

## Post-COVID seizure: A new feature of “long-COVID”

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### ABSTRACT

Novel coronavirus SARS-CoV-2 has created unprecedented healthcare challenges. Neurologic deficits are often an important presenting symptom. To date, the only reported post-infectious COVID-19 manifestations of neurologic disease include cognitive deficits and dysfunction of the peripheral nervous system. Here we report that seizure can also be a post-COVID-19 or “long-COVID” complication. We present a 71-year-old man with hypertension, diabetes mellitus, and COVID-19 diagnosed by RT-PCR who initially presented with posterior circulation stroke-like symptoms, which completely resolved after emergent thrombolysis. Six days later, the patient returned with seizure activity, supported by radiographic and electroencephalographic studies. Notably, he was negative for SARS-CoV-2, and no other provoking factor was uncovered after a comprehensive work-up. To our knowledge, this is the first report of post-infectious seizures after a case of COVID-19, highlighting the potential importance of monitoring for neurologic symptoms in COVID-19 patients, even after convalescence.

### 1. Case description

A 71-year-old man with hypertension and diabetes mellitus presented to emergency services within three hours of witnessed sudden onset dysconjugate gaze, ptosis, vertical diplopia, nausea, and vomiting. Computed tomography (CT) angiography with perfusion imaging was remarkable for severe right vertebral artery stenosis and normal perfusion (Fig. A). Shortly after thrombolysis administration, all symptoms resolved. An RT-PCR test for SARS-CoV-2 was positive on admission, and mild interstitial pulmonary disease was evident on chest x-ray in the absence of respiratory symptoms. Additional work-up, including stroke labs, echocardiography, and cardiac telemetry, was otherwise unremarkable. He was discharged home without neurological deficits. Six days later, the patient was found confused and incontinent by family members and was emergently returned to the hospital. Repeat CT angiography with perfusion demonstrated new hyperemia in the bilateral frontal lobes suggestive of recent seizure (Fig. 1A). Electroencephalogram (EEG) captured several seizures manifesting as lateralized, right

central predominant, sharply-contoured rhythmic delta activity at 1–3 Hz that spread to the temporal, then frontal lobes bilaterally (Fig. B 1–4). On this admission, repeat testing for SARS-CoV-2 virus using the same PCR platform and testing protocol was negative. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was unrevealing (Fig. C). Studies to evaluate for toxic, metabolic, inflammatory, and infectious processes from serum and cerebrospinal fluid were remarkable only for the patients known mild chronic hyponatremia, which was stable from labs dating back three years (Table 1). The patient’s seizures were managed with intravenous loading of anti-epileptics. He ultimately required both phenytoin and levetiracetam, but he returned to his neurologic baseline after achieving therapeutic anti-epileptic drug levels and was discharged home.

### 2. Discussion

To our knowledge, this is the first report of a COVID-19 patient whose presenting symptoms were primarily neurological without

