI)	197/999 (20%, 95%*CI*17 – 22%)	17.1%, 95% CI
Midwest, *N* (%, 95% CI)	209/999 (21%, 95%*CI*18 – 24%)	20.8%, 95% CI
South, *N* (%, 95% CI)	413/999 (41%, 95%*CI*38 – 44%)	38.3%, 95% CI
West, *N* (%, 95% CI)	180/999 (18%, 95%*CI*16 – 21%)	23.9%, 95% CI

**https://data.census.gov/cedsci/profile?q=United%20States&g=0100000US, accessed February 6, 2021.*

sample) (Neuro-QoL, 2021). Higher T-scores indicate worse self-reported health for the anxiety, depression, fatigue, and sleep metrics, while lower scores indicate worse self-reported health for the cognitive function metric.

Statistical Analyses

This study was powered to detect a T-score mean difference of five points between COVID-19 positive and negative subjects (based on the average conditional minimal detectable change for Neuro-QoL anxiety and depression T-scores), assuming a United States COVID-19 positivity rate of 4%, power of 0.80, alpha of 0.05, and sample size of 820 participants. Patients were coded as having a worse than average NeuroQoL metric if their T-score was >55 (for anxiety, depression, fatigue, or sleep), or <45 (for cognition) based on data from reference populations (where mean T-score is set at 50 and the average minimal clinically significant difference in scores is 5) (Neuro-QoL, 2021).

Demographics, past medical history, stressors and new or worsened symptoms within the past month and NeuroQoL T-scores were compared between COVID-19 status groups using Chi-squared, Fisher's Exact and Kruskal–Wallis non-parametric tests, as appropriate. Backwards step-wise, multivariable logistic regression models were constructed to predict worse than average Neuro-QoL scores (dichotomized at T-score >55 for anxiety, depression, fatigue or sleep and <45 for cognition) using the following covariates: age, race, ethnicity, sex, years of education, region of United States (U.S. Census Bureau Map of the United States Showing Census Divisions and Regions, 2021), population center (urban, suburban, and rural), COVID-19 status (negative, prolonged, positive but not prolonged), history of lung disease, history of depression/mood/thought disorder, and individual stressors within the last month (social isolation, financial insecurity, unemployment, food insecurity, homelessness, death of family member/friend, illness of family member/friend, fear of illness, new disability, education disruption, increased caregiver responsibilities, lack of access to childcare, political conflict with family/friends/colleagues, relationship issues with household, and domestic abuse/violence). This study was deemed IRB exempt per the NYU Langone Hospitals IRB. All analyses were conducted using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY, United States).

RESULTS

Of 1,000 responses, 999 were included in analysis and one duplicate was removed. Data were complete in 99.7% of responses. The average age was 45 years (range 18–84), 49% were male, and 77% were white. Respondents closely approximated United States census statistics for age, gender, race and region of United States, however, fewer Hispanics participated in this survey than are represented in the general United States population (**Table 1**). Overall, 76/999 (7.6%, 95% CI 6.0–9.4%) reported having COVID-19, either diagnosed by laboratory test (*N* = 46/76, 61%, 95% CI 49–72%) or by exposure to a known COVID-19 contact followed by typical symptoms (*N* = 30/76, 39%, 95% CI 28–51%). There were no statistically significant differences in demographics between patients who were diagnosed by laboratory or symptom-based criteria (**Supplementary Table 2**), however, those with symptom-based diagnoses tended to have COVID earlier in the pandemic, were more often from urban areas and were more often from the Northeast. This may reflect the limited COVID-19 testing that was available during the beginning of the pandemic in New York City region. No respondents were hospitalized for COVID-19. Of those with reported COVID-19, 19/76 (25%, 95% CI 16–36%) reported prolonged COVID-19 symptoms lasting a median of 4 months (range 1–13). Of these 19, 13 (68%) had laboratory confirmation and 6 (32%) had a COVID-19 exposure followed by typical symptoms. At least one stressor was identified in 676/999 (68%, 95% CI 65–71%) subjects within the last month and 648/999 (65%, 95% CI 62–68%) reported at least one

TABLE 2 | Characteristics of survey participants (*N* = 999).

	Prolonged COVID-19 symptoms[#] *N* = 19	COVID-19 positive[^] without prolonged symptoms *N* = 57	COVID-19 negative *N* = 923	*P**	*P*[¶]
Demographics					
Age, median (IQR)	32 (22–51)	44 (28–56)	45 (31–60)	**0.010**	**0.013**
Sex (male), *N* (%)	6 (32%)	37 (65%)	447 (48%)	**0.017**	0.172
Race, *N* (%)				**0.039**	0.283
White	13 (68%)	50 (88%)	702 (76%)		
Black	3 (16%)	7 (12%)	120 (13%)		
Asian	0	0	68 (7%)		
Native American/Alaskan Native	0	0	4 (0.4%)		
Pacific Islander/Native Hawaiian	0	0	2 (0.2%)		
Other	3 (16%)	0	23 (3%)		
Unknown/prefer not to answer	0	0	4 (0.4%)		
Ethnicity, *N* (%)				**<0.001**	**0.023**
Hispanic	5 (26%)	3 (5%)	39 (4%)		
Non-Hispanic	14 (74%)	54 (95%)	868 (96%)		
Years of education, median (IQR)	15 (14–16)	16 (14–18)	16 (14–17)	0.265	0.928
Region of United States**, *N* (%)				0.276	0.102
North East	4 (21%)	10 (18%)	183 (20%)		
Mid-West	2 (11%)	13 (23%)	194 (21%)		
South	11 (58%)	29 (51%)	373 (40%)		
West	2 (11%)	5 (9%)	173 (19%)		
Population center, *N* (%)				0.310	0.179
Urban	10 (53%)	20 (35%)	263 (29%)		
Suburban	8 (42%)	30 (53%)	506 (55%)		
Rural	1 (5%)	7 (12%)	152 (17%)		
Time from COVID diagnosis to survey, median (IQR)	4 months (2–9 months)	2 months (<1–6 months)	–	0.255[ϒ]	
Past medical history, *N* (%)					
None	13 (68%)	32 (56%)	532 (58%)	0.621	0.790
Hypertension	3 (16%)	14 (25%)	243 (26%)	0.565	0.499
Diabetes	1 (5%)	4 (7%)	100 (11%)	0.497	0.330
Coronary artery disease	1 (5%)	0	24 (3%)	0.351	1.00
Peripheral artery disease	1 (5%)	0	8 (1%)	0.101	0.511
Arrhythmia	1 (5%)	3 (5%)	26 (3%)	0.486	0.278
Lung disease (COPD/asthma)	2 (11%)	8 (14%)	50 (5%)	**0.021**	**0.019**
Cancer	1 (5%)	6 (11%)	44 (5%)	0.159	0.101
Venous thromboembolism	0	0	14 (2%)	0.557	0.617
Chronic liver disease	0	0	4 (0.4%)	0.848	1.00
Chronic kidney disease	1 (5%)	1 (2%)	11 (1%)	0.287	0.260
Anemia	3 (16%)	5 (9%)	61 (7%)	0.251	0.233
Neurological/psychiatric history, *N* (%)					
None	6 (32%)	33 (58%)	535 (58%)	0.070	0.260
Stroke	1 (5%)	1 (2%)	8 (1%)	0.137	0.173
Head trauma	0	1 (2%)	23 (3%)	0.740	1.00
Seizure/epilepsy	0	1 (2%)	11 (1%)	0.828	1.00
Dementia	0	0	0	—	—
Fibromyalgia	2 (11%)	1 (2%)	30 (3%)	0.170	0.734
Chronic fatigue syndrome	0	0	0	—	—
Depression	11 (58%)	17 (30%)	252 (27%)	**0.013**	0.075
Anxiety	8 (42%)	18 (32%)	283 (31%)	0.562	0.520
Other mood disorder (e.g., bipolar)	5 (26%)	1 (2%)	47 (5%)	**<0.001**	0.284
Thought disorder	1 (5%)	0	4 (0.4%)	**0.011**	0.327

(Continued)

TABLE 2 | Continued

	Prolonged COVID-19 symptoms[#] *N* = 19	COVID-19 positive[^] without prolonged symptoms *N* = 57	COVID-19 negative *N* = 923	*P**	*P*[¶]
Stressors in the last month, *N* (%)					
Total number, median (IQR)	3 (1–5)	2 (0–4)	1 (0–3)	0.083	0.076
None	4 (21%)	19 (33%)	306 (33%)	0.538	0.606
Social isolation	7 (37%)	15 (26%)	323 (35%)	0.400	0.287
Unemployment	6 (32%)	6 (11%)	110 (12%)	**0.032**	0.322
Financial insecurity	10 (53%)	17 (30%)	225 (24%)	**0.014**	**0.031**
Homelessness	0	54 (5%)	15 (2%)	0.112	0.143
Food insecurity	1 (5%)	4 (7%)	39 (4%)	0.598	0.336
Death of family member/friend	3 (16%)	6 (11%)	89 (10%)	0.660	0.546
Illness of family member/friend	4 (21%)	15 (26%)	160 (17%)	0.215	0.118
Fear of illness	7 (37%)	15 (26%)	252 (27%)	0.641	0.757
Domestic abuse/violence	1 (5%)	4 (7%)	12 (1%)	**0.003**	**0.007**
Relationship problems in household	3 (16%)	13 (23%)	108 (12%)	**0.043**	**0.028**
New disability	0	0	0	—	—
Lack of access to childcare	0	4 (7%)	24 (3%)	0.111	0.158
Increased caregiver responsibilities	4 (21%)	6 (11%)	84 (9%)	0.201	0.244
Education disruption	0	5 (9%)	72 (8%)	0.430	1.00
Political conflict with family/friends	7 (37%)	11 (19%)	140 (15%)	**0.028**	0.070
Qualitative Symptoms in the last month, *N* (%)					
Total number, median (IQR)	6 (2–9)	2 (0–7)	1 (0–4)	**<0.001**	**<0.001**
None	1 (5%)	17 (32%)	371 (41%)	**0.004**	**0.009**
Brain fog, difficulty concentrating, forgetfulness	9 (47%)	16 (28%)	205 (22%)	**0.023**	**0.033**
Post-exertional brain fog	8 (42%)	6 (11%)	57 (6%)	**<0.001**	**<0.001**
Headache	9 (47%)	20 (35%)	201 (22%)	**0.003**	**0.001**
Cough	3 (16%)	13 (23%)	64 (7%)	**<0.001**	**<0.001**
Vision abnormalities	5 (26%)	4 (7%)	69 (8%)	**0.010**	0.180
Shortness of breath	5 (26%)	10 (18%)	62 (7%)	**<0.001**	**<0.001**
Wheezing	4 (21%)	5 (9%)	25 (3%)	**<0.001**	**<0.001**
Irregular heart beat	4 (21%)	8 (14%)	49 (5%)	**0.001**	**0.001**
Chest pain	7 (37%)	7 (12%)	34 (4%)	**<0.001**	**<0.001**
Fatigue	8 (42%)	21 (37%)	246 (27%)	0.088	**0.031**
Post-exertional malaise/fatigue	5 (26%)	8 (14%)	55 (6%)	**<0.001**	**0.001**
Joint pain	7 (37%)	12 (21%)	150 (16%)	**0.042**	0.056
Muscle pain/aches	7 (37%)	15 (26%)	182 (20%)	0.098	0.055
Difficulty sleeping	6 (32%)	18 (32%)	269 (29%)	0.904	0.654
Persistent loss taste/smell	4 (21%)	8 (14%)	11 (1%)	**<0.001**	**<0.001**
Fever	2 (11%)	8 (14%)	16 (2%)	**<0.001**	**<0.001**
Dizziness/lightheadedness	5 (26%)	6 (11%)	49 (5%)	**<0.001**	**0.004**
Anxiety	10 (53%)	21 (37%)	258 (28%)	**0.025**	**0.018**
Depression	8 (42%)	15 (26%)	243 (26%)	0.305	0.456
Impact due to symptoms, *N* (%)					
No limitations on activities	1 (5%)	24 (42%)	468 (51%)	**<0.001**	**0.003**
Interfering with work	10 (53%)	21 (37%)	163 (18%)	**<0.001**	**<0.001**
Interfering with household responsibilities	13 (68%)	21 (37%)	239 (26%)	**<0.001**	**<0.001**
Limiting leisure activities	12 (63%)	21 (37%)	229 (63%)	**<0.001**	**<0.001**

[#]*Symptoms lasting ≥ 1 month in COVID-19 positive patients; 12/17 (71%) had laboratory confirmed SARS-CoV-2 infection.* [^]*COVID-19 positive = laboratory confirmed or exposure to known COVID-19 positive person and subsequent symptoms consistent with COVID-19.* **Compares COVID-19 positive with prolonged symptoms (N = 17), COVID-19 positive without prolonged symptoms (N = 57) and COVID-19 negative (N = 906) using Kruskal–Wallis test for continuous variables and Chi-Squared test for binary and categorical variables.* [¶]*Compares COVID-19 positive and negative groups Mann–Whitney U/Wilcoxon rank sum.* [ϒ]*Compares COVID-19 subjects with and without prolonged symptoms.* ***North East = Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania; South = Maryland, Delaware, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Mississippi, Alabama, Florida, Arkansas, Louisiana, Texas, Oklahoma; Midwest = Ohio, Michigan, Indiana, Illinois, Wisconsin, Minnesota, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota; West = Alaska, Hawaii, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Idaho, Nevada, California, Oregon, Washington. Bold indicates P < 0.05.*

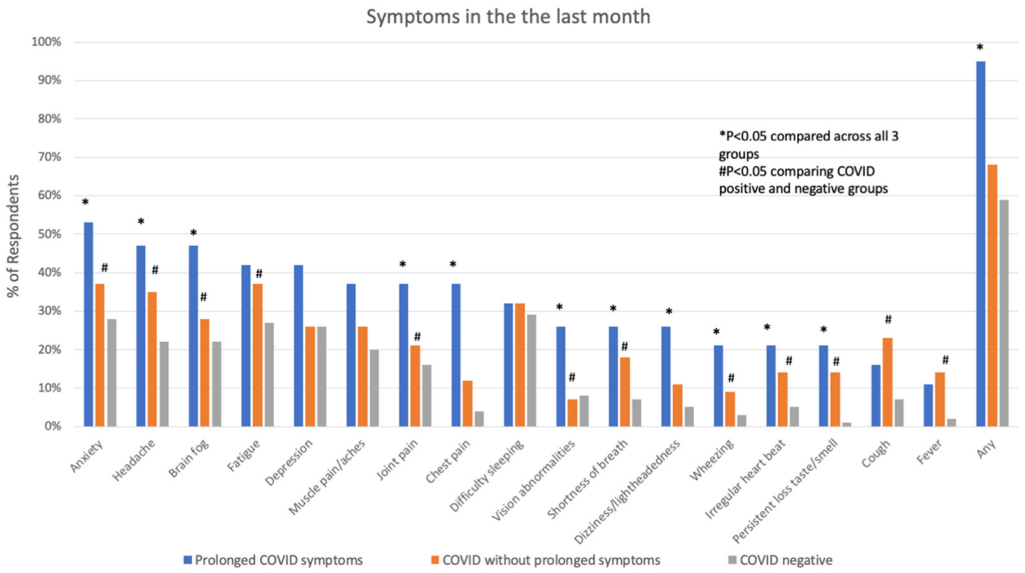

FIGURE 1 | Symptoms in the month prior to interview in subjects with prolonged COVID-19 symptoms, COVID-19 without prolonged symptoms and COVID-19 negative subjects. *$P < 0.05$ comparing across all three groups; #$P < 0.05$ comparing COVID positive to COVID negative.

