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Acute Neurologic Complications of COVID-19 and Postacute Sequelae of COVID-19

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KEYWORDS

• Neurologic complications • Long-COVID • Cerebrovascular complications
• Neuro-COVID

KEY POINTS

- Neurologic complications of COVID-19 are common. They can occur in patients with mild to severe COVID-19.
- Cerebrovascular complications, such as acute ischemic stroke, are seen in about 1.5% of all patients with COVID-19, whereas cerebral sinus venous thrombosis is rare, and intracerebral hemorrhage can occur as a consequence of therapeutic anticoagulation or because of hemorrhagic transformation of acute ischemic stroke. Stroke systems of care must be adapted to provide the same high-quality care for patients with COVID-19 to uphold time is brain by providing rapid access to testing and personal protective equipment.
- Coma and prolonged disorders of consciousness may be seen in patients with COVID-19 as a consequence of viral infection, as prolonged use of sedative drips and delayed metabolism of these medications are due to hepatorenal dysfunction. Delirium is common in COVID-19. Compliance with the intensive care unit liberation bundle or the A2F bundle was lower than during the first and second waves of COVID-19, and lack of family visitation may have been an important contributor to increased incidence of delirium.
- Neurologic complications in postacute sequelae of COVID-19 range from persistent fatigue, headaches, brain fog, depression, anxiety, postural orthostatic tachycardia even in patients with mild disease to an overlap with postintensive care syndrome in intensive care unit survivors, highlighting the need for long-term follow-up.

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ACUTE NEUROLOGIC COMPLICATIONS OF COVID-19 AND POSTACUTE SEQUELAE OF COVID-19

Three hundred forty million people have suffered from the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 [COVID-19]), across the world at the time of publication, and 5.57 million deaths have occurred since the beginning of the pandemic.[1] COVID-19 is a multisystem viral sepsis syndrome that can affect different organ systems with symptoms ranging from mild to life threatening.[2] Neurologic complications are commonly described and may occur as direct or indirect consequences of the viral infection, complications of treatment, or, in some cases, may be incidental associations. These insults do not just occur in the acute phases, with ongoing sequelae occurring and/or persisting for weeks to months after the initial infection, often as part of a syndrome known as postacute sequelae of COVID-19 (PASC) or long-COVID.[3–8] Critically ill patients have a higher likelihood of neurologic complications than patients with mild COVID-19.[3,4]

The recognition and diagnosis of these neurologic complications are challenging, particularly in the context of overstrained medical systems, where an underrecognition or delays in diagnosis of neurologic complications may contribute to poor outcomes.[5]

In this review, the authors highlight acute neurologic complications of COVID-19 as well as neurologic manifestations of PASC.

In the first section of this review, the authors discuss overall epidemiology, pathophysiology, and risk factors for neurologic manifestations followed by a discussion of specific neurologic manifestations.

EPIDEMIOLOGY

The risk of neurologic manifestations increases with hospitalization and higher severity of COVID-19 infection, although even patients with mild initial disease may have neurologic sequelae. These include non-life-threatening but debilitating symptoms ranging from anosmia, dysgeusia, fatigue, malaise, headaches to stroke, encephalitis, and Guillain-Barre syndrome (GBS), among others (**Table 1**).

The understanding of the neurologic complications of COVID-19 comes mainly from observational studies. **Table 1** summarizes neurologic complications described in some of the larger cohort studies of hospitalized patients. In a systematic review and meta-analysis (n = 13,480 patients and a third of these patients with severe COVID-19), the most common neurologic manifestations were myalgia (22%), dysgeusia (20%), anosmia (18%), headache (12%), dizziness (11%), encephalopathy (9.4%), and stroke (2.5%). Myalgia, elevated creatine kinase and lactate dehydrogenase, and acute stroke were significantly more common in severe cases.[6,7]

RISK FACTORS FOR ACUTE NEUROPSYCHIATRIC COMPLICATIONS AND POSTACUTE SEQUELAE OF COVID-19

Older patients, multiple comorbidities, Hispanic patients, south Asian, black, and mixed ethnicity patients, and patients with preexisting neurologic disorders have a higher risk of developing neurologic complications of acute COVID-19. Additional risk factors for PASC include age greater than 40 years, white ethnicity, and female sex.[8] A systematic review identified the following risks for neuropsychiatric consequences of PASC[9]

- For depression and/anxiety (seen in 20%–40% of survivors): Women, those with infected family members, postinfectious physical symptoms, severe infection, elevated inflammatory markers, prior psychiatric diagnoses

Table 1
Summary of neurologic manifestations in cohort studies

Study	Varatharaj et al	Meppiel et al	Frontera et al	Chou et al
No. of patients with neurologic complications	153	222	606	2439/3054
Encephalopathy, %	23	30	51	51
Stroke, %	62	26 (ischemic strokes)	14	3
Seizures/status epilepticus	Not reported	9.5%	12%	1%
Acute inflammatory central nervous system syndromes, %	9	9.5	0	1
PNS disease	5%	6.8%	Not reported	6%
Other	Neuropsychiatric disorders 23/125 patients	Not reported	Hypoxic brain injury 11%	Coma 17%

