CASE REPORT

Two encephalopathic patients with COVID-19 and elevated intracranial pressure

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COVID-19, the disease caused by infection with SARS-Cov-2, has proven capable of affecting the central nervous system. Encephalopathy is a well-described phenomenon among COVID-19 patients, but there are few cases in the medical literature that include measurement of intracranial pressure in such patients. In this article, we report two adult patients hospitalized with COVID-19 who developed acute encephalopathy; both underwent lumbar puncture and were found to have significantly elevated intracranial pressure. One of the patients experienced complete, sustained recovery from encephalopathy after normalization of intracranial pressure. These cases, in conjunction with our review of similar cases outlined in other articles, led us to conclude that future research incorporating measurement of opening pressure of encephalopathic patients with COVID-19 may provide information about the pathophysiology of the neurologic manifestations of the disease, particularly in patients on hemodialysis.

Keywords: COVID-19, Communicable Diseases, Diagnostic Techniques and Procedures, Infectious Diseases, Neurologic Manifestations

Abbreviations: COVID-19, Coronavirus disease 2019; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ABG, arterial blood gas; CT, computerized tomography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; cm H2O, centimeters of water; WBC, white blood cell; RBC, red blood cell; HPF, high-powered field; EKG, electrocardiogram; NSTEMI, non-ST elevation myocardial infarction; TSH, thyroid stimulating hormone; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension.

INTRODUCTION

This article describes two patients with end-stage renal disease on hemodialysis who were hospitalized with COVID-19 and developed acute encephalopathy early in their hospitalization. Both patients underwent lumbar puncture and were found to have significantly elevated intracranial pressure. Although little is known about the pathophysiology of encephalopathy in COVID-19, current literature cites two other cases of elevated intracranial pressure in hospitalized patients with COVID-19.

CASE PRESENTATION

CASE 1: A 48-year-old man with end stage renal disease on hemodialysis and a history of mitral and aortic valve replacement

presented to the emergency room with complaints of worsening fatigue and shortness of breath associated with dry cough, fevers, and chills. Review of systems included hiccups but was otherwise unrevealing; he denied headache, visual change, nausea, diarrhea, or urinary abnormalities. He was febrile to 39C (102.2F), with an oxygen saturation of 84% on room air. Respirations were non-labored, and his affect was described as flat, but he was fully alert and oriented, and his neurologic exam was otherwise normal. PCR for SARS-Cov-2 was positive. He was started on supplemental oxygen and admitted to the hospital.

The patient was stared on dexamethasone 6 milligrams daily and transfused one unit of convalescent plasma. On hospital day 2, he continued to complain of hiccups, for which he was prescribed low dose baclofen. He underwent hemodialysis that day to stay on his usual dialysis schedule. That night he developed transient hypotension.

By the next morning (day 3), blood pressure had normalized and oxygenation had improved, but the patient was more somnolent and confused. His altered mental state was attributed to baclofen which was immediately discontinued; however, the patient became progressively more encephalopathic over the next 3 days despite undergoing hemodialysis twice more without any further hypotension. ABG showed pH 7.46, pCO2 32, and pO2 of 60 on room air. On hospital day 7, he had generalized flaccid weakness and was poorly responsive to all verbal and physical stimuli. Eye exam revealed a disconjugate gaze, with left eye esotropia. CT of the head revealed no acute process.

The patient underwent lumbar puncture, which revealed an opening pressure of 38 cm H2O. Four tubes of CSF were collected and CSF was drained to a closing pressure of 18 cm H2O. At the end of the procedure, the patient turned onto his back and asked where he was. He was able to answer questions appropriately and moved all 4 extremities purposefully. Disconjugate gaze had resolved completely. Within 2 hours he was fully alert, sitting up and eating lunch, interacting normally and calling relatives on his cell phone.

CSF indices were normal (glucose 64, protein 31.3, 1 WBC (lymphocyte) / HPF, 0 RBC) and CSF culture was negative. An MRI of the brain without contrast was done a few days later revealing (1) an acute punctate infarction in the right corona radiata, and (2) a small focus of extra-axial susceptibility along the high left frontoparietal vertex, consistent with a calcified vascular embolism, without any signal abnormality in the underlying brain parenchyma. MRV of the head was negative for venous sinus thrombosis. He had no neurologic deficits and no further episodes of confusion. He was discharged from the hospital in his normal state of health. At follow up several weeks later he had no complaints of headache and no neurologic or cognitive deficits.