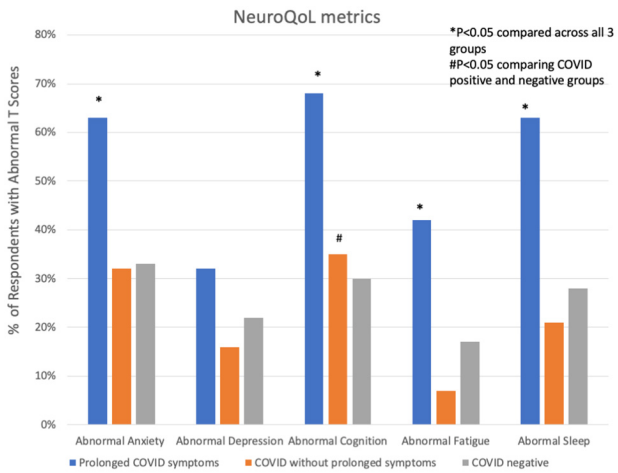

FIGURE 2 | Abnormal NeuroQoL T-scores in subjects with prolonged COVID-19 symptoms, COVID-19 without prolonged symptoms and COVID-19 negative subjects. Abnormal T-scores were defined as: T-score > 55 for anxiety, depression, fatigue, or sleep and <45 for cognition. *$P < 0.05$ comparing across all three groups; #$P < 0.05$ comparing COVID positive to COVID negative.

new/worsened symptom since the onset of the pandemic. Overall, worse than average Neuro-QOL scores for anxiety, depression, fatigue, cognition and sleep occurred in 335/999 (34%, 95% CI 31–37%), 220/999 (22%, 95% CI 19–25%), 164/999 (16%, 95% CI 14–19%), 313/999 (31%, 95% CI 29–34%), and 279/999 (28%, 95% CI 25–31%), respectively.

Comparing respondents with a history of COVID-19 to those without, those with COVID were younger, more often Hispanic, and more often had a history of lung disease (**Table 2**). COVID-19 respondents had a significantly higher number of symptoms, specifically brain fog, headache, shortness of breath, cough, wheezing, chest pain, irregular heartbeat, fatigue, post-exertional malaise/brain fog, persistent loss of taste/smell, fever, dizziness/lightheadedness, and anxiety (**Figure 1**). These symptoms were more likely to interfere with work or household responsibilities compared to COVID negative respondents. COVID-19 respondents also had significantly higher rates of financial insecurity, domestic violence/abuse, or relationship problems with members of their household, though the total number of stressors experienced did not differ between COVID positive and negative groups (**Figure 2**).

Participants with prolonged COVID-19 symptoms were more often younger, female, Hispanic, and had a history of depression, mood or thought disorder (**Table 2**). Stressors including unemployment, financial insecurity and political conflict were also more common in this group (**Figure 2**). The most common symptoms in the prolonged COVID-19 group were anxiety (53%), brain fog/difficulty concentrating/forgetfulness (47%), and headache (47%). This group experienced a greater number of symptoms in the prior month and were more disabled by these symptoms (symptoms interfered with work, household, or leisure activities) compared to other non-prolonged and COVID-19 negative respondents (**Figure 3**).

In univariate analyses, COVID-19 positive subjects (including those with and without prolonged symptoms) had significantly worse subjective measures of cognitive function than COVID-19 negative respondents, though NeuroQoL measures of fatigue, anxiety, depression and sleep symptoms did not differ between groups. Those with prolonged COVID-19 had significantly worse NeuroQoL T-scores and higher rates of worse than average symptoms of anxiety, cognition, fatigue and sleep than other

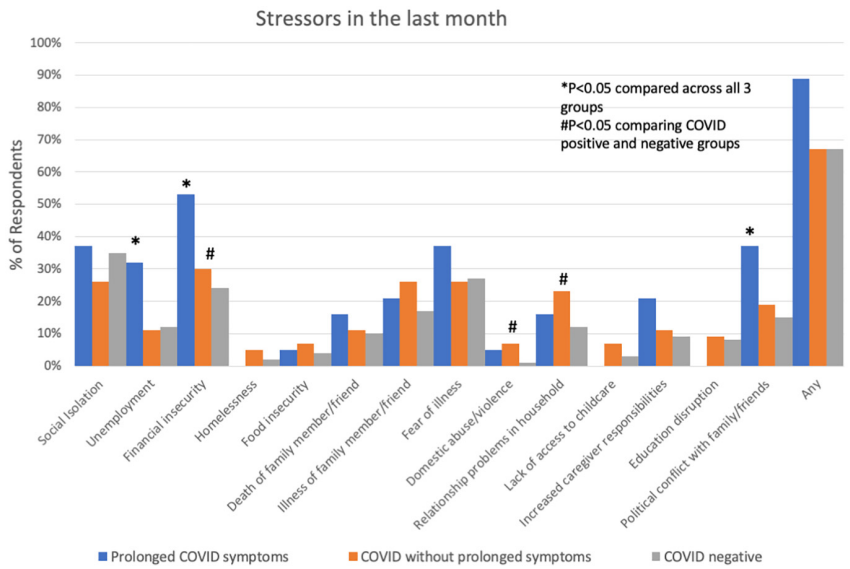

FIGURE 3 | Socio-economic stressors in the month prior to interview in subjects with prolonged COVID-19 symptoms, COVID-19 without prolonged symptoms and COVID-19 negative subjects. *$P < 0.05$ comparing across all three groups; #$P < 0.05$ comparing COVID positive to COVID negative.

groups (**Table 3**). After adjusting for demographic, past medical history and stressor covariates in multivariable logistic regression analysis, COVID-19 status (prolonged vs. not-prolonged vs. negative) was independently associated with worse Neuro-QoL cognitive dysfunction scores (adjusted OR 1.52, 95% CI 1.01–2.28, $P = 0.047$, **Table 4**), but there were no significant differences in quantitative measures of anxiety, depression, fatigue, or sleep. The most consistent factors significantly associated with worse NeuroQoL metrics across a variety of domains were: younger age, female gender, history of depression, social isolation, and relationship problems with members of the household (**Table 4**).

We next explored the relationship of age with socio-economic stressors, symptoms and Neuro-QoL T-scores. Age was negatively correlated with both the number of symptoms (Spearman correlation coefficient −0.105, $P = 0.001$) and stressors (Spearman correlation coefficient −0.131, $P < 0.001$) experienced by subjects in the month prior to the survey. Notably, unemployment (Spearman correlation coefficient −0.146, $P < 0.001$) and financial insecurity (Spearman correlation coefficient −0.129, $P < 0.001$) were most strongly associated with younger age. Additionally, older respondents were less likely to report limitations in their routine activities due to symptoms (OR 0.98, 95% CI 0.97–0.99, $P < 0.001$). Overall, while age was inversely related to worse Neuro-QoL T-scores in multivariable analyses (**Table 4**), there was a suggestion of a bimodal distribution of worse T-scores for depression, cognition and sleep with peaks around ages 30 and again at 60–65 (**Figure 4**).

TABLE 3 | Neuro-QoL T-scores by COVID-status (*N* = 999).

Metric	Prolonged COVID-19 symptoms *N* = 19	COVID-19 without prolonged symptoms *N* = 57	COVID-19 negative *N* = 923	*P**	*P*¶
Anxiety T-score, median (IQR) Anxiety T-score > 55, *N* (%)	56.8 (51.4–62.6) 12/19 (63%)	53.3 (45.1–56.8) 18/57 (32%)	51.4 (45.9–57.6) 305/923 (33%)	0.007	0.201
Depression T-score, median (IQR) Depression T-score > 55^, *N* (%)	51.3 (46.8–56.7) 6/19 (32%)	46.8 (36.9–53.2) 9/57 (16%)	47.9 (43.1–53.6) 205/923 (22%)	0.113	0.834
Cognition T-score, median (IQR) Cognition T-score <45^, *N* (%)	41.9 (38.9–48.3) 13/19 (68%)	47.1 (42.4–54.2) 20/57 (35%)	50.9 (43.9–59.0) 280/923 (30%)	<0.001	0.001
Fatigue T-score, median (IQR) Fatigue T-score > 55^, *N* (%)	54.4 (48.4–57.6) 8/19 (42%)	43.8 (40.7–50.8) 4/57 (7%)	45.6 (39.5–52.3) 152/922 (17%)	0.004	0.370
Sleep T-score, median (IQR) Sleep T-score > 55^, *N* (%)	58.0 (50.4–62.8) 12/19 (63%)	47.3 (42.8–53.1) 12/57 (21%)	48.9 (41.7–55.6) 255/922 (28%)	0.004	0.432

*IQR = interquartile range. ^T-scores > 50 indicate worse than average self-reported health for anxiety, depression, fatigue and sleep compared to a reference United States population. T-scores > 50 indicate better self-reported cognitive function compared to a reference United States population. *Krusal–Wallis non-parametric test of continuous variable T-scores across all three COVID-19 status categories (prolonged COVID-19, non-prolonged COVID-19, COVID-19 negative. ¶Mann–Whitney U/Wilcoxon rank sum comparing COVID-19 positive and negative groups.*

TABLE 4 | Multivariable logistic regression models predicting worse than average Neuro-QoL metrics among subjects with prolonged COVID-19 symptoms (*N* = 19), COVID-19 without prolonged symptoms (*N* = 57), and COVID-19 negative (*N* = 923) subjects.

Variable	Adjusted Odds Ratio (95% CI)	*P*
Neuro-QoL anxiety scores worse than average (T-score > 55)		
Age	0.96 (0.95–0.97)	<0.001
Sex (male)	0.71 (0.51–0.98)	0.034
Years of education	0.92 (0.86–0.98)	0.009
History of depression/mood/thought disorder	3.48 (2.49–4.88)	<0.001
Social isolation	1.79 (1.27–2.53)	0.001
Relationship problem with member of household	2.64 (1.63–4.27)	<0.001
Fear of illness	1.98 (1.38–2.84)	<0.001
Neuro-QoL depression scores worse than average (T-score > 55)		
Age	0.97 (0.96–0.98)	<0.001
History of depression/mood/thought disorder	4.81 (3.38–6.84)	<0.001
Social isolation	1.93 (1.35–2.67)	<0.001
Unemployment	1.75 (1.10–2.80)	0.012
Relationship problem with member of household	1.70 (1.07–2.72)	0.025
Neuro-QoL fatigue scores worse than average (T-score > 55)		
Age	0.98 (0.97–0.99)	0.002
Sex (male)	0.63 (0.43–0.93)	0.021
Years of education	0.89 (0.82–0.96)	0.003
History of depression/mood/thought disorder	3.35 (2.27–4.95)	<0.001
History of lung disease (asthma/COPD)	2.29 (1.16–4.50)	0.017
Social Isolation	1.69 (1.12–2.54)	0.012
Relationship problem with member of household	2.35 (1.44–3.85)	0.001
Fear of illness	1.63 (1.07–2.47)	0.022
Political conflict with family/friends/colleagues	1.61 (1.02–2.56)	0.043
Neuro-QoL cognitive dysfunction scores worse than average (T-score <45)		
Age	0.97 (0.96–0.98)	<0.001
Years of education	0.92 (0.86–0.98)	0.007
History of depression/mood/thought disorder	3.46 (2.49–4.79)	<0.001
Social Isolation	2.30 (1.66–3.19)	<0.001
Food insecurity	2.42 (1.15–5.07)	0.020
Illness of family member/friend	1.74 (1.18–2.57)	0.005
Political conflict with family/friends/colleagues	1.66 (1.10–2.51)	0.016
COVID-19 status (negative, positive/no prolonged symptoms, positive with prolonged symptoms)	1.52 (1.01–2.28)	0.047
Neuro-QoL sleep scores worse than average (T-score > 55)		
Age	0.98 (0.97–0.99)	<0.001
Sex (male)	0.60 (0.44–0.83)	0.002
Hispanic ethnicity	2.25 (1.14–4.56)	0.020
History of depression/mood/thought disorder	3.24 (2.33–4.50)	<0.001
Education disruption	2.09 (1.21–3.61)	0.008
Social Isolation	1.74 (1.24–2.43)	0.001
Death of family member/friend	1.70 (1.04–2.81)	0.036
Food insecurity	3.07 (1.49–6.32)	0.002
Political conflict with family/friends/colleagues	1.86 (1.23–2.80)	0.003

(Continued)

TABLE 4 | Continued

Covariates included in backward stepwise logistic regression analysis: age, sex, race (white versus other), ethnicity, years of education, region of United States, population center (rural, suburban, urban), COVID-19 status (negative, prolonged, positive but not prolonged), history of lung disease, history of depression, mood or thought disorder, and stressors within the last month (social isolation, financial insecurity, unemployment, food insecurity, homelessness, death of family member/friend, illness of family member/friend, fear of illness, new disability, education disruption, increased caregiver responsibilities, lack of access to childcare, political conflict with family/friends/colleagues, relationship issues with household, domestic abuse/violence). Variables not shown were not significant and did not remain in the final model.

DISCUSSION

This study is the first, to our knowledge, to establish baseline quantitative measures of the prevalence of common symptoms of "long-hauler" syndrome – including cognitive dysfunction, fatigue, anxiety, depression, and sleep disorders – in a representative population of community-dwelling United States residents with and without a history of COVID-19. Furthermore, this is one of the first studies to examine the impact of psychosocial stressors on quantitative measures of subjective cognitive status, mood, and sleep. We found worse than average NeuroQoL scores occurred in ∼30% of subjects *without* COVID-19 across a range of domains. We further demonstrated that financial and social stressors, which may be exacerbated by the pandemic, predict worse NeuroQoL outcomes independent of COVID-19 status. However, a history of COVID-19, and particularly prolonged COVID-19, was associated with significantly worse subjective cognitive dysfunction scores, even after adjusting for baseline differences in demographics, past medical history and stressors. Indeed, most of the abnormalities in NeuroQoL metrics were driven by the subgroup of COVID-19 patients with protracted symptoms. Though there was an association of COVID-19 status with subjective cognitive dysfunction, other socio-demographic factors, including younger age, female gender, history of depression, social isolation and relationship problems with members of the household, were much stronger predictors of worse NeuroQoL metrics.

