Epilepsy & Behavior Reports 16 (2021) 100447

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

A presumed case of new-onset focal seizures as a delayed complication of COVID-19 infection

Sihyeong Park *, Haroon Majoka, Ajaz Sheikh, Imran Ali

Department of Neurology, University of Toledo, Toledo, OH, USA

ARTICLE INFO

Article history:
Received 17 December 2020
Revised 15 March 2021
Accepted 16 March 2021
Available online 31 March 2021

Keywords:
Temporal lobe epilepsy
COVID-19
SARS-CoV-2

ABSTRACT

Previously seizures have been reported as presenting neurological manifestation with COVID-19 infection. There is a growing literature on the delayed neurologic effects of COVID-19 infection. Here, we report a case with insidious onset of focal impaired awareness seizures associated with left temporal epileptiform interictal and ictal discharges consistent with focal epilepsy; occurring within a short time frame of the diagnosis of COVID-19 infection. This may be possibly a post COVID-19 inflammatory syndrome manifesting as new onset focal epilepsy with focal non-motor seizures with impaired awareness. As implicated by presentation with seizure as in our case, longterm follow-up studies are warranted to further investigate if the patients who acquire COVID-19 infection are at increased risk of developing epilepsy as a delayed manifestation.

1. Introduction

The current pandemic associated with the coronavirus (COVID-19) with predominantly respiratory manifestations (SARS-COV-2) has been increasingly associated with neurological complications. Encephalopathy, seizures, stroke, myalgia and many other manifestations have been noted over the last year in patients with COVID-19 [1]. Seizures [2] or status epilepticus [3] can occur in the acute phase of the illness with potentially resulting from hypoxia or acute neurologic injury [4]. There is a reported case of refractory status epilepticus which was presumed to be post-inflammatory in etiology after COVID-19 infection [5]. Acute disseminated encephalomyelitis (ADEM) [6], acute inflammatory demyelinating polyneuropathy (AIDP) [7], myasthenia gravis [8], encephalitis [9], multisystem inflammatory syndrome in adults (MIS-A) [10] as well as delayed post hypoxic necrotizing leukoencephalopathy [11] have been described as delayed manifestations of COVID infection. Still, the data regarding the long term effects of the virus remain unknown in comparison to the complications during acute illness

Seizures associated with COVID-19 have been noted in 1–2% of patients in large series [12]. We report a case with insidious onset of focal impaired awareness seizures associated with left temporal epileptiform interictal and ictal discharges consistent with focal epilepsy; occurring within a short time frame of the diagnosis of COVID-19 infection.

2. Case presentation

A 45-year-old right-handed woman with no prior history of seizures, presented with 3-week history of dry cough and burning chest pain. She had a positive nasopharyngeal swab test by PCR for SARS-CoV-2. There was no documented seizure-like activity during that hospitalization. Her symptoms improved and she eventually tested negative for COVID five weeks later. Subsequently, she developed paroxysmal episodes of paresthesia involving her right upper extremity and palpitations that were associated with staring and confusion. Her neurological exam was reported as normal. Due to concerns for seizures, sequential CT head and MRI of brain with and without contrast were obtained and were unremarkable. She also underwent routine EEG recording, which did not reveal any epileptiform discharges.

Approximately, 6 weeks after negative COVID test, she had a witnessed episode of focal to bilateral tonic-clonic seizure that involved jerking movements of her arms and legs, lasting for a few minutes, associated with loss of consciousness and urinary incontinence. This was preceded by headache, chest discomfort, along with a feeling of anxiety and dizziness. She was admitted to another hospital for workup, and notable lab results include white blood cell count $14.4 \times 10^3/mm^3$ [4.4×10^3–10.5×10^3], absolute neutrophil count $12{,}200/mm^3$ [1,800–7,700], normal basic metabolic panel, serum ammonia 50 μmol/L [11–35], and

* Corresponding author.
E-mail address: sihyeong.park@utoledo.edu (S. Park).

