Neurological Complications with COVID-19: A Contemporaneous Review

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Abstract

The COVID-19 pandemic is raging across the world, affecting 212 Countries and Territories around the world. It has infected more than 3.7 million people with a mortality rate of around 7%. Although the causative virus, the SARS-CoV-2 is primarily a respiratory pathogen, recent observational studies have documented a high rate of neurological complications associated with COVID-19. We searched PubMed databases from December 01, 2019 to June 9, 2020 for articles published on "COVID 19" OR "coronavirus" with targeted search words. We also search preprint servers for neurological complications of COVID-19. Neurological manifestations are seen in around 36%–45% of patients with COVID-19 and can involve almost every part of the central nervous system (CNS) from the hemispheres, cranial or peripheral nerves, spinal cord, and muscle. The mechanisms vary from direct viral invasion of the CNS, to a dysregulated host immune response to molecular mimicry to multiorgan dysfunction. In many patients, neurological manifestations preceded other systemic features or the diagnosis of COVID-19. Sick patients with COVID-19 will require ICU care and many patients may present first to the neurocritical care ICU and receive a diagnosis of COVID-19 later. Hence, it is important for all healthcare personnel to be aware of the myriad neurological manifestations of this infection, so as to initiate appropriate infection control practices and refine investigation and treatment protocols.

Keywords: COVID-19, COVID-19 and brainstem involvement, COVID-19 and central respiratory failure, COVID-19 and cranial neuropathy, COVID-19 and Cytokine storm, COVID-19 and encephalitis, COVID-19 and encephalopathy, COVID-19 and GBS, COVID-19 and myalgia, COVID-19 and myelitis, COVID-19 and neurological complications, COVID-19 and Pediatric inflammatory multisystem syndrome (PIMS), COVID-19 and PIMS, COVID-19 and respiratory failure, COVID-19 and sHLH, COVID-19 and shock, COVID-19 and stroke

Introduction

The Coronaviruses are large, enveloped, RNA viruses with three genera: alpha, beta, and gamma coronaviruses.[1] The current Coronavirus 2019 (COVID-19) pandemic is caused by the SARS-CoV-2 virus, a beta-coronavirus. The other notable family members of the beta-coronavirus—SARS-CoV-1 (2002-3) and MERS-CoV (2012 onwards)—have recently caused severe respiratory disease in humans. The disease, COVID-19 is derived from the acronym- CO (for corona) VI (virus) D (disease) and 19 (year of viral identification). SARS-CoV-2 is primarily a respiratory pathogen and, hence, neurological complications were missed during the early stages of the pandemic. However, subsequent observational studies have shown a high incidence of neurological complications in COVID-19 infections (~36%).[2] As of June 9, 2020, the World Health Organisation situation report on COVID-19 reports more than 7 million cases and over 400,000 deaths with a worldwide average mortality rate of ~ 5.89% (range: 0.27%–16.18%).

In the US, the CDC COVID-19 Response Team found that 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19 were among adults aged ≥65 years with the highest percentage of severe outcomes among persons aged ≥85 years.[1] In the largest Chinese cohort of 72,314 patients with confirmed 44, 415 cases, 81% had mild infection, 14% had severe illness, and 5% had critical illness.[3] Around the world, healthcare systems have been overwhelmed by the sheer volume of patients admitted to hospitals and ICUs. Nearly a quarter (26%) of patients require ICU admission due to respiratory failure or other issues.[4] In addition, some patients present directly to the Neurocritical care unit with primary neurological complications. Health-care workers are disproportionately affected, especially with repeated exposures and inadequate Personal protective equipment (PPE). Hence, all neurocritical care physicians should be aware of the numerous clinical manifestations of COVID-19. We have reviewed the contemporary literature on neurological complications associated with COVID-19.