The relationship between stressors, heightened inflammatory response, mood disorders, cognitive abnormalities and neurodegenerative disease has been well established (Watt and Panksepp, 2009; Cunningham, 2011; Murray et al., 2011, 2012; Jack et al., 2018; Nation et al., 2019; Parnetti et al., 2019; Sweeney et al., 2019; Jones et al., 2020). Indeed, elevated IL-6 levels, which correlate with COVID-19 severity (Aziz et al., 2020; Frontera et al., 2020, 2021; Pairo-Castineira et al., 2021; Zhu et al., 2021), have been associated with depression and alterations in activity in the subgenual cingulate cortex (Drevets et al., 2008; Harrison et al., 2009). Other symptoms, including fatigue, malaise, myalgias, and joint pain, commonly

FIGURE 4 | Distribution of Neuro-QoL T-scores by age. There is a suggestion of a bimodal peak in worse depression, cognitive and sleep score with peaks around ages 30–35 and again around ages 60–65.

referred to as "sickness behavior", are thought to be triggered by proinflammatory cytokines (IL-1α, IL-1β, IL-6, and TNFα) generated as an innate immune response (Watt and Panksepp, 2009). The inflammatory response generated by pandemic-related stressors may represent the mechanistic underpinning of debilitating symptoms in patients that did not have COVID-19, though more data is needed to support this hypothesis. Among patients with a history of COVID-19, the inflammatory response or cytokine release syndrome associated with infection (Aziz et al., 2020; Leisman et al., 2020; Pairo-Castineira et al., 2021; Zhu et al., 2021) may synergize with a stressor-related inflammatory response to amplify and prolong post-viral symptoms.

Prolonged COVID-19 symptoms occurred in 25% of participants and were disabling, lasted months following diagnosis, and interfered with work and household responsibilities. The most common protracted symptoms reported in our study were anxiety, headache, "brain fog," and fatigue, which have also been observed in other cohorts (Carfì et al., 2020; Huang et al., 2021; Mahmud et al., 2021; Tenforde et al., 2021). During the timeframe of this survey there were 26,779,193 United States confirmed COVID-19 cases (U. S. Johns Hopkins Coronavirus Resource Center, 2021), representing 8.1% of the total United States population (U.S. Census Bureau and U.S. World Population Clock, 2021). Our study detected a 7.6% COVID-19 positivity rate, which closely approximates population-based prevalences. Extrapolating from the 25% rate of prolonged symptoms among COVID-19 subjects in our study, there could be as many as 6,694,798 people in the United States currently experiencing post-acute sequelae of COVID-19 or "long-hauler" syndrome. Other countries have also documented prolonged symptoms following SARS-CoV-2 infection. A study conducted in the United Kingdom identified higher rates of stroke, dementia, mood and anxiety disorders 6-months after COVID-19 diagnosis compared to contemporaneous patients diagnosed with a different respiratory tract infections (Taquet et al., 2021). Similarly, a Chinese study found that 6-months after hospital discharge for COVID-19, 63% of patients had fatigue or muscle weakness, 26% had sleep abnormalities and 23% had anxiety or depression (Huang et al., 2021).

While we initially hypothesized that NeuroQoL metrics would be worse among older respondents, in fact, we detected the opposite. Older participants had fewer post-COVID symptoms and were less likely to have limitations in their activities due to symptoms. Older participants also reported fewer stressors. It is possible that the synergistic relationship between viral and stressor-related inflammatory responses was more pronounced in younger respondents. Financial insecurity and unemployment issues were significantly more common in those with prolonged COVID symptoms and these stressors were also inversely correlated with age, perhaps because younger people are less established in their careers, or have less savings. We did, however, detect the suggestion of a bimodal peak, where NeuroQoL scores for depression, sleep and subjective cognitive function appeared to worsen around ages 60–65. The underlying mechanisms related to abnormal scores in these different age ranges may differ and further evaluation is merited.

Limitations of this study include the fact that people who complete online surveys may not be representative of the general United States population in unmeasurable ways. This may limit generalizability to the United States population as a whole. However, our respondent population did closely approximate easily measured United States demographic data, though Hispanics were underrepresented. Second, it is possible we underestimated the prevalence of prolonged COVID symptoms

since some of the respondents may have been diagnosed with COVID close to the time of the survey and hence not accrued enough time to qualify for prolonged COVID symptoms. Though the median time from COVID diagnosis to the survey was not statistically different between patients with or without prolonged symptoms, the median time interval was twice as long for those with prolonged symptoms compared to those without (4 versus 2 months). Third, cognitive function and financial stressors may be even worse than we measured, since the ability to complete an online survey requires access to technology and computer competence. Despite this, 29% of respondents reported unemployment, financial insecurity, food insecurity, or homelessness within the month prior to completing the survey, indicating that this was not a rarified group of respondents. Fourth, patients hospitalized with more severe COVID-19 may have substantially different outcomes than this cohort of non-hospitalized community dwellers. Fifth, the number of patients with COVID-19 was relatively small, as was the number of respondents with prolonged-COVID symptoms. However, we powered our survey for an even smaller positivity rate and our data provides important epidemiological information regarding the prevalence of post-acute COVID symptoms. Sixth, because this was a survey we had to rely on self-reported COVID status. Methodologically, obtaining laboratory proof of SARS-CoV-2 infection from all respondents would not have been feasible and our definition of COVID status was the only pragmatic option to obtain data rapidly on a large scale during a pandemic. Because respondents with symptom-based diagnoses tended to be from urban areas, the Northeast and had COVID earlier in the pandemic, it is possible that this group represents the first wave in the New York City area before testing was widely available. Last, NeuroQoL metrics are subjective measures of self-reported health. Objective measures of cognitive dysfunction using formal neuropsychological testing are needed to identify domains of dysfunction, which would guide therapeutic intervention.

CONCLUSION

Prolonged symptoms lasting a medina of 4 months occurred in 25% of COVID-19 positive participants. NeuroQoL cognitive dysfunction scores were significantly worse among COVID-19 positive subjects, even after accounting for demographic and stressor covariates. Fatigue, anxiety, depression, and sleep scores did not differ between COVID-19 positive and negative respondents. Major factors associated with worse NeuroQoL metrics across a variety of domains were younger age, female gender, history of depression, social isolation, and relationship problems with members of the household.

DATA AVAILABILITY STATEMENT

The data will be made available to investigators upon reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NYU IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JF designed the study, analyzed the data, and drafted the manuscript. AL, KM, JL, DK, RH, SY, SM, TW, LB, and SG contributed to the conceptual design of the study, data interpretation, and critical revision of the manuscript. All authors approved the submitted version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.690383/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

SYSTEMATIC REVIEW
published: 02 August 2021
doi: 10.3389/fnagi.2021.653694

Age-Associated Neurological Complications of COVID-19: A Systematic Review and Meta-Analysis

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The outbreak of the novel and highly infectious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in hundreds of millions of infections and millions of deaths globally. Infected individuals that progress to coronavirus disease-19 (COVID-19) experience upper and lower respiratory complications that range in severity and may lead to wide-spread inflammation and generalized hypoxia or hypoxemia that impacts multiple organ systems, including the central and peripheral nervous systems. Since the SARS-CoV-2 outbreak, multiple reports continue to emerge that detail neurological symptoms, ranging from relatively mild (e.g., impaired taste and/or smell) to severe (e.g., stroke), suggesting SARS-CoV-2 may be neurotropic and/or contribute to nervous system injury through direct and/or indirect mechanisms. To gain insight into the types of neurological complications associated with SARS-CoV-2 infection and their possible relationship with age, sex, COVID-19 severity, and comorbidities, we performed a systematic review of case reports and series published in 2020 – April 4, 2021 of infected patients with neurological manifestations. Meta-analyses were conducted using individual patient data from reports where these data could be extracted. Here, we report neurological injury occurs across the lifespan in the context of infection, with and without known comorbidities, and with all disease severities, including asymptomatic patients. Older individuals, however, are more susceptible to developing life-threatening COVID-19 and cerebrovascular disease (CVD), such as stroke. A mild but inverse correlation with age was seen with CNS inflammatory diseases, such as encephalitis, as well as taste and/or smell disorders. When reported, increased age was also associated with comorbid cardiovascular risk factors, including hypertension, diabetes mellitus, and lipid disorders, but not with obesity. Obesity did correlate with development of critical COVID-19. Discussion into potential pathophysiological mechanisms by which neurological symptoms arise and long-term consequences of infection to the nervous system is also provided.

Keywords: brain, COVID-19, cerebrovascular events, SARS-CoV-2, encephalopathy, aging brain

OPEN ACCESS

Edited by:
Agustín Ruiz Laza, Fundació ACE, Spain

Reviewed by:
Jukka Jolkkonen, University of Eastern Finland, Finland
Miguel Calero, Instituto de Salud Carlos III (ISCIII), Spain

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Received: *15 January 2021*
Accepted: *08 June 2021*
Published: *02 August 2021*

Citation:
Sullivan BN and Fischer T (2021) Age-Associated Neurological Complications of COVID-19: A Systematic Review and Meta-Analysis. Front. Aging Neurosci. 13:653694. doi: 10.3389/fnagi.2021.653694

INTRODUCTION

Infectious disease, ranging in severity from symptoms of a mild cold to severe acute respiratory distress are attributed to coronaviruses (CoV)s. The majority of this large family of viruses are transmitted among non-human species, however, occasional zoonosis has resulted in seven known CoV strains that infect and cause disease in humans. Of these, three human CoVs (huCoVs) strains have emerged over the past two decades that can promote severe disease and even death. Severe acute respiratory coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS)-CoV, emerged in 2003 and 2012, respectively, causing significant global illness and mortality (Drosten et al., 2003; Memish et al., 2013). In December 2019, a novel CoV strain, now designated SARS-CoV-2, was first reported to infected humans and cause severe disease, termed CoV disease-19 (COVID-19). While most individuals with COVID-19 experience mild to moderate symptoms, others develop more severe disease, leading to death in a subset of these patients. Rapid transmission of the virus has resulted in a global pandemic resulting in hundreds of millions of infections and millions of deaths, worldwide, that remains on-going at the time of this review (Huang et al., 2020; WHO, 2021).

Although primarily considered a virus impacting the respiratory system, an increasing number of case studies have highlighted substantial neurological consequences of SARS-CoV-2 infection. Indeed, the Centers for Disease Control (CDC) lists new confusion or the inability to arouse as indicators of severe COVID-19 presentation, necessitating emergency medical attention (CDC, 2020). Early reports from Wuhan, China alerted the neuroinvasive potential of SARS-CoV-2, as multiple patients developed headache and dizziness, anosmia, and/or ageusia, which were often reported as initial symptoms of infection and disease (Chen N. et al., 2020; Huang et al., 2020; Mao et al., 2020; Yang et al., 2020). In addition, acute onset of more serious neurological symptoms, including altered mental status (encephalopathy), meningoencephalitis, demyelinating diseases, and stroke are increasingly reported in SARS-CoV-2 infected patients (Al-Olama et al., 2020; Farhadian et al., 2020; Lodigiani et al., 2020; Lu et al., 2020; Scullen et al., 2020; TunÇ et al., 2020). Many reports that reveal the age of the subjects studied suggest that patients older than 50 years are more likely to experience severe neurological complications, however, varying new onset neurological manifestations have also been reported among younger individuals and appear to be a common complication of COVID-19. As such, there is a critical need for investigating the impact of COVID-19 on the central nervous system (CNS). Here, we present evidence for a direct or indirect role of SARS-CoV-2 in promoting neurological disease in individuals across the lifespan via a systematic review of the literature and meta-analyses. We also discuss potential pathophysiology of SARS-CoV-2-associated CNS injury and the potential for long-term neurological complications of infection in recovered patients, including the potential impact of disease on pathological brain aging.

METHODS

Search Strategy and Study Selections

A systematic review was conducted for the purposes of identifying the population of COVID-19 patients diagnosed with new onset neurological condition(s) during the disease course. This review was designed and organized in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (Moher et al., 2009). The database PubMed-NCBI was systematically searched for peer-reviewed literature presenting original clinical data of COVID-19 patients diagnosed with a neurological condition. The search of PubMed-NCBI alone is considered comprehensive and reliable, as over 90% of MEDLINE is covered by this database, thus the search of additional databases was deemed unnecessary (Williamson and Minter, 2019). Manuscripts published from 2019 to April 4, 2021 were interrogated using the following search terms: ("COVID-19" OR "SARS-CoV-2") AND ("Brain" OR "Neuro" OR "Stroke" OR "Seizure" OR "Anosmia" OR "Ageusia" OR "Guillain-Barré" OR "Headache" OR "Dizziness" OR "Confusion" OR "Impaired Consciousness" OR "Seizure" OR "Encephalopathy" OR "Meningitis") NOT "review." The search was restricted to full text peer-reviewed reports available in English containing original clinical data. Preprint articles were not included. The purpose of this systematic review and meta-analysis was to assess the type and incidence of neurological complications of COVID-19 in relation to age. As such, only published articles with original clinical data containing the following criteria were included: (1) age of patient(s) featured in the study, (2) a diagnosis of new onset neurological manifestations, and (3) laboratory-confirmed SARS-CoV-2 infection. Exclusion criteria included: (1) any known pre-existing neurological conditions, (2) known co-current viral or parasitic infection, and/or (3) opinions, viewpoints, personal anecdotes, and reviews. Seizure was reported in a SARS-CoV-2 positive 6-week-old male (Dugue et al., 2020), however, this case was excluded from analysis because a history of seizure could not be ruled out, due to the young age. An 80-year-old woman with Alzheimer's dementia, who developed stroke (Xiong et al., 2020) and a 52-year-old HIV-infected woman with posterior reversible encephalitic syndrome (PRES) (Anand et al., 2020a) were also excluded from analyses, as these comorbidities could not be ruled-out as significant confounders to the development of neurological disease in the context of COVID-19.

Data Extraction and Synthesis

Articles vetted for inclusion were independently reviewed by BNS and TF, and the following information was extracted for analysis: age, gender, neurological manifestation, COVID-19 symptom severity, comorbidities, and presence of virus in CSF or autopsied brain. All data were captured and maintained in a Microsoft Excel workbook. Any disagreement regarding inclusion was resolved by discussion.

