ANNUAL REVIEWS

Annual Review of Medicine

Neurologic Manifestations and Complications of COVID-19

Matthew K. Hensley,[1] Desiree Markantone,[2] and Hallie C. Prescott[3,4]

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15232, USA; email: hensleymk2@upmc.edu

[2]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA; email: desiree.markantone@gmail.com

[3]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109, USA; email: hprescot@med.umich.edu

[4]VA Center for Clinical Management Research, HSR&D Center of Innovation, Ann Arbor, Michigan 48109, USA

ANNUAL REVIEWS CONNECT

www.annualreviews.org

- Download figures
- Navigate cited references
- Keyword search
- Explore related articles
- Share via email or social media

Annu. Rev. Med. 2022. 73:113–27

First published as a Review in Advance on August 20, 2021

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-042320-010427

Copyright © 2022 by Annual Reviews. All rights reserved

Keywords

neurology, neurologic manifestations, COVID-19, SARS-CoV-2, stroke

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a global pandemic. Beyond the well-described respiratory manifestations, SARS-CoV-2 may cause a variety of neurologic complications, including headaches, alteration in taste and smell, encephalopathy, cerebrovascular disease, myopathy, psychiatric diseases, and ocular disorders. Herein we describe SARS-CoV-2's mechanism of neuroinvasion and the epidemiology, outcomes, and treatments for neurologic manifestations of COVID-19.

INTRODUCTION

Since its identification in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly to become a global pandemic, with nearly 31 million coronavirus disease 19 (COVID-19) cases and 557,000 deaths in the United States as of April 8, 2021 (1). While respiratory manifestations of SARS-CoV-2 infection are well described (2–6), neurologic manifestations have received less attention (7, 8). However, in case series and cohort studies, neurologic manifestations have been reported in 14–57% of patients hospitalized with COVID-19 (8–10), with taste and smell disturbance reported in many patients with milder disease (11). In this review, we describe the spectrum of neurologic manifestations, their epidemiology, their outcomes, and future research directions to inform understanding and management.

MECHANISMS OF NEUROINVASION

While transmission of SARS-CoV-2 respiratory disease has been the subject of much attention and study (5, 12), data on neuroinvasion of SARS-CoV-2 are sparse. Thus, the current understanding of SARS-CoV-2 neuroinvasion is largely extrapolated from other coronaviruses. For example, human coronavirus (HCoV) OC43 can invade peripheral nerve terminals, spread retrograde via axonal transport, and eventually gain access to the central nervous system in mouse models (13). Human cellular data suggest that coronaviruses thrive in dopaminergic neurons (14). Transsynaptic (neuron-to-neuron) spread is hypothesized to cause neurologic manifestations while also contributing to respiratory disease due to its effects on the cardiorespiratory centers within the brainstem (15). Another postulated mechanism for neurologic manifestations of SARS-CoV-2 is spread via spike protein attachment to glycoproteins on the endothelial cell surface, with resultant storage in vesicles and transfer across the blood–brain barrier (16). An in vitro mouse model demonstrated significant uptake of the S1 spike protein across the blood–brain barrier, but the clinical significance of this finding remains unclear. Further supporting the potential importance of blood–brain barrier passage, SARS-CoV-2 virus has been detected within the neural capillary endothelial cells during autopsy in some studies (17). However, other autopsy studies have found little evidence of active viral replication within the central nervous system (18, 19). Additional mechanisms may involve uptake in non-neuronal cells, such as sustentacular cells in the olfactory epithelium, leading to anosmia (20). Finally, coronaviruses can infect leukocytes (21), thereby providing a pathway from the blood to the brain during periods of high inflammation and capillary leak. At this time, the exact mechanisms for the various neurologic manifestations of COVID-19 remain a focus of ongoing research.

NEUROLOGIC SIGNS AND SYMPTOMS

A large proportion of patients with COVID-19 experience neurologic signs and symptoms, including loss or alteration of taste and smell, headache, acute brain dysfunction (e.g., delirium, encephalopathy), acute psychiatric manifestations (e.g., psychosis), cerebrovascular disease, seizures, myopathy, and ocular disorders (**Figure 1**, **Table 1**). A case series of 214 patients hospitalized with COVID-19 in Wuhan, China, in January and February 2020 reported that 78 (36.4%) patients had at least one neurologic manifestation confirmed after adjudication by three neurologists (10).

Alteration in Taste and Smell

Absent or diminished senses of smell (anosmia/hyposmia) and taste (ageusia/hypogeusia) are well-described neurologic manifestations of COVID-19 (22) and may be the sole presenting symptom(s) in up to 3% of outpatients diagnosed with COVID-19 (23). Loss of smell and/or

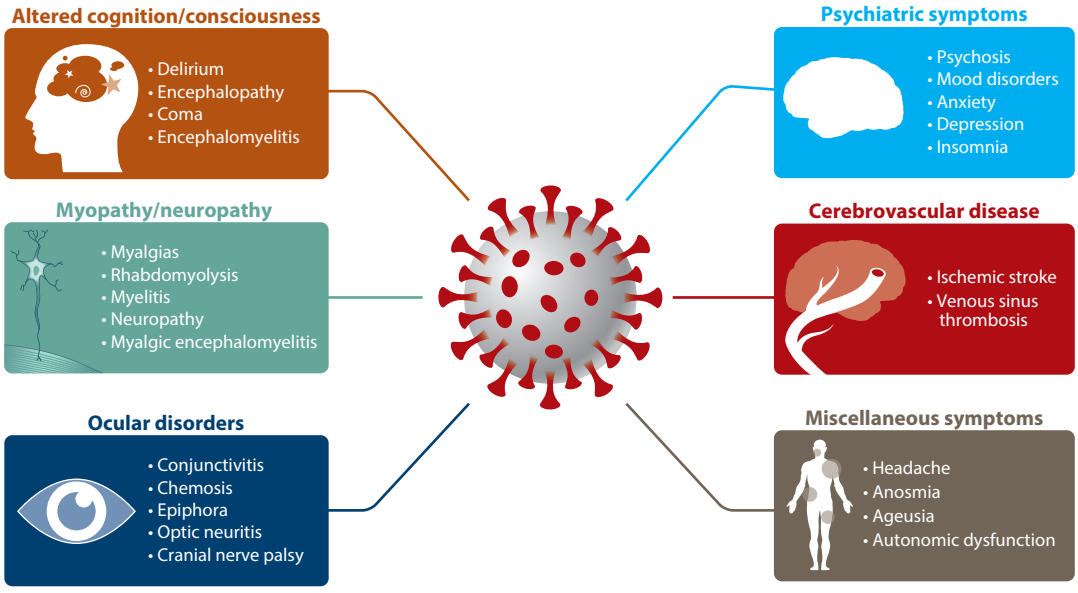

Figure 1

The spectrum of neurologic diseases as a result of COVID-19.