https://doi.org/10.1016/j.ebr.2021.100447
2589-9864/

negative urine drug screen. Lumbar puncture was performed and CSF obtained was clear. CSF analysis showed WBC 1/mm^3 [0–5], RBC 48/mm^3 [0–1], glucose 68 mg/dL [41–70], and total protein 34 mg/dL [15–45]. Meningitis panel was negative. CT of the brain was unremarkable. MRI of brain with and without contrast was obtained, and did not show radiological evidence of mesial temporal sclerosis or any other pathology (Fig. 1). She was also evaluated by cardiology due to palpitations, and her ejection fraction (EF) on echocardiogram was normal during the acute phase of COVID-19 infection. Later, her EF was found to be low at 45–50%, and she received colchicine for presumed inflammatory cardiomyopathy. Eventually, her EF had partially improved to 55–60%, with her baseline EF being 60–65%. She has had persistent palpitations with no other explanation found after extensive cardiac evaluation at two tertiary centers.

She was then transferred to our epilepsy monitoring unit for characterization of her seizure-like episodes. Her personal history was reviewed, and was found negative for developmental delay, febrile seizures, head trauma, CNS infections or tumors, stroke, or family history of seizures. Interictal EEG recordings showed epileptiform discharges in the form of sharp wave and spike-slow wave discharges arising from the left anterior temporal region (Fig. 2). Two clinical seizures were recorded on video EEG. She had a focal to bilateral tonic-clonic seizure during sleep. At the beginning of the seizure, significant sinus tachycardia was noted on the EKG, as the heart rate increased from 60 beats per minute (BPM) to 110 BPM. This was followed by extension of her left arm and followed by guttural vocalizations; right arm was extended and left flexed. Subsequently whole body tonic posturing, followed by clonic jerking was seen for approximately 40 seconds. Post-ictal confusion lasted for 15 minutes. No lateralized post-ictal weakness was observed. Electrographically, this seizure began as 5 to 6 hertz rhythmic sharp waves in the left anterior temporal region, after an 8–10 second period of background attenuation. These discharges increased in amplitude and decreased in frequency to about 4 Hz over next 20 seconds, rapidly spreading to the rest of left hemisphere, before the background was obscured by dense EMG artifact from generalized tonic seizure. This activity eventually spread to the right hemisphere, just prior to appearance of diffuse EMG artifact (Fig. 3a, 3b, 3c). Her second seizure was featured by her typical aura of palpitations, paresthesia of the right arm, followed by loss of awareness. This was associated with electrographic findings of rhythmic 5–6 Hz sharp wave discharges in the left anterior temporal region, that later evolved into rhythmic 1–2 Hz delta activity over the left temporal region. There was no spread to the right hemisphere. Sinus tachycardia was again noted on the EKG channel, as heart rate increased from 80 BPM to about 115 BPM. She was diagnosed with left temporal lobe epilepsy and was started on oxcarbazepine 600 mg twice a day which was later switched to lacosamide 200 mg twice a day, due to side effects. The patient reported improvement with lacosamide with approximately 50% reduction in the frequency of her seizure. She has also been intolerant to additional antiseizure medications including topiramate.

3. Discussion

This case highlights the possibility of new onset focal epilepsies as a delayed CNS manifestation in patients with recent COVID-19 infection. Our patient developed focal onset non-motor seizures, and later focal to bilateral tonic-clonic seizures weeks after developing symptomatic COVID-19 infection. Although in our case there was no evidence of any active neurologic illness associated with COVID-19 infection, the possibility of this being a delayed manifestation cannot be completely excluded, especially in the absence of any other identified risk factor. One of the limitations of this case report is absence of testing for inflammatory markers at the time of the clinical presentation with a generalized tonic clonic seizure although the CSF analysis was normal. Another limitation is that we did not have ability to perform CSF-PCR and antibody testing in the CSF. However, the data on CSF positivity rates for PCR and antibody testing is conflicting and not necessarily consistent with myriad of clinical presentations [13,14]. It is also very likely that the seizure onset was earlier than reported due to subtle nature of her focal seizures with impaired awareness and lack of motor manifestations until approximately 6–8 weeks later.