- For posttraumatic stress disorder (PTSD) (20%–30% of survivors): Women, younger age, critically ill, past psychiatric history, obesity, type 2 diabetes mellitus, autoimmune disorders
- For cognitive issues, such as memory loss, concentration difficulties, difficulties with multitasking, processing speed (20%–30% of survivors): Delirium, older age

PATHOPHYSIOLOGY

COVID-19 can be thought of as having the following phases, which include an early viremic phase during which patients may remain asymptomatic for the first 48 to 72 hours followed by a prothrombotic, inflammatory phase, followed by an immune dysregulatory state (**Fig. 1**, **Table 2**).[10]

The COVID-19 spike protein attaches to the ACE2 receptor on various organs and activates an inflammatory cascade. It also attaches to the ACE2 receptor on endothelium and activates a prothrombotic state.[11] By binding to ACE2, the SARS-CoV-2 virus may damage vascular endothelial cells by inhibiting mitochondrial function and endothelial nitric oxide synthetase activity, leading to secondary cardiovascular and cerebrovascular effects.[12] It is possible that because the density and concentration of ACE2 receptors are limited in the central nervous system (CNS), direct viral invasion may be a rare phenomenon. Consistent with this, viral particles have been identified very rarely in the brain in autopsy studies. Whether this is a consequence of low viral invasion or that by the time these patients died they had progressed from the early viremic to the inflammatory or prothrombotic state is not known.[7,13,14] Acute demyelinating encephalomyelitis (ADEM).

Inflammation

In an autopsy series, microglial activation, microglial nodules and neuronophagia, was observed in most of the brains. They were thought to not result from direct viral infection of brain parenchyma, but more likely from systemic inflammation, perhaps with synergistic contribution from hypoxia/ischemia.[7,13]

A postmortem study (n = 43) found that neuropathologic changes in patients with COVID-19 seem to be mild, with pronounced neuroinflammatory changes in the

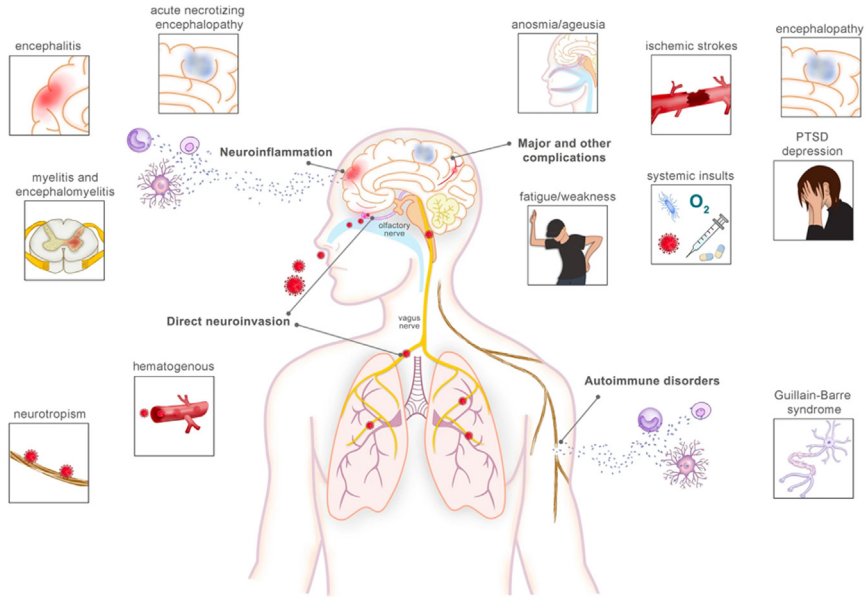

Fig. 1. Potential mechanisms and complications of neuroCOVID. (*From* Newcombe VFJ, Dangayach NS, Sonneville R. Neurological complications of COVID-19. Intensive Care Med. 2021;47(9):1021-1023. https://doi.org/10.1007/s00134-021-06439-6; with permission)

Table 2
Mechanism of injury and clinical examples of neurologic complications

Mechanism/Cause	Example
Direct viral invasion into the CNS	• Infectious encephalitis, meningitis, myelitis
Parainfectious, immune-mediated	• ADEM • Transverse myelitis • Guillain-Barré syndrome
Neurologic complications of systemic disease	• Hypercoagulability → ischemic stroke • Hypoxic respiratory failure → hypoxic brain injury • Sepsis → encephalopathy/delirium
Exacerbation of baseline neurologic disorder	• Epilepsy: increased seizure frequency/status epilepticus • Multiple sclerosis flare
Treatment-associated neurologic complications	• Anticoagulation → CNS hemorrhages • Steroids & paralytic medications → critical illness neuropathy/myopathy • Sedatives → delirium/encephalopathy
Thrombotic complications	• Stroke: arterial and venous
Associated with critical illness	• Postintensive care syndrome
Unclear	• Long-COVID

brainstem being the most common finding. There was no evidence for CNS damage directly caused by SARS-CoV-2.[14] Inflammation around blood vessels but not viral particles in a study that included n = 8 postmortem samples suggests that COVID-19 is associated with endotheliopathy and microvascular injury.[15] Patients with coma or prolonged disorders of consciousness (DOC) may have a higher systemic inflammatory burden as compared with patients who do not have coma or DOC.[16]