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METHODS

We searched PubMed databases from December 01, 2019 to June 9, 2020 for relevant articles. The following search strategy and keywords were used (in the title/abstract) were used: "COVID 19" OR "coronavirus" OR "Novel coronavirus" OR "SARS-CoV-2," AND "brain" OR "CNS" OR "neurologic" OR "stroke" OR "peripheral nervous system" OR, " "encephalitis" OR "encephalopathy" OR "seizure" OR "ataxia" OR "myelopathy" OR neurological complications. We also searched the "gray literature," the preprint servers (medRxiv and bioRxiv) which contain nonpeer reviewed preprints on SARS-CoV-2. A total of 3141 articles (2522 medRxiv, 619 bioRxiv) were retrieved. Furthermore, we reviewed the references of retrieved articles for additional articles that may not have been indexed yet.

PATHOPHYSIOLOGY OF NEUROLOGICAL COMPLICATIONS OF COVID-19

The SARS-CoV-2 has viral spike (S) glycoproteins that bind the angiotensin-converting enzyme 2 (ACE2) receptor to enter the human host. The serine protease TMPRSS2 is additionally required for S protein priming. SARS-CoV-2 binds with a 10–20 fold higher affinity than its predecessor, the SARS-CoV virus.[5,6] ACE2 receptors are integral parts of the renin-angiotensin system and are a counterpoise to angiotensin-converting enzyme 1 (ACE1) and angiotensin II. Angiotensin II has proinflammatory and vasoconstrictive effects and promotes organ damage.

ACE2 receptors are expressed in human airway epithelia, lung parenchyma, vascular endothelia, kidney cells, and small intestine cells. After binding to the ACE2 receptors, the complex is endocytosed, leading to a depletion of ACE2 receptors. This skews the balance in favor of ACE1 receptors and angiotensin II. Vasoconstriction, proinflammatory, and procoagulation effects are enhanced. In the nervous system, ACE2 receptors are present in the glial cells (microglia, astrocytes, oligodendrocytes) neurons, and skeletal muscle.[7,8]

SARS-CoV2 entry into the central nervous system (CNS) might occur hematogenously, via axoplasmic spread, or direct viral invasion. The virus can cross the blood–brain barrier (BBB) by transcytosis across endothelial cells and pericytes via endocytic vesicles. It can also directly infect endothelial or epithelial cells and pass across the BBB or blood-CSF barrier in the choroid plexus. It can also utilize a "trojan horse mechanism" by lurking inside leucocytes (microglial precursor cell leukocytes) that are transported across the BBB. The neurotropism and neurovirulence of Coronaviruses are well known and the first SARS-CoV virus was also shown to enter the CNS retrogradely through the olfactory epithelium (trans-cribriform spread).[9,10]

A unique "sepsis-induced coagulopathy" (SIC) is seen in severe COVID-19. This hypercoagulopathy is characterized by elevated D-dimer and fibrinogen levels, elevated prothrombin time, increased D-dimer levels, and a high incidence of multiorgan failure without overt bleeding. In SIC, which is a prodromal phase of disseminated intravascular coagulation (DIC), hypofibrinogenemia and bleeding manifestations are conspicuously absent (unlike DIC).[11] By using the International Society of Thrombosis and Hemostasis scoring system score for SIC and a DIC score, these two disorders can be differentiated with alterations in therapeutic strategies.

Another insight into stroke is offered by the pulmonary findings reported in acute COVID-19. SARS-CoV2 attacks both the alveolar epithelial cells as well as the vascular endothelial cells. The diffuse endothelial attack induces an inflammatory cell accumulation, widespread microangiopathy, and microthrombosis. The host response initiates an accelerated reactive intussusceptive angiogenesis. By this process, a single blood vessel divides into two blood vessels by extending the capillary wall into the lumen of an existing vessel, and splitting it into two vessels, greatly increasing the number of new vessels in the face of overwhelming microthrombosis.[12]

