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Neurologic complications of COVID-19

Posted August 14, 2020

ABSTRACT

Human coronaviruses, including SARS-CoV-2, have the ability for neurotropism. Commonly reported neurologic complications of SARS-CoV-2 infections include encephalopathy, neuromuscular disorders, and acute cerebrovascular disorders. Other complications, such as postinfectious demyelination, encephalitis, and seizures, occur less often, but are probably under-reported given the lack of diagnostic information, such as cerebrospinal fluid sampling and electroencephalogram monitoring. Clinicians should have a high clinical suspicion for associated neurologic complications in a COVID-19–infected patient.

INTRODUCTION

The public health crisis caused by the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues to overwhelm nations across the world. Members of the coronavirus family share several features including the large spike glycoproteins that inspired the Latin corona (or crown) name. Molecular analyses of SARS-CoV-2 have discovered that the spike glycoproteins are essential for viral entry via the angiotensin-converting enzyme 2 (ACE2) receptor.[1,2] Expression of ACE2 receptors are seen in many cell types, including the neurons and glial cells of the brainstem, raising suspicion for possible neurotropism of SARS-CoV-2. There is substantial evidence for SARS-CoV-2–related neurologic complications through direct and indirect neurotropism.[1,2]

The statements and opinions expressed in COVID-19 Curbside Consults are based on experience and the available literature as of the date posted. While we try to regularly update this content, any offered recommendations cannot be substituted for the clinical judgment of clinicians caring for individual patients.

doi:10.3949/ccjm.87a.ccc058

Common neurologic complications in patients with coronavirus disease 2019 (COVID-19), resulting from SARS-CoV-2 infection, are presented below.

ACUTE ENCEPHALOPATHY

Encephalopathy is a global cerebral dysfunction associated with infection, fever, pharmacologic exposure, and metabolic derangement. This altered functional state is a relatively common presenting symptom of severe COVID-19 disease, ranging from 7.5% to 65%.[3,4]

Careful examination and appropriate neurological work-up is necessary for patients with acute encephalopathy that is not explained by their clinical condition. This was highlighted in a study of 13 patients with COVID-19 and unexplained encephalopathy, in whom brain magnetic resonance imaging (MRI) showed leptomeningeal enhancement in 8 patients and frontotemporal hypoperfusion in 11 patients.[5]

Encephalopathy

Presentation:	Altered mental status
Supportive testing:	MRI: Normal; EEG: Abnormal (slowing); CSF: Normal; CSF: SARS-CoV-2 negative
Treatment:	Supportive; treat underlying COVID-19

CSF = cerebrospinal fluid; EEG = electroencephalogram; MRI = magnetic resonance imaging

ACUTE CEREBROVASCULAR DISEASES

A stroke prevalence of 2.5% to 6% in hospitalized patients with COVID-19 has been reported.[4,6,7] In a

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study of 221 hospitalized patients with COVID-19 in Wuhan, China, those with acute stroke were more likely to be older, present with severe infection, and have cardiovascular risk factors, including a history of stroke.[6] In this report, intracranial hemorrhage was much less common than acute ischemic strokes.

Acute ischemic stroke

Occurrences of acute ischemic stroke were reported during the SARS-CoV and MERS-CoV epidemics. In patients with COVID-19, a case series from New York City reported large-vessel ischemic stroke in 5 patients younger than 50 years of age.[7] Each presented with acute stroke symptoms with lymphopenia and elevated inflammatory markers on admission labs, but 2 had no COVID-19 symptoms.

The presence of lupus anticoagulants and prolonged activated partial-thromboplastin time have also been frequently reported among hospitalized COVID-19 patients, with a prevalence of 45% to 91% for lupus anticoagulants.[8,9] While there is no clear association of lupus anticoagulants with thrombosis in these studies, a case series that reported the presence of antiphospholipid antibodies in 3 critically ill COVID-19 patients with bilateral cerebral infarcts in multiple vascular territories.[10] This suggests that an acquired antiphospholipid syndrome was the underlying cause, but unlike the reported series of large artery strokes in 5 young patients,[7] these patients with antiphospholipid antibodies were over 60 years of age.

These reports show that the presence of antiphospholipid antibodies varies in patients with COVID-19, but they are likely higher than expected in the general population. As the clinical significance is not yet known, these laboratory tests should not be routinely checked in COVID-19 patients without thrombosis.

Other causes of ischemic stroke, such as viral-induced central nervous system (CNS) vasculitis, have been questioned in COVID-19 patients with brain lesions in vascular patterns but without clear cerebrovascular etiology. A postmortem histological analysis of 3 patients with COVID-19 revealed lymphocytic endotheliitis within the endothelial cells of multiple organs, including lung, heart, kidney, small intestine, and liver.[11] Endotheliitis can cause microcirculatory vasoconstriction and endothelial dysfunction with consequential ischemia and apoptosis. Histopathologic analysis of the central nervous system is still needed to determine if COVID-19–related CNS vasculitis can occur due to lymphocytic endotheliitis.