Table 1 Onset and recovery of neurologic COVID-19 symptoms

Neurologic manifestation	Prevalence	Timing of onset	Recovery
Alteration in taste/smell (26)	~50% of all patients diagnosed with COVID-19	3 days after onset of systemic symptoms	30% recovery 8 days after resolution of other symptoms
Headache (8)	12–15% of all patients diagnosed with COVID-19	4 days after onset of other symptoms	Possibly up to 6 weeks after resolution of other symptoms
Encephalopathy (8, 10)	14% of hospitalized patients with COVID-19	Unknown	Unknown
Psychosis/mood disorder (55)	~6% of all patients diagnosed with COVID-19	14–90 days after onset of systemic symptoms	Unknown
Stroke (10, 59)	1–5% of patients hospitalized with COVID-19	Initial symptom but also after resolution of systemic symptoms	Unknown
Seizure (74, 75)[a]	<1% of patients hospitalized with COVID-19	Unknown	Unknown
Myelopathy (79, 80, 82)[a]	<1% of patients hospitalized with COVID-19	5–10 days after onset of systemic symptoms	Unknown
Myopathy (8)	17% of patients hospitalized with COVID-19, 1% rhabdomyolysis	12 days after onset of other systemic symptoms	Unknown
Ocular symptoms (97, 98)[a]	30% of patients hospitalized with COVID-19	Initial symptom but may also be concurrent with other symptoms	Unknown
Dysautonomia, postural orthostatic tachycardia syndrome, orthostatic intolerance (96)	Unknown	Unknown	Symptom improvement in 85% at 6–8 months after COVID-19 resolution

[a]Low quality of evidence; estimates may not be generalizable.

taste is reported to occur in 5–88% of patients across cohorts (8, 10, 23–25). For example, in a study of 417 European patients hospitalized with mild–moderate COVID-19, 85.6% and 88.0% reported olfactory or gustatory dysfunction, respectively (24). A recent meta-analysis of 27 (smell) and 20 (taste) studies including up to 20,541 patients with COVID-19 estimated the prevalence of smell and/or taste alterations (26): Loss of smell was estimated to occur in 54.5% (95% CI 39.3–69.3) of patients with COVID-19 in North America and 48.5% (95% CI 33.8–63.3) globally. Loss of taste, reported in 20 studies (8,001 patients), was estimated to occur in 53.2% (95% CI 44.8–61.7) and 38.6% (95% CI 7.9–75.3) of patients with COVID-19 in Europe and North America, respectively. Loss of both smell and taste (5,977 patients across 13 studies) was estimated to occur in 31.3% (95% CI 13.6–52.2) and 66.8% (95% CI 56.2–76.7) of patients with COVID-19 in Europe and North America, respectively (26).

In a study of 59 patients hospitalized in Italy, rates of olfactory and gustatory dysfunction were higher in women than in men (52.6% versus 25.0%, $p = 0.04$) and in younger patients than in older patients (median age 56 versus 66 years, $p = 0.035$) (25). Additionally, olfactory and gustatory dysfunction is more common in milder forms of COVID-19 (8), though this finding may simply reflect the difficulty of assessing taste and smell among critically ill patients. Interestingly, in a study of 103 patients diagnosed with COVID-19 over a 6-week period in Switzerland, olfactory loss was not associated with rhinitis or nasal obstruction (27).

The timing of olfactory/gustatory symptoms is variable (**Table 1**). In 103 patients in Switzerland, olfactory loss occurred a median of 3 days after the onset of other COVID-19 symptoms, but the lag ranged from 0 to 12 days (27). In a study of 417 hospitalized, non–critically ill patients in Europe, olfactory/gustatory dysfunction preceded the onset of other symptoms in 12%, was concurrent with other symptoms in 22%, and occurred after other symptoms in 65% (24). In this same study, 155 of 247 (63%) patients with clinically resolved disease (absence of general or systemic symptoms) had persistent olfactory dysfunction. Of the 59 patients assessed for subsequent olfactory recovery, 19 (31.9%) recovered smell within 8 days of other symptom resolution (24).

The mechanism of olfactory and gustatory dysfunction in COVID-19 is a subject of debate. While direct neuroinvasion is possible, invasion of the olfactory epithelium likely contributes to diminished smell (20). In a study examining murine and human olfactory epithelium (sustentacular and basal cells but not sensory neurons), the abundance of CoV-2 receptor ACE2 and spike protein protease TMPRSS2 was similar to the amounts seen in respiratory epithelium (20). This finding suggests a potential alternate route for neuroinvasion, further supported by olfactory bulb enhancement on magnetic resonance imaging (MRI) in a COVID-19 patient with anosmia (28), which resolved after smell returned to normal.

At present, the main recommendation for olfactory and gustatory dysfunction is supportive care, as most patients recover spontaneously with time. However, olfactory retraining, with repeated sniffing of common scents, may be helpful for patients with prolonged smell impairment (29). In a study of 417 patients diagnosed with COVID-19 in Europe, most (70.2%) received no therapy for olfactory loss, 16.7% were treated with nasal saline, and 8.1% were treated with nasal corticosteroids (24). Treatment for gustatory loss was even less common, with only four patients receiving L-carnitine (24). Nasal corticosteroids and fatty acid supplementation are currently being investigated for treatment of anosmia (NCT04484493, NCT04495816).