Prothrombotic

COVID-19 is thought to be an endotheliopathy and triggers a prothrombotic state. Of note, patients with COVID-19 acute respiratory distress syndrome (ARDS) had a higher level of various prothrombotic factors and thrombotic events, as compared with non-COVID-19 patients.[17]

Treatment Effects

Severely ill patients with COVID-19 are at a high risk of encephalopathy and intensive care–acquired weakness. These neurologic consequences were much higher than expected in these patients and likely explained by the prolonged needs for sedation, immobilization, and social isolation, increasing the risk of delirium and postintensive care syndrome (PICS). Although some of these factors may have been related to the severity of the underlying illness, others were likely due to the decreased compliance with the A2F bundle due to concerns for staff safety, shortage of personal protective equipment (PPE), medications, and limitations of family visitation.[18,19]

SPECTRUM OF NEUROLOGIC COMPLICATIONS

Neurologic complications can be broadly categorized under cerebrovascular disease, CNS inflammatory disease, demyelinating disease, encephalopathy, peripheral neuropathy, taste/smell disorders, and other.[20]

Fig. 2 describes a few potential ways of classifying neurologic complications of COVID-19.

NEURODIAGNOSTIC STUDIES, NEUROMONITORING

Early diagnosis of neurologic complications in patients with COVID-19 will rely on focused bedside neurologic examinations. Such focused clinical examinations can then guide a judicious utilization of imaging and electrophysiologic studies. However,

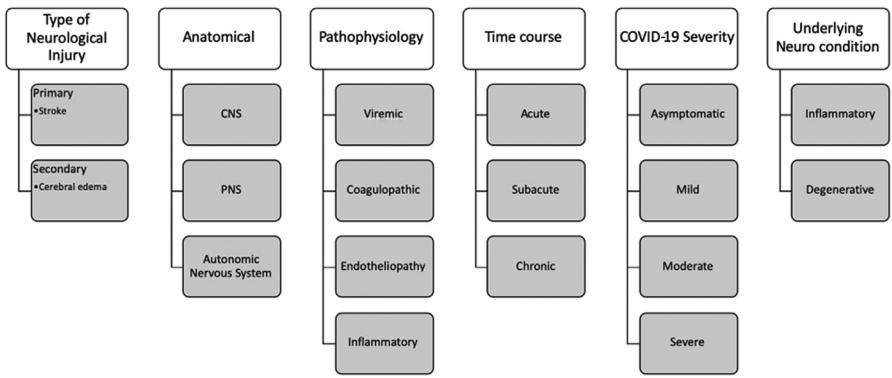

Fig. 2. Classifying neurologic complications of COVID-19. PNS, Peripheral Nervous System.

the pandemic has posed specific challenges in this clinical neuromonitoring with a reduction in both frequency of clinical examinations and compliance of bundles of care, which include choice and depth of sedation and choice of pain control when patient numbers are high.

Imaging Findings

Critically ill patients with COVID-19 may not be stable hemodynamically or from a ventilation/oxygenation perspective to tolerate lying flat for several minutes in an MRI scanner. Performing computed tomographic (CT) scans in such patients suspected of having neurologic complications may be the first step in diagnosis. Given the risk of cerebrovascular complications in these patients, it may be pertinent to perform vessel imaging for the arterial and venous systems at the same time as the CT or MRI session.

Common imaging findings described in patients with severe COVID-19 have included leukoencephalopathy, ischemia/infarction with patterns of large vessel occlusion, leptomeningeal enhancement, encephalitis, hemorrhage in locations not typical for hypertension (lobar and/or cortical, which raises the question of whether it is secondary to anticoagulation), and perfusion abnormalities.[21] Another key finding in patients with coma/DOC has been microhemorrhages.[22] In another case series, 25/115 hospitalized patients with COVID-19 had cerebral microbleeds documented on MRI, often with concomitant leukoencephalopathy. These were most common in patients with more severe respiratory illness.[23]

Other findings have included findings typical for posterior reversible encephalopathy syndrome, hypoxic ischemic encephalopathy.[24] In a retrospective multicenter study (n = 64), MRI abnormalities have included leptomeningeal enhancement in 17% and encephalitis in 13%; 46% of MRI studies was normal.[25]

Cerebrospinal Fluid Studies and Biomarkers

Pleocytosis is usually not seen in cerebrospinal fluid (CSF) of patients with COVID-19. Studies have demonstrated that CSF findings could range from being inflammatory to the only abnormality being an elevated protein. In a case-control study that included n = 18 CSF samples from patients with COVID-19, the investigators described an absence of pleocytosis as well as an absence of increased proinflammatory markers or cytokines (IL-6, ferritin, or D-dimer). They also found that in non-COVID-19 stroke patients and COVID-19 stroke patients there was a similar increase in proinflammatory cytokines (IL-6, TNFα, IL-12p70).[26]

