

Neurological and Neuromuscular Manifestations in SARS-CoV-2: Review of Literature and Case Series

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization in March 2020. It binds to the ACE-2 receptor and transmembrane serine protease 2 and is highly virulent. There are many sequelae of this virus, including neurological consequences. We have performed a literature review of the neurological sequelae of COVID-19 with relation to neuroimaging and then present a case series.

Case Series: Seven cases were seen by neurology consultants at the Hospital for Special Surgery in New York City between February and May of 2020; 5 met criteria. The majority of these consultations were called for encephalopathy. Some had neuroimaging of brain MRI or head CT, which all showed microvascular disease. One case had prior imaging without microvascular disease.

Summary/Conclusion: It is known that vascular disease is a risk factor for severe COVID-19 infection. This case series demonstrates presence of microvascular disease in patients with encephalopathy. We know that microvascular disease can be a risk factor for toxic metabolic encephalopathy. It is unclear if the microvascular disease was present prior to infection, although at least one patient had prior imaging without microvascular disease. More research is needed to determine if COVID-19 infection can cause vascular disease.

Keywords

Neuroimaging, COVID-19, SARS-CoV-2, Neurological sequelae, Neuromuscular

Introduction

The 2019 coronavirus (COVID-19) is caused by SARS-CoV-2, a single stranded RNA betacoronavirus enveloped in a 60-140nm lipid bilayer. It binds to the ACE-2 receptor and transmembrane serine protease 2 and was declared a pandemic in March 2020 [1]. This paper is a literature review of its neurological sequelae with focus on neuroimaging, then a case series of patients seen by neurology consultants at the Hospital for Special Surgery in New York City from February until May, 2020.

Literature Review

COVID-19 arose in humans around December 2019 near Wuhan, China and likely originated in bats [2]. It is unclear exactly how patient zero contracted

the SARS-CoV-2 virus, but it is postulated that transmission occurred at a wildlife wet market. Genetic analysis of this virus shows that it is of the genera betacoronavirus, along with SARS and MERS [2]. Infection occurs when the virus binds to the ACE-2 receptor or transmembrane serine protease 2 in lung epithelium. Direct infection of T-cells and macrophages occurs, activating them [3]. A cascade up-regulates pro-inflammatory cytokines, such as IL-1, IL-6, IL-10 and TNF- α , and down-regulates anti-inflammatory cytokines, such as IFN- γ [3]. Typical symptoms include fever, cough, and dyspnea, but can develop into ARDS in about 1 week [2]. Through molecular mimicry between virus and myelin basic protein, demyelination occurs [3].

In a 214 patient case series from Wuhan, 36.4% of patients had neurologic signs [4]. They include headache (8%), confusion (9%), dizziness (16%), stroke (5.7%), ataxia, seizure (1 patient), anosmia (5.6%), ageusia (5.1%), visual disturbance, neuralgia, rhabdomyolysis and muscular weakness (17%) [4]. Animal models demonstrate respiratory failure due to brainstem involvement [3]. Neurologic signs can be due to primary neurologic invasion or secondary injury, most commonly due to inflammation [4]. There are two possible mechanisms for nervous system spread: hematogenous spread or retrograde transport up axons [5]. Cytokine storm facilitates blood brain barrier breakdown and therefore hematogenous spread [6].

Central Nervous System Manifestations/Sequelae

Strokes are reported in patients with COVID-19, usually as a secondary neurological manifestation [4]. Cardiotoxicity due to cytokine storm, hypercoagulability and direct myocardial invasion all serve as cardiac risk factors for stroke [4]. Direct invasion of vascular epithelium is possible. A case series from NEJM showed a cohort of five COVID-19 patients under 50 presented over a 2 week period with strokes. The average number of stroke patients under 50 in a given 2 week period at their institution is less than 1 [7]. SARS-CoV-2 RNA has been detected in CSF [2]. Autopsies of COVID-19 patients showed hyperemic, edematous brain tissue with degeneration of neurons [4]. Dysregulation of ACE-2 receptors has been implicated in animal models of autoimmune encephalomyelitis [3]. MRI brain shows thalamic and brainstem hyperintensities [5]. COVID-19 encephalitis may manifest with seizures, as it did in this case report of a 6-week old [8]. This patient's EEG showed interictal abnormalities of excessive temporal sharp waves, and intermittent delta vertex slowing. One patient in a study of 214 SARS-CoV-2 positive subjects had seizure [4].