Headaches

The incidence of headaches in patients with COVID-19 ranges from 8% to 15.4% across studies of hospitalized and nonhospitalized patients (30–34). However, there is little information regarding headache characteristics (e.g., timing, duration, severity) or treatments. The ALBACOVID

registry abstracted data for 841 patients admitted with laboratory-confirmed SARS-CoV-2 to two Spanish hospitals in March 2020 and collected data on neurologic manifestations. Among patients in this registry, headache and myalgias occurred a mean of 4 days after onset of other COVID-19 symptoms (8). One review estimated that up to 10% of outpatients with COVID-19 have headache at onset prompting them to seek medical care and reported that many COVID-19-related headaches are refractory to common analgesic therapies but typically abate after 3–9 days (31). However, other reviews have proposed that headaches may take up to 6 weeks to fully resolve (7). At present, only supportive care, including typical analgesics, is recommended for treatment, but ongoing studies are examining the role of nerve block (NCT04636034).

Alteration in Cognition or Consciousness

Acute brain dysfunction resulting in altered consciousness or cognition due to COVID-19 is defined variably across studies and may include entities such as coma, delirium, encephalopathy, confusion, somnolence, stupor, or coma. The incidence of acute brain dysfunction among patients hospitalized with COVID-19 ranges from 7.5% to 13.9% across cohorts (8, 10). In critically ill patients, the incidences of coma (81.6%) and delirium (55%) are much higher, though similar to rates of acute brain dysfunction reported in prepandemic cohorts of critically ill patients (35). For example, in a study of 275 patients hospitalized with COVID-19 in the United States and receiving invasive mechanical ventilation, delirium was diagnosed in 81.7% of patients by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) tool (36). In studies predating the COVID-19 pandemic, acute delirium has been associated with increased risk of long-term cognitive impairment (37). Presumably, patients with COVID-19 and acute delirium are likewise at increased risk for downstream cognitive impairment, but longitudinal studies to confirm this hypothesis are still in process.

A significant contributor to acute brain dysfunction is the use of sedative medications to facilitate invasive mechanical ventilation. In a series of 24 critically ill patients hospitalized with COVID-19 in Seattle, Washington, the average duration of invasive mechanical ventilation for COVID-19-related respiratory failure was 10 days [interquartile range (IQR) 7–12 days], indicating the possibility of prolonged exposure to deliriogenic sedative medications (2). In a larger cohort of 533 patients intubated for respiratory failure due to COVID-19 in 18 hospitals across the Netherlands in March 2020, median duration of mechanical ventilation was 13.5 days (IQR 7.5–22.5) (38). Indeed, despite strong evidence to support minimization of sedation in critically ill patients, the depth and duration of sedation increased during the pandemic. High patient volumes and infection control precautions make it more difficult for nurses to remain at bedside, so deeper sedation may be used to mitigate risk of self-extubation and other complications (39). Among 2,088 mechanically ventilated patients with COVID-19-related respiratory failure treated in 69 centers in 14 countries, 1,481 (70.9%) patients were treated for a median of 7 days (IQR 4–11) with propofol infusions, while 1,337 (64.0%) were treated for a median of 7 days (IQR 4–12 days) with benzodiazepine infusions—which are associated with increased risk for delirium (35). While the impact of deeper sedation, longer sedation, and increased use of benzodiazepines in COVID-19 is not yet known, these sedation practices are expected to result in increased acute and chronic brain dysfunction (40).

Encephalitis (inflammation of brain tissue) and meningitis (inflammation of the tissues that surround the brain and spinal cord) have also been reported in the setting of SARS-CoV-2 infection. These are rare complications of COVID-19, whose exact incidence is unknown. Patients with encephalitis and/or meningitis from COVID-19 have presented in various ways, ranging from classic signs of meningeal irritation (e.g., nuchal rigidity) (41), to atypical presentations including akinetic mutism (42), psychosis (43), seizures (44), and coma with impaired oculocephalic reflex

(45). While some case reports of encephalitis/meningitis found elevated protein and pleocytosis on cerebrospinal fluid (CSF) analysis (42), these features were not observed consistently. Similarly, there have been conflicting reports on whether SARS-CoV-2 is detectable (44, 46) or not (42, 45) in CSF. Additionally, authors have postulated a postinfectious autoimmune cause for encephalitis (47). Radiographic features in COVID-19-related encephalitis are reported to include hemorrhage (48) as well as varied T2 FLAIR (fluid-attenuated inversion recovery) hyperintensities (44, 45). Brain histopathologic findings at autopsy have included both hemorrhagic and demyelinating lesions, with varying degrees of axonal injury (49). Treatments reported in case series have included steroids and intravenous immune globulin (42, 45, 48), but the data are insufficient to show whether these are beneficial. Similarly, registry data will be important for assessment of long-term outcomes (8).

Posterior reversible encephalopathy syndrome, more commonly described in patients with hypertension or calcineurin inhibitor exposure, has been recently described in patients with COVID-19 (50, 51). However, mechanisms, treatment, and outcomes remain unknown.

Psychiatric Manifestations

Case series and case reports describe a broad range of psychiatric manifestations of COVID-19 (52–54), including suicidal ideation, psychosis, insomnia, hallucinations, agitation, and polydipsia. While psychiatric symptoms are rarely presenting symptoms of COVID-19, they may develop in the weeks to months after COVID-19 onset. In a retrospective cohort including more than 62,000 hospitalized and nonhospitalized patients with COVID-19 in the United States, 5.8% (95% CI 5.2–6.4) had a new psychiatric diagnosis (psychosis, anxiety, mood disorder, insomnia) coded in a healthcare encounter in the 14–90 days following COVID-19 diagnosis (55). Compared to patients with influenza matched on 28 variables (including age, race, sex, obesity, and cancer), patients diagnosed with COVID-19 had nearly twofold higher odds of a new psychiatric diagnosis in the subsequent 14–90 days. Most new psychiatric diagnoses have occurred in patients without pre-existing depression, mood, or psychotic disorders (52, 53). However, patients with pre-existing psychiatric diagnoses may also experience worsening of symptoms or develop additional psychiatric diagnoses after COVID-19 (55). Treatments thus far have not differed from standard psychiatric care (53, 54).