In a small case series of patients with moderate to severe COVID-19, an unusual pattern of marked CSF inflammation emerged, in which soluble markers of neuroinflammation (neopterin, β2-microglobulin, and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein[NfL]) was increased. However, white cell response and other immunologic features typical of CNS viral infections were absent.[27] In patients with COVID-19 with neurologic manifestations, CSF pleocytosis was found to be associated with parainfectious or postinfectious encephalitis and polyradiculitis. Elevations in anti-GD1b and anti-Caspr2 autoantibodies[28] and myelin-associated glycoprotein[29] may be seen raising the possibility of SARS-CoV-2–induced secondary autoimmunity.

Serum Biomarkers

Serum markers of brain injury including neurofilament light (NFL), glial fibrillary acidic protein (GFAP), and total Tau have been found to be increased in a severity-dependent manner in hospitalized patients, with elevations persisting at 4-month follow-up.[29] In

these patients, elevations in NFL and GFAP were associated with elevations of proinflammatory cytokines, as well as autoantibodies. Another case-control study that included plasma samples from n = 57 patients at less than 48 hours of COVID-19 hospitalization, and 20 matched controls investigated levels of 6 brain injury molecules (BIMs), 2 endothelial injury molecules (EIMs), and chemokines/cytokines. Three BIMs: MAP2, NSE, and S100B; 2 EIMs: sICAM1 and sVCAM1; and 7 chemokines and cytokines: GRO, IL10, sCD40L, IP10, IL1Ra, MCP1, and TNFα, were significantly (P<.05) elevated in the COVID-19 cohort compared with controls.[30]

In summary, pleocytosis is not seen in CSF of patients with COVID-19 with encephalopathy, but protein levels can be elevated with oligoclonal bands. Elevated plasma and CSF levels of cytokines, GFAP, and NFL in COVID-19 are thought to reflect a proinflammatory systemic and brain response that involves microglial activation and subsequent neuronal damage.[27] Further evidence for inflammatory mechanisms comes from imaging findings, which showed meningeal enhancement and diffuse white matter abnormalities as well as microhemorrhages.[13] It should be noted that several of these biomarkers are not being measured routinely as part of clinical care, and further understanding of when, how high, and the meaning of elevations is required before use in clinical practice.

NON-LIFE-THREATENING BUT POTENTIALLY DISTRESSING SYMPTOMS

Anosmia/Dysgeusia

A meta-analysis of 83 studies involving more than 27,000 patients reported that olfactory dysfunction occurs in 48% of cases.[31] Olfactory bulb involvement was described on postmortem brain MRI earlier in the pandemic.[32] Most patients recover from anosmia and dysgeusia.[33–35]

Whether this high incidence of anosmia will be seen in patients with other COVID-19 variants remains to be seen.

Headache

Headache is a common symptom of COVID-19. A meta-analysis that included n = 3598 patients showed that headache was present in 11% to 14% of patients infected with COVID-19.[36] Earlier studies from China reported a lower incidence of headache at about 6.5% to 8%.[37–39] In a cohort study of n = 47 patients with COVID-19, 64% had headaches. Bilateral headache localization was reported by 94% of patients; headache severity was determined as severe in 53%, and constant headaches with median period of 15 days occurred in 15% of cases.[40]

LIFE-THREATENING NEUROLOGIC COMPLICATIONS

Stroke

There have been several cohort studies and meta-analyses describing the risk of stroke and outcomes in patients with COVID-19. Before the COVID-19 pandemic, it was already known that sepsis and related inflammation can trigger strokes.[41,42]

In one of the earlier reports of stroke in COVID-19, which included n = 108,571 patients with COVID-19, acute stroke occurred in 1.4% (95% confidence interval: 1.0–1.9). The investigators compared the risk of stroke in patients with COVID-19 with those with influenza and concluded that more patients with COVID-19 suffer from stroke as compared with patients with influenza (0.9%).[43]

The first cases of large vessel occlusion were described in young, asymptomatic, or mild COVID-19 cases. Subsequent studies have shown that the average age of patients with COVID-19 with stroke may be slightly lower than the average age in non-

COVID-19 stroke patients, but stroke is not as common in young patients (<50 years of age). Also, COVID-19 stroke patients tend to have a higher comorbidity burden.[44–46] Mechanisms of stroke can vary from thromboembolic, large-artery atherosclerosis, COVID-19–associated myocarditis, to arrhythmias, cryptogenic.[24,47] In a review that included n = 46 studies with 129,491 patients, COVID-19 stroke patients were younger, tend to be men, and have an increased stroke severity, compared with stroke patients in the prepandemic period. The investigators found no difference in rates of intravenous thrombolysis but found that patients with COVID-19 were more likely to undergo thrombectomy.[48,49] Stroke systems of care had to be adapted to COVID-19–related staff safety, PPE, and staff shortages. The American Heart Association released a statement to provide guidance to health systems to provide expeditious access to thrombectomy.[49]