Several mechanisms have been proposed as an underlying mechanism for COVID-19-related seizures, including neurotropism, the entry of pro-inflammatory cytokines into the nervous system, and post-infectious immune-mediated disorders

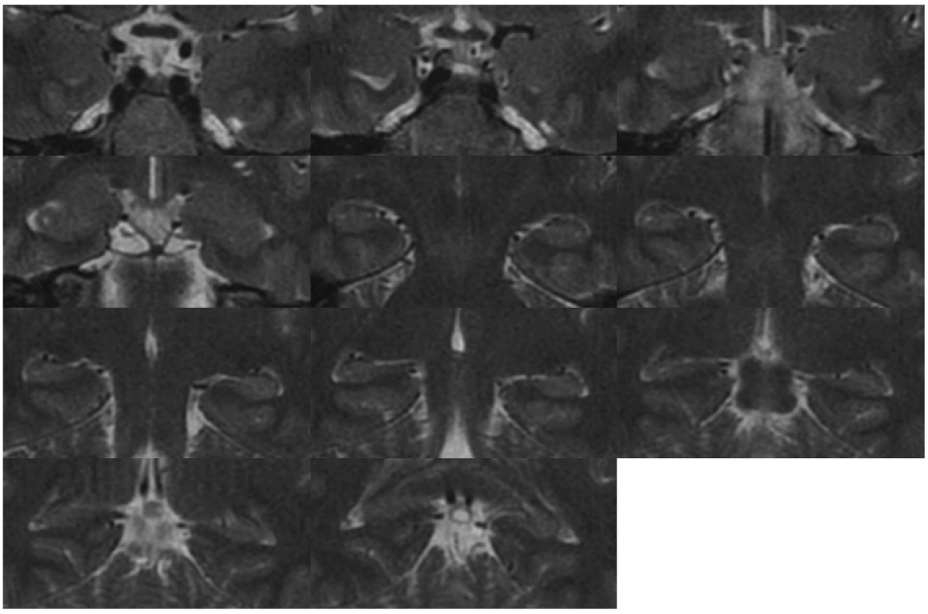

Fig. 1. Coronal T2 images of hippocampi (1.5 T, TR = 7094 ms, TE = 87.1 ms). No obvious sclerosis or atrophy was noted.

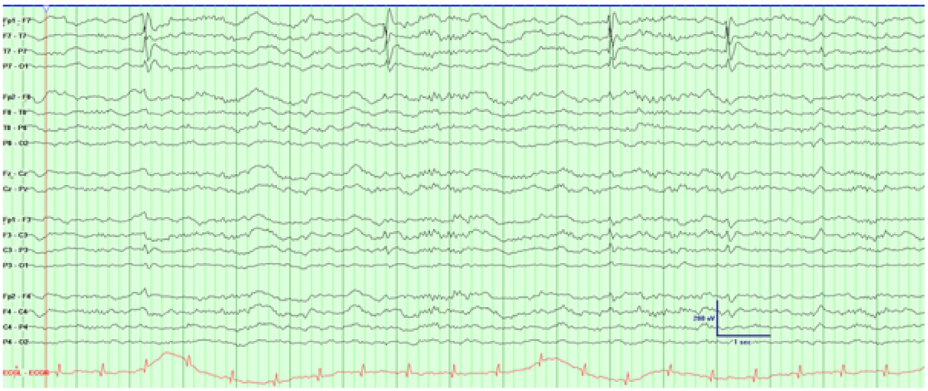

Fig. 2. Interictal EEG. An interictal EEG during sleep with standard 10–20 placement, bipolar montage, band-pass filter of 1–50 Hz, sensitivity 10 μV/mm, showing spike-slow wave discharges arising from the left temporal region.