The COVID-19 pandemic has also impacted the psychological and emotional health of healthcare workers and the public at large. One New York City emergency medicine physician committed suicide in the spring of 2020, and her death was widely viewed to be the result of the extreme stresses endured as a result of COVID-19—both as a patient and as a physician (56). Since spring 2020, there has been widespread advocacy for enhanced access to mental health services to address the growing burden of patients with new or worsened psychiatric symptoms as a result of the pandemic (57, 58). One way to improve our comprehensive care for patients would be to increase virtual access to mental health resources, particularly for healthcare workers (58).

Hypercoagulability

Across several cohorts, ischemic stroke has been diagnosed in 1–5% of patients hospitalized with COVID-19 (8, 10, 59), with <1% having hemorrhagic cerebrovascular disease (8). In a study of 3,402 emergency room visits or hospitalizations in New York City, comparing COVID-19 (n = 1,916) to influenza (n = 1,486), COVID-19 was estimated to confer a sevenfold increased chance of stroke [odds ratio (OR) 7.6, 95% CI 2.3–25.2] (60). Another observational cohort of 277 patients with stroke hospitalized in New York City found that 105 (38.0%) patients had COVID-19 (61). Stroke patients with COVID-19 compared to those without were more likely to have lobar

Table 2 Clinical trials to address neurologic manifestations of COVID-19[a]

Manifestation	National Clinical Trial number	Population	Intervention	Trial status
Headache	NCT04636034	Adults with persistent headache after COVID-19	Sphenopalatine nerve block versus sham procedure	Recruiting
Anosmia	NCT04495816	Adults with anosmia from COVID-19	Omega-3 fatty acids versus placebo	Recruiting
Anosmia	NCT04484493	Adults with anosmia from COVID-19	Mometasone nasal spray versus placebo	Completed
Stroke	NCT04406090	Adults with COVID-19 admitted with stroke	Mechanical thrombectomy (retrospective)	Completed
Delirium	NCT04513314	Adult patients mechanically ventilated with COVID-19 and delirium	Valproate and quetiapine versus standard of care	Not yet recruiting

[a]ClinicalTrials.gov search date February 25, 2021. Search terms included combinations of "COVID-19" and "headache," "anosmia," "taste," "stroke," "encephalopathy," "delirium," "seizure," "eye," and "ocular."

location of their stroke, with increased inpatient mortality (33% versus 12.9%, $p < 0.0001$), worsening neurologic exam while admitted (51.9% versus 21.0%, $p < 0.0001$), and greater likelihood of admission to the ICU (58.7% versus 44.7%, $p = 0.025$) (61). Nearly all strokes in these cohorts were cryptogenic or cardioembolic in etiology (60, 61). While pre-existing comorbidities such as atrial fibrillation and hypertension presumably increase risk, it is hypothesized that SARS-CoV-2 infection directly increases risk of stroke through hypercoagulability, vasculitis, and acute cardiovascular dysfunction (62). Additionally, patients hospitalized with COVID-19 have been noted to have frequently abnormal coagulation parameters, including positive lupus anticoagulant (63), elevated D-dimer, and elevated fibrin degradation products (64). It is possible that these abnormal coagulation parameters may predict or directly contribute to risk of cerebrovascular disease in COVID-19, but more research is needed to examine the extent to which these laboratory abnormalities are markers versus mediators of cardiovascular outcomes in COVID-19.

The severity of strokes in patients with COVID-19 may differ from that in patients without COVID-19—although it is unclear whether this difference is driven by delays in presentation during the pandemic or by true differences in stroke pathophysiology. A retrospective cohort of 3,556 patients hospitalized with COVID-19 in New York City compared COVID-19 patients with ischemic stroke ($n = 32$) to historical controls ($n = 80$) (59). Patients with COVID-19 had higher National Institutes of Health Stroke Scale scores on admission (OR per point increase 1.23, 95% CI 1.05–1.44), as well as increased odds of in-hospital mortality (OR 40.7, 95% CI 5.44–298.01) (59). Based on these data, some authors have advocated that young individuals presenting with stroke without risk factors should be evaluated for COVID-19 (65). Treatment for stroke remains the same with or without COVID-19, but investigators are assessing the safety, feasibility, and efficacy of thrombectomy for management of acute ischemic stroke in patients with COVID-19 (NCT04406090) (**Table 2**).

Additional case reports and series have demonstrated an association between COVID-19 and cerebral venous sinus thrombosis (66–68). One series of eight patients hospitalized with COVID-19 across seven different centers and four countries (United States, Egypt, Spain, and Romania) found that 50% ($n = 4$) presented with headache, and 25% ($n = 2$) had focal neurologic deficits (68). Median time of onset from COVID-19 diagnosis was 3 days (IQR 0.75–3 days), and the superior sagittal sinus was the most common site of thrombosis (75%, $n = 6$).

Roughly 20–50% of hospitalized patients with COVID-19 have abnormal coagulation parameters (69), including elevated D-dimer, prolonged prothrombin time, and thrombocytopenia.

It has been debated whether these abnormalities indicate hypercoagulability or consumptive disseminated intravascular coagulation (DIC). A study of 183 patients hospitalized with COVID-19 in China demonstrated thrombocytopenia (23.8%), elevated D-dimer (85.7%), low fibrinogen (28.6%), and prolonged prothrombin time (47.6%) among decedents, consistent with DIC (64). In a study in an ICU in Italy comparing 22 patients to 44 healthy controls, bloodwork and thromboelastography revealed increased D-dimer (5,343 ng/L versus 225 ng/L, $p < 0.0001$), higher fibrinogen (517 mg/dL versus 297 mg/dL, $p < 0.0001$), shorter clot formation time (57 s versus 70 s, $p = 0.0002$), and higher clot firmness (68 mm versus 62 mm, $p < 0.0001$) (70). Results were replicated on repeat assessment of the same patients, with elevated D-dimer (4,877 ng/mL), elevated fibrinogen (680 mg/dL), and thromboelastography consistent with hypercoagulability (70). Peripheral smears would support a hypercoagulable state rather than a consumptive process, but definitive conclusions cannot be made presently (71).

