Journal of Investigative Medicine High Impact Case Reports
Volume 10: 1–5

DOI: 10.1177/23247096221111778
journals.sagepub.com/home/hic
SAGE

Catastrophic Neurological Complications in 2 Patients With Sickle Cell Disease and COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection is commonly associated with neurological complications. Patients with sickle cell disease are at increased risk of developing neurologic complications throughout their lifetimes and often have underlying cardiopulmonary comorbidities that may predispose them to poor outcomes during serious infections. In this case series, we describe 2 patients with sickle cell disease who developed devastating neurologic complications following SARS-CoV-2 infection, which ultimately led to brain edema and death. We highlight the unusual manifestations of coronavirus disease 2019 in patients with sickle cell disease and address the risk of these patients to develop catastrophic neurologic injury due to COVID-19, if not recognized promptly.

Keywords

COVID-19, sickle cell, neurological complications

Background

Patients with coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), commonly present with respiratory symptoms including cough and dyspnea. However, within the first few months of the COVID-19 pandemic, the association of COVID-19 with neurological complications became evident.[1,2] It is now recognized that both acute and chronic neurological complications often develop in patients with COVID-19.[3,4]

Acute neurological complications of COVID-19 can manifest in either the central or peripheral nervous system.[2-5] Central nervous system manifestations include non-inflammatory encephalomyopathy, strokes (ischemic and hemorrhagic), encephalitis,[2,3,5,6] and less commonly cerebral edema and herniation.[7-10] Acute peripheral nervous system manifestations include ageusia, anosmia, myositis, and neuropathies (e.g. Guillain-Barré syndrome).[3,5]

Although the mechanism by which SARS-CoV-2 affects the nervous system is not well understood, several possible processes have been suggested, including virus-induced hypercoagulable and hyperinflammatory states. In addition, coronaviruses are known to have direct neuroinvasive and neurotropic abilities.[1] Severe acute respiratory syndrome coronavirus binds to angiotensin-converting enzyme (ACE)-2 inhibitor receptors, which are found in many tissues, including those in the central nervous system.[1] It appears most likely that the neurological manifestations of COVID-19 are due to the hyperinflammatory and hypercoagulable state that is caused by SARS-CoV-2, rather than direct neuroinvasion.

Sickle cell disease is a group of disorders caused by a point mutation in the beta globin gene that results in a hemoglobin S (HbS) allele.[11,12] This mutation changes the hemoglobin structure, causing red blood cells to sickle. Individuals who are homozygous for hemoglobin S (HbSS) have more

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Received March 7, 2022. Revised June 11, 2022. Accepted June 18, 2022.

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severe disease compared with those who are compound heterozygous for hemoglobin S and C (HbSC). Approximately 100 000 Americans have sickle cell disease, with approximately two-thirds having the HgSS genotype.[13] Patients with sickle cell disease are relatively immunocompromised and are at a higher risk of infection, due to functional asplenism.[14] They also often have underlying cardiopulmonary comorbidities that may predispose them to poor outcomes in the setting of serious infections.[15] For these reasons, COVID-19 illness presents significant challenges for patients with sickle cell disease.

Sickle cell disease complications can affect many organs, including the kidneys (leading to end-stage renal disease), eyes (resulting in retinopathy), bone (resulting in avascular necrosis), and central nervous system.[12] Patients with sickle cell disease are at increased risk of developing neurologic complications throughout their lifetimes, and these are often associated with increased morbidity and mortality.[11,16-18] Strokes (ischemic and hemorrhagic), headache (acute and chronic), silent cerebral ischemia, epilepsy, cerebral venous sinus thrombosis, posterior reversible encephalopathy syndrome, cerebral fat embolism, and moyamoya disease are among the numerous neurological complications that occur in patients with sickle cell disease.[11,16-18]

Silent cerebral infarcts occur in 39% of patients with sickle cell disease by the time they are 18 years old.[17] Ischemic strokes occur in approximately 11% of children with sickle cell disease who do not receive adequate screening and prophylaxis to reduce their stroke risk. Hemorrhagic strokes occur in 3% of children and 10% of adults with sickle cell anemia. In addition, in comparison with the general population, epilepsy is 2 to 3 times more common in patients with sickle cell disease.

Most of the approximately 8000 patients with sickle cell disease who reside in the state of Georgia live in the Atlanta metro area,[19] and many receive medical care at Emory Healthcare, which is Georgia's most advanced tertiary care system. In this case series, we discuss 2 patients with sickle cell disease who received medical care within the Emory Healthcare system.