Mortality in patients with stroke and COVID-19 is higher than in non-COVID-19 patients with a similar stroke burden.[48] A multicenter study from n = 31 centers in the United States that included n = 230 stroke patients found that only 33% of them were younger than 60 years of age. Of the patients, 102/203 (50%) had poor outcomes with an observed mortality of 38.8% (35/219).[50] The in-hospital mortality for COVID-19 stroke patients was about 38.1% and for intracerebral hemorrhage (ICH) was 58.3%.[50]

Good outcome has been reported for patients who develop malignant cerebral edema concurrent with COVID-19, and so infection should not be used to exclude patients from this potentially life-saving surgery.[51]

Hemorrhagic Stroke

Intracerebral hemorrhage

ICH is less common than ischemic stroke after COVID-19, comprising approximately 20% of strokes, and its incidence ranges from 0.2% to 0.86%.[52,53] This rate is higher than the worldwide incidence of ICH, which is 24.6/100,000 person-years or 0.02% per person-year.[54] In patients with COVID-19 with stroke, less than 20% have ICH.[55] The pooled incidence of ICH in a systematic review was 0.7% in patients with COVID-19 that included n = 23 studies and n = 148 COVID-19 ICH patients.[56]

In a study that analyzed data from Vizient Clinical Data Base comparing n = 559 patients with ICH-COVID-19 and 23,378 non-COVID-19 ICH controls from 194 hospitals, patients with ICH-COVID-19 had a longer hospital stay (21.6 vs 10.5 days), a longer intensive-care stay (16.5 vs 6.0 days), and a higher in-hospital death rate (46.5% vs 18.0%). Patients with COVID-19 with ICH or subarachnoid hemorrhage (SAH) were more likely to be a racial or ethnic minority, diabetic, and obese and to have higher rates of death and longer hospital length of stay when compared with controls.[57] A patient level pooled meta-analysis that included n = 139 patients with ICH with COVID-19, the investigators found that the ICH in these patients had different characteristics compared with ICH not associated with COVID-19, including frequent lobar location (67%) and multifocality (36%), a high rate of anticoagulation, and high mortality.[58] In a systematic review,[59] older age, non-Caucasian race, respiratory failure requiring mechanical ventilation, and therapeutic anticoagulation were identified as risk factors for ICH.[60]

Subarachnoid hemorrhage

In a study where the investigators analyzed data from the Vizient database comparing COVID-19 SAH cases versus non-COVID-19 SAH controls, there were 212 SAH-COVID patients and 5029 controls from 119 hospitals. The hospital (26.9 vs 13.4 days) and intensive-care (21.9 vs 9.6 days) length of stays and in-hospital death rate (42.9% vs 14.8%) were higher in the SAH-COVID cohort than in controls.[57] In another cohort study that included data from 62 health care facilities using the Cerner

deidentified COVID-19 data set, there were n = 86 (0.1%) and n = 376 (0.2%) patients with SAH among 85,645 patients with COVID-19 and 197,073 patients without COVID-19, respectively. The investigators found that there was no increase in the risk of SAH in patients with COVID-19 but higher mortality probably driven by systemic complications (31.4% vs 12.2%).[61]

Cerebral sinus venous thrombosis

In a case series from New York City at the height of the COVID-19 pandemic's first wave (March through May 2020), cerebral sinus venous thrombosis (CSVT) was diagnosed in 12 of 13,500, for a frequency of 0.088 per million as compared with CSVT in the general population is 5 per million annually.[62] In a systematic review of n = 34,331 patients with COVID-19, the estimated frequency of CSVT was 0.08%.[63] The superior sagittal and transverse sinuses were the most common sites for acute CVST.[64] CSVT and vaccine induced thrombocytopenia (VITT) are discussed later in this review.[64]

Extracorporeal membrane oxygenation and neurologic complications

In a systematic review on neurologic complications in extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 that included n = 1322 patients from case series and retrospective cohort studies, the prevalence of intracranial hemorrhage (ICH), ischemic stroke, and hypoxic ischemic brain injury was 5.9% (n = 78), 1.1% (n = 15), and 0.3% (n = 4), respectively. The overall mortality of the 1296 ECMO patients in the 10 studies that reported death was 36% (n = 477), and the mortality of the subset of patients who had a neurologic event was 92%.[65]

In a multicenter case-control study of ECMO patients, the investigators included 29/142 (20%) patients with ICH versus 4/68 (6%) non-COVID-19 patients with ICH on ECMO. Half of the patients with COVID-19 had a clinically significant ICH and a third of them suffered in-hospital mortality. The overall intensive care unit (ICU) mortality in the presence of ICH of any severity was 88%. This study showed a 6-fold increased adjusted risk for ICH and a 3.5-fold increased incidence of ICH in patients with COVID-19 on ECMO, versus non-COVID-19 patients.[66] In another study that included ARDS patients on ECMO comparing COVID-19 versus non-COVID-19 patients, ICH was detected in 10% of patients with ARDS. Despite statistically higher rates of antiplatelet therapy and therapeutic anticoagulation in patients with COVID-19, there was a similar rate of ICH in patients with ARDS owing to COVID-19 compared with other causes of ARDS.[67]