While serial measurements of coagulation parameters (D-dimer, fibrinogen, thromboelastography) are used to assess patient trajectories in some hospitals, it is unclear that such monitoring improves outcomes. Similarly, the optimal anticoagulation approach remains unclear. Deep vein thrombosis prophylaxis is clearly indicated for hospitalized patients with COVID-19, and randomized clinical trials suggest that full-dose anticoagulation may be beneficial before patients become critically ill (72). However, once patients are critically ill, empiric full-dose anticoagulation increases risk for complications (73). A preliminary search of ClinicalTrials.gov using the search terms "COVID-19" and "anticoagulation" yielded 25 ongoing investigations into the role of full-dose anticoagulation for COVID-19 as of January 24, 2021, so treatment approaches may be refined further once these trial results are available.

Seizures

There are limited data on the impact of COVID-19 on the development or progression of seizures. In a study of 304 patients hospitalized with COVID-19 in China, only two patients had seizure-like activity, one attributed to an acute stress reaction and the other to hypocalcemia (74). In a cohort of 6,147 inpatients and outpatients diagnosed with COVID-19 in Iran, seizures occurred in only 5 (0.08%) patients (75). Of these five, none had a history of epilepsy, four presented with seizures, and four ultimately died of COVID-19. All five patients were critically ill, so seizures may simply be a reflection of severe illness rather than SARS-CoV-2 specifically.

In a single-center US cohort of 1,043 patients hospitalized with COVID-19, seven (0.7%) presented with seizures, including three who had no preceding infectious symptoms and four who had no history of epilepsy (76). Only one patient had a brain MRI due to status epilepticus, which demonstrated gyriform diffusion restriction and leukoencephalopathy (76). Electroencephalogram testing was similarly limited but demonstrated seizures in one patient and encephalopathy in another. In most cases, patients had metabolic derangements that may have contributed to their seizures.

Movement Disorders

It is suspected that patients with pre-existing movement disorders may be at higher risk of acquiring SARS-CoV-2 infection due to their disease as well as residence in high-risk settings such as nursing facilities or long-term care homes, but it is unknown whether SARS-CoV-2 infection increases risk of developing movement disorders or exacerbates pre-existing movement disorders such as Parkinson's disease. In a cohort of 79,049 patients with COVID-19 (inpatient and outpatient), including 694 (0.9%) with pre-existing Parkinson's disease, there was a 27% increase in odds of death among patients with Parkinson's disease compared to those without (OR 1.27, 95%

CI 1.04–1.53) (77). By contrast, in a cohort of 9,470 patients in Italy [including 880 (9.3%) with Parkinson's disease or symptoms], Parkinson's disease was not associated with increased risk of death [hazard ratio (HR) 0.8, 95% CI 0.3–2.3] but was associated with increased risk of hospitalization (HR 1.51, 95% CI 1.1–2.1) for COVID-19 (78).

Peripheral Nervous System Disorders

Demyelinating diseases are a rare but increasingly well-recognized complication of COVID-19. A case series of five patients hospitalized with COVID-19 in Italy describes the natural history of Guillain-Barre syndrome (GBS) after SARS-CoV-2 infection (79). The patients experienced lower limb weakness, then progressive tetraplegia occurring 5–10 days after onset of infectious symptoms. CSF protein levels were normal in 40% of patients ($n = 2$), and none of the five had detectable SARS-CoV-2 in CSF. Compound action potentials (measured by nerve conduction testing) were reduced, and two patients had prolonged motor distant latencies. Evaluation was consistent with axonal variant in three patients and demyelinating variant in the other two (80). All five patients were treated with intravenous immune globulin and steroids. Short-term follow-up (4 weeks) revealed that only one patient was discharged and able to ambulate independently (79). Another group utilized plasmapheresis for a patient with GBS associated with COVID-19 due to concerns of hypercoagulability with intravenous immune globulin (81). Other cases have reported a longer time from disease onset, with GBS occurring roughly 3 weeks after COVID-19 symptoms started (82). Long-term outcomes are unknown.

In the ALBACOVID registry of 841 patients hospitalized with COVID-19 in Spain, 142 (17%) patients experienced myalgias during hospitalization (8), 73 (9.2%) had elevated creatine phosphokinase, and 9 (1.1%) had rhabdomyolysis. Myopathy occurred later in the course of illness, a median of 12 days after onset, and was associated with prolonged ICU stay (OR 1.3, 95% CI 1.02–1.71) (8). Beyond the ALBACOVID registry, data on myopathy come from case reports (83–85). It has been postulated that SARS-CoV-2 directly targets myofibers leading to viral myositis and breakdown, as opposed to cross-reactivity between virus and myofibers leading to autoimmune destruction (84), and may predispose to prolonged weakness (86). There are no data thus far regarding long-term outcomes of COVID-19-related myopathy.

Critically ill patients with respiratory failure due to COVID-19 are sometimes placed in the prone position, increasing risk for brachial plexopathy due to prolonged pressure and injury (87). However, a recent case report identified brachial plexopathy in a COVID-19 survivor who was not proned, with no identifiable source other than hypercoagulability-induced thrombi leading to ischemia of the vasa nervorum (88). Short-term 3-month follow-up revealed improvement in strength and reinnervation, though with some residual deficits.

Transverse Myelitis, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, and Autonomic Dysfunction

Rarely, patients with recent COVID-19 have represented with progressive weakness, hypesthesia, and urinary retention, ultimately being diagnosed with transverse myelitis ($n = 2$) (89, 90). Weakness occurred nearly one week after COVID-19 diagnosis. MRI revealed T2 hyperintensity within the spinal cord, with elevated protein in the CSF, negative oligoclonal bands, and negative SARS-CoV-2 polymerase chain reaction testing. Steroids were the treatment of choice in these cases, but duration of treatment and long-term outcomes are unknown at present.

Beyond the acute manifestations of COVID-19, some patients experience long-lasting and debilitating fatigue following COVID-19 (91). In a telephone survey of 471 patients hospitalized with COVID-19 in Michigan, 40% reported being unable to return to normal activities by

2 months posthospitalization (92). Furthermore, in a telephone survey of 270 outpatients with mild COVID-19, 35% had not returned to their normal state of health by 2–3 weeks after diagnosis. The term "long COVID" was coined by patients early in the pandemic to describe the life-altering consequences of COVID-19, including persistent fatigue (93). The pathophysiology and natural history of fatigue following COVID-19 remain unclear, but some have questioned whether SARS-CoV-2 can cause myalgic encephalomyelitis or chronic fatigue syndrome.