Encephalitis is another serious manifestation of COVID-19. Detection of SARS-CoV-2 virus in CSF has occurred [2]. Post-mortem studies of COVID-19 patients' brains showed hyperemic, edematous brain tissue with degeneration of neurons [4]. SARS-CoV viral RNA was seen in brain tissue in 2003 [3]. Dysregulation of ACE-2 receptors has been implicated in animal models of autoimmune encephalomyelitis. MRI brain shows hyperintensities invariably in bilateral thalami [5]. A case report of a patient presenting with confusion and meningeal signs was diagnosed

with encephalitis [12]. Encephalitis may manifest with seizures.

A case report of a COVID-positive 6 week old with a 3-minute event of tonic stiffening and upgaze showed interictal abnormalities on EEG of excessive temporal sharp waves, intermittent delta vertex slowing [8]. A 24 year-old presented in convulsive status epilepticus, found to have COVID-19. CSF OP was 32 and the rest of the CSF analysis was normal [13]. Brain MRI showed diffusion restriction along the wall of the right temporal horn, and FLAIR revealed hyperintensity of the right mesial structures common in herpes encephalitis [13]. Several case reports of a patients in their 70's with no seizure history, who presented in convulsive and non-convulsive status epilepticus [14, 15].

In a report of 99 patients from Wuhan, 9% had confusion, which is thought to be a function of disease severity [2]. A case series of 58 patients in France with encephalopathy presented with confusion (65%), agitation (69%), corticospinal tract signs (67%), or dysexecutive syndrome (36%) [16]. Imaging of confused patients in our case series revealed non-specific findings, such as microvascular disease. Although microvascular disease, hypoxia, critical illness, multiorgan failure and old age can be risk factors for encephalopathy, it is unclear if microvascular disease always precedes encephalopathy in COVID-19.

A case report demonstrated hemorrhagic necrotizing encephalopathy as another serious neurologic complication of COVID-19 [6]. MRI shows rim enhancing hemorrhagic lesions in bilateral thalami, medial temporal lobes and subinsula. CT shows hypoattenuation in symmetric regions that include the thalami [6].

Peripheral Nervous System Manifestations/Sequelae

COVID-19 has been linked to cases of Guillain-Barré syndrome (GBS) and other inflammatory neuropathies, which sometimes precede are concurrent with the respiratory illness. Molecular mimicry between viral RNA and myelin basic protein is the proposed mechanism of demyelination of both the central and peripheral nervous systems [5]. A case series from Italy of 5 patients [9] and a single case report from Iran [10] with GBS have been reported. The syndrome began with typical symptoms with neurological symptoms beginning 5-10 days later. Evolution of GBS symptoms occurred over about 3 days. The majority of cases were typical GBS, but two were Miller Fischer variant [9, 11]. MRI lumbar spine with gadolinium showed cauda equine enhancement [9]. Unfortunately, treatment with IVIG or PLEX did not result in favorable outcomes in the majority of these cases. Three patients required another treatment and one recovered one month post treatment. Two remained tetraplegic.

Myopathy or myositis can occur as a late manifestation of COVID-19 and is associated with multi-organ damage [5]. Direct damage is implicated by the presence of ACE-2 receptors in skeletal muscle [4]. Significantly elevated CK (and other muscle markers), CRP, and D-dimer can be seen [4]. Critical illness myopathy is associated with multi-organ

damage [4]. A case report from Wuhan describes a patient with leg weakness and pain 9 days into his COVID-19 illness, which was treated with aggressive hydration, PLEX, then IVIG with rapid improvement [12].

