

Spontaneous intracranial hemorrhage presenting in a patient with vitamin K deficiency and COVID-19: illustrative case

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BACKGROUND Coronavirus disease 2019 (COVID-19) is known to cause more severe symptoms in the adult population, but pediatric patients may experience severe neurological symptoms, including encephalopathy, seizures, and meningeal signs. COVID-19 has also been implicated in both ischemic and hemorrhagic cerebrovascular events. This virus inhibits angiotensin-converting enzyme 2, decreasing angiotensin (1–7), decreasing vagal tone, disrupting blood pressure autoregulation, and contributing to a systemic vascular inflammatory response, all of which may further increase the risk of intracranial hemorrhage. However, there has only been one reported case of intracranial hemorrhage developing in a pediatric patient with COVID-19.

OBSERVATIONS The authors discuss the first case of a pediatric patient with COVID-19 presenting with intracranial hemorrhage. This patient presented with lethargy and a bulging fontanelle and was found to have extensive intracranial hemorrhage with hydrocephalus. Laboratory tests were consistent with hyponatremia and vitamin K deficiency. Despite emergency ventriculostomy placement, the patient died of his disease.

LESSONS This case demonstrates an association between COVID-19 and intracranial hemorrhage, and the authors have described several different mechanisms by which the virus may potentiate this process. This role of COVID-19 may be particularly important in patients who are already at a higher risk of intracranial hemorrhage, such as those with vitamin K deficiency.

<https://thejns.org/doi/abs/10.3171/CASE20163>

KEYWORDS intracranial hemorrhage; vitamin K deficiency bleeding; coronavirus disease 2019; COVID-19; case report; coagulopathy

In March 2020, SARS-CoV2 (coronavirus disease 2019 [COVID-19]) was declared a global pandemic.¹ Since the initial outbreak, the virus has spread throughout the world with more than 65 million confirmed cases and 1.5 million deaths reported worldwide.² This virus is known to cause more severe symptoms in adults than in children, and common symptoms include fever, cough, shortness of breath, fatigue, myalgias, vomiting, diarrhea, and anosmia.³⁻⁵ In the adult population, there is also an increased association between the COVID-19 virus and cerebrovascular disease.⁶⁻¹⁰ In the pediatric population, neurological symptoms most often include mild symptoms such as headache, myalgia, and fatigue. More severe symptoms, including seizures, encephalopathy, and meningeal signs, have also been reported but are much less common.¹¹ To date, there has only been one reported case of a pediatric patient with COVID-19 who developed intracranial hemorrhage.¹² In this case, the patient presented with significant symptoms, including fever, respiratory insufficiency, fatigue, and

nausea. His hemorrhage was not discovered until after he was in critical condition with acute renal failure requiring pressors and fresh frozen plasma administration. We present the first case of a pediatric patient with COVID-19 presenting to the hospital with an acute intracranial hemorrhage.

Illustrative Case

A 5-week-old male presented to the hospital after he was noted to have 2 days of progressive lethargy, pallor, and poor tone. The patient was from a Mennonite community and did not receive vitamin K at birth. Upon initial evaluation in the emergency department, the patient was noted to be lethargic with a bulging but compressible fontanelle and a fixed right gaze deviation with reports of seizure activity en route to the hospital. Intravenous Keppra was administered at a dose of 60 mg/kg. Noncontrast computed tomography (CT) scans of the head demonstrated extensive subdural hematomas, most prominently over the

ABBREVIATIONS ACE2 = angiotensin-converting enzyme 2; COVID-19 = coronavirus disease 2019; CT = computed tomography; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; VKDB = vitamin K deficiency bleeding.

INCLUDE WHEN CITING Published March 15, 2021; DOI: 10.3171/CASE20163.

SUBMITTED December 18, 2020. **ACCEPTED** December 29, 2020.

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tentorium bilaterally, along the falx, and extending inferiorly toward the foramen magnum. There was also moderate intraventricular hemorrhage within the bilateral lateral ventricles and the 3rd and 4th ventricles, with prominent hydrocephalus (Fig. 1).