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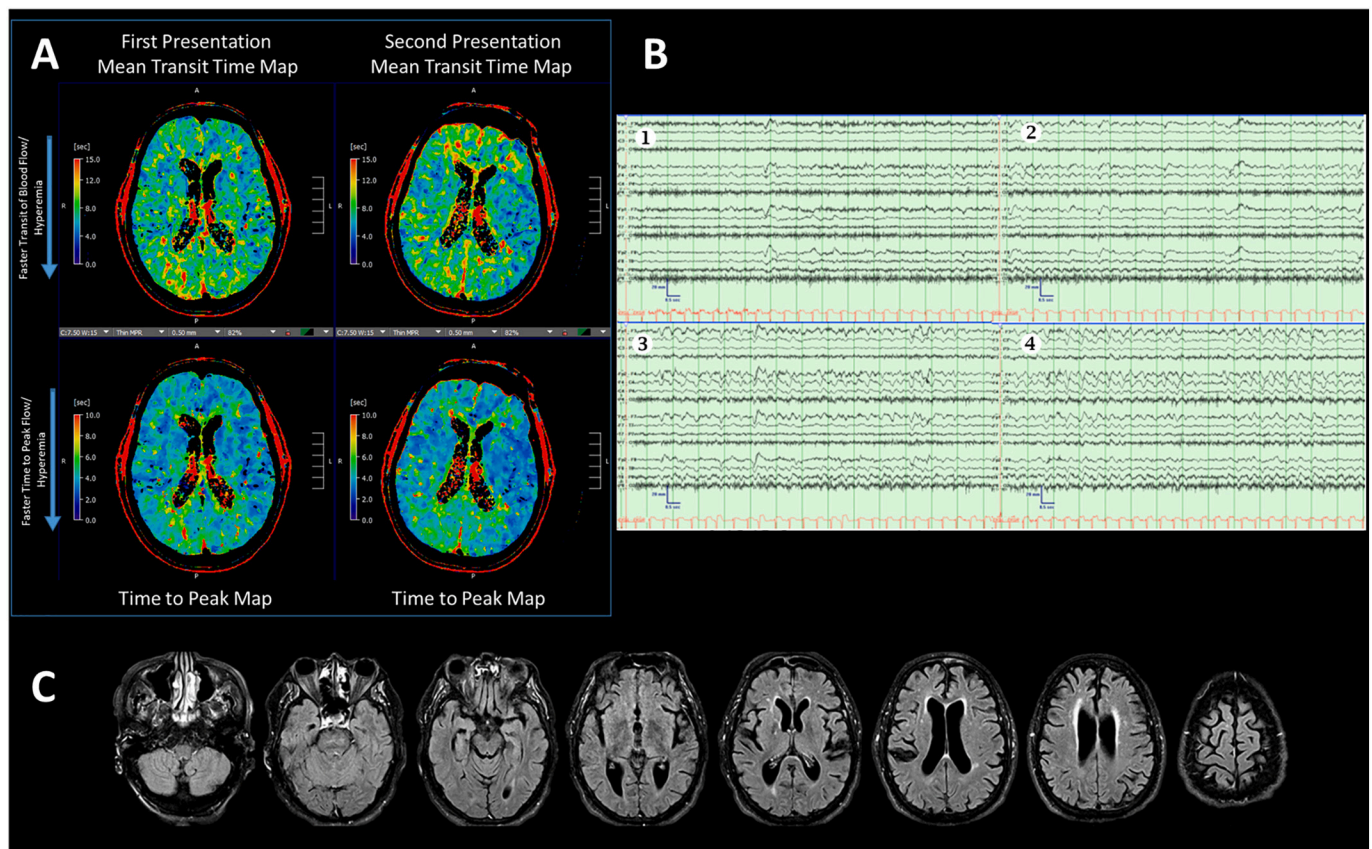
clinically significant respiratory disease and who later returned during the convalescent period of COVID-19 with seizures unexplained by other identifiable causes. It is believed that the patient's initial presentation was a thrombolysis-aborted posterior circulation stroke or transient ischemic attack given reasonable clinical suspicion and severe vertebral artery stenosis. Furthermore, the patient's deficits rapidly resolved after thrombolysis and were not accompanied by confusion or memory loss. Thus, these clinical symptoms from the first admission were more consistent with a cerebrovascular etiology. MRI of the brain was negative; however, it's worth noting that infarcts in the posterior circulation territory can be missed on MRI, particularly if they are small in size [1]. The patient's return presentation was consistent with seizure, both subjectively and objectively. CT perfusion images obtained during the second presentation on the same CT scanner using the same imaging protocol produced characteristic features of seizure such as increased cerebral blood flow to the frontal lobes later correlated with areas of epileptiform activity on EEG. While it is possible that the patient's two presentations reflect a singular progressive neurologic disorder, the imaging and clinical presentations suggest otherwise [2,3]. Both stroke and seizure have independently been associated with COVID-19 [3–9].

In the initial study from Wuhan, China 214 patients with COVID-19 revealed neurological complications in 36%, the most common being ischemic stroke [7]. Multiple factors contribute to neurological manifestations in COVID-19, such as COVID-19 coagulopathy, endothelial cell dysfunction, and thrombosis. Still, the precise causative mechanisms for COVID-19 associated neurologic manifestations are unclear [10,11]. The association between stroke and COVID-19, in particular, is thought

to be caused by SARS-CoV-2 triggered inflammation and thrombosis [12]. Others have previously reviewed the association between COVID-19 and stroke [12], so the case discussion here will focus on the association between COVID-19, seizure, and “long-COVID” neurologic symptoms.

The mechanisms behind COVID-19 associated seizure are also not fully understood [13,14]. A growing number of studies have reported a possible association between seizures and COVID-19 through multiple pathways, including direct neuroinvasion of the SARS-CoV-2 virus via olfactory neuron axonal transport and hematogenous spread via disruption of the blood brain barrier [15–17]. Other indirect factors may also contribute to the cause of seizures in COVID-19, including features such as hypoxia, multiorgan failure, and metabolic derangements typically seen in severe disease [14,18,19]. Of growing concern are reports that there may be an association between in-hospital mortality and new-onset seizures with COVID-19, such as in our patient [20,21].