To reduce the effects of heterogeneity among the case reports, neurological diagnoses/symptoms were evaluated and categorized as cerebrovascular disease (CVD), peripheral neuropathy, encephalopathy, demyelinating disease, smell and/or taste disorder, and CNS inflammatory disease. The category "other" was included to capture patients who exhibited neurological symptoms, but the underlying cause was not determined or identified. This is expanded in **Supplementary Table 1**. Dichotomous outcomes were created for each category of CNS disease for statistical tests. Reported comorbidities were also reduced to dummy variables for assessing potential relationships with hypertension (HTN), diabetes mellitus (DM), lipid disorder, obesity, none, and other. This is expanded in **Supplementary Table 2**. For analyses, comorbidities were scaled based on their overall relationship with CVD, which had the strongest association with age and COVID-19 severity. Scores were designed as follows: None = 0, other = 1, obesity = 2, lipid disorder = 3, DM = 4, HTN = 5. This allowed for the inclusion of multiple reported comorbidities by synthesizing a "comorbidity score" for each patient equal to the sum of the individual scores. For example, a patient with HTN and DM would have a comorbidity score = 9. "None" includes only reports that specifically stated no comorbidities. Reports that did not include comorbidities were excluded from analyses that required these data. COVID-19 severity was converted to ordinal variables as follows: asymptomatic = 0, mild = 1, moderate = 2, severe = 3, critical = 4.

Statistical Analyses

Statistical tests were performed using Prism 9 for MacOS (v9.1.1) and the on-line statistics software, Intellectus Statistics (2021)[1]. Graphs were constructed with Prism and Microsoft Excel. Summary statistics for individual patient data were calculated for each variable. A general assessment of the relationship between age and each neurological disease category was conducted through simple linear regression using dummy coding (dichotomous outcomes) for the neurological disease category. Pearson correlation matrices were constructed to assess pair-wise relationships between variables. Cohen's standard was used to evaluate the strength of the relationships, where coefficients between ± 0.10 and ± 0.29 represent a small effect size, coefficients between ± 0.30 and ± 0.49 represent a moderate effect size, and coefficients of ± 0.50 and above indicate a large effect size (Cohen, 1998). The result of the correlations was examined using Holm corrections to adjust for multiple comparisons based on $\alpha = 0.05$. Analysis of variance (ANOVA) was conducted to assess if there were significant differences in COVID-19 severity or comorbidities score between the levels of neurological disease category. Tukey pairwise comparisons were conducted for all significant effects based on $\alpha = 0.05$. For each statistical test, only data from patients with all variables investigated were included. Cases with missing data were excluded from analysis. As such, the *n* for each test or summary is reported.

[1]https://analyze.intellectusstatistics.com

RESULTS

Search Results and Population Characteristics

Of an initial 4,611 records retrieved, 4,372 were excluded as per our exclusion criteria (**Figure 1**). A total of 239 articles were included in an overall assessment for the prevalence of neurological conditions reported in all patients with confirmed COVID-19 (n = 2,307) (**Figure 2**). The prevalence of COVID-19 patients with neurological conditions were assessed by age (years) from a total of 230 articles (n = 584) in which individual ages could be extracted (**Table 1**). Patient diagnoses were categorized under the following general neurological conditions: cerebrovascular disease (CVD), peripheral neuropathies, encephalopathies, demyelinating diseases, smell and/or taste disorders, and CNS inflammatory diseases. An additional category of "other" was ascribed to patients who exhibited neurological symptoms, but the underlying cause was not determined or identified (**Figure 2**). Smell and/or taste disorders were the most prevalent neurological manifestation with 1,303 cases identified, or 56.5% of the total. CVD, including stroke and microhemorrhages, was seen less frequently, but impacted approximately one quarter of the total (n = 584). Each of the remaining neurological conditions comprised less than ten percent of the total reported with encephalopathy and "other" accounting for 5.3% (n = 122) and 6.8% (n = 156), respectively. Less prevalent, but nonetheless significant neurological conditions also reported include peripheral neuropathy [e.g., Guillain-Barré Syndrome (GBS) and critical illness neuromyopathy (CIM)], CNS inflammatory disease (e.g., encephalitis and myelitis), and demyelinating disease [e.g., multifocal demyelinating lesions and acute disseminated encephalomyelitis (ADEM)], constituting a respective 3.3% (n = 75), 2.1% (n = 49), and 0.8% (n = 18) of the total subjects.

Summary of Individual Patient Data for Meta-Analyses

Data of 510 patients were extracted from 227 published reports, from which age and neurological complication could be matched. When possible, sex, COVID-19 severity, comorbidities, and the presence of detectable virus in cerebrospinal fluid (CSF) were also captured. As described above, neurological diagnoses were broadly categorized under CVD, CNS inflammatory disease, demyelinating disease, encephalopathy, peripheral neuropathy, taste/smell disorders, and other. Frequencies and percentages of individual diagnoses included under these categories are listed in **Supplementary Table 1**. The most frequently reported CVD was stroke of various types (n = 230, 89%). Among CNS inflammatory diseases, meningoencephalitis was most frequently observed (n = 22, 47%). Acute disseminated encephalomyelitis (ADEM) was the most frequently reported demyelinating disease (n = 9, 60%). Within the category of encephalopathy, a diagnosis of various types of encephalopathy were reported with the highest frequency (n = 47, 83%), while different manifestations of GBS were the most frequently

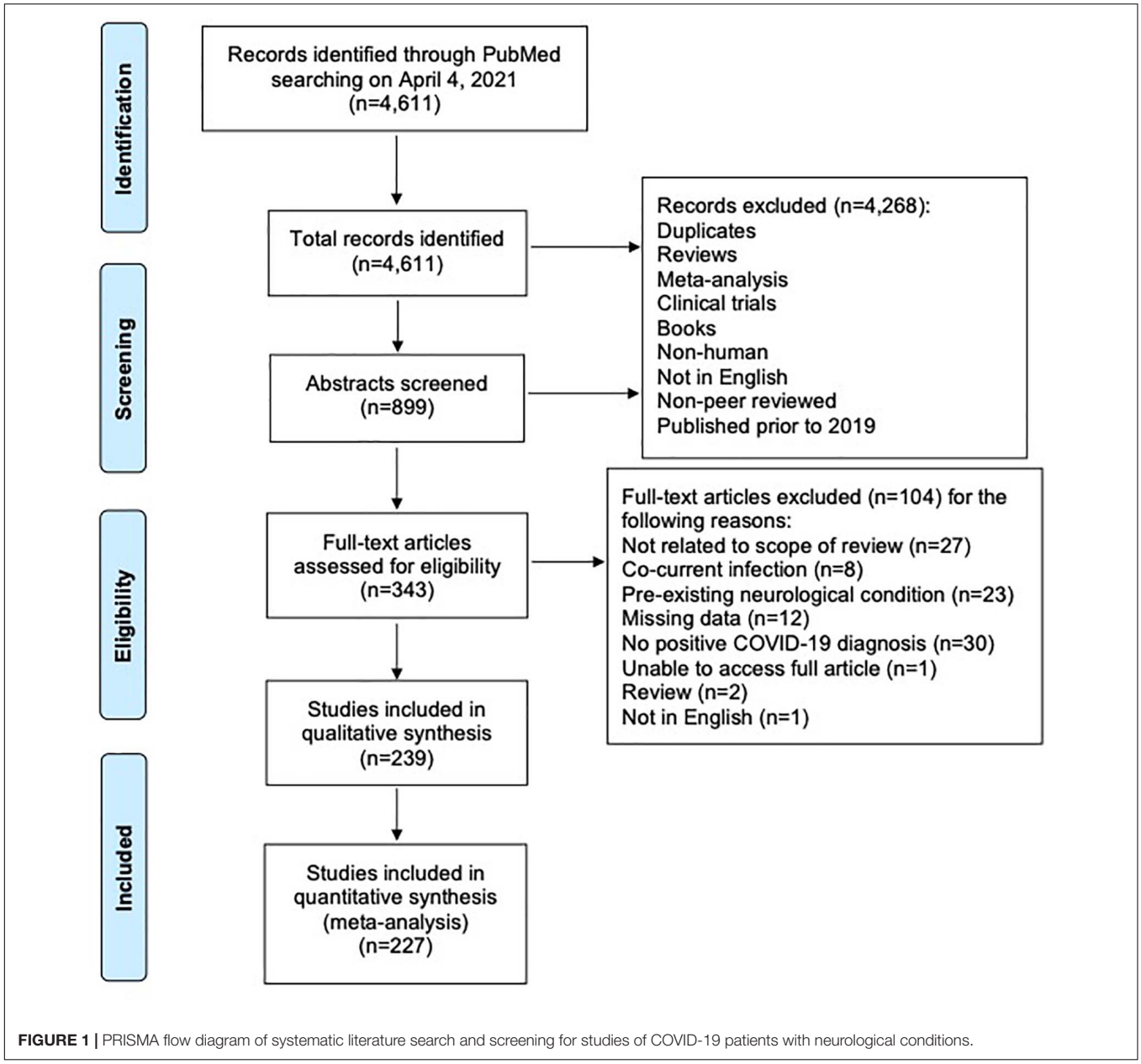

FIGURE 1 | PRISMA flow diagram of systematic literature search and screening for studies of COVID-19 patients with neurological conditions.

observed peripheral neuropathy (n = 54, 84%). Loss of smell (anosmia) was the most frequent complication of taste/smell disorders (n = 11, 31%) and various manifestations of headache (n = 18, 49%) were the most frequently reported neurological manifestation categorized as "other," which includes neurological manifestations for which the underlying cause was not identified.

Comorbidities were reported for 363 of the 510 patients for which individual patient data could be extracted. Risk factors for cardiovascular disease, including hypertension (HTN), diabetes mellitus (DM), obesity, and hyperlipidemia, were the most frequent comorbidities among COVID-19 patients with neurological manifestations (**Supplementary Table 2**). To assess the association of the stated comorbidities with neurological manifestations, comorbidities were limited to HTN, DM, obesity, and lipid disorders, which includes hyperlipidemia, dyslipidemia, and hypercholesterolemia. All other reported comorbidities were included as "other."

Although the number of males outnumbered females, the mean age did not differ significantly between the two sexes, or from the mean age of a cohort of individuals for which sex was not specified (**Table 2**). Summary statistics for individual patient data were calculated for each variable, and frequencies and percentages were split by sex and reported in **Table 3**. Frequencies and percentages were only calculated on available data (n/a = not available excluded). This is reflected in the n reported for each variable. The most frequently observed

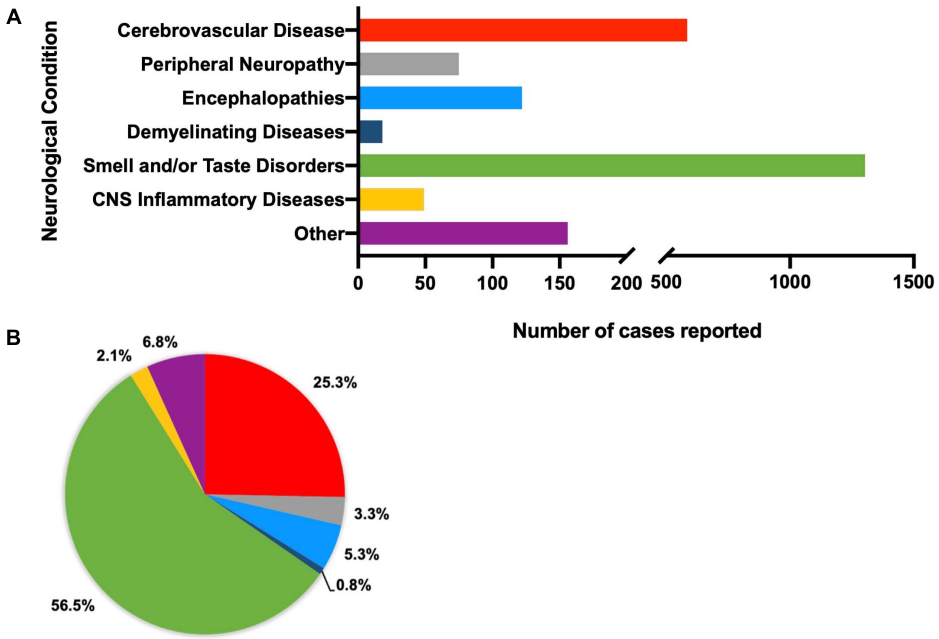

FIGURE 2 | Total number **(A)** and percent of **(B)** reported neurological conditions occurring in patients, regardless of demographics (total *n* = 2,390). Individual diagnoses have been categorized as cerebrovascular diseases (*n* = 592), peripheral neuropathies (*n* = 75), encephalopathies (*n* = 175), demyelinating diseases (*n* = 23), smell and/or taste disorders (*n* = 1,303), CNS inflammatory diseases (*n* = 45), and other (neurological symptoms that cannot be attributed to a specific neurological condition, such as headache, seizure, ataxia, aphasia) (*n* = 177).

neurological disease category for all patients regardless of sex, specified or not, was cerebrovascular disease (*n* = 257, 50% of total). Moderate COVID-19 severity was most often reported for all male and female subjects, however, patients for which sex was not specified (*n* = 57), severe COVID-19 was most frequently reported. Although no comorbidities (none) appear to be most frequently reported among all subjects (*n* = 131, 36%), when taken together, HTN, with and without additional comorbidities, is most frequently reported *in toto* (*n* = 165, 45%), as well as separately among males (*n* = 96, 46%) and persons for which sex was not specified (*n* = 27, 57%). No comorbidities (none) and HTN, with and without additional comorbidities, were equally reported among females (*n* = 42, 39%). CSF was assessed for detectable virus in 122 of the total 510 patients but only identified in four cases (**Table 3**), which included a 31-year-old male and a 74-year-old female with altered mental status (encephalopathy), a 24-year-old male with meningoencephalitis, and a 68-year-old male who developed stroke (Cebrián et al., 2020; Kamal et al., 2020; Moriguchi et al., 2020; Saitta et al., 2020).

Finally, frequencies and percentages were calculated for neurological disease category split by COVID-19 severity (*n* = 495; **Table 4**). Regardless of disease severity, CVD was the most frequently observed category of neurological disease, which may reflect a more serious injury, such as stroke, being more likely to prompt a case report. It is important to note, that CVD was reported in the context of SARS-COV-2 infection among individuals with few or no other symptoms typically associated with COVID-19.

Age-Associated Neurological Complications of COVID-19

Neurological conditions were evaluated by age, where the individual age or cohort age range was able to be determined and stratified to assess the overall frequency of specific types of neurological complications affecting children (<19 years), young adults (19–50 years), and older adults (>50) infected with SARS-CoV-2 (**Figure 3**). More specific details relating the number and percent of COVID-19 patients diagnosed with neurological conditions are stratified by decade of age and included in **Table 1**. Overall, patients 60–69 years showed the greatest population with neurological conditions (*n* = 154) and those less than or equal to 9 years of age had the least (*n* = 7) (**Table 1** and **Figure 4**). Age and other available population characteristics of multicenter, retrospective, and observational studies with large cohorts reporting neurological conditions from which individual matched patient data could not be discerned is detailed in **Supplementary Table 3**. Instances where data were able to be extracted from these reports is detailed.