With the sheer volume of patients presenting to hospitals, neurological involvement could be coincidental in many patients with COVID-19. Yet, there is precedence, with similar neurological manifestations in the earlier SARS and MERS epidemics.[13] SARS-CoV-2 is thought to affect the nervous system via multiple mechanisms. The neurological conditions associated with COVID-19 can be broadly classified as those due to direct virus-induced pathology, those secondary to the immune response directed against the virus (virus-induced neuro-immunopathology), or those due to the systemic response/homeostatic imbalance. Neurological complications are seen in around 36%–45% of patients and are more frequent in patients with severe illness.[14,15] In around 4% of patients with COVID-19, neurological complications are the primary cause of death.[16]

Retrograde olfactory axonal spread to the CNS is one pathway for direct viral entry. COVID 19 may also be able to hijack the retrograde axonal transport pathways from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways and "fast track" to the medullary cardiorespiratory center. This could account for the acute respiratory failure in some patients with COVID-19.[17] Hematogenous viral dissemination and CNS entry via the cerebral microvascular endothelial cells into the cerebral parenchyma has also been documented by transmission electron microscopy of postmortem specimens.[18] In some patients, the multiorgan failure, severe systemic illness, and sepsis produce an encephalopathy or delirium as well as skeletal muscle injury and neuropathies. A secondary cytokine storm develops as a hyperinflammatory host response to the viral infection by around day 10. Correspondingly, levels of CNS inflammatory mediators increase, exacerbating CNS injury. Even after recovery or even an asymptomatic SARS-COV-2 infection, a postinfectious multisystem or neurological syndrome can supervene as reports of a pediatric inflammatory multisystem

syndrome (PIMS) have started trickling in, a month or more after the supposed recovery.[19,20] Patients who already have underlying neurological comorbidities may experience a recrudescence, severe exacerbation or worser outcome with the COVID-19. Around 8% of patients in literature have had underlying neurological illnesses and this cohort experienced a higher rate of secondary neurological complications varying from 6%–36%.[21] A major issue with neurological data reported in the literature has been the use of data drawn retrospectively from electronic medical records, incomplete documentation, and case reporting as well as the absence of comprehensive CSF or magnetic resonance imaging (MRI) imaging due to logistical reasons. Thus, a large part of symptomatology was assessed from subjective accounts.

Until now, neuropathology data was lacking in this pandemic. However, an upcoming study has looked at postmortem brain pathological findings in patients who expired from COVID-19. It has revealed extensive subcortical micro and macrobleeds, grey and white matter edema suggestive of posterior reversible encephalopathy syndrome (PRES), as well as nonspecific deep white matter changes. An asymmetric olfactory bulb was found in 21% of patients. The multifocal parenchymal bleeds were probably triggered by DIC. The authors postulate a direct virus-induced or cytokine-induced endothelial disturbance (due to the widespread expression of ACE2 receptors in endothelial cells). They could not detect any brainstem involvement either by MRI or on autopsy in their cohort.[22]

Clinical manifestations of COVID-19

An unknown proportion of patients remain asymptomatic after infection. Symptomatic patients develop clinical illness after an incubation period of around about 5 days (median range: 3–7 days, with a maximum of 14 days). These patients develop fever, cough, fatigue, headache, myalgia, anosmia, and dyspnea. Around 81% of patients have a mild illness, 14% develop severe COVID-19 with ARDS, and 5% develop critical illness with ARDS and macrophage activation syndrome (MAS).[3] COVID-19 progresses along a continuum from mild to critical illness and clinical staging of COVID-19 is useful to plan a therapeutic strategy.[23] By around the middle of the second week (~day 10), critically ill pSARS and features of a systemic hyperinflammation [MAS, cytokine storm, or secondary hemophagocytic lymphohistiocytosis (sHLH)] [Figure 1].