Urgent laboratory tests were obtained and were remarkable for a prothrombin time (PT) of >100.0 sec, an activated partial thromboplastin time (aPTT) of 142.3 sec, and an international normalized ratio (INR) of >8.4. Platelet count was $614 \times 10^3/\mu\text{L}$, fibrinogen was 408 mg/dL, and sodium was 122 mEq/L. The pediatric hematology team was urgently consulted and recommended intravenous vitamin K and prothrombin complex concentrate administration. The patient was started on Diamox and Decadron, and he was scheduled to undergo urgent ventriculostomy placement in the operating room because of his extensive coagulopathy. Prior to this, the patient was admitted to the pediatric intensive care unit, was urgently intubated, and underwent placement of arterial and central venous lines.

Following intubation, the patient developed fixed and dilated pupils. An emergency fontanelle tap was performed using a 22-gauge spinal needle. Approximately 5 mL of cerebrospinal fluid was removed, with improvement of pupillary size and reactivity. The patient was then brought to the operating room and underwent emergency placement of a right frontal ventriculostomy. He was then started on continuous electroencephalography, which demonstrated encephalopathy and depressed cortical activity with no seizures.

A repeat head CT scan was performed the following morning that demonstrated stable hemorrhage with good catheter placement within the right lateral ventricle (Fig. 2). COVID-19 polymerase chain reaction testing was performed at admission and noted to be positive, though the patient did not have any respiratory symptoms related to his COVID-19 infection. Cerebrospinal fluid cultures and broad encephalitis panels were sent from the ventriculostomy and were negative.

Upon presentation, there was no evidence of external trauma. Ophthalmology was consulted and noted no evidence of papilledema or retinal hemorrhages, lowering the suspicion for nonaccidental trauma. The patient's examination remained poor throughout his admission, though his intracranial pressure remained low. Repeat noncontrast head CT scanning was performed on hospital day 6 and demonstrated stable subdural and intraventricular hemorrhage, but diffuse infarct throughout the entire cerebral hemispheres bilaterally with associated cerebral edema was noted (Fig. 3). Because of the devastating findings on this CT scan, the decision was made to pursue comfort measures.

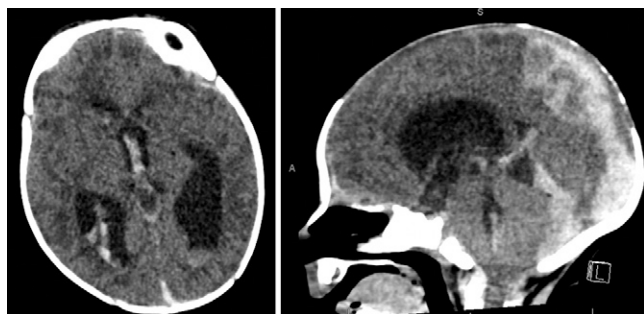


FIG. 1. Axial (left) and sagittal (right) CT scans without contrast demonstrating bilateral tentorial and parafalcine subdural hematomas and intraventricular hemorrhage with associated hydrocephalus.

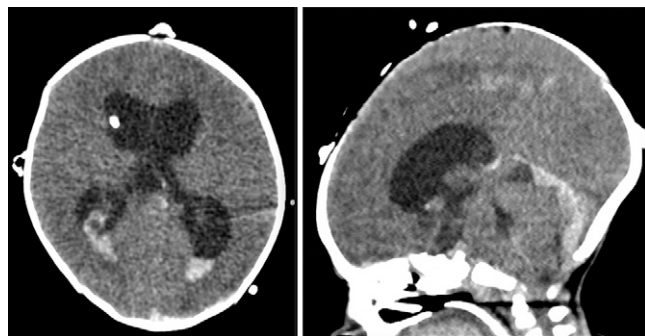


FIG. 2. Axial (left) and sagittal (right) CT scans without contrast following ventriculostomy placement, demonstrating mildly improved hydrocephalus with persistent subdural and intraventricular hemorrhage.