Linear regression analyses were conducted to assess whether age significantly predicted any category of neurological complications of SARS-CoV-2 infection (**Figure 5**). The results of the linear regression model were significant for CVD, $F(1,508) = 30.08$, $p < 0.001$, $r^2 = 0.06$, indicating that approximately 6% of the variance in CVD is explainable by increased age (**Figure 5A**). In contrast, taste/smell disorder was associated with decreased age, $F(1,508) = 28.73$, $p < 0.001$, $r^2 = 0.05$, indicating that approximately 5% of the variance in this category is explainable by age (**Figure 5F**). A mild, but

TABLE 1 | Total number ($n = 584$) and percent of each neurological condition reported in patients diagnosed with COVID-19 per decade of age.

Age range	**≤ 9**	**10–19**	**20–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**≥ 80**
#Cases reported	**7**	**22**	**19**	**60**	**72**	**100**	**154**	**121**	**29**
Neurological diagnosis	***N* (%)** [reference]								
Cerebrovascular diseases	**2 (28.6)** (Xiong et al., 2020; Tiwari et al., 2021)	**3 (13.6)** (Asif and O' Mahony, 2020; Gulko et al., 2020; Dakay et al., 2021)	**3 (15.8)** (Cavalcanti et al., 2020; de Sousa et al., 2020; Dakay et al., 2021)	**19 (31.7)** (Al Saiegh et al., 2020; Cavalcanti et al., 2020; Cezar-Junior et al., 2020; Chia et al., 2020; Diaz-Segarra et al., 2020; Fara et al., 2020; Kantonen et al., 2020; Oxley et al., 2020; Pisano et al., 2020; Trifan et al., 2020a,b; Vu et al., 2020; Wang et al., 2020; Al-Mufti et al., 2021; Sabayan et al., 2021; Shah et al., 2021)	**31 (43.1)** (Agarwal et al., 2020; Anzalone et al., 2020; Cavalcanti et al., 2020; de Almeida Lima et al., 2020; Fabbri et al., 2021; Frisullo et al., 2020; Gupta et al., 2020; Heman-Ackah et al., 2020; Lapergue et al., 2020; Nicholson et al., 2020; Oxley et al., 2020; Patel et al., 2020; Sabayan et al., 2021; Toledano-Massiah et al., 2020; Trifan et al., 2020a; TunÇ et al., 2020; Wang et al., 2020; Yaghi et al., 2020; Al-Mufti et al., 2021; Fu et al., 2021; Mullaguri et al., 2021)	**46 (46.0)** (Avci et al., 2020; Beyrouti et al., 2020; Cezar-Junior et al., 2020; D'Anna et al., 2020; Diaz-Segarra et al., 2020; Fabbri et al., 2021; Fara et al., 2020; Fayed et al., 2020; Heman-Ackah et al., 2020; Jaunmuktane et al., 2020; Kremer et al., 2020a; Lapergue et al., 2020; Mansour et al., 2020; Morassi et al., 2020; Motoie et al., 2020; Nepal et al., 2020; Nicholson et al., 2020; Panico et al., 2020; Sangalli et al., 2020; Sugiyama et al., 2020; Toledano-Massiah et al., 2020; Trifan et al., 2020a; Wang et al., 2020; Xiong et al., 2020; Yaghi et al., 2020; Al-Mufti et al., 2021; Fu et al., 2021; Harrogate et al., 2021; Mousa-Ibrahim et al., 2021; Mullaguri et al., 2021; Prasad et al., 2021; Sabayan et al., 2021)	**70 (45.5)** (Al Saiegh et al., 2020; Anand et al., 2020a; Azpiazu Landa et al., 2020; Beyrouti et al., 2020; Bigliardi et al., 2020; Bolaji et al., 2020; Cannac et al., 2020; Cezar-Junior et al., 2020; Co et al., 2020; D'Anna et al., 2020; Díaz-Pérez et al., 2020; Diaz-Segarra et al., 2020; Guillan et al., 2020; Gulko et al., 2020; Hemasian and Ansari, 2020; Imoto et al., 2020; Jaunmuktane et al., 2020; Kantonen et al., 2020; Kremer et al., 2020a; Lapergue et al., 2020; Morassi et al., 2020; Nicholson et al., 2020; Roy-Gash et al., 2020; Saitta et al., 2020; Shawkat et al., 2020; Shoskes et al., 2020; Siepmann et al., 2021; Soldatelli et al., 2020; Trifan et al., 2020a; TunÇ et al., 2020; Vattoth et al., 2020; Wang et al., 2020; Xiong et al., 2020; Yaghi et al., 2020; Yong et al., 2020; Al-Mufti et al., 2021; Fabbri et al., 2021; Garví López et al., 2021; Khan et al., 2021; Mousa-Ibrahim et al., 2021; Sabayan et al., 2021)	**69 (57.0)** (Agarwal et al., 2020; Al-Dalahmah et al., 2020; Avula et al., 2020; Azpiazu Landa et al., 2020; Beyrouti et al., 2020; Burkert and Patil, 2020; Cezar-Junior et al., 2020; D'Anna et al., 2020; Fara et al., 2020; Fayed et al., 2020; Gonçalves et al., 2020; Kremer et al., 2020a; Mohamed et al., 2020; Morassi et al., 2020; Papi et al., 2020; Sangalli et al., 2020; Trifan et al., 2020a; TunÇ et al., 2020; Viguier et al., 2020; Xiong et al., 2020; Yaghi et al., 2020; Zayet et al., 2020; Al-Mufti et al., 2021; Fabbri et al., 2021; Harrogate et al., 2021; Mousa-Ibrahim et al., 2021; Mullaguri et al., 2021; Robles, 2021; Sabayan et al., 2021)	**21 (72.4)** (Alay et al., 2020; Avula et al., 2020; Beyrouti et al., 2020; D'Anna et al., 2020; Gonçalves et al., 2020; Kantonen et al., 2020; Kremer et al., 2020a; Xiong et al., 2020; Zayet et al., 2020; Al-Mufti et al., 2021; Sabayan et al., 2021; Siepmann et al., 2021)

(Continued)

TABLE 1 | Continued

Age range	≤ 9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥ 80
Peripheral neuropathies		**2 (9.1)** (Khalifa et al., 2020; Manji et al., 2020)	**2 (10.5)** (Hutchins et al., 2020; Toscano et al., 2020)	**6 (10.0)** (Ameer et al., 2020; Dinkin et al., 2020; Gutiérrez-Ortiz et al., 2020; Homma et al., 2020; Lantos et al., 2020; Rajdev et al., 2020)	**8 (11.1)** (Bigaut et al., 2020; Khaja et al., 2020; Liberatore et al., 2020; Tiet and AlShaikh, 2020; Velayos Galán et al., 2020; Abolmaali et al., 2021; Manganotti et al., 2021; Nanda et al., 2021)	**15 (15.0)** (Assini et al., 2020; Barrachina-Esteve et al., 2020; Chan et al., 2020; Gale et al., 2020; Gutiérrez-Ortiz et al., 2020; Hirayama et al., 2020; Korem et al., 2020; Manganotti et al., 2020; Naddaf et al., 2020; Petrelli et al., 2020; Rana et al., 2020; Sancho-Saldaña et al., 2020; Toscano et al., 2020; Webb et al., 2020; Abolmaali et al., 2021; Nanda et al., 2021)	**12 (7.8)** (Abrams et al., 2020; Assini et al., 2020; Bracaglia et al., 2020; Juliao Caamaño and Alonso Beato, 2020; Sedaghat and Karimi, 2020; Senel et al., 2020; Tankisi et al., 2020; Toscano et al., 2020; Wada et al., 2020; Zhao et al., 2020; Bueso et al., 2021; Nasuelli et al., 2021)	**16 (13.2)** (Alberti et al., 2020; Bigaut et al., 2020; Coen et al., 2020; Dinkin et al., 2020; Fernández-Domínguez et al., 2020; Marta-Enguita et al., 2020; Su et al., 2020; Toscano et al., 2020; Manganotti et al., 2021; Nanda et al., 2021; Nasuelli et al., 2021)	**2 (6.9)** (Abolmaali et al., 2021; Manganotti et al., 2021)
Encephalopathies	**2 (28.6)** (Abel et al., 2020; De Paulis et al., 2020)		**2 (10.5)** (Agarwal et al., 2020; Babar et al., 2020)	**7 (11.7)** (Benameur et al., 2020; Dakay et al., 2020; Kamal et al., 2020; Kantonen et al., 2020; Pascual-Goñi et al., 2020; Radnis et al., 2020; Zayet et al., 2021)	**9 (12.5)** (Fischer et al., 2020; Franceschi et al., 2020; Hosseini et al., 2020; Muccioli et al., 2020; Ordoñez-Boschetti et al., 2020; Radnis et al., 2020; Scullen et al., 2020; Edén et al., 2021; Matos et al., 2021)	**11 (10.0)** (Abenza-Abildúa et al., 2020; Anand et al., 2020a; Anzalone et al., 2020; Chaumont et al., 2020b; Dixon et al., 2020; Naaraayan et al., 2020; Nicolas-Jilwan and Almaghrabi, 2020; Priftis et al., 2020; Scullen et al., 2020; Harrogate et al., 2021; Perrin et al., 2021)	**25 (16.2)** (Benameur et al., 2020; Chaumont et al., 2020b; Delorme et al., 2020; Díaz-Pérez et al., 2020; Franceschi et al., 2020; Kakadia et al., 2020; Kantonen et al., 2020; Pascual-Goñi et al., 2020; Princiotta Cariddi et al., 2020; Radnis et al., 2020; Roy-Gash et al., 2020; Scullen et al., 2020; Shoskes et al., 2020; Vaschetto et al., 2020; Yong et al., 2020; Edén et al., 2021; Garví López et al., 2021; Perrin et al., 2021; Zayet et al., 2021)	**14 (1.6)** (Alkeridy et al., 2020; Balestrino et al., 2020; Butt et al., 2020; Cebrián et al., 2020; Chaumont et al., 2020b; Delorme et al., 2020; Farhadian et al., 2020; Hosseini et al., 2020; Morassi et al., 2020; Soysal and Kara, 2020; Edén et al., 2021; Harrogate et al., 2021; Mullaguri et al., 2021; Perrin et al., 2021)	**2 (6.9)** (Kantonen et al., 2020; Edén et al., 2021)

(Continued)

TABLE 1 | Continued

Age range	≤ 9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥ 80
Demyelinating diseases		**1 (4.5)** (de Miranda Henriques-Souza et al., 2021)		**2 (3.3)** (Agarwal et al., 2020; McCuddy et al., 2020)	**2 (2.8)** (Lopes et al., 2020; Pessoa Neto et al., 2020)	**7 (7.0)** (Abdi et al., 2020; Brun et al., 2020; Langley et al., 2020; Lopes et al., 2020; McCuddy et al., 2020; Parsons et al., 2020; Chang et al., 2021)	**4 (2.6)** (Jaunmuktane et al., 2020; Kakadia et al., 2020; Wada et al., 2020; Khan et al., 2021)	**3 (2.5)** (Cani et al., 2021; McCuddy et al., 2020; Reichard et al., 2020)	
Smell and/or Taste disorder		**8 (36.4)** (Chiu et al., 2005; Erdede et al., 2020; Hatipoglu et al., 2020; Mak et al., 2020)	**5 (26.3)** (Babar et al., 2020; Laurendon et al., 2020; Pissurno et al., 2020; Politi et al., 2020; Smith et al., 2020)	**9 (15.0)** (Faber et al., 2020; Gilani et al., 2020; Homma et al., 2020; Vargas-Gandica et al., 2020)	**8 (11.1)** (Bigaut et al., 2020; Gane et al., 2020; Gilani et al., 2020; Sampaio Rocha-Filho and Voss, 2020; Vargas-Gandica et al., 2020; Manganotti et al., 2021; Matos et al., 2021)	**4 (4.0)** (Melley et al., 2020; Panico et al., 2020; Vargas-Gandica et al., 2020)	**10 (6.5)** (Chow et al., 2020; de Oliveira et al., 2020; Hjelmesæth and Skaare, 2020; Jacob et al., 2020; Vargas-Gandica et al., 2020; Bueso et al., 2021; Edén et al., 2021)	**4 (3.3)** (Bigaut et al., 2020; Manganotti et al., 2021)	**2 (6.9)** (Hjelmesæth and Skaare, 2020; Vargas-Gandica et al., 2020)
CNS inflammatory diseases	**3 (42.9)** (Kaur et al., 2020; Raj et al., 2020; Kim et al., 2021)	**4 (4.5)** (Lin et al., 2020; Natarajan et al., 2020; Bektaş et al., 2021)	**3 (15.8)** (Elkhaled et al., 2020; Laurendon et al., 2020; Moriguchi et al., 2020)	**7 (11.7)** (Álvarez Bravo et al., 2020; Benameur et al., 2020; Efe et al., 2020; Handa et al., 2020; Fumery et al., 2021; Povlow and Auerbach, 2021)	**5 (6.9)** (Agarwal et al., 2020; Ghosh et al., 2020; Heller et al., 2020; Kadono et al., 2020; Fabbri et al., 2021)	**13 (13.0)** (Águila-Gordo et al., 2020; Kremer et al., 2020a; Monti et al., 2020; Picod et al., 2020; Poyiadji et al., 2020; Fabbri et al., 2021)	**18 (11.7)** (Chaumont et al., 2020a; Chow et al., 2020; Hanafi et al., 2020; Kremer et al., 2020a; Munz et al., 2020; Sotoca and Rodríguez-Álvarez, 2020; Vaschetto et al., 2020; Fabbri et al., 2021)	**6 (5.0)** (Kremer et al., 2020a; Fabbri et al., 2021)	**1 (3.4)** (Kremer et al., 2020a)
Other		**4 (18.2)** (Hatipoglu et al., 2020; Seth and Kushwaha, 2020)	**4 (21.1)** (Anand et al., 2020b; Lyons et al., 2020; Silva et al., 2020)	**10 (16.7)** (Dinkin et al., 2020; Kantonen et al., 2020; Noro et al., 2020; Pascual-Goñi et al., 2020; Silva et al., 2020; Tu et al., 2020)	**9 (12.5)** (Anand et al., 2020b; Sampaio Rocha-Filho and Voss, 2020; Silva et al., 2020; Fabbri et al., 2021)	**4 (4.0)** (Fasano et al., 2020; Ortiz-Seller et al., 2020; Fabbri et al., 2021)	**15 (9.7)** (Anand et al., 2020b; de Oliveira et al., 2020; Jacob et al., 2020; Kantonen et al., 2020; Le Guennec et al., 2020; Ottaviani et al., 2020; Pascual-Goñi et al., 2020; Silva et al., 2020; Fabbri et al., 2021)	**9 (7.4)** (Anand et al., 2020b; Dinkin et al., 2020; Elgamasy et al., 2020; Logmin et al., 2020; Vollono et al., 2020; Fabbri et al., 2021)	**1 (3.4)** (Kantonen et al., 2020)

TABLE 2 | Summary statistics for age of patients *in toto* and by sex.