sHLH is associated with higher blood levels of proinflammatory cytokines [interleukin (IL)-6, IFNγ, tumor necrosis factor-alpha, IL-8, IL-10, and IL-2R].[24] sHLH is a hyperinflammatory syndrome with a fulminant and fatal hypercytokinemia that induces multiorgan dysfunction and failure. Utilizing a standard algorithm such as the "HScore" and an online calculator will help clinicians to monitor and follow up sHLH.[25,26] The "HScore" calculates a composite score from "the body temperature, organomegaly, number of cytopenias, levels of triglycerides, ferritin, fibrinogen, serum aspartate aminotransferase, presence of underlying immunosuppression,
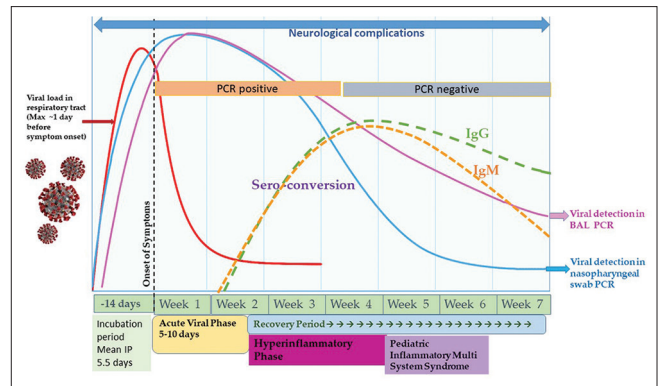
Figure 1: Graph showing the interaction of the viral and host response in patients with COVID-19

and hemophagocytosis on a bone marrow aspirate." HScores >169 are 93% sensitive and 86% specific for HLH. In contrast to a rapid and coordinate innate response to a viral infection, a dysregulated and excessive immunological storm causes extensive collateral damage to the human body.[27]

These patients develop pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure (acute kidney and cardiac injury), sepsis, or neurological complications. The viral load peaks in the first week of illness and gradually declines by the second week. The antibody response (both IgG and IgM antibodies) starts to increase by day 10 and patients often seroconvert within 3 weeks.[28] The viral load is directly proportional to the age of the patient—reflecting both a lower immunity in this group as well as a higher expression of ACE2 receptors in older patients.[29] Host cellular micro-RNAs (miRNAs) tiny molecules that directly target viral 3'UTR and coding regions of the viral genome and have a profound antiviral effect. Older patients as well as patients with comorbidities show lower amounts of human miRNAs targeting COVID-19.[30] Hence, the SARS-CoV-2 is able to penetrate and replicate more efficiently within the host. These factors might explain the increasing severity of disease in the elderly. Comorbidities such as diabetes, hypertension, obesity, cardiovascular disease, COPD, obesity, and chronic kidney disease also increase the likelihood of a severe illness.[31-33]

Neurological complications

General neurological complaints reported in COVID-19 include dizziness (16.8%) and headache (8%–34%).[18,22] An encephalopathy or an acute multifactorial delirium is found in more than 25% of ICU patients. Predisposing factors include prolonged hospital and ICU stays and compounded by the relative isolation, direct CNS viral invasion, effects of multiorgan failure, social and environmental isolation during ICU care as well as unusual positions for respiratory care including prone positioning.[34,35] A "cytokine storm" also contributes to the encephalopathy. Older patients and those with preexisting neurological conditions have residual neurocognitive deficits even after recovery from the acute illness Table 1.[2]

COVID-19 and pediatric neurological complications

Children are less affected than adults (<1.7% of total cases in the US), but experience the same clinical course as adults.[36] In the aftermath of the pandemic, young children with a previously asymptomatic infection with SARS-CoV-2 have been reported to develop a PIMS, 1 month after the curve in a region. This hyperinflammatory syndrome presents with features of a persistent fever and can resemble an atypical Kawasaki disease, toxic shock syndrome, or MAS. It is thought to be due to a "postinfectious immune response." Of a cohort of seven patients from the UK, one patient (a 14-year old) developed ACA and MCA infarctions and succumbed to the illness. These children can also present with alteration of sensorium, severe headache, meningismus (40%), extreme weakness and/or inability to walk or stand, severe generalized extremity pain, and strokes in the context of a warm vasoplegic shock.[19,20,37] Thus, delayed neurological complications in children can be anticipated if this "hyperinflammatory shock syndrome" resurges after this epoch.

