Toddler With New Onset Diabetes and Atypical Hemolytic-Uremic Syndrome in the Setting of COVID-19

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This is a novel case of a 16-month-old boy with a history of prematurity with intrauterine growth restriction, severe failure to thrive, microcephaly, pachygyria, agenesis of the corpus callosum, and postnatal embolic stroke, who presented with new-onset diabetes mellitus with diabetic ketoacidosis in the setting of severe acute respiratory syndrome coronavirus 2 infection, with a course complicated by atypical hemolytic syndrome (aHUS). This patient demonstrated remarkable insulin resistance in the period before aHUS diagnosis, which resolved with the first dose of eculizumab therapy. There is increasing evidence that COVID-19 is associated with thrombotic disorders and that microangiopathic processes and complement-mediated inflammation may be implicated. In this case report, we describe a pediatric patient with COVID-19 and a new complement-mediated microangiopathic thrombotic disease. Because whole-exome sequencing and extensive workup returned without a clear etiology for aHUS, this is likely a COVID-19 triggered case of aHUS versus an idiopathic case that was unmasked by the infection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease (COVID-19), typically affects adults and presents with severe respiratory disease.1 Children typically have milder forms of the disease. Shekerdemian et al2 reported that of the 48 children admitted to 46 North American PICUs from March 14 to April 3, 2020, with COVID-19, 83% had preexisting conditions and most had respiratory symptoms. Three children in this cohort presented with diabetic ketoacidosis (DKA), which mimics reports in adults.3,4 Not only does diabetes appear to be a risk factor for COVID-19, the virus also appears to trigger new cases of diabetes and complicate management of existing diabetes.5–7

COVID-19 is also associated with a prothrombotic state with increased risk of thrombosis and disseminated intravascular coagulation.8,9 Although other viruses, such as H1N1 influenza, have been associated with thrombotic microangiopathies (TMAs), and infection can be a relapse trigger in patients with TMA due to atypical hemolytic-uremic syndrome (aHUS), there has not yet been definitive evidence linking COVID-19 with TMAs. Autopsy of patients with COVID-19 revealed that 3 out of 21 patients had generalized TMAs.10 There is growing speculation that TMAs play a large role in COVID-19.11–13

In this case, we describe a toddler who presented with COVID-19, DKA, and aHUS treated with eculizumab. This is the first COVID-19 presentation of its kind.

CASE
This is a case of a 16-month-old boy with history of prematurity at 34

abstract

Dr Alizadeh participated in clinical care of the patient, conceptualized the manuscript and the clinical implications of the case, and drafted the initial manuscript; Drs DeCourcey and Traum participated in the clinical care of the patient, conceptualized the manuscript and the clinical implications of the case; Dr Trissal participated in the clinical care of the patient and created and reviewed the hematology slide; Drs O’Halloran, Alghamdi, and Chen participated in the clinical care of the patient; and all authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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DOI: https://doi.org/10.1542/peds.2020-016774

Accepted for publication Sep 29, 2020

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

weeks’ gestation, intrauterine growth restriction, severe failure to thrive, microcephaly, pachygyria, agenesis of the corpus callosum, postnatal embolic stroke with residual cranial nerve IV palsy, retinopathy of prematurity, and multiple dysmorphisms without a unifying genetic disorder (previous chromosomal microarray revealed large areas of homozygosity). He was in his usual state of health until a day before presentation, when he developed fever, emesis, and respiratory distress. On presentation he was toxic, appearing with fever, tachycardia, and tachypnea. Laboratory evaluation revealed a metabolic acidosis with venous pH of 7.0, Pco2 of 17 mm Hg, bicarbonate of 4 mmol/L, anion gap of 40, glucose of 805 mg/dL, elevated β-hydroxybutyric acid, and hemoglobin A1c of 9.5%, confirming the diagnosis of DKA. Antibody testing obtained on admission revealed positive glutamic acid decarboxylase, zinc transporter 8, and islet antigen-2 antibodies, confirming type 1 diabetes without anti-insulin antibodies. Additional laboratory tests revealed a white blood cell count of 33 000 with neutrophil predominance, elevated procalcitonin of 3 ng/mL (normal range: <0.09), and hypernatremia (sodium 158 mmol/L). Chest radiograph was unremarkable, and the result of nasopharyngeal SARS-CoV-2 PCR testing was positive.

