COVID-19 Encephalitis in a Young Adult Male Treated with Combination Therapy: A Case Report

Victor J. Guerrero, MD[1] and Angelito H. Reyes, Jr., MD, FPNA[2]

ABSTRACT

Coronavirus disease 2019 (COVID-19) infection primarily affects the respiratory system leading to majority of intensive care unit admissions; nevertheless, neurologic manifestations and complications occur and are now being reported. We present a case of a 19-year-old male who tested positive for COVID-19 and manifested with headache, drowsiness and eventually went into coma. Cerebrospinal fluid analyses during the early course of illness showed predominance of lymphocytes but were negative for COVID-19 and other viral or bacterial organisms. Cranial MRI showed bright signals in the splenium of the corpus callosum. The patient was treated with a combination of antivirals, convalescent plasma therapy and high dose steroid therapy. Progressive improvement in clinical status was observed after the combination therapy including high-dose steroid, suggesting a possible inflammatory mechanism of COVID-19-related encephalitis. The diagnosis of COVID-19 encephalitis can be challenging but it must be considered in any COVID-19 positive patient presenting with symptoms of encephalitis, such as fever, seizures or altered sensorium. Anticipation of long-term care should also be taken into consideration since the long-term sequelae of CNS COVID-19 are largely unknown.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection primarily affects the respiratory system leading to majority of intensive care unit admissions due to acute respiratory distress syndrome (ARDS). [1] As the number of confirmed COVID-19 cases continue to rise, reports of patients presenting with neurologic manifestations including olfactory dysfunction, headache, acute cerebrovascular disease and impaired awareness are increasing. [2-4] Few case reports documented the occurrence of encephalitis in COVID-19 infected individuals without severe pulmonary manifestation.[5,6] In this paper, we present a case of COVID-19 patient presenting with headache and decreased sensorium.

CASE PRESENTATION

This is a case of a 19-year-old Filipino male who presented with headache, generalized body weakness and diarrhea without associated fever, cough, colds, dyspnea, dizziness, nausea and vomiting. The patient has no known co-morbidities, is a non-smoker and non-alcoholic beverage drinker with no family history of similar condition. Three days after the initial symptoms, the patient consulted a nearby health facility and was advised to stay for quarantine due to suspicion of COVID-19 infection. The patient had oropharyngeal swab for SARS-CoV-2 reverse transcriptase-polymerase-chain-reaction (RT-PCR) test done. Six days later, the patient had persistence of headache and generalized body weakness, now associated with loss of appetite, hence the patient was transferred to a tertiary hospital for admission. At the time of admission, initial vital signs were as follows: blood pressure of 130/70, heart rate of 68 beats per minute, respiratory rate of 20 cycles per minute, temperature of 36.7 C and oxygen saturation of 98% at room air. On

[1] Resident-in-training, Department of Internal Medicine, De La Salle University Medical Center, Philippines
[2] Consultant Neurologist, Section of Neurology, Department of Internal Medicine, De La Salle University Medical Center, Philippines