Agitation and bilateral corticospinal tract signs have been seen in around 69% and 67% of acute COVID-19 infections, respectively. More than one-third of patients (36%) had a residual frontal dysexecutive syndrome. MRI brain showed leptomeningeal space enhancement in 62%, bilateral frontotemporal hypoperfusion in all patients who underwent perfusion imaging, and minor acute ischemic strokes in 23%. EEG showed a diffuse bifrontal slowing, whereas CSF was noninflammatory in all patients and negative for SARS-CoV-2.[38]

Cranial neuropathies

Although chemosensory abnormalities such as hypo or ageusia (5.6%) and hypo or anosmia (5.1%) were initially reported only in a few patients, more recent focused studies have shown a very high incidence ranging from 19%–88% of patients with 18% reporting chemosensory abnormalities as the initial manifestations of COVID-19.[6] The abrupt onset of these disorders in the absence of upper respiratory symptoms (coryza) or nasal obstruction is thought to be more specific for COVID-19. Detailed testing has also revealed a high incidence (~46%) of oral chemesthetic abnormalities. Oral chemesthesis refers to defects in sensations such as burning, cooling, or tingling in the mouth that are induced by herbs or spices. Impairment of chemesthesis was always found with gustatory or olfactory loss, whereas the reverse was not found (isolated gustatory or olfactory dysfunction with normal chemesthesis could occur). This dissociation between olfaction, gustation, and chemesthesis, likely depends upon the relative affliction of the three chemosensory pathways subserved by the olfactory nerve, chorda-tympani/glossopharyngeal nerves, and trigeminal sensory afferents, respectively, by the SARS-CoV-2 virus.[39] One study has shown that only the olfactory support cells, stem cells, and perivascular cells of the olfactory epithelium and bulb express two key genes involved in CoV-2 entry, ACE2 and TMPRSS2. The olfactory sensory neurons or olfactory bulb neurons themselves do not express these genes. These findings suggest that SARS-CoV-2 infects predominantly the nonneuronal support cell types, leading to a reversible olfactory dysfunction.[40] Direct viral involvement of the olfactory area (posterior gyrus rectus) has recently been noted in MRI of a patient with acute anosmia and dysgeusia.[3] Similarly, ACE2 receptors are expressed in tongue keratinocytes; however, it is unclear if taste receptor cells or cranial nerves carrying taste or chemesthetic information are infected by SARS-CoV-2.[41] Mono or poly cranial neuropathies have been described with acute COVID-19 infection with MRI showing oculomotor or optic nerve sheath enhancement or enlargement.[42]

Neurological respiratory failure and respiratory center dysfunction

Many patients with severe COVID-19 develop dyspnea, ARDS, and require mechanical ventilation. Surprisingly, in Wuhan, more than 62% of severe cases and 46% of those who required mechanical ventilation or died did not complain of dyspnea.[1,9,43] Sudden death due to central respiratory failure is likely due to damage to the medullary cardiorespiratory center and loss of the hypoxic respiratory drive. It is thought to be caused by brainstem damage by retrograde axonal viral transport.[44] Severe hypoxemia due to ARDS or sepsis has been associated with a hypoxic/ischemic encephalopathy in ~20% of deceased patients with COVID-19.[20] Peripheral respiratory failure due to Guillain–Barre syndrome (GBS) has also been reported with acute COVID-19.[20]