A less serious sequela of COVID-19 is anosmia or ageusia. Post-viral anosmia occurs in 40% of a sample of 99 patients in Wuhan and can be permanent [1]. Coronaviruses can invade CN1 via the cribriform plate. Invasion of the olfactory bulb can lead to decreased volume on brain MRI [17]. The remainder of anosmia is caused by nasal turbinate obstruction of CN1 observed on imaging, after invasion via ACE-2 receptors on microvillar Bowman's gland cells [1, 3]. This differs from post-infectious anosmia in that there is no ageusia and it is temporary.

Case Series

Seven cases were seen by neurology consultants at the Hospital for Special Surgery in New York City between February and May of 2020. Two were excluded for lack of neuroimaging. The majority of these consultations were called for encephalopathy after extubation. They had typical symptom onset initially with subsequent confusion, described mainly as inattentiveness and poor short term memory. Five had neuroimaging of brain MRI or head CT, which all showed microvascular disease (Figures 1 and 2). There were two cases of watershed infarctions (Figure 3). One case had prior imaging without microvascular disease. Most had a past medical history that can lead to microvascular disease, but one had no prior history. Please refer to the table 1 for more details.



Figure 1: Repeat CT head for confusion in case #2 showing mild parenchymal volume loss, small vessel ischemic changes and atherosclerosis of the internal carotid.

Discussion

It is known that vascular disease is a risk factor for severe COVID-19 infection. This case series demonstrates presence

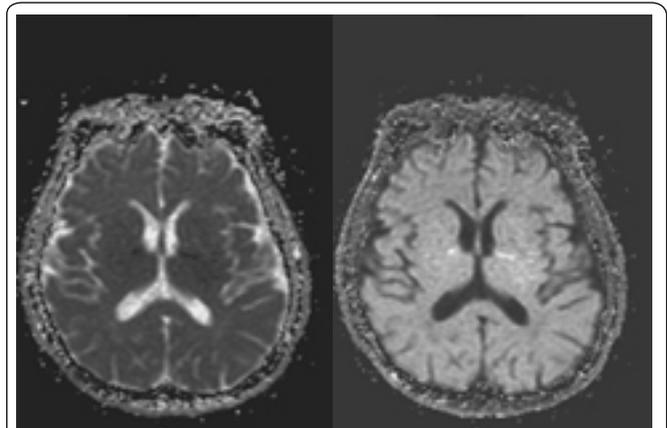


Figure 2: MRI from case #4, showing subsinsular white matter disease.