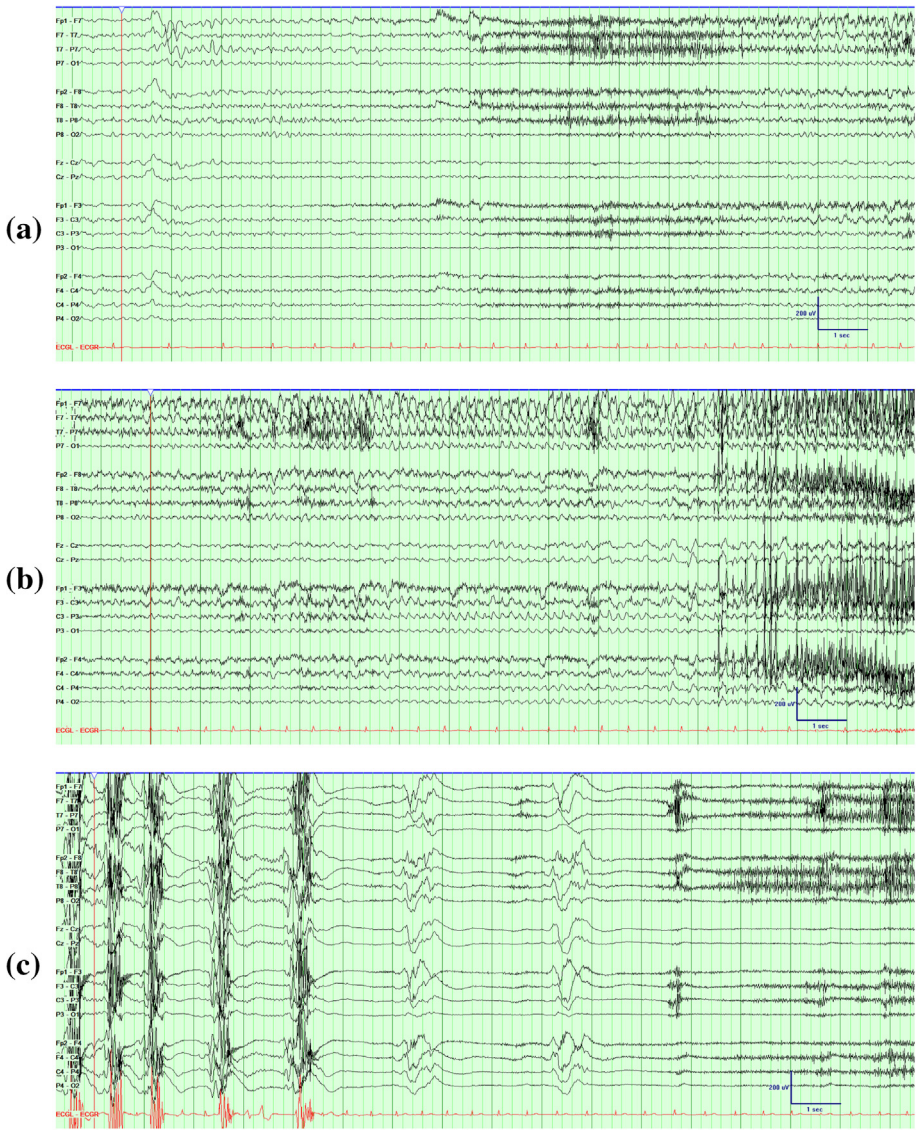

Fig. 3. a–c. Serial ictal EEGs. a. Onset of seizure. EEG during sleep, with the same setting as mentioned in Fig. 1, showing a sharp wave discharge in the left anterior temporal region followed by diffuse background attenuation. The EKG channel showed significant tachycardia at the beginning of the seizure. b. Consolidation of seizure. An EEG epoch showing rhythmic 5–6 Hz sharp waves in the left anterior temporal region. These sharp discharges increased in amplitude and spread to the other temporal channels. This was then superimposed by dense EMG artifact from tonic phase. c. Termination of seizure. Generalized bursts of frontally dominant poly sharp-slow discharges leading to diffuse suppression of the background.

[15,16]. There are accumulating data regarding various manifestations of post-COVID inflammatory responses, including ADEM [6] and GBS [7]. In addition, a recent case report described a patient who developed refractory status epilepticus which was presumed to be post-inflammatory in etiology after COVID-19 infection [5]. Also, cases of multisystem inflammatory syndrome in children (MIS-C), a postviral inflammatory syndrome, have been described in the absence of active infection [17]. Although information is limited regarding other acute inflammatory markers, our patient's neutrophilia persisted after she developed seizures, and there was no clear evidence of infection. Neutrophilia is also well described in cases of MIS-C [17]. Given persistent neutrophilia as well as initial diagnosis of inflammatory cardiomyopathy, an indolent inflammatory process cannot be excluded. In addition, mild memory impairment and intermittent tachycardia has persisted in our patient. A prospective study has demonstrated changes in the hippocampus and cingulate gyrus on MRI at a 3-month follow-up [18], suggesting delayed neurologic injury related to COVID-19 infection.