Objective

In this case series, we describe 2 patients who had sickle cell disease: one had the HbSS genotype, while the other had the HbSC genotype. Both patients developed catastrophic neurologic complications following SARS-CoV-2 infection, which ultimately led to brain edema, herniation, and death. Both patients were treated at the beginning of the pandemic, prior to COVID-19 vaccine availability, and prior to authorized COVID-19-specific therapeutics.

This report was derived from a retrospective chart review. The goal for sharing the details of these 2 cases is to draw attention to the fact that sickle cell disease patients can present with vaso-occlusive crises as their sole manifestation of the COVID-19 infection, and that they may be at increased risk of developing catastrophic neurologic injury due to COVID-19.

Description of Cases

Patient 1

A 23-year-old woman with a history of HbSS and asthma presented with upper extremity pain consistent with previous vaso-occlusive crises. Laboratory values on the day of admission included hemoglobin 8.4 g/dL, white blood cell (WBC) count 7.8 (10E3/μL), platelet count 295 × 10E3/μL, sodium 138 mmol/L, potassium 3.7 mmol/L, bicarbonate 24 mmol/L, blood urea nitrogen (BUN) 9 mg/dL, creatinine 0.55 mg/dL, and glucose 125 mg/dL. Aminotransferases were normal, as was her initial chest radiograph (CXR), and initial blood cultures showed no growth. She was treated with intravenous hydration, nonsteroidal anti-inflammatory drugs, and opiates. On hospital day 2, she developed vomiting, diarrhea, tachycardia, and oxygen desaturation to 92% on ambient air. Repeat CXR revealed bibasilar opacities. A nasopharyngeal polymerase chain reaction (PCR) swab was positive for SARS-CoV-2. Blood cultures showed no growth. She acutely decompensated, necessitating emergent tracheal intubation for hypoxemic respiratory failure. Post-resuscitation, her arterial blood gas on 40% FIO_2 showed pH 7.37/pCO_2 34/pO_2 135. During the intubation, she became asystolic and required cardiopulmonary resuscitation. Return of spontaneous circulation was obtained after 3 minutes. She was treated with therapeutic hypothermia for 24 hours. Post-resuscitation, the patient underwent automated red cell exchange.

The patient did not regain neurologic function during the remainder of her hospital course. Following the cessation of sedative medications and after correction of all metabolic abnormalities, her neurological examination on hospital day 8 showed absent brainstem reflexes consistent with brain death. Brain computed tomography (CT) showed severe cerebral edema and brain herniation. Care was withdrawn on hospital day 13.

Patient 2

A 31-year-old woman with a history of HbSC, chronic deep vein thrombosis/pulmonary embolism (on dabigatran), and asthma presented to an outside hospital with diffuse pain similar to prior vaso-occlusive crises. Initial laboratory values included hemoglobin 10.3 g/dL, WBC count 16.2 × 10E3/μL, platelet count 332 × 10E3/μL, sodium 141 mmol/L, potassium 3.4 mmol/L, bicarbonate 26 mmol/L, BUN 10 mg/dL, creatinine 0.7 mg/dL, glucose 103 mg/dL, and lactic acid 0.9 mmol/L. Her aminotransferases were normal. Prothrombin time (PT) and partial thromboplastin time (PTT) were first obtained on hospital days 10 and 4,