Sex	Mean age (years)	*SD*	*n*	SE_M	Min (years)	Max (years)
All subjects	55.37	18.16	510	0.80	2	94
Male	55.55	17.75	278	1.06	2	94
Female	54.33	19.99	175	1.51	3	92
Not specified	57.67	13.74	57	1.82	31	93

nonetheless statistically significant inverse relationship between age and CNS inflammatory disease or other was also observed. Approximately 1% of the variance in observation of COVID-19 patients with CNS inflammatory disease [$F(1,508) = 7.19$, $p = 0.008$, $r^2 = 0.01$] or other [$F(1,508) = 6.70$, $p = 0.01$, $r^2 = 0.01$] is also explainable by decreased age (**Figures 5D,G**). Age did not explain a significant proportion of variation in the observed frequencies of encephalopathy, peripheral neuropathy, or demyelinating disease (**Figures 5B,C,E**).

Relationship of Age, COVID-19 Severity, and Comorbidities on Neurological Manifestations of COVID-19

A Pearson correlation analysis was conducted among age, sex, each category of neurological disease, COVID-19 severity, and individual comorbid factors to assess the relationships among these variables and displayed as heat maps based on the coefficient between variables (**Figure 6**). Cases with incomplete data for the variables being assessed were excluded from analysis, resulting in a different *n* for each analysis.

In agreement with the linear regression analyses, a significant positive correlation between age and CVD was seen ($p < 0.001$) with a coefficient (r_p) of 0.24, indicating a small effect size (**Figure 6A**). Small effect size was also observed with age and CNS inflammatory disease ($r_p = -0.12$, $p = 0.008$), smell and/or taste disorder ($r_p = -0.23$, $p < 0.001$), and other ($r_p = -0.11$, $p = 0.01$), all of which show a negative correlation with age (**Figure 6A**). The relationship between age and COVID-19 severity was statistically significant for all disease severities (**Figure 6B**). A negative relationship was observed between age and asymptomatic ($r_p = -0.13$, $p = 0.005$), mild ($r_p = -0.15$, $p < 0.01$), or moderate ($r_p = -0.09$, $p = 0.046$) COVID-19 severity, while a positive correlation was seen between age and severe ($r_p = 0.18$, $p < 0.001$) or critical ($r_p = 0.11$, $p = 0.013$) disease (**Figure 6B**).

Apart from obesity, the relationship between age and comorbidities was statistically significant for all types examined (**Figure 6C**). A moderate effect size ($r_p = -0.40$, $p < 0.001$) between age and stated no comorbidities (none) was observed, indicating that as age increases, the category of "none" tends to decrease. In contrast, the significant positive relationship between age and HTN ($r_p = 0.37$, $p < 0.001$), DM (0 $r_p = 0.16$, $p = 0.002$), or lipid disorders ($r_p = 0.11$, $p = 0.042$), suggests comorbid cardiovascular risk factors may contribute to the increased risk for CVD and/or severe-critical COVID-19 observed. Although the relationship between age and "other" was found to be statistically significant with a small effect size ($r_p = 0.12$, $p = 0.023$), the wide variety of conditions included in this category do not point to any one condition as being significant.

Relationships among all variables were also assessed and displayed in **Figure 7**. This revealed additional associations with neurological disease among patients for which all variables were available ($n = 350$). Age retained the strongest relationship with CVD, however, a significant positive correlation of CVD with HTN ($r_p = 0.16$, $p = 0.002$), DM ($r_p = 0.13$, $p = 0.014$), lipid disorders ($r_p = 0.19$, $p < 0.001$), and severe COVID-19 ($r_p = 0.19$, $p < 0.001$) were also seen. Encephalopathy correlated positively with severe COVID-19 ($r_p = 0.18$, $p = 0.001$) and was seen most frequently among individuals with comorbid conditions categorized as "other" ($r_p = 0.11$, $p = 0.033$). CNS inflammatory disease showed a positive correlation with moderate COVID-19 severity ($r_p = 0.17$, $p = 0.002$), as well as patients without comorbid disease ($r_p = 0.17$, $p = 0.001$). No significant relationship between comorbidities and demyelinating disease was observed, however, it did correlate with critical COVID-19 ($r_p = 0.22$, $p < 0.001$). These results, however, may be less reliable due to a low number of patients within this neurological disease category ($n = 12$). There appears to be a small positive relationship between demyelinating disease and obesity, however, this did not reach statistical significance. Like demyelinating disease, obesity had a positive association with critical COVID-19 ($r_p = 0.30$, $p < 0.001$). Peripheral neuropathy correlated with mild COVID-19 ($r_p = 0.19$, $p < 0.001$) but not with any comorbid condition. Interestingly, impaired taste/smell only reached significant positive associations with asymptomatic COVID-19 ($r_p = 0.19$, $p < 0.001$) and no comorbidities ($r_p = 0.24$, $p < 0.001$). Although the reason for this is unclear, in the absence of more critical symptoms, impairments in taste and/or smell may be more discernable by patients.

Effect of COVID-19 Severity and Comorbidities on Neurological Disease Outcome

In addition to age, COVID-19 severity and comorbidities appeared to associate with the observance of specific neurological disease (**Figure 7**). Multivariate analysis of covariance (MANCOVA) to assess if there were significant differences in the linear combination of COVID-19 severity and comorbidities score between the levels of neurological disease category after controlling for age were attempted, however, these tests failed assumptions of homogeneity of covariance and covariate-independent variable independence.

TABLE 3 | Frequencies and percentages of neurological disease, COVID-19 severity, comorbidities, and detectable virus in CSF by sex.

Variable	*n*	Female	Male	Not specified
Neurological disease category	**510**			
Cerebrovascular disease		68 (39%)	133 (48%)	56 (98%)
CNS inflammatory disease		20 (11%)	26 (9%)	0 (0%)
Demyelinating disease		6 (3%)	8 (3%)	1 (2%)
Encephalopathy		25 (14%)	32 (12%)	0 (0%)
Taste/smell disorders		21 (12%)	15 (5%)	0 (0%)
Peripheral neuropathy		19 (11%)	44 (16%)	0 (0%)
Other		16 (9%)	20 (7%)	0 (0%)
COVID-19 severity	**495**			
Asymptomatic		20 (12%)	16 (6%)	3 (5%)
Mild		21 (12%)	44 (16%)	2 (4%)
Moderate		61 (36%)	73 (27%)	10 (18%)
Severe		31 (18%)	67 (25%)	35 (61%)
Critical		37 (22%)	68 (25%)	7 (12%)
Comorbidities (reclassified)	**363**			
None		42 (39%)	78 (37%)	11 (23%)
DM		2 (2%)	17 (8%)	2 (4%)
DM, lipid disorder		1 (1%)	1 (0%)	2 (4%)
DM, obesity		1 (1%)	0 (0%)	0 (0%)
DM, other		1 (1%)	1 (0%)	1 (2%)
HTN		20 (19%)	27 (13%)	8 (17%)
HTN, DM		5 (5%)	24 (11%)	0 (0%)
HTN, DM, lipid disorder		1 (1%)	3 (1%)	5 (11%)
HTN, DM, lipid disorder, other		0 (0%)	1 (0%)	3 (6%)
HTN, DM, obesity		1 (1%)	4 (2%)	0 (0%)
HTN, DM, obesity, lipid disorder, other		1 (1%)	0 (0%)	0 (0%)
HTN, DM, obesity, other		1 (1%)	2 (1%)	0 (0%)
HTN, DM, other		2 (2%)	6 (3%)	0 (0%)
HTN, lipid disorder		1 (1%)	10 (5%)	5 (11%)
HTN, lipid disorder, other		3 (3%)	0 (0%)	2 (4%)
HTN, obesity		1 (1%)	4 (2%)	0 (0%)
HTN, obesity, lipid disorder		0 (0%)	1 (0%)	0 (0%)
HTN, obesity, lipid disorder, other		1 (1%)	0 (0%)	0 (0%)
HTN, obesity, other		0 (0%)	1 (0%)	0 (0%)
HTN, other		5 (5%)	13 (6%)	4 (9%)
Lipid disorder		1 (1%)	1 (0%)	3 (6%)
Lipid disorder, other		0 (0%)	1 (0%)	0 (0%)
Obesity		4 (4%)	5 (2%)	1 (2%)
Obesity, other		5 (5%)	0 (0%)	0 (0%)
Other		8 (7%)	9 (4%)	0 (0%)
Virus in CSF	**122**			
No		50 (98%)	67 (96%)	1 (100%)
Yes		1 (2%)	3 (4%)	0 (0%)

Due to rounding errors, column wise percentages may not equal 100%. CNS, Central nervous system; DM, Diabetes mellitus; HTN, Hypertension; CSF, Cerebral spinal fluid.

As such, ANOVAs were performed separately to assess whether there were significant differences in COVID-19 severity or comorbidities score by neurological disease category. This demonstrated significant differences in the mean COVID-19 severity and comorbidities score among the different neurological disease categories (**Figure 8**). Demyelinating disease, CVD, and encephalopathy had the highest mean COVID-19 severity and comorbidities score, while loss of taste/smell had the lowest for both, demonstrating a relationship between disease severity and comorbid conditions. To aid viewing, neuronal disease categories were reordered by increasing mean of the two variables (**Figure 8**).

TABLE 4 | Frequencies and percentages of observed neurological disease split by COVID-19 severity (*n* = 495).

Neurological disease category	**Asymptomatic**	**Mild**	**Moderate**	**Severe**	**Critical**
Cerebrovascular disease	18 (46%)	25 (37%)	55 (38%)	88 (66%)	58 (52%)
CNS inflammatory disease	2 (5%)	4 (6%)	15 (10%)	6 (5%)	17 (15%)
Demyelinating disease	1 (3%)	1 (1%)	1 (1%)	2 (2%)	10 (9%)
Encephalopathy	4 (10%)	7 (10%)	10 (7%)	24 (18%)	12 (11%)
Loss of taste/smell	7 (18%)	10 (15%)	16 (11%)	0 (0%)	3 (3%)
Peripheral neuropathy	5 (13%)	15 (22%)	19 (13%)	12 (9%)	12 (11%)
Other	2 (5%)	5 (7%)	28 (19%)	1 (1%)	0 (0%)

Due to rounding errors, column wise percentages may not equal 100%.

DISCUSSION

Neurological manifestations are a significant complication of SARS-CoV-2 infection and COVID-19. Although many anecdotal and case study reports have suggested relationships between neurological complications of disease with age, disease severity, and comorbid conditions, significant associations among these variables remain unclear. Through a systematic review of peer-reviewed, published patient reports spanning the entirety of 2020 through April 4, 2021, and meta-analyses, we report that while smell and/or taste disorders are the most common neurological manifestation of SARS-CoV-2 infection, CVD, manifesting almost entirely as stroke, is a major neurological complication of infection, affecting just over a quarter of individuals in this study. Other clinically significant CNS complications, broadly categorized as encephalopathy, CNS inflammatory disease, demyelinating disease, and peripheral neuropathy have been reported less frequently. Other symptoms, including headache, seizure, aphasia, and ataxia have also been reported in connection with infection without identification of the underlying cause and are categorized as "other" in this report.

When investigating a potential relationship between the type of neurological disorder and age, smell and/or taste disorders remained the most common neurological complication affecting infected individuals 50 years of age and younger. For infected individuals over 50, however, CVD became the most common neurological injury, where it was observed in over half of

individuals in this age group. Linear regression analysis, however, suggests only 6% of the variance in CVD is explainable by age. Known risk factors for vascular disease, HTN and DM, as well as critical COVID-19, showed a positive correlation with CVD but with a small effect size. Additionally, stroke affected individuals across the lifespan, including individuals with reported no comorbidities and/or asymptomatic disease. Together, this suggests other factors, which may include virus and/or the host's response to infection, contribute to the development of CVD.

Although there is currently no clear indicator as to which patients will suffer stroke, several risk factors for stroke in aged individuals have been reported in COVID-19 patients, such as coagulopathy, elevated D-dimer levels, and vascular endothelial dysfunction. A large retrospective study evaluating risk factors for mortality of COVID-19 patients found coagulopathy to be a significant indicator, affecting ∼50% of non-survivors (Zhou et al., 2020). Additionally, marked elevation (<0.5 μg/L) of D-dimer, a by-product of blood clotting that is often elevated in response to acute vascular disease, has been reported in COVID-19 patients and found to be predictive of severe disease and mortality (Gao et al., 2020; Han et al., 2020; Huang et al., 2020; Mao et al., 2020; Zhou et al., 2020).

Endothelial cell infection and/or injury may also contribute to increased risk for CVD with COVID-19. ACE2, the principal receptor used for viral entry, is reportedly expressed by endothelial cells throughout the body, including brain (Hamming et al., 2004; To and Lo, 2004), indicating the potential for viral infection in the endothelium in the CNS. In support of this notion, a post-mortem investigation reported the presence of endothelial cell infection and endotheliitis across the vascular beds of several organs (Varga et al., 2020). Although the brain was not evaluated in this study, the presence of endothelial infection of multiple organs reveals the potential for widespread disruption of vascular homeostasis, increasing the susceptibility of infected patients to CVD. Interestingly, endotheliopathy without evidence of infection has been reported in a cohort of COVID-19 patients (mean age = 62 years), which was associated with severe disease (Goshua et al., 2020). This suggests that the host response to infection may sufficiently promote endothelial cell inflammation and injury, without direct involvement of the virus.

In agreement with endotheliopathy in the CNS, several autopsy and neuroimaging reports demonstrate the presence of brain microvascular lesions and microhemorrhages in COVID-19 patients (Conklin et al., 2020; Fitsiori et al., 2020; Kremer et al., 2020b; Lee et al., 2020; Lin et al., 2020; Radmanesh et al., 2020; Shoskes et al., 2020). Autopsy findings reveal intact endothelium, suggesting that microbleeds may form due to inflammation of endothelial cells that allows for extravasation of red blood cells into the brain parenchyma (Goshua et al., 2020; Pugin et al., 2020). Cerebral microhemorrhages are associated with age and systemic disease, increasing the risk for microhemorrhage development in older patients with COVID-19. Moreover, the integrity of the blood-brain barrier (BBB) decreases with age and is posited to precede and contribute to the development of CVD (Li et al., 2018). The mechanisms of BBB dysfunction in aging are not completely clear; however, small atheromatous plaques, HTN, and endothelial cell inflammation are believed to play a prominent role and may help explain why individuals with underlying comorbidities, including DM and HTN, appear to be at greater risk for developing more severe COVID-19. Additionally, chronic, subclinical inflammation is a common feature of aging that increases the susceptibility of individuals to age-related disease (Franceschi et al., 2000). Chronic inflammation can induce cellular stress and injury that weakens tissues and reduces the ability of cells to counter additional insults. It is reasonable, therefore, that aging-associated inflammation promotes endotheliitis and endotheliopathy, leading to increased "leakiness" of the vasculature that is made more severe with COVID-19.