There is a growing literature on the delayed effects of COVID-19 which includes but is not limited to ADEM [6], AIDP [7], myasthenia gravis [8], and MIS-A [10]. As implicated by delayed presentation with seizure as in our case, long-term follow-up studies are warranted to further investigate if the patients who acquire COVID-19 infection are at increased risk of developing epilepsy as a delayed manifestation.

4. Conclusion

We believe that this is the first report of a patient with a possible post COVID-19 inflammatory syndrome manifesting as new onset focal epilepsy. In the absence of any clear other risk factor and with potential temporal relationship of the seizures, the association with COVID-19 infection is quite likely.

In this era of COVID pandemic, knowing if the patient had COVID-19 infection would be helpful when evaluating new-onset seizure patients even weeks after diagnosis as the mid to long term events of this infection are currently unknown. Additionally, based on our case, inflammatory markers should be assessed in patients with recent COVID-19 infections and neurological symptoms or disorders.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Salahuddin H, Afreen E, Sheikh IS, Lateef S, Dawod G, Daboul J, et al. Neurological predictors of clinical outcomes in hospitalized patients with COVID-19. Front Neurol 2020;11. 585944.
[2] Asadi-Pooya AA. Seizures associated with coronavirus infections. Seizure 2020;79:49–52.
[3] Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. Seizure 2020;78:109–12.
[4] Anand P, Al-Faraj A, Sader E, Dashkoff J, Abdennadher M, Murugesan R, et al. Seizure as the presenting symptom of COVID-19: a retrospective case series. Epilepsy Behav 2020;112. 107335.
[5] Carroll E, Neumann H, Aguero-Rosenfeld ME, Lighter J, Czeisler BM, Melmed K, et al. Post-COVID-19 inflammatory syndrome manifesting as refractory status epilepticus. Epilepsia 2020;61(10). e.135–e139.
[6] Zhang T, Rodricks MB, Hirsh E. COVID-19-Associated acute disseminated encephalomyelitis – a case report. medRxiv. 2020:2020.2004.2016.20068148.
[7] Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barre syndrome associated with SARS-CoV-2. N Engl J Med. 2020;382(26):2574–6.
[8] Huber M, Rogozinski S, Puppe W, Framme C, Höglinger G, Hufendiek K, et al. Postinfectious onset of myasthenia gravis in a COVID-19 patient. Front Neurol. 2020;11. 576153.
[9] Khoo A, McLoughlin B, Cheema S, Weil RS, Lambert C, Manji H, et al. Postinfectious brainstem encephalitis associated with SARS-CoV-2. J Neurol Neurosurg Psychiatry 2020;91(9):1013–4.
[10] Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69(40):1450–6.
[11] Radmanesh A, Derman A, Ishida K. COVID-19-associated delayed posthypoxic necrotizing leukoencephalopathy. J Neurol Sci 2020;415. 116945.
[12] Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. Epilepsia 2020;61(6). e49–e53.
[13] Benameur K, Agarwal A, Auld SC, Butters MP, Webster AS, Ozturk T, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and Coronavirus Disease, Atlanta, Georgia, USA, 2020. Emerg Infect Dis 2020;26(9):2016–21.
[14] Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020;382(23):2268–70.
[15] Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? the potential mechanisms. Mult Scler Relat Disord 2020;46:102535. https://doi.org/10.1016/j.msard.2020.102535.
[16] Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143(10):3104–3120.
[17] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324(3):259–69.
[18] Lu Y, Li X, Geng D, Mei N, Wu P-Y, Huang C-C, et al. Cerebral micro-structural changes in COVID-19 patients – an MRI-based 3-month follow-up study. EClinicalMedicine 2020;25. 100484.