Similarly, there is burgeoning interest in understanding autonomic dysfunction after COVID-19 (94, 95). Observations of heightened sympathetic activity, with accompanying loss of parasympathetic activity (vagal tone), have led some researchers to postulate that changes in sympathetic activity contribute to morbidity and mortality associated with COVID-19, similar to other diseases such as heart failure, diabetes, and hypertension.

Postural orthostatic tachycardia syndrome has similarly been described in case series of patients who have recovered from COVID-19 (96). Of 20 patients who presented to a dysautonomia clinic with persistent respiratory and cardiovascular symptoms after resolution of COVID-19, 70% were female with a median age of 40 (interquartile range 25–65 years) (96). Six patients (30%) had a prior confirmed positive COVID-19 test, while others were deemed by their primary care provider to have had COVID-19 based on prior clinical symptoms. None were hospitalized during their acute illness. After resolution of their acute illness, most patients experienced fatigue, postural tachycardia, orthostatic intolerance defined as abnormal tilt table test, dizziness, and exercise intolerance. After evaluation in the dysautonomia clinic, 15 patients (75%) were diagnosed with postural orthostatic tachycardia syndrome, 3 (15%) with neurocardiogenic syncope, and 2 (10%) with orthostatic hypotension (96). Sixteen (80%) required pharmacologic treatment including beta blockers, fludrocortisone, midodrine, and ivabradine. Seventeen (85%) reported residual symptoms at 6–8 months after COVID-19, with 3 (15%) returning to work full time and 5 (25%) able to work full time from home.

Ocular Disorders

The incidence of ocular manifestations among patients with COVID-19 varies across cohorts, with estimated incidence of up to 30% in patients hospitalized with COVID-19 (97, 98). Symptoms include irritation (chemosis), excessive tearing (epiphora), and ocular secretions indicative of conjunctivitis. In a series of 38 patients hospitalized with COVID-19 in China, 12 (31.6%) patients had ocular symptoms prior to systemic symptoms (98). There have been reports of ocular transmission of COVID-19, but there is not enough information currently to determine if tears can actually transmit virus between patients (99).

CONCLUSIONS

There is a broad range of potential neurologic manifestations of SARS-CoV-2, most commonly seen among patients requiring hospitalization. The most common manifestations are alterations in taste and smell, headache, disorders of consciousness/cognition, and neuropsychiatric manifestations (8). Rarer manifestations include transverse myelitis, seizures, rhabdomyolysis, cranial nerve palsy, and GBS. To date, there are limited data on long-term outcomes and scant evidence that treatment for COVID-19-related neurologic manifestations should differ from the standard treatment of these conditions outside of COVID-19. Registries and databases will provide more information on the incidence and outcomes of neurologic manifestations moving forward, but trials are needed to inform and refine treatment approaches. Similarly, there has been a call to develop an international registry to track outcomes and inform treatment options for patients suffering from the neurologic sequelae of COVID-19 (100). As vaccination (101) becomes more

widespread, we anticipate that the incidence of COVID-19 and COVID-19-related neurologic manifestations will decrease, but management of longer-term neurologic complications of COVID-19 will remain an enduring clinical challenge, given the number of patients with recovered COVID-19 around the world.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government. This material is the result of work supported with resources and use of facilities at the Ann Arbor VA Medical Center.

LITERATURE CITED

1. CDC (Cent. Dis. Control Prev.). 2020. COVID data tracker. *Centers for Disease Control and Prevention*. **https://covid.cdc.gov/covid-data-tracker/#datatracker-home**
2. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. 2020. Covid-19 in critically ill patients in the Seattle region—case series. *N. Engl. J. Med.* 382:2012–22
3. Cummings MJ, Baldwin MR, Abrams D, et al. 2020. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 395(10239):1763–70
4. McMichael TM, Currie DW, Clark S, et al. 2020. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. *N. Engl. J. Med.* 382(21):2005–11
5. Wiersinga WJ, Rhodes A, Cheng AC, et al. 2020. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 324(8):782–93
6. Ziehr DR, Alladina J, Petri CR, et al. 2020. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am. J. Respir. Crit. Care Med.* 201(12):1560–64
7. Ellul MA, Benjamin L, Singh B, et al. 2020. Neurological associations of COVID-19. *Lancet Neurol.* 19(9):767–83
8. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. 2020. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. *Neurology* 95(8):e1060–70
9. Helms J, Kremer S, Merdji H, et al. 2020. Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med.* 382(23):2268–70
10. Mao L, Jin H, Wang M, et al. 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 77(6):683–90
11. Zubair AS, McAlpine LS, Gardin T, et al. 2020. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* 77(8):1018–27
12. Prather KA, Wang CC, Schooley RT. 2020. Reducing transmission of SARS-CoV-2. *Science* 368(6498):1422–24
13. Dubé M, Le Coupanec A, Wong AHM, et al. 2018. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J. Virol.* 92(17):e00404-18
14. Yang L, Han Y, Nilsson-Payant BE, et al. 2020. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell* 27(1):125–36.e7
15. Li Y-C, Bai W-Z, Hashikawa T. 2020. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol.* 92(6):552–55
16. Rhea EM, Logsdon AF, Hansen KM, et al. 2020. The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice. *Nat. Neurosci.* 24:368–78

17. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. 2020. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J. Med. Virol.* 92(7):699–702
18. Kantonen J, Mahzabin S, Mäyränpää MI, et al. 2020. Neuropathologic features of four autopsied COVID-19 patients. *Brain Pathol.* 30(6):1012–16
19. Solomon IH, Normandin E, Bhattacharyya S, et al. 2020. Neuropathological features of Covid-19. *N. Engl. J. Med.* 383(10):989–92
20. Brann DH, Tsukahara T, Weinreb C, et al. 2020. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci. Adv.* 6(31):eabc5801
21. Gu J, Gong E, Zhang B, et al. 2005. Multiple organ infection and the pathogenesis of SARS. *J. Exp. Med.* 202(3):415–24
22. Howard J, Guy J. 2020. Doctors say loss of sense of smell might be Covid-19 symptom. *CNN Health*, Mar. 23. **https://www.cnn.com/2020/03/23/health/coronavirus-symptoms-smell-intl/index.html**
23. Spinato G, Fabbris C, Polesel J, et al. 2020. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 323(20):2089–90
24. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. 2020. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur. Arch. Otorhinolaryngol.* 277(8):2251–61
25. Giacomelli A, Pezzati L, Conti F, et al. 2020. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin. Infect. Dis.* 71(15):889–90
26. Ibekwe TS, Fasunla AJ, Orimadegun AE. 2020. Systematic review and meta-analysis of smell and taste disorders in COVID-19. *OTO Open* 4(3):2473974X20957975
27. Speth MM, Singer-Cornelius T, Oberle M, et al. 2020. Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. *Otolaryngol. Head Neck Surg.* 163(1):114–20
28. Politi LS, Salsano E, Grimaldi M. 2020. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol.* 77(8):1028–29
29. Whitcroft KL, Hummel T. 2020. Olfactory dysfunction in COVID-19: diagnosis and management. *JAMA* 323(24):2512
30. Huang C, Wang Y, Li X, et al. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223):497–506
31. Bolay H, Gül A, Baykan B. 2020. COVID-19 is a real headache! *Headache* 60(7):1415–21
32. Guan W, Ni Z, Hu Y, et al. 2020. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 382(18):1708–20
33. Zhu J, Ji P, Pang J, et al. 2020. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. *J. Med. Virol.* 92(10):1902–14
34. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. 2020. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J. Clin. Med.* 9(4):941
35. Pun BT, Badenes R, Heras La Calle G, et al. 2021. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir. Med.* 9(3):239–50
36. Ely EW, Shintani A, Truman B, et al. 2004. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 291(14):1753–62
37. Girard TD, Jackson JC, Pandharipande PP, et al. 2010. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit. Care Med.* 38(7):1513–20
38. Botta M, Tsonas AM, Pillay J, et al. 2021. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. *Lancet Respir. Med.* 9(2):139–48
39. Hanidziar D, Bittner EA. 2020. Sedation of mechanically ventilated COVID-19 patients: challenges and special considerations. *Anesth. Analg.* 131(1):e40–41
40. Iwashyna TJ, Ely EW, Smith DM, et al. 2010. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 304(16):1787–94
41. Ye M, Ren Y, Lv T. 2020. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav. Immun.* 88:945–46

42. Pilotto A, Odolini S, Masciocchi S, et al. 2020. Steroid-responsive encephalitis in coronavirus disease 2019. *Ann. Neurol.* 88(2):423–27
43. Bernard-Valnet R, Pizzarotti B, Anichini A, et al. 2020. Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection. *Eur. J. Neurol.* 27(9):e43–44
44. Moriguchi T, Harii N, Goto J, et al. 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94:55–58
45. Parsons T, Banks S, Bae C, et al. 2020. COVID-19-associated acute disseminated encephalomyelitis (ADEM). *J. Neurol.* 267(10):2799–802
46. Huang YH, Jiang D, Huang JT. 2020. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav. Immun.* 87:149
47. Paterson RW, Brown RL, Benjamin L, et al. 2020. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 143(10):3104–20
48. Poyiadji N, Shahin G, Noujaim D, et al. 2020. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology* 296(2):E119–20
49. Reichard RR, Kashani KB, Boire NA, et al. 2020. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol.* 140(1):1–6
50. Princiotta Cariddi L, Tabaee Damavandi P, Carimati F, et al. 2020. Reversible encephalopathy syndrome (PRES) in a COVID-19 patient. *J. Neurol.* 267(11):3157–60
51. Franceschi AM, Arora R, Wilson R, et al. 2020. Neurovascular complications in COVID-19 infection: case series. *Am. J. Neuroradiol.* 41(9):1632–40
52. Mirza J, Ganguly A, Ostrovskaya A, et al. 2020. Command suicidal hallucination as initial presentation of coronavirus disease 2019 (COVID-19): a case report. *Psychosomatics* 61(5):561–64
53. Smith CM, Komisar JR, Mourad A, et al. 2020. COVID-19-associated brief psychotic disorder. *BMJ Case Rep.* 13(8):e236940
54. Ferrando SJ, Klepacz L, Lynch S, et al. 2020. COVID-19 psychosis: a potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response? *Psychosomatics* 61(5):551–55
55. Taquet M, Luciano S, Geddes JR, et al. 2020. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* 8(2):130–40
56. Romo V. 2020. NYC emergency room physician who treated coronavirus patients dies by suicide. *NPR*, Apr. 28. **https://www.npr.org/sections/coronavirus-live-updates/2020/04/28/847305408/nyc-emergency-room-physician-who-treated-coronavirus-patients-dies-by-suicide**
57. Bao Y, Sun Y, Meng S, et al. 2020. 2019-nCoV epidemic: address mental health care to empower society. *Lancet* 395(10224):e37–38
58. Reger MA, Stanley IH, Joiner TE. 2020. Suicide mortality and coronavirus disease 2019—a perfect storm? *JAMA Psychiatry* 77(11):10193–94
59. Yaghi S, Ishida K, Torres J, et al. 2020. SARS-CoV-2 and stroke in a New York healthcare system. *Stroke* 51(7):2002–11
60. Merkler AE, Parikh NS, Mir S, et al. 2020. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) versus patients with influenza. *JAMA Neurol.* 77(11):1366–72
61. Dhamoon MS, Thaler A, Gururangan K, et al. 2021. Acute cerebrovascular events with COVID-19 infection. *Stroke* 52(1):48–56
62. Spence JD, de Freitas GR, Pettigrew LC, et al. 2020. Mechanisms of stroke in COVID-19. *Cerebrovasc. Dis.* 49(4):451–58
63. Harzallah I, Debliquis A, Drénou B. 2020. Lupus anticoagulant is frequent in patients with Covid-19. *J. Thromb. Haemost.* 18(8):2064–65
64. Tang N, Bai H, Chen X, et al. 2020. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J. Thromb. Haemost.* 18(5):1094–99
65. Fifi JT, Mocco J. 2020. COVID-19 related stroke in young individuals. *Lancet Neurol.* 19(9):713–15
66. Dakay K, Cooper J, Bloomfield J, et al. 2021. Cerebral venous sinus thrombosis in COVID-19 infection: a case series and review of the literature. *J. Stroke Cerebrovasc. Dis.* 30(1):105434