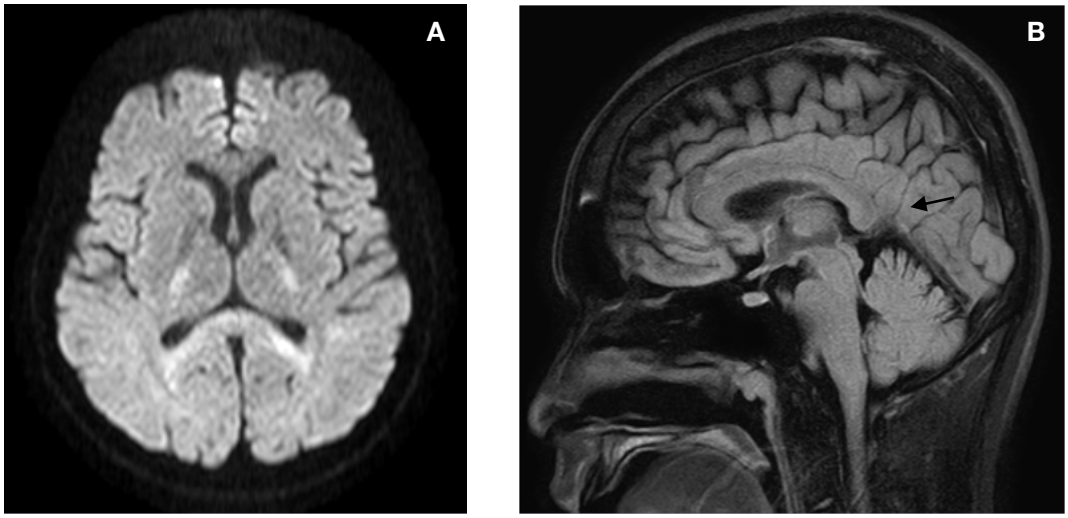
physical examination, the patient was awake, weak looking, with dry oral mucosa, clear breath sounds, normal heart rate and regular rhythm and follows commands. However, no focal neurologic deficit nor meningeal signs were noted. Complete blood count (CBC) showed normal white blood cell count with neutrophilic predominance, elevated C-reactive protein, normal ferritin and negative human immunodeficiency virus (HIV) 1 and 2 antibody test. Chest x-ray and cranial computed tomography (CT) scan were both unremarkable. Patient was started on empiric intravenous antibiotics and anti-viral medications (ceftriaxone 2g IV every 12 hours and acyclovir 10 mg/kg IV every 8 hours). He was also given valproic acid for seizure prophylaxis. On day 9 of illness, he underwent lumbar puncture which showed cerebrospinal fluid (CSF) that is clear, colorless, with leucocyte of 12/cu.mm (88% lymphocyte), no red blood cell, protein of 49.4 mg/dl, glucose of 50.58 mg/dl. CSF culture and India ink were both negative of organisms. On day 10, the patient was noted to have decreased sensorium and desaturation hence an endotracheal intubation was done. Septic work-up including blood and ET aspiration cultures were done. Procalcitonin was slightly elevated at 1.072 ng/ml. Antibiotics were shifted to piperacillin-tazobactam 4.5g IV every 8 hours and ciprofloxacin 400mg IV every 12 hours, pending culture results. The result of the RT-PCR test for SARS-CoV-2 turned out to be positive and the patient was started on remdesivir 200mg IV loading dose then 100mg IV once daily, enoxaparin 0.4 cc subcutaneously once daily and due to episodes of desaturation, intravenous dexamethasone 4mg IV once daily was also started. The patient was advised transfer to an institution capable of convalescent plasma therapy (CPT).

On the 15th day of illness, the patient received CPT. Repeat blood examinations showed leukocytosis with segmenter predominance hence piperacillin-tazobactam was shifted to meropenem and ciprofloxacin was continued. Repeat ET aspiration gram stain and culture were done. Cranial CT scan with contrast was unremarkable. On the 17th day of illness, neurology service started methylprednisolone pulse therapy (MPPT) 1g every 4 hours x 5 days. After the 1st dose of MPPT, the patient had an acute episode of desaturation with noted frothy ET secretions, diaphoresis and rales on both lung fields. Patient was then given furosemide with noted relief and MPPT was placed on hold. On the 19th day of illness, MPPT was resumed at 250mg IV q6, then after 1 infusion, the patient was noted to have episodes of premature ventricular contractions on cardiac monitor hence succeeding doses of MPPT were no longer given. Repeat lumbar puncture was done and CSF analysis including gram stain, culture, india ink, CALAS and viral panel for West Nile virus, Japanese encephalitis virus, enterovirus, herpes simplex virus 1 and 2 were all unremarkable. CSF COVID RT-PCR result was also negative. CSF and serum immunoglobulin G were also normal. Result of electroencephalogram showed presence of generalized, moderate slowing of the background activity. On the 23rd day of illness, the patient started to have more frequent eye openings but still with no regards. On the 26th day of illness, patient was more awake and tries to communicate by raising his eyebrows. In the interim, progressive improvement in sensorium and ability to communicate non-verbally were noted. On the 28th day of illness, patient was extubated, had prolonged wakefulness, able to verbally communicate. On the 32nd day of illness, cranial MRI was done and revealed subtle bright signals in FLAIR and DWI which appears dark on ADC seen along the splenium suggestive of mild restriction in diffusion sequences (Figure 1). On the 33rd day of illness, patient was discharged.