Discussion

Vitamin K is an important vitamin that is directly involved in the production of multiple factors involved in the coagulation cascade.¹³ In adults, vitamin K is obtained from leafy green vegetables and produced by intestinal flora. However, infants have a diminished ability to produce vitamin K because of differences in their intestinal flora, and those who are exclusively breast fed are at particularly high risk of vitamin K deficiency.^{14,15}

Vitamin K deficiency was previously known as “hemorrhagic disease of the newborn.”¹⁶ Since it was first discovered, much has been learned about the pathophysiology of vitamin K deficiency, and there are now several different classifications. Early-onset vitamin K deficiency bleeding (VKDB) is classified as ranging from 0 to 24 hours, classic VKDB ranges from 2 to 7 days, and late-onset VKDB ranges from 2 to 12 weeks.^{13,14,17} Secondary causes of late-onset VKDB may include chronic diarrhea, hepatobiliary lesions, or chronic antibiotic usage. However, late-onset VKDB is often secondary to exclusive breastfeeding and, in those circumstances, is classified as idiopathic. The majority of cases of late-onset VKDB are idiopathic, and two large nationwide surveys in Japan indicated that idiopathic cases are nearly 7.5 times higher than secondary causes.^{13,18,19}

VKDB is known to cause bleeding in a variety of locations, including the gastrointestinal tract, the skin (often noted at peripheral intravenous lines), or the central nervous system. In the early Japanese surveys,

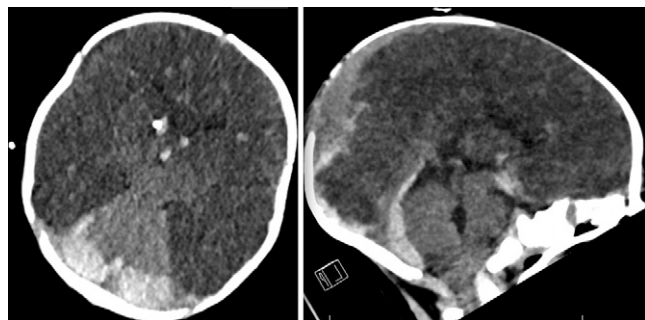


FIG. 3. Axial (left) and sagittal (right) CT scans without contrast demonstrating resolution of hydrocephalus but extensive bilateral supratentorial infarction and associated cerebral edema.

the rate of intracranial hemorrhage was reported to be approximately 83%, and the fifth Japanese survey published in 2011 demonstrated a rate of 63.4%.^{19,20} Pooni et al. published a study of 42 infants from India and noted a 71% rate of intracranial hemorrhage.²¹ A study from Germany published by Sutor et al. demonstrated an intracranial hemorrhage rate of 58%.²² Multiple studies from Turkey have also demonstrated a high rate of intracranial hemorrhage with subsequent neurological symptoms secondary to late-onset VKDB.^{23,24} Given concerns of the deleterious effects of hemorrhage from VKDB, the administration of prophylactic vitamin K has been extensively studied and is known to be efficacious.^{17,25–29}

The COVID-19 pandemic has resulted in a significant burden on the healthcare system, and the virus causes severe respiratory symptoms, particularly in the elderly population.³ Furthermore, this virus has been linked to many cases of cerebrovascular disease, most notably in the adult population. Sweid et al.⁷ published a retrospective study of 22 adult patients with COVID-19 and acute stroke or hemorrhage. Of these patients, 17 had acute ischemic strokes, 3 had a ruptured cerebral aneurysm, and 2 patients had cerebral venous sinus thromboses.⁷ Oxley et al. noted that there was an association of large vessel occlusion in young adults with COVID-19.⁶ Nawabi et al. published the largest series to date of patients with intracranial hemorrhage and COVID-19.⁸ They presented 18 patients and found that the presence of intracranial hemorrhage typically correlated with the severity of the patient's COVID-19 symptoms, and only 2 of these patients presented with hemorrhage prior to presentation with respiratory symptoms.⁸

There are several mechanisms by which the COVID-19 virus may contribute to increased rates of intracranial hemorrhage. First, the virus is known to bind to angiotensin-converting enzyme 2 (ACE2), thereby inhibiting it.^{30–32} When ACE2 is inhibited, it is no longer able to convert angiotensin II into angiotensin (1–7). When produced, angiotensin (1–7) plays an important role in neuroprotection and increasing vagal tone.^{33–35} Therefore, the inhibition of ACE2 results in decreased angiotensin (1–7) and an overall reduction in the renin-angiotensin-aldosterone system, increasing systolic blood pressure. All of these effects may further predispose patients to intracranial hemorrhage.