In addition to CVD, more frequent observations of clinically significant encephalopathy and peripheral neuropathy are also seen in patients over 50 years. Patients with encephalopathy, which is broadly characterized as disease or damage to the brain that affects brain function, present with altered mental status ranging from mild confusion to more severe dementia or coma. Several case reports detail infected patients presenting with acute encephalopathic episodes, irrespective of COVID-19 severity, including acute necrotizing encephalopathy and posterior reversible encephalopathy syndrome (PRES). Encephalopathy accounted for only 5.3% of the total population of COVID-19 patients with neurological manifestations and 10.4% of those over 50 years of age. It is highly probable, however, that due to the strong inflammatory response to infection in the periphery, which can negatively impact the CNS, encephalopathy among infected individuals occurs more frequently but not widely reported in case studies.

Peripheral neuropathy, including Guillain-Barré syndrome (GBS) and critical illness neuromyopathy, have emerged as one of the more serious neurological complications of COVID-19 infection. GBS is a neuromuscular disorder defined as an acute paralytic neuropathy, often preceded by an infection, and clinically characterized by symmetric weakness of the limbs (Yuki and Hartung, 2012). This disease is considered, primarily, to be an affliction of the peripheral nerves that has a 5% fatality rate and results in the severe disability of up 20% of GBS patients (Hughes et al., 2007; Yuki and Hartung, 2012). Critical illness neuromyopathy is characterized by muscle wasting and paralysis and often culminates into a severely disabling weakness of the muscles and/or paralysis (Latronico et al., 2007; Guarneri et al., 2008). In this review, we found that peripheral neuropathy was most frequent among older adults (6.6%, $n = 44$), with zero cases of critical illness neuromyopathy reported in patients younger than 60 years of age.

Less frequent observations of CNS inflammatory disease, demyelinating disease, and smell and/or taste disorders was seen among older adults, as compared to younger adults and patients under 19 years of age (children). CNS inflammatory disorders, which includes encephalitis, myelitis, and meningitis, was most frequently reported among patients under 19 years, while demyelinating disease was similar in frequency among the three age categories. Interestingly, the demyelinating disease, acute disseminated encephalomyelitis (ADEM), which is a rare but serious complication of viral infection most commonly

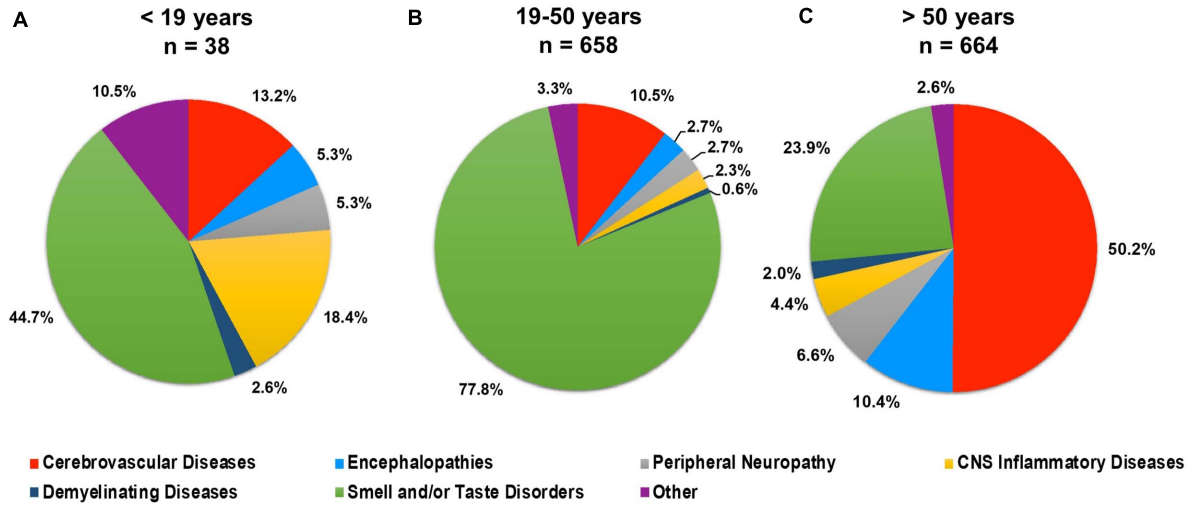

FIGURE 3 | Percent of total neurological conditions (n = 1,360) occurring in **(A)** children (<19 years), **(B)** young adults (19–50 years), and **(C)** older adults (>50 years) diagnosed with COVID-19.

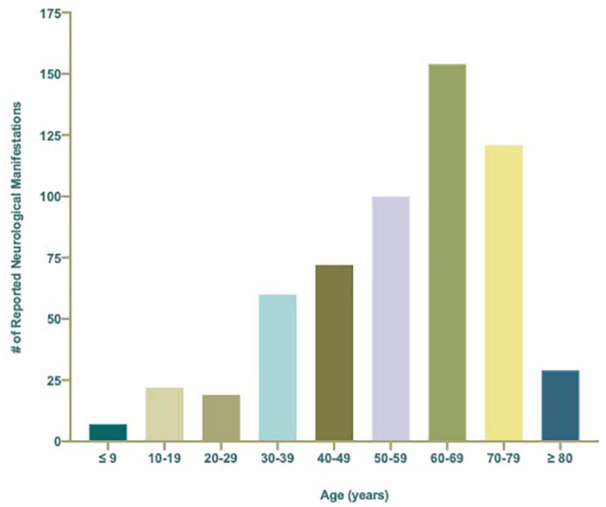

FIGURE 4 | Total number (n = 584) of reported neurological manifestations occurring in patients with COVID-19 per decade ranging from ≤9 to ≥80 years of age.

affecting young children, was seen more frequently in older adults (72.8%, n = 8), as compared to younger adults (18.1%, n = 2) and children (9.1%, n = 1), in this review. Impaired smell and/or taste was seen at a high frequency in all age groupings but was the principal manifestation affecting children and young adults and the second most common complication among individuals over 50 years.

Pathophysiology of Neurological Involvement

How SARS-CoV-2 infection promotes the development of neurological complications is unclear and may involve several factors (**Figure 9**). Brain autopsy and CSF analyses seldom report detectable virus in the CNS compartment, however, the neuroinvasive character of other huCoVs suggest SARS-CoV-2 may also infect the CNS (Arbour et al., 2000) and has been demonstrated in a limited number of infected individuals (Filatov et al., 2020; Moriguchi et al., 2020; Poyiadji et al., 2020; Schurink et al., 2020). While the presence of virus in the CNS compartment and mechanism of entry is not fully elucidated, it is highly likely that SARS-CoV-2 is able to gain access to the brain through nasal epithelial cells. ACE2 is highly expressed in nasal epithelium, pointing to the olfactory bulb as a probable point of entry (Sungnak et al., 2020). Infected olfactory epithelial cells may then transfer virus to closely situated olfactory neurons, allowing for retrograde axonal transport into the CNS compartment. In support of this, unilateral oblation of the olfactory bulb prior to intranasal inoculation of a neurotropic coronavirus prevented CNS entry and viral spread in mouse brain (Perlman et al., 1990).

Hematological entry of virus into the CNS also cannot be ruled out. SARS-CoV-2 has been detected in endothelial cells throughout the body of infected subjects and, given the prevalence of endothelial ACE2 expression, SARS-CoV-2 may be found in brain endothelium (Hamming et al., 2004; Varga et al., 2020). Post-mortem analyses of human and non-human primate brain revealed hCoV-299E in brain endothelial cells (Cabirac et al., 1995). Viral infection of the endothelial cells by coronavirus has been found to cause inflammation of the endothelial cells which disrupts vascular homeostasis and coagulation, suggesting an increased risk for CVD, as a result (Cabirac et al., 1995; Varga et al., 2020).

Even in the absence of direct neuronal or neural cell infection, hypoxia/hypoxemia, coagulopathy, and uncontrolled inflammation or "cytokine storm" can also negatively impact the CNS and cognition (**Figure 9**). Indeed, most clinical evidence suggests neurological complications of COVID-19 are due to secondary effects of infection, including reduced O_2

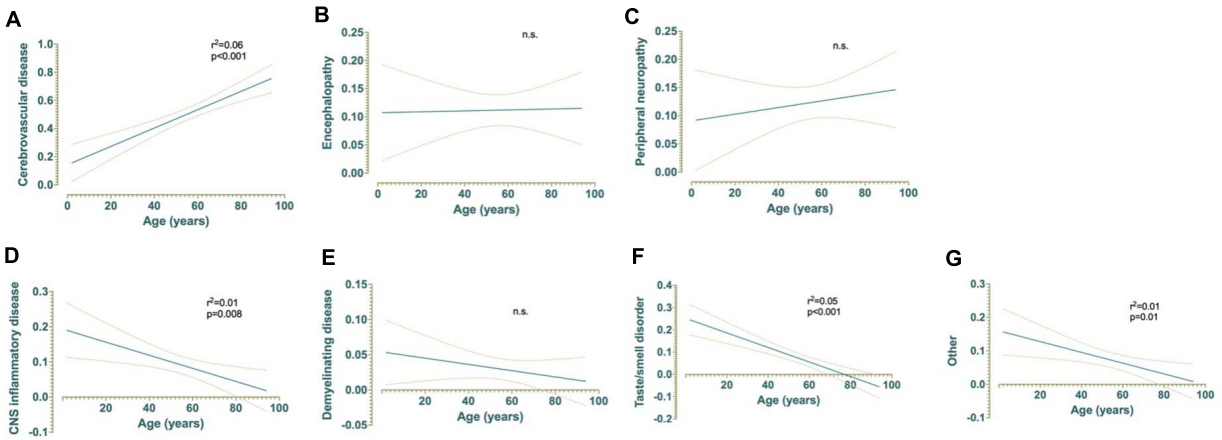

FIGURE 5 | Simple linear regressions demonstrating the effect of age on **(A)** cerebrovascular disease, **(B)** encephalopathy, **(C)** peripheral neuropathy, **(D)** CNS inflammatory disease, **(E)** demyelinating disease, **(F)** taste and/or smell disorders, and **(G)** other non-specific neurological symptoms and their relationships with age (years) for patients with COVID-19 (n = 510).

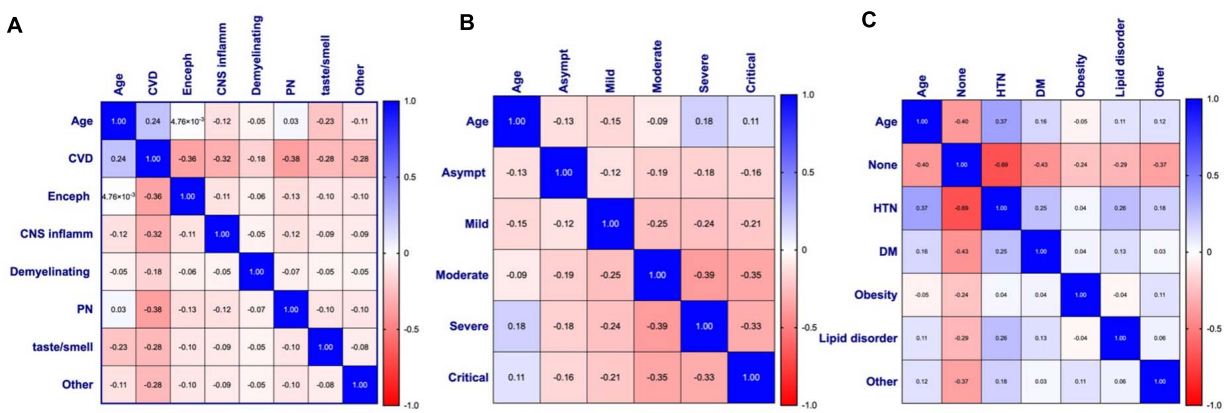

FIGURE 6 | Pearson's correlation matrices and heat maps for **(A)** age and neurological disease (n = 510), **(B)** age and COVID-19 symptom severity (n = 495), and **(C)** age and comorbidities (n = 363) of patients with COVID-19 and diagnosed with a neurological condition(s). Pearson's correlation coefficients are displayed and assigned color based on the distance from zero, with blue representing positive and red representing negative correlations. CVD, Cerebrovascular disease; Enceph, Encephalopathy; CNS inflamm, Central nervous system inflammatory disease; PN, Peripheral neuropathy; Asympt, Asymptomatic; HTN, Hypertension; DM, Diabetes mellitus.

and hyperimmune responses, often referred to as "cytokine storm." Serum levels of pro-inflammatory cytokines [e.g., interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α)] in COVID-19 patients are significantly predictive and/or correlative to the severity of infection and mortality (Chen T. et al., 2020; Gao et al., 2020; Huang et al., 2020; Zhou et al., 2020). Previously, SARS-CoV patients with severe disease were found to have elevated levels of pro-inflammatory cytokines and chemokines, and reduced levels of anti-inflammatory cytokines (IL-10), in comparison to patients with mild disease (Chien et al., 2006). Indeed, virus-associated diseases of the nervous system, such as acute necrotizing encephalopathy, are associated with high levels of pro-inflammatory cytokines in serum and CSF. As such, elevated pro-inflammatory cytokines in serum of severe COVID-19 patients may promote inflammation in brain and contribute to the neurological manifestations of disease (Kansagra and Gallentine, 2011; Sun et al., 2019).

Long-Term Impact of COVID-19 on the Nervous System

The long-term consequences of COVID-19-associated nervous system injury and/or dysfunction is currently unknown, however, reports continue to emerge describing persistent symptoms of disease months after resolution of infection, including impaired smell and/or taste, chronic fatigue, and impaired cognition. Long-term complications of infection are referred to as post-acute sequelae of COVID-19 (PASC) or Long COVID and evidence for this complication is seen with other viruses that induce neurological disease, including human immunodeficiency virus (HIV), West Nile virus, and multiple herpes- and picornaviruses.