67. Garaci F, Di Giuliano F, Picchi E, et al. 2020. Venous cerebral thrombosis in COVID-19 patient. *J. Neurol. Sci.* 414:116871
68. Abdalkader M, Shaikh SP, Siegler JE, et al. 2021. Cerebral venous sinus thrombosis in COVID-19 patients: a multicenter study and review of literature. *J. Stroke Cerebrovasc. Dis.* 30(6):105733
69. Lee SG, Fralick M, Sholzberg M. 2020. Coagulopathy associated with COVID-19. *CMAJ* 192(21):E583
70. Panigada M, Bottino N, Tagliabue P, et al. 2020. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. *J. Thromb. Haemost.* 18(7):1738–42
71. Abou-Ismail MY, Diamond A, Kapoor S, et al. 2020. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. *Thromb. Res.* 194:101–15
72. NIH (Natl. Inst. Health). 2021. *Full-dose blood thinners decreased need for life support and improved outcome in hospitalized COVID-19 patients*. News release, Jan. 22, NIH, Bethesda, MD. **https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients**
73. NIH (Natl. Inst. Health). 2020. *NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients*. News release, Dec. 22, NIH, Bethesda, MD. **https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients**
74. Lu L, Xiong W, Liu D, et al. 2020. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. *Epilepsia* 61(6):e49–53
75. Emami A, Fadakar N, Akbari A, et al. 2020. Seizure in patients with COVID-19. *Neurol. Sci.* 41(11):3057–61
76. Anand P, Al-Faraj A, Sader E, et al. 2020. Seizure as the presenting symptom of COVID-19: a retrospective case series. *Epilepsy Behav*. 112:107335
77. Zhang Q, Schultz JL, Aldridge GM, et al. 2020. Coronavirus disease 2019 case fatality and Parkinson's disease. *Mov. Disord.* 35(11):1914–15
78. Vignatelli L, Zenesini C, Belotti LMB, et al. 2021. Risk of hospitalization and death for COVID-19 in people with Parkinson's disease or parkinsonism. *Mov. Disord.* 36(1):1–10
79. Toscano G, Palmerini F, Ravaglia S, et al. 2020. Guillain-Barré syndrome associated with SARS-CoV-2. *N. Engl. J. Med.* 382(26):2574–76
80. Hadden RD, Cornblath DR, Hughes RA, et al. 1998. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. *Ann. Neurol.* 44(5):780–88
81. Abrams RMC, Kim BD, Markantone DM, et al. 2020. Severe rapidly progressive Guillain-Barré syndrome in the setting of acute COVID-19 disease. *J. Neurovirol.* 26(5):797–99
82. Arnaud S, Budowski C, Ng Wing Tin S, et al. 2020. Post SARS-CoV-2 Guillain-Barré syndrome. *Clin. Neurophysiol.* 131(7):1652–54
83. Samies NL, Pinninti S, James SH. 2020. Rhabdomyolysis and acute renal failure in an adolescent with coronavirus disease 2019. *J. Pediatr. Infect. Dis. Soc.* 9(4):507–9
84. Meegada S, Muppidi V, Wilkinson DC, et al. 2020. Coronavirus disease 2019-induced rhabdomyolysis. *Cureus* 12(8):e10123
85. Jin M, Tong Q. 2020. Rhabdomyolysis as potential late complication associated with COVID-19. *Emerg. Infect. Dis.* 26(7):1618–20
86. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. 2020. Multiorgan and renal tropism of SARS-CoV-2. *N. Engl. J. Med.* 383:590–92
87. Sánchez-Soblechero A, García CA, Ansotegui AS, et al. 2020. Upper trunk brachial plexopathy as a consequence of prone positioning due to SARS-CoV-2 acute respiratory distress syndrome. *Muscle Nerve* 62(5):E76–78
88. Han CY, Tarr AM, Gewirtz AN, et al. 2021. Brachial plexopathy as a complication of COVID-19. *BMJ Case Rep.* 14(3):e237459
89. Chow CCN, Magnussen J, Ip J, et al. 2020. Acute transverse myelitis in COVID-19 infection. *BMJ Case Rep*. 13(8):e236720
90. Munz M, Wessendorf S, Koretsis G, et al. 2020. Acute transverse myelitis after COVID-19 pneumonia. *J. Neurol.* 267(8):2196–97

91. Komaroff AL, Bateman L. 2021. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front. Med.* 7:1132
92. Chopra V, Flanders SA, O'Malley M, et al. 2020. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann. Intern. Med.* 174(4):576–78
93. Perego E, Callard F, Stras L, et al. 2020. Why we need to keep using the patient made term "Long Covid." *BMJ Opin. Blog*, Oct. 1. **https://blogs.bmj.com/bmj/2020/10/01/why-we-need-to-keep-using-the-patient-made-term-long-covid**
94. Dani M, Dirksen A, Taraborrelli P, et al. 2021. Autonomic dysfunction in "long COVID": rationale, physiology and management strategies. *Clin. Med.* 21(1):e63–67
95. Del Rio R, Marcus NJ, Inestrosa NC. 2020. Potential role of autonomic dysfunction in Covid-19 morbidity and mortality. *Front. Physiol.* 11:561749
96. Blitshteyn S, Whitelaw S. 2021. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol. Res.* 69(2):205–11
97. Bertoli F, Veritti D, Danese C, et al. 2020. Ocular findings in COVID-19 patients: a review of direct manifestations and indirect effects on the eye. *J. Ophthalmol.* 2020:4827304
98. Wu P, Duan F, Luo C, et al. 2020. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 138(5):575
99. Peng M, Dai J, Sugali CK, et al. 2020. The role of the ocular tissue in SARS-CoV-2 transmission. *Clin. Ophthalmol.* 14:3017–24
100. Román GC, Reis J, Spencer PS, et al. 2020. COVID-19 international neurological registries. *Lancet Neurol.* 19(6):484–85
101. Polack FP, Thomas SJ, Kitchin N, et al. 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* 383:2603–15