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LETTER TO THE EDITOR

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Comparison of clinical characteristics of a patient with Epstein–Barr virus-associated seizure and patients with COVID-19-associated seizure

To the Editor,

EBV and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent of COVID-19, are different viruses, but the infected host responses may share important features. Primary EBV infection, infectious mononucleosis, in young adults typically presents with some combination of oropharyngitis, lymphadenopathy, splenomegaly, fever, malaise and fatigue, but it can present with seizures.[1,2] COVID-19 typically presents with some combination of fever, cough, dyspnea, anosmia, ageusia, headache, nausea, vomiting and diarrhea, but in young adults it may present with seizures, which can be hypothesized to be due to microvascular thrombosis or reversible obstruction from hyperviscosity similar to what happens in the lungs.[3,4]

A 23-year-old male construction worker was brought to hospital on a Sunday morning after having a seizure at church lasting 1–2 min, manifested by staring blankly, jaw clenching and muscle twitching. On arrival, the patient's pulse was 136/minute, blood pressure 142/88 mmHg, respirations 24/min and temperature 35.8°C. He had slurring speech with left-sided facial droop. His white blood cell count was 8810/mm^3 (44% neutrophils, 4% bands, 45% lymphocytes, 3% atypical lymphocytes), platelets 176,000/mm^3, international normalized ratio (INR) 1.25, and comprehensive metabolic panel normal. Testing for SARS-CoV-2 was not done; this was several years before COVID-19. Urine toxicology screen was negative for illicit drugs. Chest X-ray showed no abnormalities. Noncontrast computed tomography showed no definite findings of infarction or hemorrhage. Shortly after arrival, the patient became unresponsive; he was intubated and placed on ceftriaxone, doxycycline, acyclovir, dexamethasone, acetaminophen, fosphenytoin, levetiracetam, propofol and fentanyl. Lumbar puncture yielded clear, colorless cerebrospinal fluid (CSF) with 4 white blood cells/mm^3, 2 red blood cells/mm^3, protein 51.2 mg/dl, and glucose 63 mg/dl. CSF was negative for HSV1, HSV2, VZV, human herpesvirus 6, cytomegalovirus, enterovirus, parechovirus, Hemophilus influenzae, meningococcus, and pneumococcus.

The patient had had progressive malaise and fatigue for at least a week, uncharacteristically taking afternoon naps. Starting 4 days prior, he had 4 consecutive days of headache. One day prior, he had nausea and dizziness. The patient used no alcohol or tobacco. Late on hospital day 1, his temperature reached a peak of 38.8°C. Brain MRI with gadolinium showed no abnormalities. Electroencephalogram showed diffuse slowing with a few spikes of sharp wave activity. On hospital Day 2, arterial blood showed pH 7.321, PCO_2 43.2 mmHg, and PO_2 60 mmHg on FiO_2 0.30 and positive end-expiratory pressure of 8 cm H_2O. Chest X-ray showed no infiltrates. Echocardiogram showed normal left and right ventricular function, but dilated inferior vena cava. The patient gradually improved. He was weaned off mechanical ventilation and was discharged from hospital on Day 5, but blood drawn that day was positive for infectious mononucleosis antibodies (Monospot, Mono Screen). Confirmatory testing was negative for immunoglobulin G (IgG) against Epstein–Barr virus nuclear antigen and IgG against Epstein–Barr virus viral capsid antigen (VCA), but positive for immunoglobulin M against EBV VCA.

Neurological manifestations of primary EBV infection occur in 1%–5% of patients and include encephalitis.[2] 45%–48% of children with EBV encephalitis have seizures.[5,6] EBV encephalitis often produces minimal evidence of inflammation in the CSF. In a report of 48 adult patients with EBV encephalitis, 19% had seizures, 71% had less than 10 white blood cells/mm^3 of CSF and 81% had normal CSF protein.[7] This is similar to encephalitis with COVID-19. In six patients with COVID-19 who underwent lumbar puncture, all had less than 3 white blood cells/mm^3 of CSF and normal CSF protein.[8] Seizures occur in 0.08% of patients with COVID-19.[9] Stroke in patients with COVID-19 is often attributed to the hypercoagulable state induced by SARS-CoV-2 infection causing microvascular or macrovascular, arterial or venous, thrombosis or thromboembolism.[10] This may also explain the condition publicized as “happy hypoxia,” better termed “silent hypoxemia,” characterized by hypoxemia without dyspnea for which COVID-19 is notorious.[11] Thrombi in pulmonary microvasculature are hypothesized to cause ventilation-perfusion mismatch and hypoxemia without increased work of breathing that would trigger dyspnea.[11] Hyperviscosity without thrombosis due to high levels of acute phase reactant proteins could produce this effect without chest radiographic infiltrates and be reversible.[12] If reversible microvascular obstruction occurs in the lungs, it could presumably also occur in brain, leading to temporary ischemia and seizures. This could explain multiple features of the case we report: mildly elevated INR, arterial hypoxemia with normal chest radiograph, and dilated inferior vena cava suggestive of elevated right atrial pressure, possibly due to elevated pulmonary arterial

pressure from thrombosis or hyperviscosity-induced obstruction. These features are eerily similar to COVID-19 suggesting the possibility that EBV infection could cause seizures with pathophysiology similar to COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Larry Nichols conceived the idea, researched the medical literature about it, and composed most of the manuscript. Merritt Thompson collected the case data and composed a draft of the case presentation. Gretchen L. Bentz critiqued the case presentation and manuscript.

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