Delirium/encephalopathy

In a systematic review that included n = 48 studies with 11,553 patients with COVID-19 from 13 countries, the pooled prevalence, incidence, and mortalities for delirium in patients with COVID-19 were 24.3%, 32.4%, and 44.5%, respectively.[68]

In a hospitalized cohort of patients with COVID-19 of n = 419, about 80% of them were diagnosed with a neurologic complication anytime from presentation to later during their hospitalization, and 30% of these patients had encephalopathy.[69] In addition, these patients often require longer ventilation with prolonged sedation and paralysis than used in many common ICU conditions.

In a cohort study that included patients with severe COVID-19, 84% patients were found to have neurologic symptoms, mainly delirium.[70] In a subsequent study (n = 140 patients), 70% developed agitation during ICU stay. In addition, more than half (17/28) of the patients had MRI abnormalities, and more than half (18/28) had an inflammatory CSF profile. Electroencephalogram showed only nonspecific findings.[71]

Delirium was present in 55% patients in the COVID-D cohort study of n = 2088 critically ill patients with COVID-19. Mechanical ventilation, use of restraints,

benzodiazepine, opioid, and vasopressor infusions, and antipsychotics were each associated with a higher risk of delirium the next day, whereas family visitation (in person or virtual) was associated with a lower risk of delirium.[19]

Coma/encephalitis

Among patients with COVID-19 with a disorder of consciousness (DoC), coma, serum inflammatory markers were higher as compared with patients with COVID-19 without coma.[72] After cessation of sedatives, patients with severe respiratory failure secondary to COVID-19 may have a prolonged period of unconsciousness, which may be weeks before complete recovery.[73] In a prospective, longitudinal study, consecutive critically ill patients with COVID-19 with a DoC unexplained by sedation or structural brain injury, who underwent a brain MRI, were enrolled. In addition to structural imaging, the investigators performed a resting state functional MRI and diffusion MRI to evaluate functional and structural connectivity, as compared with healthy controls and patients with DoC resulting from severe traumatic brain injury. Of the 12 patients included in this study, one died shortly after enrollment, and the rest recovered consciousness between 0 and 25 days after stopping all sedatives.[74] Given the long length of recovery time seen, caution is advised when prognosticating in these patients.

POSTINTENSIVE CARE SYNDROME AND POSTACUTE SEQUELAE OF COVID-19

PICS has been described as the unintended consequences of critical care with new or worsening impairments in the physical, cognitive, or mental health domains.[75,76]

In a single-center, observational cohort study, 294 of 622 patients, including both COVID-19 and non-COVID-19 patients (median age, 64 years; 36% women); 16% and 13% of these patients reported probable PTSD, 29% and 20% probable anxiety, and 32% and 24% probable depression at 1 and 3 months after hospital discharge, respectively. The investigators found a similar risk of neuropsychiatric consequences in both COVID-19 and non-COVID-19 hospitalized patients, concluding that there is a need for long-term follow-up for hospitalized patients during this pandemic to focus on the needs of both of these cohorts.[69]

Of COVID-19 survivors, 90% suffered from impairments to one or more PICS domains in a prospective cohort from New York City.[77] At 3 months of follow-up, 87.5% (28/32) had not regained their baseline level of daily activities in a cohort study of COVID-19 ICU survivors, and 40% patients had impairments in multiple domains.[78]

Similar problems can be seen in all those who require critical care. PICS is a common constellation of physical, psychological, and cognitive problems experienced by those who have been in critical care, with holistic rehabilitation programs required for each component.[79]

Patients and caregivers should be educated to monitor for persistent symptoms (**Fig. 3**) and followed up in a multidisciplinary fashion to address the needs of patients with PASC. Dedicated COVID-19 centers may not be widely available in all countries; however, awareness of such centers, along with the ability to follow up via telehealth, may have help to bridge the gap in meeting the needs of COVID-19 survivors. Studies have shown that about half of the patients with COVID-19 will develop PASC.[80] Similar to acute COVID-19, PASC could also include multisystem manifestations. Recognizing that COVID-19 survivors will have multisystem needs, COVID-19 survivors need to be followed up in multidisciplinary clinics. For critical care survivors, impairments in different domains (physical, cognitive, behavioral) have long been characterized as PICS. Clinics developed for survivors of critical illness offer a model to address PASC survivorship for both acute and nonhospitalized patients with COVID-19 for