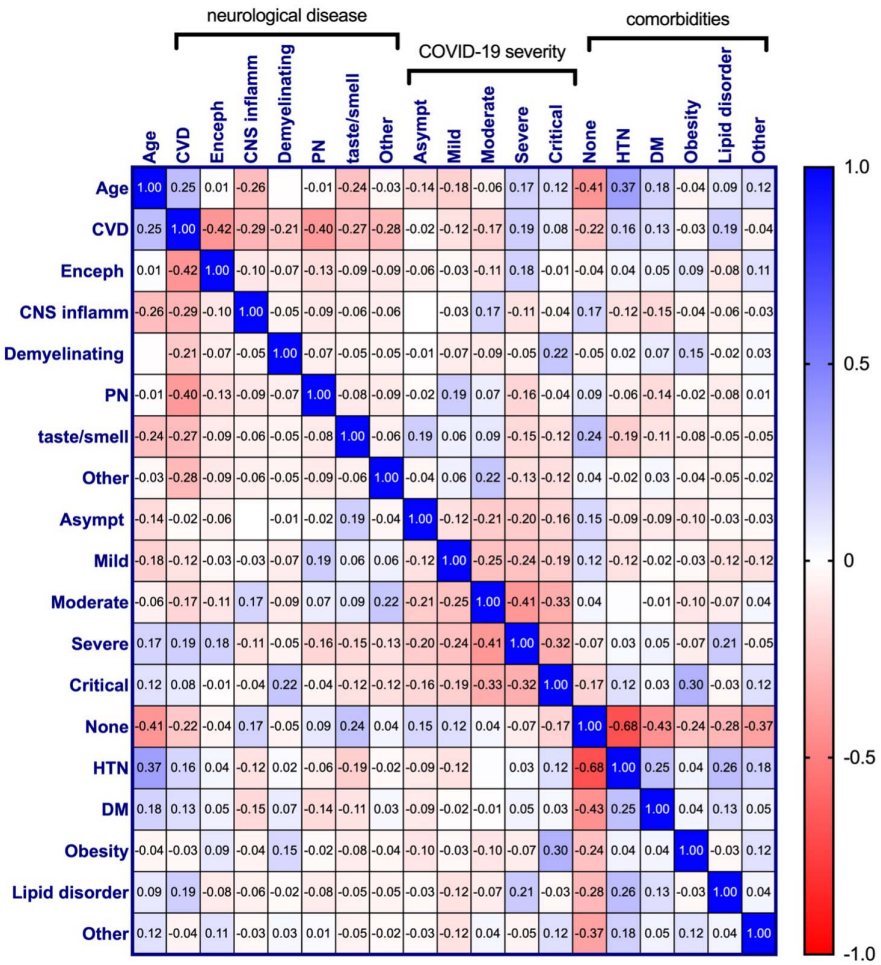

FIGURE 7 | Pearson correlation matrix for age, neurological disease, COVID-19 symptom severity, and comorbidities of COVID-19 patients diagnosed with a neurological condition(s) (n = 303). Pearson's correlation coefficients are displayed and assigned color based on the distance from zero, with blue representing positive and red representing negative correlations. CVD, Cerebrovascular disease; Enceph, Encephalopathy; CNS inflamm, Central nervous system inflammatory disease; PN, Peripheral neuropathy; Asympt, Asymptomatic; HTN, Hypertension; DM, Diabetes mellitus.

It is not entirely clear if SARS-CoV-2 directly infects neurons and/or non-neuronal cells of the CNS and, if so, whether virus is eradicated from these sites with recovery of COVID-19. The significance of this important consideration is seen in a single case report of a 78-year-old woman who recovered from COVID-19 but succumbed to a sudden cardiac arrest prior to hospital discharge (Yao et al., 2020). Although this individual had three consecutive SARS-CoV-2 PCR negative nasopharyngeal swabs, postmortem investigation of multiple tissues, excluding brain, revealed residual virus in lung (Yao et al., 2020). These findings suggest that the virus may not be completely cleared in some patients that appear to have recovered and raises the possibility that SARS-CoV-2 may evade immune surveillance, at least to some degree. It is important to note that replication-competency of virus found in lung of this patient was not determined and remains an important scientific and clinical question. This would have major implications for the brain if replication-competent virus persists in the CNS compartment after recovery. Even an abortive infection, if present, could negatively impact cell function and impair brain homeostasis. Alternatively, or in addition to direct viral involvement, chronic neuroinflammation can contribute to impaired brain homeostasis through production of soluble factors that directly and/or indirectly impair neuronal function. Clinical follow-up and prospective observational studies are critical for assessing long-term neurological outcomes of patients recovered from COVID-19. While this is a likely standard for follow-up of individuals who were diagnosed with serious neurological manifestations, functional and cognitive decline may continue after recovery among COVID-19 patients for whom neurological disease was not identified. There is significant evidence that supports the notion that these individuals, particularly those recovered from severe COVID-19, may have difficulty performing critical functions long after recovery, including reduced job performance and/or ability to attend to activities of daily living, that may worsen over time.

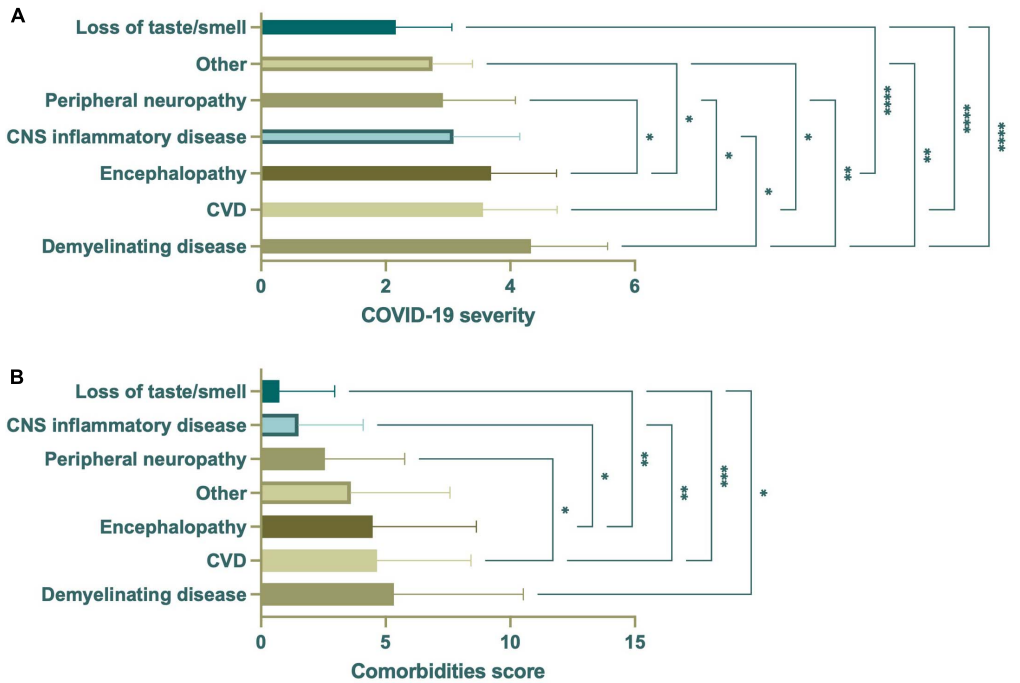

FIGURE 8 | ANOVA of COVID-19 severity or comorbidities score by neurological disease category (n = 350). Significant differences in mean COVID-19 severity **(A)** were seen among all neurological disease categories. Demyelinating disease had the highest mean, with CVD and encephalopathy second and third. Similarly, demyelinating disease had the highest mean comorbidities score, with CVD and encephalopathy second and third **(B)**. Loss of taste/smell had the lowest mean COVID-19 severity and comorbidities score. Data were derived from the same subjects. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

Limited studies are available that investigate the long-term neurological consequences of COVID-19 and do not include neurological assessments but have relied on neuropsychological testing and self-reports. A large cross-sectional study involving cognitive assessments of subjects who had recovered from COVID-19 demonstrated impairment in a variety of cognitive domains and a lower global cognitive performance score, with worsening performance associated with the severity of respiratory disease (Hampshire et al., 2020). This may suggest irreversible injury to the brain due to reduced oxygen and/or chronic subclinical unresolved neuroinflammation, two factors that play a major role in pathologic brain aging. Importantly, minor deficits were even seen among individuals who had experienced only mild respiratory symptoms. Additional follow-up of these individuals is needed to assess the course of symptoms with increased recovery time. It is important to note that testing was performed on-line, rather than by a board-certified neuropsychologist. In a separate assessment of self-reports from subjects at 6-month post-infection, sleep difficulties, anxiety, and depression were the most commonly reported complaints, in addition to fatigue and muscle weakness (Huang et al., 2021).

Evidence of injury at the level of the CNS is very limited at this time, however, a functional imaging study of patients with persistent anosmia following recovery of SARS-CoV-2 infection displayed reduced metabolism in bilateral limbic cortices and the insular cortex of the left hemisphere, as compared to controls (Donegani et al., 2021). This suggests brain involvement in SARS-CoV-2-associated anosmia that may also impact cognitive function, as these brain regions are involved in multiple cognitive processes, including learning and memory, word, face, and body recognition, and consciousness. The insular cortices are also involved in taste, which is often impaired in SARS-CoV-2 infection, alone or concurrent with impaired smell, which may implicate injury within in this region among individuals suffering loss of taste and/or smell. With the potential for controlling the SARS-CoV-2 pandemic with the world-wide introduction of multiple vaccines, more comprehensive follow-up of recovered patients is likely to become an urgent public health concern, including neurological work-up and neuropsychological and/or psychiatric assessments.

This systematic review of the literature and meta-analysis has demonstrated that neurological manifestations are a common complication of SARS-CoV-2 infection and COVID-19 that effects individuals across the lifespan, with all severities of COVID-19, and with or without comorbidities. Consistently emerging case reports and retrospective studies detailing the neurological impact of COVID-19, point to the necessity for investigating the impact of hyperimmune responses and/or reduced oxygen more thoroughly on neuronal injury. In addition, the neuroinvasive potential of the virus should not be ruled outs, as neurological conditions may be seen as a presenting symptom of infection and arise in the absence of respiratory disease. Further, as SARS-CoV-2 infection can lead to devastating neurological diseases irrespective of age, sex, or comorbidities, targeted studies of the COVID-19 population are imperative to better understand and elucidate the true impact of COVID-19 on the CNS. COVID-19 patients

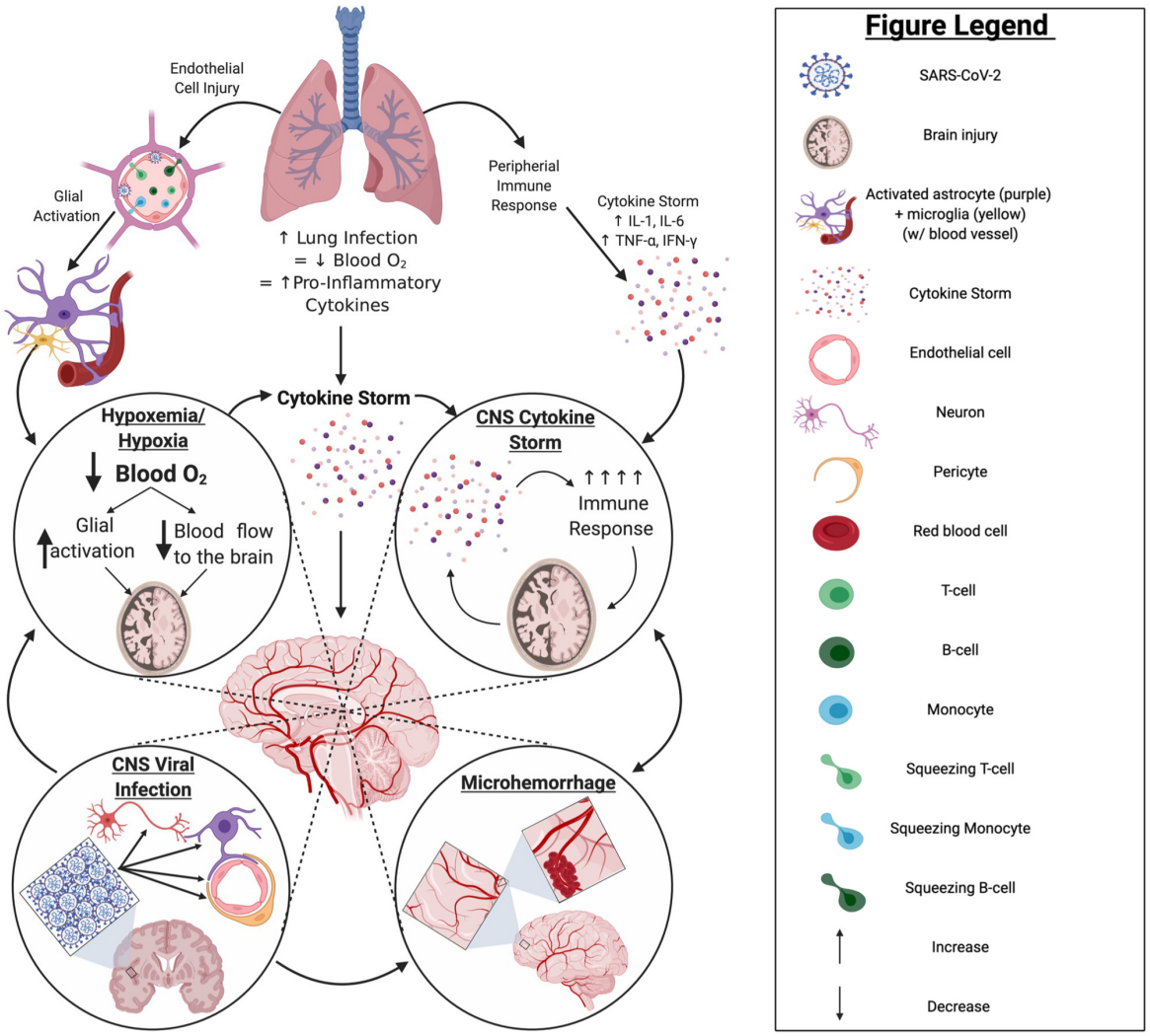

FIGURE 9 | COVID-19 pathology in the CNS: primary impacts and potential mechanisms. Infection by SARS-CoV-2 primarily impacts the lungs, often leading to a hypoxic state and resulting in a robust increase in proinflammatory cytokine production. This may ultimately cause a "cytokine storm" and/or activate glia in the brain. Should such events occur, there is potential for hypoxemia or hypoxia, exacerbated "cytokine storm," and/or infiltration of peripheral immune cells through endothelial cell infection to occur within the brain; any of which can result in significant brain injury to the infected patient. Although currently unclear, if SARS-CoV-2 can establish a productive or even non-productive infection within the CNS compartment, persistent inflammation and/or impaired cell function may result, increasing the potential for serious injury of the brain and/or pathological brain aging. Created with BioRender.com.

need to be followed for potential long-term neurological sequelae after recovery from infection, including pathologic brain aging, that likely plays a key role in PASC. With multiple vaccines now available, we may continue to see a reduction in new cases and/or disease severity, however, the potential for CNS complications remains a major clinical and public health concern.

AUTHOR CONTRIBUTIONS

BS and TF contributed to the writing of the article, figure and table preparation, and final assembly. Both authors contributed to the article and approved the submitted version.

FUNDING

TF was supported by P51OD011104 through the NIH, Office of Research Infrastructure Programs (ORIP).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.653694/full#supplementary-material

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