Stroke

Presentation:	Acute presentation with focal motor, sensory or speech disturbance
Supportive testing:	MRI: Abnormal, lesion located in a vascular distribution
Treatment:	No society guidelines for COVID-19–specific stroke treatment 1. Acute ischemic stroke treatment: thrombolytic and endovascular therapy should be considered. No society guidelines on stroke prevention. Therapeutic anticoagulation should be considered on a case-by-case basis. 2. Acute hemorrhagic stroke (rare): standard treatment with blood pressure control. 3. Cerebral venous sinus thrombosis: standard treatment with full-dose therapeutic anticoagulation, evaluate for other thrombosis sites.

MRI = magnetic resonance

Venous thromboembolism

Studies show that patients with severe COVID-19 also may be at risk for thromboembolic events from COVID-19–associated coagulopathy (CAC).[12,13] In hospitalized patients with COVID-19, the increased coagulation activity is marked by increased D-dimer concentrations.[3,12,13] Furthermore, patients with COVID-19 and cerebrovascular disease had higher D-dimer levels than those without cerebrovascular disease (6.9 mg/L vs 0.5 m/L, $P < .001$).[13] At this time, however, it is unclear if elevated D-dimer levels in patients with COVID-19 are directly associated with either or both arterial and venous ischemic stroke. The reported incidence of cerebral venous sinus thrombosis has been much lower than that of acute ischemic stroke (0.5% vs 5%).[14]

CENTRAL NERVOUS SYSTEM INFECTIONS

Encephalitis, meningitis

Encephalitis is characterized by brain inflammation that can cause morbidity and mortality if left untreated.[15] In acute viral encephalitis, viral replication occurs in the brain tissue leading to significant central nervous system insults. In-vivo studies of mice have shown that the human coronavirus can infect

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neurons and subsequently cause persistent infection in human neural-cell lines.[16]

The first case of COVID-19–associated meningoencephalitis was reported in a 24-year-old male with no prior medical history who suffered convulsive seizures in the setting of presumed SARS-CoV-2 infection with paranasal sinusitis.[17] Lumbar puncture results depicted a neutrophilic pleocytosis and detected SARS-CoV-2 infection. A brain MRI depicted diffusion restriction of the inferior horn of the right lateral ventricle with fluid-attenuated inversion recovery (FLAIR) hyperintensities of the right mesial temporal lobe and hippocampus. He was diagnosed with meningoencephalitis and started on empiric antibiotic coverage but remained critically ill.

Interestingly, an autopsy study on 8 patients with confirmed SARS-CoV-2 infection reported that all the patients had SARS genome detected in the cytoplasm of hypothalamic and cortex neurons.18 The low reported rate of CNS infection in patients with COVID-19 is likely an underestimation as performing a lumbar puncture in patients with severe COVID-19 infection requires a substantial risk-benefit consideration.

Encephalitis, meningitis

Presentation:	Headache, nuchal rigidity, seizures, focal neurologic deficits; plus altered mental status for encephalitis
Supportive testing:	MRI: Abnormal, WM changes noted; EEG: Abnormal (slow, +/- focal epileptiform discharges); CSF: Pleocytosis, elevated protein; CSF: SARs-CoV-2, positive
Treatment:	Remains unclear; Role for corticosteroids?

CSF = cerebrospinal fluid; EEG = electroencephalogram; MRI = magnetic resonance; WM = white matter

Postinfectious demyelination

Acute disseminated encephalomyelitis (ADEM) is a monophasic, demyelinating disease of the central nervous system characterized by multifocal white matter demyelination in the setting of a rapidly, progressive encephalopathy. An antecedent infectious process prior to the CNS symptoms is common; however, the cause is typically only found in a small percentage of cases. Two cases of probable ADEM have been reported in the COVID-19 population with bilateral, extensive, nonenhancing T2-FLAIR signal changes noted in the cerebral white matter, involving the subcortical brain parenchyma and cervical spinal cord.[19,20] The cerebrospinal fluid (CSF) SARS-CoV-2 polymerase chain reaction test was negative in both cases. One patient was treated with intravenous immunoglobulin and the other with a 5-day course of high-dose corticosteroid with a 10-day taper; neurologic improvement was noted in both patients.

Acute necrotizing hemorrhagic encephalopathy

Acute disseminated encephalomyelitis

Presentation:	Headache, acute neurologic symptoms
Supportive testing:	MRI: Hyperintense FLAIR lesions with variable enhancement
Treatment:	2 case reports showing improvement with the following: • 5 days of IVIG (0.4 g/kg/day)[19] • 5 days of IV dexamethasone (20 mg/day) with a 10-day taper[20]

FLAIR = fluid-attenuated inversion recovery; IV = intravenous; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging

A recent case report presented details of a SARS-CoV-2–infected woman in her late-50s who presented with fever, cough, and altered mental status.[21] Her noncontrast brain CT imaging depicted symmetric hypoattenuation in the bilateral medial thalami with a normal CT angiogram and venogram. MRI imaging demonstrated hemorrhagic, enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. A CSF analysis revealed negative bacterial cultures and viral testing. The reason for not performing SARS-CoV-2 CSF test was not reported. Based on imaging and clinical context, she was given a diagnosis of probable acute necrotizing hemorrhagic encephalopathy and started on IV immunoglobulin therapy. No further information is available on her clinical course.