MENINGOENCEPHALITIS AND ENCEPHALOPATHY

Patients with meningoencephalitis may either show a normal CSF or a florid CSF inflammatory response (average of ~ 26 cells/cmm^3 with very high CSF protein levels).[45,46] Although most cases have not shown a SARS-CoV2 CSF-RT PCR positivity, two cases of meningoencephalitis have been associated with a positive SARS-CoV2 CSF reverse transcription-polymerase chain reaction (RT-PCR) confirming CNS penetration of this virus.[47,48] Furthermore, one case has demonstrated viral particles within neuronal cytoplasmic vesicles as well as microvascular endothelial cell blebs-lending credence to a hematogenous viral spread across the BBB.[49] Rhombencephalitis has been reported in one case of acute COVID-19 with spontaneously resolving brainstem dysfunction and MRI hyperintensities extending from the right inferior cerebellar peduncle, extending to involve a small portion of the upper cord.[50] This patient also resolved spontaneously without any specific treatment and unfortunately CSF RT PCR could not be obtained. Hence, it could not be determined if this was an infective or an immune-mediated rhombencephalitis.

Immune-mediated CNS complications with acute COVID-19 infection have also been reported. A case of immune-mediated steroid-responsive encephalopathy presenting as akinetic mutism has also been reported. The CSF showed inflammatory findings and MRI and CSF SARS-CoV-2RT PCR were normal.

EEG showed generalized slowing and an empirical trial of IV methylprednisolone 1 g/day for 5 days resulted in a dramatic recovery.[51]

Two cases of acute hemorrhagic necrotizing encephalopathy (ANE) has now been described in COVID-19. In a middle-aged woman, MRI showed symmetric, multifocal cerebral and cerebellar lesions, especially involving the thalamus with an intralesional hemorrhage and a contrast enhancing rim. These lesions were hypodense on computed tomography (CT). This parainfectious ANE in COVID-19 was thought to be due to a cytokine storm.[52,53] ANE is associated with a number of viral infections and is classically associated with massive cytokine dysregulation or a cytokine storm rather than a direct viral brain invasion or injury. Although this report lacked specific clinical details, most cases of ANE are associated with systemic features of hypercytokinemia such as systemic inflammatory response syndrome, multiple organ failure, and DIC.[54]

CSF studies were normal and SARS-CoV2 RTPCR could not be performed. Corticosteroids were deferred in the first case due to an ongoing COVID-19 infection and viral replication, whereas IV methylprednisolone (IVMP) 1 g/day was initiated in the second case. In spite of IVMP, the second patient expired due to multiple complications.

COVID-19 and stroke

Stroke in acute COVID-19 infection occurs more frequently in severe disease and older patients, increasing morbidity and mortality. Conversely, patients with prior history of stroke have a 2.5-fold increase in the odds of developing a severe COVID-19 infection.[11] Stroke is often accompanied by multiorgan injury, higher CRP, D-dimer, and ferritin levels as well as lower lymphocyte and platelet levels. An abnormal inflammatory and hypercoagulable state coupled with immunosuppression and vascular endothelial dysfunction due to direct viral invasion and dysregulated host response are potential reasons for strokes.[55] Viral cardiac injury also increases the risk of cardioembolic stroke.[56] Direct viral invasion is unlikely as CSF SARS-CoV2 RT-PCR is negative.[57]

A capillary endothelitis may be seen in the brain also as evidenced by multiple microhemorrhages or a leukoencephalopathy.[58] A viral infection associated antiphospholipid antibodies (aPL) syndrome has been found in three patients with multifocal cerebral infarcts and multiple limb ischemia and accounts for an additional stroke mechanism in COVID-19.[59]

Patients developed stroke by about 10 days from the onset of COVID-19 infection (range: 1–29 days). Lacunar strokes, large vessel occlusions (LVO), or embolic strokes can be seen. LVO patients tended to be younger and sicker with a median age of 46 and mean NIHSS of 24 as compared to non-LVO patients who were older (median age: 62 years).[60] LVO patients may also have very high D-dimer levels (≥1000 µg/L). Patients with LVO could also have multi-arterial territorial infarctions or concurrent peripheral venous thrombosis.[61] As many patients