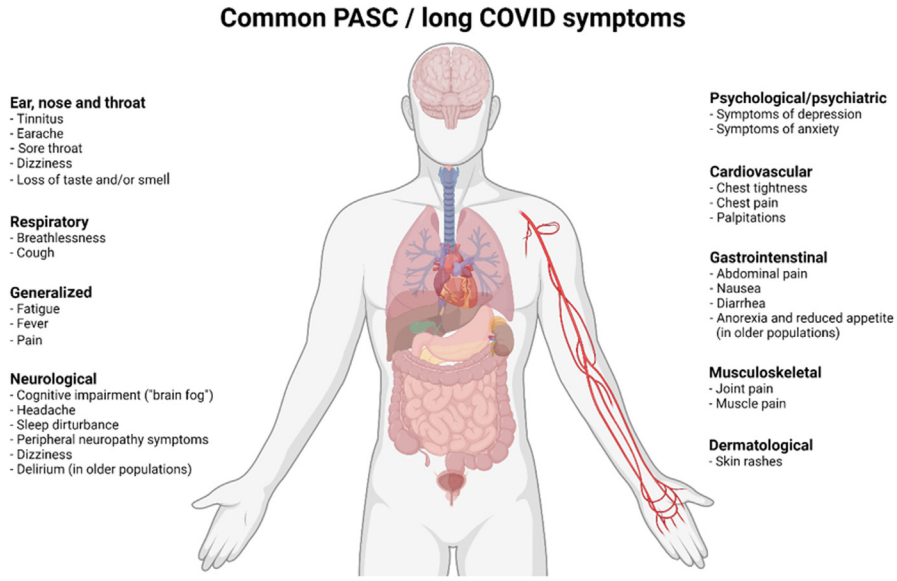

Fig. 3. Common PASC symptoms. (*From* Newcombe VFJ, Dangayach NS, Sonneville R. Neurological complications of COVID-19. Intensive Care Med. 2021;47(9):1021-1023. https://doi.org/10.1007/s00134-021-06439-6; with permission)

better understanding the trajectory, clustering of symptoms as well as providing an opportunity to pool data to inform survivorship trajectories. A multidisciplinary program of care should include access to rehabilitation services, social work and welfare support, pharmacy, subspecialty care via direct inclusion or targeted referrals, and structured peer support program with trained moderators; coordination with primary care is essential.[73]

PASC clinics also offer research opportunities that should be harnessed to inform knowledge of survivorship trajectories after SARS-CoV-2 infection, and to improve service innovation and delivery.[81] Although resources for follow-up and rehabilitation will vary between and within countries, awareness and innovations like telehealth may help bridge the gap in meeting the needs of COVID-19 survivors. Symptom assessment could be performed between 4 and 6 weeks and at 12 weeks after discharge, along with screening for neuropsychiatric symptoms in addition to follow-up for other organ system involvement, for example, pulmonary, hematological, along with early referral for ongoing clinical trials, and for physical, occupational, and cognitive therapy.[82]

NEUROLOGIC COMPLICATIONS OF VACCINES

There are several approved COVID-19 vaccines being used in different parts of the world. Different systems are used in different parts of the world to track and report adverse events owing to vaccines for, for example, in the United States, the Vaccine Adverse Events Reporting Systems (VAERS), in the United Kingdom, Coronavirus Yellow Card reporting Web site (https://coronavirus-yellowcard.mhra.gov.uk/).

Any patient or health care provider can report side effects of vaccines through the Centers for Disease Control and Prevention (CDC) through VAERS; patients, providers, and manufacturers can also report complications to the Food and Drug Administration Adverse Event Reporting System. The most common neurologic symptoms included dizziness, headache, pain, muscle spasms, myalgia, and paresthesias,

which are expected to occur as acute, transient effects of the vaccination. Rare cases of tremor, diplopia, tinnitus, dysphonia, seizures, and reactivation of herpes zoster have been reported. In order of reporting frequency in 2021, there are facial palsy, GBS, stroke, transverse myelitis, and acute disseminated encephalomyelitis in the VAERS database.[83] Transient episodes of headaches, myalgias, and fatigue were reported in about 5% of participants in clinical trials.[84]

From the United Kingdom, in a self-controlled case series study to investigate hospital admissions from neurologic complications in the 28 days after a first dose of ChAdOx1nCoV-19 (AstraZeneca) (n = 20,417,752) or BNT162b2 (Pfizer) (n = 12,134,782), and after an SARS-CoV-2–positive test (n = 2,005,280), there was an increased risk of GBS (incidence rate ratio [IRR], 2.90 at 15 to 21 days after vaccination) and Bell palsy (IRR, 1.29 at 15–21 days) with the AstraZeneca vaccine.[85]

There was an increased risk of hemorrhagic stroke (IRR, 1.38 at 15–21 days) with Pfizer vaccine. Another independent Scottish cohort provided further support for the association between the AstraZeneca vaccine and GBS (IRR, 2.32 at 1–28 days). There was a substantially higher risk of all neurologic outcomes in the 28 days after a positive SARS-CoV-2 test, including GBS (IRR, 5.25).[85]