Prior reports of acute necrotizing hemorrhagic encephalopathy in the setting of virulent influenza infections have been well described in the pediatric population.[22] It is pathologically distinguished from ADEM by causing blood-brain barrier breakdown without direct viral invasion or demyelination.[23]

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SEIZURES

Although new-onset seizures in a COVID-19 patient are rare, a recent case series from Cleveland Clinic described 2 acute symptomatic seizures in nonepileptic patients with COVID-19.[24] Two retrospective studies have described electroencephalogram (EEG) patterns seen in patients with acute COVID-19.[25,26] One study reported frequent sporadic interictal epileptiform discharges in 22 patients with COVID-19 using mostly continuous 8-channel EEGs;[25] however, this finding was not supported by the other study, which used standard 21-channel EEGs.[26] This study also reported a variety of other EEG findings, including continuous slowing, generalized rhythmic activity, and generalized periodic discharges.[26]

These studies support the high incidence of encephalopathy in hospitalized patients with COVID-19 and the presence of acute symptomatic seizures from an underlying metabolic or toxic process or primary CNS insult as a complication of COVID-19.

NEUROMUSCULAR DISORDERS

Critical illness polyneuropathy and myopathy

Patients in the intensive care unit (ICU) are at risk for developing severe weakness secondary to critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM) with a reported incidence of up to 44%.[27] To date, there have been no reports of definitive CIP or CIM in patients with COVID-19; however, a study from Wuhan, China, reported 23 COVID-19 patients with acute muscle injury (defined as myalgia and elevated serum creatinine kinase level above 200 U/L).[4] Thus, clinicians should have a high suspicion for CIP or CIM in patients with COVID-19 presenting with sepsis or complications leading to prolonged mechanical ventilation and ICU length of stay.

Muscle injury

Presentation:	Myalgias
Supportive testing:	CPK: elevated; Muscle biopsy: necrosis
Treatment:	Supportive: Remains unclear; Role for corticosteroids? Physical therapy

CPK = creatinine phosphate kinase

Acute inflammatory demyelinating polyneuropathy

Acute inflammatory demyelinating polyneuropathy (AIDP), more commonly known as Guillain-Barré syndrome, is an autoimmune demyelinating disorder of the peripheral nervous system usually following an antecedent infection. It is characterized by parathesias, areflexia, and ascending weakness that may lead to respiratory failure. There are several cases of patients developing AIDP after onset of COVID-19 symptoms.[28-30] A case series from Italy reported 5 patients presenting with paraplegia, facial muscle weakness, and areflexia 5 to 10 days after COVID-19 symptom onset.[28] Of those, 3 patients had pathognomonic CSF findings of albuminocytologic dissociation consistent with AIDP. All 5 patients were treated with IV immunoglobulins, but only 2 patients had clinical improvement at the time of publication. Although it is important to recognize the classic symptoms of AIDP, a case series from Spain reported 2 rare AIDP variants, including Miller Fisher Syndrome and polyneuritis cranialis.[30]

Acute inflammatory demyelinating polyneuropathy[a]

Presentation:	Flaccid paralysis +/- respiratory compromise, cranial nerve deficits
Supportive testing:	CSF: Increased protein, normal WBC; NCS: Abnormal, axonal and demyelinating variants noted
Treatment:	Standard GBS treatment with 5 days of IVIG (0.4 g/kg/day) Case series noted only minimal improvement in 2 of 5 patients post-treatment[28]

CSF = cerebrospinal fluid; GBS = Guillain-Barre syndrome; IVIG = intravenous immunoglobulin; NCS = nerve conduction study; WBC = white blood cells

[a]Also known as Guillain-Barre syndrome.

CRANIAL NEUROPATHY

Olfactory neuropathy

Anosmia and dysgeusia are common symptoms associated with COVID-19, likely secondary to the direct olfactory bulb access.[31] A study of 417 patients with mild to moderate COVID-19 symptoms in 12 European hospitals reported sudden onset olfactory and gustatory dysfunction with a prevalence of 86% and 88%, respectively.[32] There was a 25% recovery from both symptoms within 2 weeks. Anosmia and

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dysgeusia are now recognized as presenting COVID-19 symptoms by the Centers for Disease Control and Prevention.

Anosmia/dysgeusia	
Presentation:	Olfactory or taste dysfunction
Supportive testing:	Abnormal smell and taste evaluation
Treatment:	Supportive: Improvement noted by 2 weeks post-symptom onset

CONCLUSIONS

Human coronaviruses, including SARS-CoV-2, have the ability for neurotropism. Commonly reported neurologic complications in patients infected with SARS-CoV-2 include encephalopathy, neuromuscular disorders, and acute cerebrovascular disorders. Other complications, such as postinfectious demyelination, encephalitis, and seizures are likely underreported given the inability to obtain further diagnostic information, such as CSF sampling and EEG monitoring. Clinicians should have a high clinical suspicion for associated neurologic complications in a COVID-19–infected patient.

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