DISCUSSION

The respiratory system is the primary target of COVID-19 and respiratory symptoms

Figure 1. Plain Cranial Magnetic Resonance Imaging
A. Axial view on diffusion-weighted MR image and
B. Sagittal view on FLAIR MR image done on day 32 of illness showing subtle bright signals along the splenium of the corpus callosum (arrow).



remain to be the most common presentation and reason for in-hospital admission. Since the initial outbreak that happened in China in December 2019, there have been emerging reports of patients presenting with pulmonary symptoms that also have neurologic involvements.[3, 7, 8] To date, reports have shown that neurologic manifestations were associated with 12% of COVID-19 cases. [9] Neurologic symptoms commonly reported among hospitalized COVID-19 patients include myalgia (17.2%), headache (14.1%) and alteration in sensorium (13.9%). [10] It was also found out that patients presenting with severe pulmonary symptoms also had neurologic manifestations such as acute cerebrovascular events, myopathies and alterations in sensorium.[3, 10-12] In one study involving 4,711 hospitalized patients with COVID-19, results showed that the presence of altered sensorium on admission predicts a significantly higher in-hospital mortality regardless of disease severity. [11] In our patient, he initially presented with headache then progressive decreased sensorium and was in coma for several days. Occurrence of COVID-19 encephalitis in younger patients is thought to be rare. [13] In a study done in New York City involving 4,491 hospitalized patients -with COVID-19, none was diagnosed with encephalitis.[9] In a systematic review done in Spain involving 841 hospitalized patients with COVID-19, only one 57-year-old woman had encephalitis. [10]

The potential mechanism for neurotropism in COVID-19 remains to be unclear but it has been suggested that COVID-19 could reach the CNS via hematogenous route or via the upper nasal route thru the ACE2 receptors and cause varied neurologic manifestations. [10, 14-16] These receptors are also present in neurons and endothelial cells of the brain which may facilitate entry across the blood-brain barrier (BBB). [17, 18] The proposed mechanism for COVID-19 encephalitis involves direct viral injury and systemic and intrathecal inflammation. [19] This mechanism can be due to a leaky BBB caused by high levels of cytokines causing destruction and increased permeability of the BBB which in turn, may lead to inflammation and invasion. This inflammatory response causes varied neurologic manifestations including encephalitis. [5, 19, 20] Li et.al. found in a mouse model that the neurovirulence of COVID-19 rests on its ability to induce proinflammatory cytokine signaling from astrocytes and microglia. Other investigators have found that primary glial cell cultures secrete proinflammatory cytokines when exposed to

coronavirus. Cytokine storm is the most plausible mechanism of CNS dysfunction in COVID-19, especially in the setting of negative PCR on CSF.[19, 21]

In a case series conducted in Sweden involving six COVID-19 confirmed patients with neurologic symptoms, it was observed that these patients had elevated CSF biomarkers including neopterin (a marker used to determine microglia and astrocyte activation) and β2-microglobulin (a marker for monocytic activation), both of which indicate a significant CSF immune activation despite the lack of the typical elevation of IgG production in the CSF that is usually seen in viral meningitis and the lack of COVID-19 viral RNA in the CSF. This disparity between the profound CSF immune response and the lack of COVID-19 viral RNA in the CSF suggests that the neurologic abnormalities may not be due to direct viral invasion but rather a systemic hyperinflammatory response brought about by COVID-19 infection. [18]

The diagnosis of COVID-19 encephalitis can be challenging since the definitive diagnosis involves direct isolation of the virus from the CSF and the yield is very low. In three studies done to determine presence of COVID-19 in CSF using rt-PCR for SARS-CoV-2 of patients presenting with meningitis/encephalitis, all 7/7, 14/14 and 18/18 CSF samples were negative. [5, 9, 22] In a systematic review involving 304 COVID-19-confirmed patients with neurologic symptoms whose CSF was taken, only 17 (6%) tested positive for the virus. [23] This suggests that the virus can directly invade the nervous system and dissemination can only be transient.[17, 23-26] The EEG findings are also non-specific and often showed generalized slowing of background activity. [5] Cranial MRI findings in COVID-19 include signal abnormalities in the medial temporal lobe, white matter microhemorrhages and affectation of the splenium of the corpus callosum. [27] In two cases, MRI of the brain showed a lesion in the splenium of the corpus callosum which showed hyperintensity in T2 FLAIR and restriction in diffusion sequences. [28, 29] This is a typical pattern of cytotoxic lesion particularly in the splenium since this area is vulnerable to cytokinopathy due to the high concentration of cytokine, glutamate and other receptors in that region. [30, 31] The MRI findings affecting the splenium and the EEG findings were both seen in our patient. It was also reported that there were increased levels of interleukins in the CSF of patients presenting with neurologic manifestations. This can be an indication that an inflammatory reaction brought about by the cytokine storm may affect the CNS, resulting in encephalitis and the direct neuroinvasion by COVID-19 is unlikely the cause of most neurologic manifestations [23, 32, 33]