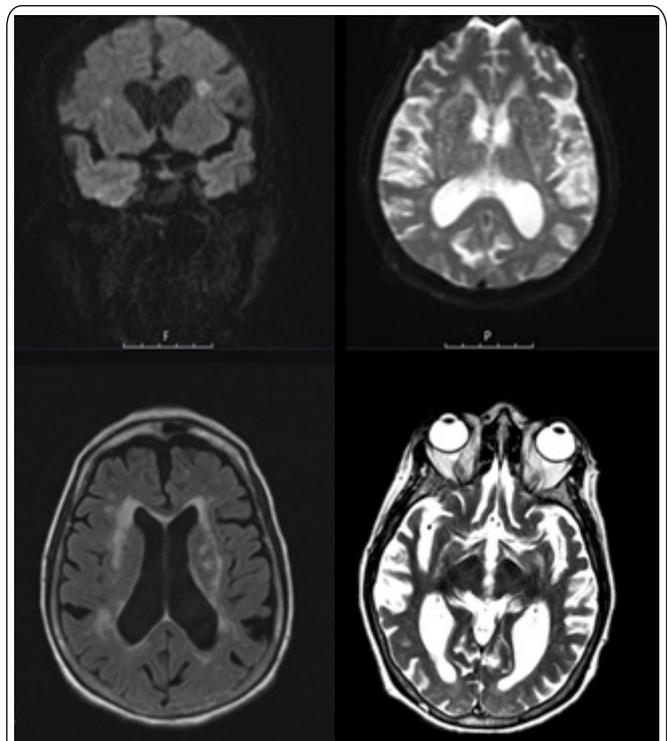


Figure 3: MRI brain from case #5, showing symmetric areas of acute infarction involving the supratentorial deep white matter of the centrum semiovale and corona radiata, likely internal border zone watershed infarcts superimposed on extensive chronic microangiopathic changes and generalized cerebral parenchymal volume loss.

of microvascular disease in patients with encephalopathy. We know that microvascular disease can be a risk factor for toxic metabolic encephalopathy. It is unclear if the microvascular disease was present prior to infection, although at least one patient had prior imaging without microvascular disease.

COVID-19 infection has been shown to invade vascular endothelium in-vitro and on autopsy [18]. Inflammatory cells, viral inclusion bodies, endotheliitis, and apoptotic bodies are observed on histopathology [18]. More research is needed to determine if direct viral invasion of the epithelium or interruption of clotting cascades by COVID-19 can cause cerebral microvascular disease, thereby making patients more

Table 1: Characteristics of patients seen with COVID-19

Age/ Sex	Case	Medical History	Presentation	Exam	Notes	Imaging	Diagnosis
59M	1	Hyperlipidemia	Dysgeusia, abnormal behavior, dizziness. Fever, anorexia, diarrhea	Inattentive, 4/5 bilateral proximal leg weakness	EEG- diffuse background slowing CSF- elevated protein (98)	MRI brain with gadolinium- mild microvascular disease	Encephalopathy
61M	2	Hypertension, diabetes mellitus type 2, coronary artery disease, hyperlipidemia and chronic kidney disease	Confusion. Fever, cough, hypoxia.	Few words, not following commands. 2 weeks later, was inattentive, poor short term memory. 4 weeks later, normal.		Normal initial CT head. CT head after confusion- chronic microvascular disease (Figure 1).	Encephalopathy
57M	3	None	Fever, cough, dyspnea, AKI, atrial fibrillation.	Generalized weakness. Mental status was intact.	Treated with hydroxychloroquine, antibiotics and tocilizumab. CK > 7,000	MRI brain- mild chronic subinsular white matter disease without stroke	Rhabdomyolysis
84M	4	Diabetes mellitus type 2 and prostate cancer metastatic to the lung	Cough, diarrhea, dyspnea, septic shock, AKI, hypernatremia and atrial flutter.	Aroused to voice, followed commands, and was diffusely weak	Treated with hydroxychloroquine.	MRI brain- subacute watershed infarcts, microangiopathic changes, and generalized cerebral parenchymal volume loss (Figure 2).	Watershed infarcts
81F	5	Hyperlipidemia	Found down. Fever, hypoxia.	Non-verbal, does not follow commands, does not withdraw to noxious stimuli in the legs.	Treated with high dose steroids and hydroxychloroquine	CT head-moderate parenchymal volume loss, severe microvascular changes, and old lacunes in the right thalamus and caudate head. MRI brain- acute bilateral watershed area infarcts superimposed on microangiopathic changes (Figure 3).	Watershed infarcts

susceptible to encephalopathy and stroke sequelae compared with other viruses.

Conclusion

In summary, there are several neurological sequelae of this coronavirus, and other coronaviruses, including stroke, encephalidites, seizure, encephalopathy, myopathy, Guillain Barre Syndrome, anosmia and ageusia. This case series demonstrated some watershed infarctions and encephalopathy with possible new white matter lesions. We know that COVID-19 has important vascular implications, whether via direct invasion or interruption of clotting cascades, that may contribute to the development of neurovascular disease. It is important for clinicians to be aware of these issues.

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