CASE 2: A 62-year-old woman with end stage renal disease on hemodialysis presented to the emergency room with complaints of shortness of breath, weakness, and malaise for several days. She denied fever, chills, chest pain, syncope, headache, nausea, or vomiting. On exam, she appeared weak and lethargic, but was otherwise alert and fully oriented without appreciable neurologic deficit. She was found to be hypoxic on room air. PCR for SARS-Cov-2 was positive and chest radiograph revealed bilateral airspace opacities. She was started on supplemental oxygen and admitted to the hospital.

The patient was started on dexamethasone 6 milligrams daily and was transfused one unit of convalescent plasma. On hospital day 3, she was more somnolent, and over the next several days became almost completely

aphasic and poorly responsive to verbal and tactile stimuli. CT of the head revealed no acute abnormality, and metabolic encephalopathy workup (including B12, TSH, thiamine) was unrevealing. All potentially sedating medications were stopped but her level of alertness did not improve. Her encephalopathy was attributed presumptively to encephalitis from COVID-19.

After two weeks the patient's level of alertness had not improved. ABG at that time showed pH of 7.45, pCO2 of 37, and pO2 of 54 on 2L BNC. A lumbar puncture was performed, revealing a markedly elevated opening pressure of 37 cm H2O. Four tubes of CSF were collected and CSF was drained to a closing pressure of 12 cm H2O. Immediately after the procedure the patient was awake enough to answer several questions, although she remained somnolent and otherwise confused.

CSF indices were as follows: glucose 83, protein 36, 9 WBC (92% lymphocytes) / HPF, 1 RBC. CSF culture was negative and an extended autoimmune encephalitis panel was completely normal. MRI revealed age-advanced brain volume loss and multifocal remote perforator infarcts in the supratentorial and infratentorial brain. MRV revealed no evidence of sinovenous occlusion. Neurosurgery was consulted and a lumbar drain was placed for continued CSF drainage. The patient had a total of 90 mL CSF drained over the next 2 days, but her mental status regressed to her prior state of near-unresponsiveness. Given poor prognosis and low likelihood of neurologic recovery, the patient's family decided to pursue comfort measures and hospice; the patient died expectedly 2 weeks later.

DISCUSSION

Encephalopathy is a well-described manifestation of COVID-19[1], the disease in humans caused by infection with SARS-Cov-2. The mechanism of encephalopathy seems to vary from patient to patient, and sometimes the exact etiology goes undiscovered. In particular, COVID-19 is associated with increased incidence of stroke[2], and venous thromboembolism[3] including venous sinus thrombosis[4]. Other proposed mechanisms of SARS-Cov-2 associated encephalopathy include direct neuronal spread within the central nervous system (as described with other respiratory syncytial viruses) and disruption of the blood-brain barrier via intravascular phenomena[5].

A review of current medical literature revealed only 2 case reports of increased intracranial pressure in hospitalized patients with COVID-19[6,7], from Brazil and Sweden, respectively. In each case, the patient presented with only respiratory symptoms, and developed encephalopathy within a few days of admission. The Brazilian patient underwent LP with finding of high ICP (40 cm H2O) and her encephalopathy resolved. The Swedish patient underwent external ventricular drain placement after brain imaging revealed cerebral edema; within hours of drain placement ICP rose above 40 cm H2O for which the drain was opened to normalize ICP. The Swedish patient's encephalopathy ultimately resolved as well. In each case, CSF examination was otherwise unrevealing.

A separate cross-sectional study, also from Brazil, examined 56 patients with COVID-19 who underwent lumbar puncture for various neurologic complaints, highlighting 13 patients whose only complaints was headache[8]. Eleven of the 13 were found to have elevated intracranial pressure (defined as intracranial pressure greater than 20 cm H2O) with otherwise normal CSF. Six of the 13 patients experienced relief of headache after LP. None of the 13 patients were encephalopathic.

Causes of increased intracranial pressure (ICP) we considered in the cases described included hypoxia, idiopathic intracranial hypertension, and viral meningitis. Hypoxia (and similarly, hypercapnia) causes increased cerebral arterial blood flow, which in some cases can result in cerebral edema with increased ICP. This phenomenon is often described in research into acute mountain sickness[9] and literature on this topic often references the "tight-fit" hypothesis, whereby anatomical variations in the skull and brain that limit compliance might predict neurologic symptoms in hypoxic patients[10]. Both patients presented were hypoxic, and although encephalopathy is not a consistent finding among hypoxic patients, we considered the "tight-fit" hypothesis as a possible explanation for their increased intracranial pressure.