The cytokine storm, with its hyperinflammatory immune response seen in severe COVID-19, seems to necessitate the use of anti-inflammatory treatments, including high-dose glucocorticoids and anti-cytokine treatments. Our patient received high-dose Methylprednisolone, but was abruptly discontinued due to adverse effects.[5] Treatment options for COVID-19-related encephalitis is mainly supportive but it may also involve the use of antivirals, plasma therapy and immunomodulators, however, outcomes of these treatment are limited. [1, 5, 26] In patients who developed encephalitis, outcome is dismal and some may develop prolonged unconsciousness and cognitive impairment, although spontaneous recoveries are still seen. [1, 5, 34]

CONCLUSION

It is known that COVID-19 may cause various neurologic manifestations, including encephalitis. It should be kept in mind that atypical symptoms of COVID-19 may occur and some patients may not present with fever and pulmonary symptoms typical of COVID-19. The diagnosis of COVID-19

encephalitis must be considered in any COVID-positive patient precenting with symptoms of encephalitis, such as fever, seizures or altered sensorium. Isolation of COVID-19 in the CSF is challenging and may often be negative. The neuropathomechanism of COVID-19-related encephalitis appears to be due to the systemic hyperinflammatory state rather than due to direct neuroinvasion by the virus. There is currently limited data on the treatment of COVID-19-related encephalitis and use of combination therapies including antivirals and high-dose glucocorticoids can be of use if there are no other options and contraindications. Anticipation of long-term care should be taken into consideration since the long-term sequelae of CNS COVID-19 is largely unknown.

REFERENCES

1. Pilotto A, Masciocchi S, Volonghi I, et al. Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2–Related Encephalitis: The ENCOVID Multicenter Study, The Journal of Infectious Diseases, Volume 223, Issue 1, 1 January 2021, Pages 28–37, https://doi.org/10.1093/infdis/jiaa609
2. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277:2251–61.
3. Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China. JAMA Neurol 2020; 77:683–90. doi: 10.1001/jamaneurol.2020.1127. PMID: 32275288; PMCID: PMC7149362.
4. Ellul MA, Benjamin L, Singh B et al. Neurological associations of COVID-19: Rapid review | Vol 19, Issue 9, P767-783, July 02, 2020; DOI:https://doi.org/10.1016/S1474-4422(20)30221-0
5. Pilotto, A., Odolini, S., Masciocchi, S., Comelli, A., Volonghi, I., Gazzina, S., Nocivelli, S., Pezzini, A., Focà, E., Caruso, A., Leonardi, M., Pasolini, M.P., Gasparotti, R., Castelli, F., Ashton, N.J., Blennow, K., Zetterberg, H. and Padovani, A. (2020), Steroid–Responsive Encephalitis in Coronavirus Disease 2019. Ann Neurol, 88: 423-427. https://doi.org/10.1002/ana.25783
6. Bernard–Valnet R, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, Cerutti–Sola J, Rossetti A.O. and Du Pasquier R. (2020), Two patients with acute meningoencephalitis concomitant with SARS–CoV–2 infection. Eur J Neurol, 27: e43-e44. https://doi.org/10.1111/ene.14298
7. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 10 2020;7(10):875-882. doi:10.1016/S2215-0366(20)30287-X
8. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. Jul 2020;doi:10.1093/brain/awaa240
9. Frontera JA, Sabadia S, Lalchan R, et al. A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City. Neurology 2021;96;e575-e586 Published Online before print October 5, 2020 DOI 10.1212/WNL.0000000000010979
10. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized

patients with COVID-19: The ALBACOVID registry. Neurology 2020;95;e1060-e1070 Published Online before print June 1, 2020. DOI 10.1212/WNL.0000000000009937