Table 1: Summary of neurological findings associated with COVID-19
Headache
Dizziness
CNS manifestations
Altered sensorium
Delirium
Impaired central respiratory drive
Meningoencephalitis
Ataxia
Seizures
Acute hemorrhagic necrotizing encephalopathy (ANE)
Steroid-responsive severe encephalopathy
Cranial nerve involvement
Hypo or anosmia
Hypo or ageusia
Oral chemesthetic impairment
Optic neuritis
Trigeminal neuralgia
Cranial neuropathies
Neuromuscular manifestations
Myalgia
Extremity paralysis
Rhabdomyolysis
Guillain Barre syndrome
Miller fisher syndrome
Acute dysautonomia
Demyelination
ADEM
Transverse myelitis
Inflammatory demyelinating disorder (IDD)
Pediatric inflammatory multisystem syndrome (PIMS)
Headache
Altered sensorium
Aseptic meningitis
Myalgia
Myositis
Stroke
Extreme weakness and/or inability to walk or stand
Severe generalized extremity pain
Movement disorders
Myoclonic storms
Generalized myoclonus or asterixis
Cerebrovascular disease
Ischemic stroke
Intracerebral hemorrhage
Cerebral venous thrombosis
Hypoxic-ischemic encephalopathy
Poststroke recrudescence (PSR)
PRES syndrome
Leukoencephalopathy
Microhemorrhages
Postviral fatigue syndrome

have conventional stroke risk factors, misattribution of all strokes to COVID-19 should be avoided and standard workup of stroke should be performed to identify other etiologies of stroke. CT scan with CT angiography is preferred to MRI (for logistical reasons). Adding CT thorax to the CT/CTA stroke

protocol can identify parenchymal lung changes even before systemic symptoms are present. Standard inclusion and exclusion guidelines should be followed in acute stroke, taking into consideration the underlying severity of COVID-19 infection and standard treatment protocols should be followed. Aspirin, clopidogrel, IV rtPA, mechanical thrombectomy, and decompressive craniectomy have all been used as required. "Protected stroke code" protocols and infection control precautions will help limit healthcare worker exposure.[62] During this pandemic, most major stroke centers have noticed a dramatic decline in the number of acute stroke cases and neurointerventional procedures and the reasons for this decline are as yet unknown.[63] Extrapolated data from the use of RAPID software in US hospitals showed a nearly 39% decline in the numbers of patients who underwent evaluation for acute stroke during a 14-day epoch during the pandemic.[64] Delayed presentation to hospitals, social isolation, and diminished access to transportation facilities in less developed nations, phobias among patients regarding hospital admission during a pandemic, and adverse media projections of the evolving situation might have an influence on the incidence of acute stroke during this epoch.

Lobar intracerebral hemorrhage has been described in a case of acute COVID-19 infection; however, it is unclear if the infection was causative or it the ICH was coincidental.[65] The risks of hemorrhagic transformation of cerebral infarcts must also be balanced against the benefits of anticoagulation in this setting.[66] A PRES syndrome with multiple cerebral hemorrhages has also been reported.[15] Widespread capillary endothelitis or a cytokine storm can also cause a diffuse leukoencephalopathy with confluent posterior predominant white matter T2/FLAIR hyperintensities and scattered microhemorrhage.[57]

Neuromuscular complications

Muscle injury (defined as myalgia with an elevated serum creatine kinase level >200 U/L) has been reported in COVID-19. Between 6% and 35% of patients complain of myalgia or fatigue.[67,68] One study detected myalgia in 24.5% and extremity paralysis in around 18.9% of patients.[4] Rhabdomyolysis has been reported with acute COVID-19 infection. Two patients had painful lower limb weakness (CPK levels >11,000 U/L) and they improved with adequate hydration and alkalinization.[69,70] In one patient, painful weakness set in on day 9 of illness, whereas, in the second patient rhabdomyolysis was the presenting symptom.