Cerebral Sinus Venous Thrombosis and Vaccine-Induced Thrombocytopenia

The initial 12 US cases of CVST with thrombocytopenia after Ad26.COV2.S vaccination were reported as serious events.[86] In the United Kingdom, up to 12 January 2022, the Medicines and Healthcare Products Regulatory Agency (MHRA) had received Yellow Card reports of 435 cases of major thromboembolic events with concurrent thrombocytopenia following vaccination with COVID-19 Vaccine AstraZeneca. Forty-nine of the 435 reports have been reported after a second dose. Of the 435 reports, 217 occurred in women, and 214 occurred in men aged from 18 to 93 years. The overall case fatality rate was 18% with 76 deaths, 6 of which occurred after the second dose. CSVT was reported in 157 cases (average age, 46 years), and 278 had other major thromboembolic events (average age, 54 years) with concurrent thrombocytopenia. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered in the United Kingdom by 12 January was 24.9 million, and the estimated number of second doses was 24.2 million. There is some evidence that the reported incidence rate is higher in women compared with men, although this is not seen across all age groups, and the difference remains small. The overall incidence of thromboembolic events with concurrent low platelets after second doses was 2.0 cases per million doses. Considering the different numbers of patients vaccinated with COVID-19 Vaccine AstraZeneca in different age groups, the data indicate that there is a lower reported incidence rate in younger adult age groups following the second dose compared with the older groups (1.0 per million doses in those aged 18–49 years compared with 2.1 per million doses in those aged 50 years and over). The scientific review concluded that there is a possible link between CVST without low platelets and COVID-19 Vaccine AstraZeneca.

Current advice from the US and UK governmental agencies, the CDC and MHRA, respectively, has been that the benefit of the vaccination outweighs the risk, and this appears to be accurate from a neurologic standpoint. In order to establish causality, clinical case definitions must be established, for example, via the Brighton collaboration guidelines for conditions recognized to be associated with vaccination and proactive clinician-led definitions in emergent conditions (such as VITT). In assessing causality, tools such as the WHO GACVS or Bradford Hill criteria,[87] may be used; however, the authors additionally propose criteria that classify associated neurologic or neuropsychiatric events into probable, possible, and unlikely cases, considering the

temporal relationship, individual risk factors, and the likelihood of an alternative cause. In such cases as the urgent SARS-CoV-2 vaccination campaign in which ongoing randomized controlled clinical trials may be unfeasible and/or unethical, epidemiologic methods of causality assessment, such as triangulation, may be used.[87]

SUMMARY

Neurologic manifestation of acute COVID-19 and PASC is common in hospitalized patients with COVID-19. Having a high clinical suspicion to screen, diagnose, and treat life-threatening neurologic complications (such as acute ischemic stroke or ICH) is needed to help frontline providers leverage existing resources appropriately. Systems of health care delivery need to be optimized to prepare for the long-term needs of COVID-19 survivors with periodic screening for neuropsychiatric manifestations and providing multidisciplinary support to help rehabilitate these patients. Adapting existing systems to help uphold the paradigm that time is brain, address barriers for implementing evidence-based bundles for liberation from the ICU can help prevent and treat acute neurologic complications, and perhaps, may help reduce the burden of PASC in ICU survivors. Patients with mild COVID-19 also remain at risk of PASC. Educating these patients to self-monitor their symptoms, increasing awareness about local multidisciplinary COVID-19 centers, engaging primary care can help patients with PASC return to their baseline.

CLINICS CARE POINTS

- Although patients with any severity of COVID-19 can suffer from neurologic complications, the incidence of these complications is much higher in patients with severe COVID-19. Early diagnosis of neurologic complications in patients with COVID-19will rely on focused bedside neurologic examinations. Such focused clinical examinations can then guide a judicious utilization of imaging and electrophysiologic studies. Stroke occurs in about 1.5% of all patients with COVID-19, and these stroke patients were younger, tend to be men, and have an increased stroke severity and worse outcomes compared with stroke patients in the prepandemic period.
- Hemorrhagic stroke may be seen in patients with COVID-19 on therapeutic anticoagulation, on extracorporeal membrane oxygenation, or spontaneously. The pattern of ICH in these patients had different characteristics compared with intracerebral hemorrhage not associated with COVID-19, including frequent lobar location (67%) and multifocality (36%), a high rate of anticoagulation, and high mortality.
- Status epilepticus, new-onset seizures, and encephalitis occur rarely in patients with COVID-19.
- Delirium may be present in more than half of the patients with severe COVID-19. There are several challenges to the implementation of the evidence-based intensive care unit liberation in these patients, including mechanical ventilation, use of restraints and benzodiazepine, opioid, and vasopressor infusions, and antipsychotics; limitations on family visitation have been associated with a higher risk of delirium.
- Patients and caregivers should be educated to monitor for persistent symptoms and followed up in a multidisciplinary fashion to address the needs of patients with postacute sequelae of COVID-19. Systems of health care delivery need to be optimized to prepare for the long-term needs of COVID-19 survivors with periodic screening for neuropsychiatric manifestations and providing multidisciplinary support to help rehabilitate these patients.

DISCLOSURE

The authors have no relevant conflicts of interest.

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