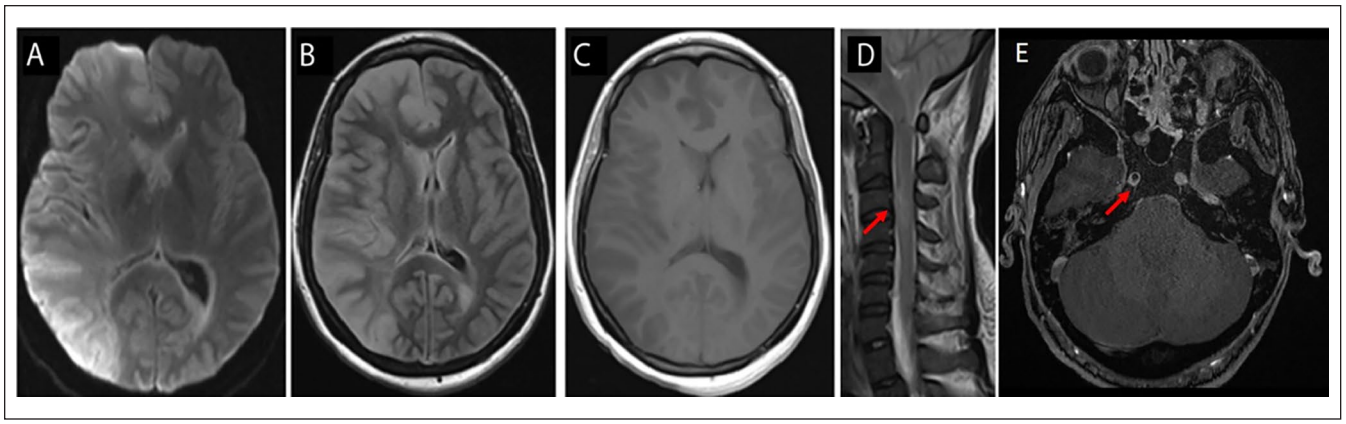

Figure 1. Patient 2 had right cerebral hemispheric restricted diffusion (diffusion-weighted imaging in panel A) and cerebral edema (fluid-attenuated inversion recovery [FLAIR] in panel B) affecting gray matter and deep gray nuclei, without enhancement (panel C), and spinal edema (shown with arrow, panel D), and an occlusive thrombus in the right internal carotid artery (shown with arrow, panel E).

respectively, with the following values: PT = 24.5 seconds (normal range: 11.5-15.1 seconds), international normalized ratio (INR) = 2.1, and PTT = 39 seconds (normal range: 23-37 seconds). The 2 sets of blood cultures that were collected at the outside hospital were negative.

Her initial CXR was notable for a right middle lobe infiltrate, and this prompted the initiation of intravenous vancomycin, piperacillin-tazobactam, and levofloxacin. Intravenous opiates were started for pain control. Her hospital course at the outside hospital was complicated by the development of acute kidney injury, acute hypoxic respiratory failure, fever, and worsening leukocytosis. Her nasopharyngeal PCR swab was positive for SARS-CoV-2 and influenza A.

The patient was started on peramivir and hydroxychloroquine; however, her leukocytosis worsened, and her fevers persisted. Due to worsening of her respiratory status despite the application of continuous bilevel positive airway pressure (BiPAP), she required endotracheal intubation and mechanical ventilation. While at the outside hospital she developed hemolytic anemia, with a nadir hemoglobin of 4.7 g/dL (normal range: 12.0-16.0 g/dL). She was transfused with 4 units of packed red blood cells (PRBCs) via simple transfusion.

The patient was transferred to our hospital for further management of her acute hypoxemic respiratory failure in the setting of confirmed COVID-19 and influenza A. At the time of her transfer, she was sedated, and throughout her admission at our hospital, she was unarousable. Laboratory values on the day of her transfer included hemoglobin 9.5 g/dL, WBC count 47.9 × 10E3/μL, sodium 145 mmol/L, potassium 3.7 mmol/L, bicarbonate 25 mmol/L, BUN 33 mg/dL, creatinine 3.3 mg/dL, and glucose 107 mg/dL. Her aminotransferases were normal. Her CXR revealed multifocal interstitial and airspace disease, compatible with pneumonia.

Given the improvement in her oxygenation by hospital day 13, paralytic and sedating medications were discontinued. Despite this, on hospital day 15, she was still comatose and had no brainstem reflexes. On hospital day 15, a lumbar puncture was done in the lateral recumbent position. It was pertinent for high opening pressure (30 cm H_2O), and cerebrospinal fluid contained 115 nucleated cells/mL, 7374 red blood cells/mL in tube 1, 342 red blood cells/mL in tube 4, elevated protein (> 200 mg/dL), and normal glucose (40 mg/dL). A meningitis/encephalitis pathogen panel was negative: it tested for *Escherichia coli*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitides*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex virus 1 and 2 (HSV-1 and HSV-2), human herpesvirus 6 (HHV-6), human parechovirus, varicella zoster virus (VZV), *Cryptococcus neoformans*, and *Cryptococcus gattii*. Cerebrospinal fluid and blood cultures were negative.

On hospital day 15, her brain magnetic resonance imaging (MRI) revealed cerebral edema and diffusion-weighted abnormalities, which were most notable in the right cerebral hemisphere (Figure 1). Brain herniation was also noted. Magnetic resonance angiography (MRA) demonstrated an occlusive thrombus with no distal flow in the right internal carotid artery. Her cervical spinal cord was edematous. There was no abnormal enhancement (Figure 1). The findings on the patient's MRI and MRA were most suggestive of encephalomyelitis, with superimposed hypoxic ischemic encephalopathy. As she had a very poor prognosis, her family decided that withdrawal of life-sustaining care would be in her best interest. She died on hospital day 16.