Both patients in our presentation had increased ICP with benign findings on CSF examination; however, we were hesitant to label their condition as pseudotumor cerebri (idiopathic intracranial hypertension, IIH)[11] even though it largely met criteria for that diagnosis. IIH can cause cognitive impairment but rarely causes severe encephalopathy[12]. Increased ICP has been described in some cases of viral meningitis[13]; the pathophysiology of this phenomenon seems to vary depending on the etiology of the meningitis[14], but impaired reabsorption of CSF through arachnoid granulations is among the mechanisms proposed. Neither patient presented had CSF findings suggestive of meningitis, but we questioned whether COVID-19 could affect the flow of CSF through arachnoid granulations.

CONCLUSION

Some hospitalized patients with COVID-19 develop encephalopathy for which the cause is unexplained. The cases presented led us to consider the possibility that increased ICP might contribute to encephalopathy in some COVID-19 patients, and that end-stage renal disease might increase the risk of said increased ICP. Future research investigating the incidence of high intracranial pressure in encephalopathic patients with COVID-19 might advance our understanding of how COVID-19 affects the central nervous system, particularly in patients with end-stage renal disease.

Notes

Potential conflicts of interest: The author reports no conflicts of interest in this work.

References

1. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221-2230. doi:10.1002/acn3.51210Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021;16(2):137-149. doi:10.1177/1747493020972922

2. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021;16(2):137-149. doi:10.1177/1747493020972922

3. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Semin Thromb Hemost. 2020;46(7):763-771. doi:10.1055/s-0040-1715456

4. Tu TM, Goh C, Tan YK, et al. Cerebral Venous Thrombosis in Patients with COVID-19 Infection: a Case Series and Systematic Review. J Stroke Cerebrovasc Dis. 2020;29(12):105379. doi:10.1016/j.jstrokecerebrovasdis.2020.105379

5. Alquisiras-Burgos, Iván et al. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-

2 Infection. Molecular neurobiology vol. 58,2 (2021): 520-535. doi:10.1007/s12035-020-02134-7

6. Noro F, Cardoso FM, Marchiori E. COVID-19 and benign intracranial hypertension: A case report. Rev Soc Bras Med Trop. 2020;53:e20200325. Published 2020 Jun 8. doi:10.1590/0037-8682-0325-2020

7. Svedung Wettervik, Teodor MD1; Kumlien, Eva MD, PhD2; Rostami, Elham MD, PhD1; Howells, Timothy PhD1; von Seth, Magnus MD, PhD3; Velickaite, Vilma MD4; Lewén, Anders MD, PhD1; Enblad, Per MD, PhD1 Intracranial Pressure Dynamics and Cerebral Vasomotor Reactivity in Coronavirus Disease 2019 Patient With Acute Encephalitis, Critical Care Explorations: August 2020 - Volume 2 - Issue 8 - p e0197 doi: 10.1097/CCE.0000000000000197

8. Silva MTT, Lima MA, Torezani G, et al. Isolated intracranial hypertension associated with COVID-19. Cephalalgia. 2020;40(13):1452-1458. doi:10.1177/0333102420965963

9. DiPasquale DM, Muza SR, Gunn AM, et al. Evidence for cerebral edema, cerebral perfusion, and intracranial pressure elevations in acute mountain sickness. Brain Behav. 2016;6(3):e00437. Published 2016 Feb 5. doi:10.1002/brb3.437

10. Wilson MH, Imray CH. The cerebral venous system and hypoxia. J Appl Physiol (1985). 2016;120(2):244-250. doi:10.1152/japplphysiol.00327.2015

11. Corbett JJ. "Pseudotumor Cerebri" by Any Other Name. Arch Ophthalmol. 2000;118(12):1685. doi:10.1001/archopht.118.12.1685

12. Yri HM, Fagerlund B, Forchhammer HB, Jensen RH. Cognitive function in idiopathic intracranial hypertension: a prospective case-control study. BMJ Open. 2014;4(4):e004376. Published 2014 Apr 8. doi:10.1136/bmjopen-2013-004376

13. Beal JC. Increased Intracranial Pressure in the Setting of Enterovirus and Other Viral Meningitides. Neurol Res Int. 2017;2017:2854043. doi:10.1155/2017/2854043

14. Kumar G, Kalita J, Misra UK. Raised intracranial pressure in acute viral encephalitis. Clin Neurol Neurosurg. 2009;111(5):399-406. doi:10.1016/j.clineuro.2009.03.004.