COVID-19 is also known to cause a widespread vascular inflammatory process.^{8,30,36} This inflammatory response has contributed to the characterization of “COVID-19–associated coagulopathy.”³⁷ This has been known to predominantly contribute to thrombotic events rather than hemorrhagic events; however, there are many described cases of hemorrhage associated with COVID-19.^{7,8,10,12} It is also well known that endothelial inflammation can contribute to increased rates of intracranial hemorrhage in acute disease processes, including posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome.^{38–40} In a similar fashion, in COVID-19, the inflammatory response within the walls of the vasculature results in damage and weakening, increasing the likelihood of rupture and associated hemorrhage.

Observations

As described above, COVID-19 has been implicated in many cases of intracranial hemorrhage and may potentiate this by inhibiting ACE2 and decreasing angiotensin (1–7), decreasing vagal tone, decreasing neuroprotective effects, increasing systolic blood pressure and disrupting blood pressure autoregulatory capacities, and contributing to a systemic vascular inflammatory response. We have described a case of a patient presenting with spontaneous intracranial hemorrhage that was significantly influenced by the patient's vitamin K deficiency. The laboratory values obtained, including PT, PTT, INR, and fibrinogen,

were consistent with late-onset VKDB. It is therefore unclear to what capacity COVID-19 influenced this process. However, this patient did not develop an intracranial hemorrhage until he developed COVID-19. This patient presented with elevated systolic blood pressure, and there was significant difficulty maintaining normotension during intubation, requiring constant titration of vasopressors and multiple fluid boluses, which is consistent with a possible disruption of the renin-angiotensin-aldosterone system. Additionally, this patient presented with hyponatremia, which has also been described in cases of COVID-19, usually related to the widespread inflammatory response and release of cytokines such as interleukin-6, which may contribute to a syndrome of inappropriate anti-diuretic hormone release and resultant hyponatremia.^{41,42} This patient's hyponatremia contributed to cerebral edema, which further increased his intracranial pressure and exacerbated his symptoms.

Given the multiple ways that COVID-19 influences the risk of hemorrhage and hyponatremia, it is reasonable to suspect that COVID-19 played a role in potentiating this process in this patient, given his already significantly increased baseline risk of intracranial hemorrhage. Even though COVID-19 has been associated with multiple cases of intracranial hemorrhage in adults and has had many different neurological manifestations in the pediatric population, this is the first reported case of a pediatric patient with COVID-19 presenting with an intracranial hemorrhage.

This patient died of his disease and is now listed as one of the more than 1.5 million COVID-19 deaths reported worldwide. Despite the important ways COVID-19 may have contributed to this patient's hemorrhage, the case also highlights the controversial classification system that many argue fails to differentiate between dying from COVID-19 and dying with COVID-19. Though certain cases of severe acute hypoxic respiratory failure and acute respiratory distress syndrome provide a clear case, there are many cases in which COVID-19 is simply one of a myriad of factors that contribute to a patient's death. This is further complicated by patients who present with significant baseline comorbidities, making them particularly susceptible to serious health effects from otherwise relatively benign disease processes.

Lessons

This case highlights the association of COVID-19 with ischemic and hemorrhagic cerebrovascular disease in both the pediatric and adult population. Particularly, patients who have a baseline increased risk of hemorrhage secondary to other processes, such as vitamin K deficiency, may have that risk further potentiated by COVID-19. Therefore, it remains important for clinicians to be aware of the effects that COVID-19 may have on the entire human body, in addition to the most commonly described pulmonary effects.

Any conclusions drawn from this case should remain tentative, given the significant limitations associated with a single case report. Additionally, D-dimer and other inflammatory markers are known to correlate with the severity of COVID-19–associated coagulopathy and would have provided further insight regarding this patient's degree of systemic inflammation. Further workup of the etiology of this patient's hyponatremia would also have been helpful, although it was not performed owing to the need for urgent correction in the setting of his intracranial hypertension.

In summary, we have reported the first case of a pediatric patient with COVID-19 presenting with an intracranial hemorrhage. It will be imperative for future research to build on this case in order to provide more definitive recommendations regarding the incidence, clinical course, and management of pediatric patients with COVID-19 and intracranial hemorrhage.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Drafting the article: Ellens. Critically revising the article: Silberstein. Reviewed submitted version of manuscript: both authors.

Approved the final version of the manuscript on behalf of both authors: Ellens. Administrative/technical/material support: Silberstein. Study supervision: Silberstein.

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