More than 12 cases of GBS have now been reported in the setting of acute COVID-19.[9,10,12,13,33,71-73] These have been parainfectious, rather than postinfectious inflammatory demyelinating neuropathies as they occur during acute COVID-19 infection. CSF was normal in most patients and negative for SARS-CoV2 RT PCR. One patient succumbed due to respiratory failure and the others have partially responded to IVIG or plasma exchange. A parainfectious Miller-fisher variant of GBS has also been described.[24] Acute dysautonomia

was noted in ~2.5% of patients due to COVID-19, but most patients had a mild disease.[15]

Demyelination

One case of steroid-responsive immune-mediated inflammatory demyelinating disorder (IDD) associated with acute COVID-19 infection has been reported.[74] MRI showed extensive cerebral, brainstem, and spinal cord demyelination without diffusion restriction or contrast enhancement. CSF parameters were normal and CSF RT PCR was negative for SARS-CoV-2 and the patient recovered dramatically with high-dose dexamethasone therapy for 20 days.

Acute disseminated encephalomyelitis (ADEM) has also been reported.[75,76] MRI showed scattered hyperintense predominantly subcortical lesions in bilateral frontoparietal white matter, anterior temporal lobes, basal ganglia, external capsules, and thalami. An elderly lady demonstrated multifocal brain, spine, and bilateral optic nerve contrast-enhancing lesions consistent with ADEM. Although the CSF was positive for SARS-CoV2 by PCR and IVMP is usually contraindicated during active viral replication, this patient made a good recovery following IVMP and oral steroids combined with IVIG.

One patient developed acute flaccid paraplegia with urinary and bowel incontinence on day 7 of an acute COVID-19 infection. Unfortunately, CSF and MRI examinations were not performed. Hence, a provisional diagnosis of acute myelitis could be made.[77] Spinal cord neuronal membranes do express ACE2 receptors; hence, a SARS-CoV-2 associated acute myelitis seems plausible.

Seizures

New onset seizures are uncommon in the setting of COVID-19, but case reports of focal, generalized, or status epilepticus have been described.[60,78,79] Known epileptics may experience breakthrough seizures or focal status epilepticus as a manifestation of acute COVID-19 infection. Thus, patients with breakthrough seizures should also be tested for SARS-CoV-2 during the pandemic and should be isolated until test results are available.[80] Very rarely, new onset seizures may signal the onset of COVID-19.[81] Seizures could have a multifactorial etiology including direct viral invasion or encephalitis, cytokine storm, septic encephalopathy, hypoxia, or polypharmacy and it may be difficult to ascertain the exact etiology.

Movement disorders

Three patients have been reported to develop generalized myoclonus along with the onset of the hyperinflammatory phase of COVID-19. This parainfectious movement disorder was characterized by spontaneous as well as stimulus sensitive generalized myoclonus as well as asterixis (positive and negative myoclonus). A "myoclonic storm" developed in one patient requiring immunotherapy with IV methylprednisolone and plasma exchange in addition to antimyoclonic drugs. EEG ruled out an epileptic myoclonus and MRI was normal

in two patients in whom it was performed. A "reticular reflex" origin of myoclonus was presumed in these cases. As CSF study was normal and immunotherapy induced a remission, a parainfectious immune-mediated brainstem pathology seems likely.[82]

CONCLUSIONS

A tremendous amount of literature on COVID-19 has been published in the last 5 months. Many neurological complications are probably not specific to COVID-19 and maybe coincidental or due to multifactorial etiologies. It is important to search diligently for other competing causes.[83] Clinicians may consider monitoring the WBC, lymphocyte, and platelet counts as well as, IL-6, D-dimer, and serum ferritin as markers of severe illness.[84] Using the HScore, one can also predict the development of sHLH. In the current pandemic, COVID-19 must be considered in the differential diagnosis of all "acute neurological conditions" as there are numerous instances of medical and paramedical personnel being caught unawares and requiring isolation or treatment, after the patient was later diagnosed with COVID-19. The high rate of nosocomial infection in Chinese cohorts (41% of patients) emphasizes the necessity of adequate PPE and abundant caution in the treatment of this infection.[85] Melior tutius paenitet! (Better safe than sorry)

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Conflicts of interest
There are no conflicts of interest.

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