Altogether, compelling questions are raised by this case of “long-COVID” seizures. It suggests that manifestations of COVID-19 may occur during convalescence when SARS-CoV-2 mRNA is no longer detectable by RT-PCR. “Long-COVID” neurological symptoms to date have included primarily cognitive deficits and neuromuscular disorders [22–24]. This case is the first report of post-COVID-19 seizures. We postulate that the post-infectious neurologic complications of prior COVID-19 infection are likely a consequence of lingering inflammation and upregulated cytokines within the central nervous system. This case also suggests that investigating for previous COVID-19 infections may be useful in the work-up of new onset neurologic disease such as seizures, especially



**Fig. 1.** Radiographic and electrographic data. There was no perfusion deficit on initial presentation as depicted by the mean transit and time to peak perfusion maps to the left (A), but on the second admission, the patient had hyperemia in bilateral frontal lobes suggestive of recent seizure activity depicted by the perfusion maps on the right which have more blue on the maps (blue areas indicate faster time intervals) in bilateral frontal lobes on both perfusion maps (A). EEG revealed lateralized, right central predominant, sharply-contoured rhythmic delta activity at 1–3 Hz that spread to the temporal, then frontal lobes bilaterally (B 1–4). MRI imaging confirmed chronic small vessel ischemic changes, but no stroke or abnormal patterns of enhancement as depicted by the post contrast fluid attenuated recovery sequence (C).

**Table 1**

Lab testing during both admissions was remarkable for positive SARS-CoV-2 PCR test during the first admission and mild chronic hyponatremia.

Initial hospital presentation	Second presentation
SARS-CoV-2 RT-PCR Test Results	
SARS-CoV-2 PCR test positive	SARS-CoV-2 PCR test negative
<b>Additional Abnormal Labs</b>	
<b>Serum Labs:</b>	<b>Serum Labs:</b>
C-reactive protein - 15.7	Sodium - 135
Vitamin D 25-41	
Sodium - 133	
<b>Normal or Negative Additional Labs</b>	
<b>Serum Labs:</b>	<b>Serum Labs:</b>
WBC - 8.8	WBC 9.9
Hemoglobin - 15 g/dL	Hemoglobin 11.1
Platelet count - 409	Platelet count 348
INR - 1.0	INR 1.1
PT - 12	aPTT -28
PTT - 28 Fibrinogen - 365	Rheumatoid factor - <10
D-dimer - 0.43	ANCA - negative
Total cholesterol - 104	ACE - <5
HDL - 33	dsDNA - negative
LDL calculated - 55	Scl 70 - negative
A1c - 6.3%	Ribonucleic protein IgG - negative
TSH - 0.269	Smith - negative
Vitamin B12-515	SSB - negative
Ethyl alcohol - 10	SSA - negative
Phosphatidylethanol -	Arbo panel - negative
Negative	ANA - negative
	Vitamin B1-353
	Ammonia - Normal
	Serial Troponins - Normal
	Cerebral Spinal Fluid labs:
	CSF WBC - 2
	CSF RBC - 0
	CSF glucose - 92
	CSF protein - 39
	HSV CSF - Negative
	entero - negative
	Blastomyces - negative
	Histoplasma - negative
	Blood cultures (from 4/26) - negative
	Cytometry - no evidence of monoclonal B-cell population
	Cryptococcal - negative
	MBP - negative
	VDRL - negative
	lyme - negative
	OCB - negative
	CSF ACE - 0.5
	EBV - negative
	VZV - negative
	CMV - negative
	Cytology - no evidence of malignancy
	Coccidioides - negative
	CSF albumin - 16
	HHV6 - negative
	CSF culture - negative
	AFB - negative
	fungal Culture - negative

during the pandemic in a patient with new onset neurologic disorder with no other identified etiology.

Diagnosing “long-COVID” complications of COVID-19 does present diagnostic challenges. Patients previously diagnosed with COVID-19, such as the patient we presented, can be tracked longitudinally. It is important to note that our patient did not have respiratory symptoms and thus was not diagnosed early during his infection. As a result, patients with mild disease may not be diagnosed with COVID-19 prior to presentation with a neurologic disorder in the “long-COVID” phase. It’s believed that the SARS-CoV-2 RT-PCR test was likely negative on the second presentation because the patient was at the later phase of the SARS-CoV-2 infection, and thus fully cleared the infection by the time of

the second presentation. The mRNA sequences used for RT-PCR testing are highly specific based on the unique genetic sequences of SARS-CoV-2 [25]. At our institution, COVID-19 antibody testing is not routinely performed since RT-PCR testing is more reliable. However, in the absence of other diagnostic tools, it may be useful to also test for antibodies that could suggest prior COVID-19 disease as part of the diagnostic work-up of new-onset neurologic disorders of unclear origin [25,26].

Given the paucity of longitudinal data on patients with neurologic manifestations of COVID-19, patients should be followed closely even if it appears they did not have severe manifestations of COVID-19 or are no longer testing SARS-CoV-2 positive. Future studies examining the relationship between mild COVID-19 symptomatology and “Long-COVID” neurologic symptoms may be informative.

#### Disclosure statement

None of the authors had any reported conflicts of interest.

#### Institution

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