11. Eskandar EN., Altschul DJ., de La Garza Ramos R, et al. Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19. Neurology. DOI: 10.1212/WNL. 0000000000011356
12. Wu Y, Xu X, Chen Z, et al.: Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020, 87:18-22. 10.1016/j.bbi. 2020.03.031
13. Al-olama, M., Rashid, A. & Garozzo, D. COVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report. *Acta Neurochir* 162, 1495–1499 (2020). https://doi.org/10.1007/s00701-020-04402-w
14. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998. doi:10.1021/acschemneuro.0c00122
15. Desforges M, Le Coupanec A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. Adv Exp Med Biol 2014;807:75–96.
16. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARSCoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020. https://doi.org/10.1002/jmv.25728.
17. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem 2008;107:1482–1494.
18. Eden A, Kanberg N, Gostner J, et al. CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms: A Case Series. Neurology 2021;96;e294-e300 Published Online before print October 1, 2020. DOI 10.1212/WNL.0000000000010977
19. Bodro M, Compta Y and Sánchez-Valle R. Presentations and mechanisms of CNS disorders related to COVID-19. Neurol Neuroimmunol Neuroinflamm 2021;8; DOI 10.1212/NXI.0000000000000923
20. Poyiadji, N.; Shahin, G.; Noujaim, D.; Stone, M.; Patel, S.; Griffith, B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology 2020.
21. Li Y, Fu L, Gonzales DM, Lavi E. Coronavirus neurovirulence correlates with the ability of the virus to induce proinflammatory cytokine signals from astrocytes and microglia. J Virol 2004;78:3398–3406.
22. Helms J, Kremer S, Merdji H. Neurologic Features in Severe SARS-CoV-2 Infection. June 4, 2020 N Engl J Med 2020; 382:2268-2270 DOI: 10.1056/NEJMc2008597.
23. Lewis, Ariane et al. Cerebrospinal fluid in COVID-19: A systematic review of the literature Journal of the Neurological Sciences 421 (2021) 117316
24. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55–58. 9.
25. Novi G, Rossi T, Pedemonte E, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. Neurol Neuroimmunol Neuroinflamm 2020;7:e797.
26. Haider A, Siddiqa A, Ali N, et al. (October 03, 2020) COVID-19 and the Brain: Acute Encephalitis as a Clinical Manifestation. Cureus 12(10): e10784. doi:10.7759/cureus.10784

27. Kremer S, Lersy F, de Sèze J, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 2020 297:2, E242-E251
28. Edjlali M, Le Gal A, Louvet M, et al. Teaching NeuroImages: Cytotoxic lesions of the corpus callosum in encephalopathic patients with COVID-19. Neurology 2020;95;1021-1022 Published Online before print September 16, 2020. DOI 10.1212/WNL.0000000000010880
29. Green C, Morrison H, Smith P, et al. Teaching Neuroimages: COVID-19-Associated Acute Disseminated Encephalomyelitis With Corpus Callosal Hemorrhage. Neurology 2021;96;e307-e308 Published Online before print October 14, 2020 DOI 10.1212/WNL.0000000000011001
30. Kobayashi N, Numaguchi Y, and Moritani T. Cytotoxic Lesions of the Corpus Callosum That Show Restricted Diffusion: Mechanisms, Causes, and Manifestations Jay Starkey, RadioGraphics 2017 37:2, 562-576
31. Rasmussen C., Niculescu I., Patel S., Krishnan A. COVID-19 and Involvement of the Corpus Callosum: Potential Effect of the Cytokine Storm? American Journal of Neuroradiology Jul 2020, DOI: 10.3174/ajnr.A6680
32. 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 Sep [*date cited*]. https://doi.org/10.3201/eid2609.202122
33. Bodro M, Compta Y, Llansó L, et al. Increased CSF levels of IL-1β, IL-6, and ACE in SARS-CoV-2-associated encephalitis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e821. Published 2020 Jul 1. doi:10.1212/NXI.0000000000000821
34. Abdo WF, Broerse CI, Grady BP, et al. Prolonged Unconsciousness Following Severe COVID-19. Neurology published online December 21, 2020. DOI 10.1212/WNL.0000000000011355