Discussion

Patients with sickle cell disease are at increased risk of developing neurologic complications throughout their lifetimes.[11,16-18] As SARS-CoV-2 has a propensity to adversely

affect the nervous system, and patients with sickle cell disease are relatively immunocompromised, there is concern that these factors increase their risk of developing neurological manifestations if they acquire this infection.

This case series describes 2 sickle cell disease patients who developed devastating neurological complications due to COVID-19 early in the pandemic when COVID-19 vaccinations and authorized COVID-19-targeted therapeutics were not available. Both patients presented with vaso-occlusive crises and received the standard treatment of opiates and hydration. Their vaso-occlusive crises were not recognized to be due to COVID-19 until later in their hospital course. The first patient underwent plasma exchange, whereas the second one received simple transfusions. Exchange transfusion should be considered early during the course of symptomatic COVID-19 infection in sickle cell disease patients, as it may significantly improve their clinical outcomes.[20,21]

The clinical course of patients with sickle cell disease and COVID-19 is varied. One case series evaluated 5 patients with sickle cell disease who were diagnosed with COVID-19 in 2020 with symptomatology that ranged from mild upper respiratory tract symptoms to an 8-day hospitalization necessitating PRBC transfusion.[22] Four of the 5 patients in this series also presented with symptoms of vaso-occlusive crises with pain in their extremities and chest. In this study, there was a 60% hospitalization rate, no patients were admitted to the intensive care unit, and none died.

A larger study by Panepinto et al[23] of 178 patients with sickle disease and COVID-19 reported that almost 90% of case patients received care through an emergency department, 69% were admitted to the hospital, 38% required a transfusion, 11% were admitted to an intensive care unit, 6% necessitated mechanical ventilation, and 2% required dialysis. The mean age of the patients was younger than 40 years old. There was a high prevalence of chronic illness, with over 10% having a history of previous stroke, pulmonary hypertension, receipt of chronic transfusion therapy, and renal disease.[23] Panepinto et al found that the severity of COVID-19 disease was as follows: 6% asymptomatic, 54% mild, 18% moderate, 17% severe, and 5% critical. In this study, 13 (7%) patients died; of those who died, the mean age was less than 40 years old and over 90% were adults. Almost 40% of the patients who died had genotypes that are typically associated with milder sickle cell disease (types HbSC or HbSβ+-thalassemia). Of those who died, 8 (61.5%) had severe or critical COVID-19 and 5 (38.5%) had mild or moderate COVID-19.

Outside of the sickle cell patient population, COVID-19 has been reported to cause various neurological complications, including brain edema in clinical series as well as neuropathological descriptions.[24-26]

This case series describes the clinical course of 2 patients with sickle cell disease and COVID-19, who though hospitalized with symptomatology of vaso-occlusive crises developed catastrophic neurological consequences with resultant death. Given the increased presence of associated comorbid conditions that already place these patients at increased risk of complications, it is essential to recognize the increased neurologic morbidity and mortality associated with COVID-19 in these patients. While knowledge of COVID-19 continues to evolve, patients with sickle cell disease are at elevated risk of poor outcomes, and further investigation is needed to define the pathophysiologic processes by which SARS-CoV-2 may lead to neurologic compromise in this patient population.

This case series also highlights the importance of COVID-19 vaccination in immunocompromised patients, including patients living with sickle disease, and the importance of early consideration of currently available authorized targeted COVID-19 therapeutics (including anti-inflammatory agents, remdesivir, and monoclonal antibodies [authorized for both treatment and prevention]).

Acknowledgments

The authors would like to thank Mary Ann Kirkconnell Hall, Senior Medical Writer, Emory Division of Hospital Medicine.

Author Contributions

KC contributed substantially to the conception and analysis of this work, as well as to drafting and revising the manuscript. KB contributed substantially to the conception, acquisition, and analysis of this work, as well as to drafting and revising the manuscript. ZW contributed substantially to the analysis of this work, as well as to drafting and revising the manuscript. YMS contributed substantially to the interpretation of the data of this work, as well as to drafting and revising the manuscript. MKM contributed substantially to the interpretation of the data of this work, as well as to drafting and revising the manuscript. FE contributed substantially to the analysis of this work, as well as to drafting and revising the manuscript. MLM contributed substantially to the analysis of this work, as well as to drafting and revising the manuscript. All authors approve the final version of this manuscript and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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