He was admitted to the PICU for DKA management, including an insulin infusion at 0.1 U/kg per hour for ~24 hours before he was transitioned to subcutaneous insulin. Because his initial tachypnea improved with correction of his acidosis, no oxygen, ventilatory support, or COVID-19–specific therapies were administered. The patient was transferred to the endocrinology wards on hospital day 4, and while on subcutaneous insulin, he developed rapidly rising insulin requirement (Fig 1A). Additional evaluation was unremarkable for other

![Figure 1](image-url)
endocrinopathies. On hospital day 6, he required readmission to the PICU for hypernatremia secondary to hypovolemia from hyperglycemia-associated osmotic diuresis. He received fluid resuscitation and was placed back on an insulin infusion for 4 days because of insulin resistance and high insulin requirements. His insulin requirement peaked at 3.5 U/kg per day, 11 days after admission, as he became increasingly ill from aHUS (details below). His total daily insulin dose decreased to 0.5 to 1 U/kg per day after eculizumab administration. Ultimately, he was discharged on a subcutaneous insulin with a total daily dose of 1 U/kg per day.

Despite having normal hemoglobin and thrombocytosis on admission, he developed progressive thrombocytopenia and anemia on days 4 to 5 of admission, with platelets falling <100K cells/µL on hospital day 10 (Fig 1B). Workup revealed reticulocytosis (13%), undetectable haptoglobin, elevated LDH (peak 3190 µ/L), and hyperbilirubinemia (peak bilirubin 1.5 mg/dL), suggestive of hemolysis. Peripheral blood smear revealed abundant schistocytes suggestive of a microangiopathic process and macrothrombocytopenia, suggesting appropriate bone marrow response to peripheral platelet clearance (Fig 2). Additional abnormalities included elevated fibrinogen (peak 557 mg/dL), elevated ferritin (peak 1493 ng/mL), and rising BUN and creatinine (peak at 39 and 0.39 mg/dL, respectively, up from baseline of 5 and 0.1 mg/dL). C3 and C4 were normal (142 and 19 mg/dL, respectively).

Initial differential diagnosis included thrombotic thrombocytopenic purpura (TTP), aHUS, and, less likely, disseminated intravascular coagulation (because he had an elevated fibrinogen and his infectious symptoms had resolved). Given the possibility of congenital TTP (hereditary ADAMTS13 deficiency), empirical fresh-frozen plasma was trialed without improvement and

**FIGURE 1**
Continued.
testing ultimately revealed normal ADAMTS13 activity. Clinically, the patient developed severe hypertension, rising BUN and creatinine, lower extremity swelling, hematuria, and nephrotic-range proteinuria (urine protein to creatine ratio of 36 mg/mg). Kidney ultrasound revealed normal sized echogenic kidneys. Echocardiogram demonstrated a structurally normal heart with normal function and a moderate pericardial effusion. His hypertension was initially refractory to calcium channel blockers, including simultaneous administration of amlodipine and nicardipine infusion due to inadequate blood pressure control and gradual increase of the dose of amlodipine. Ultimately, his hypertension was responsive to a labetalol infusion and diuresis. His final enteral antihypertensive regimen included amlodipine and labetalol.

Given clinical suspicion for aHUS with acute kidney injury, on hospital day 14, he was empirically treated with eculizumab (a monoclonal antibody which binds C5a, preventing terminal complement complex C5b–9) while awaiting complement functional studies. After the first dose of eculizumab, his progressive anemia and thrombocytopenia improved. Pre-eculizumab bloodwork revealed a low CH50 complement activity level of 3 U (normal range: 60–144), with elevated factor H, factor I, Bb fragment level, and soluble C5b–9 levels (0.45 mg/L, normal <0.3). No factor H autoantibody was detected. On discharge, he was scheduled to continue receiving eculizumab therapy every 3 weeks for aHUS.

Given his atypical COVID-19 presentation, an immunology workup was performed and was reassuring against a primary immunodeficiency. Additionally, whole-exome sequencing, including mitochondrial and complement gene sequencing, did not reveal any known genetic disorders.
DISCUSSION

This is the first case report of a child with COVID-19 developing both DKA and aHUS. Given the patient’s underlying dysmorphisms and comorbidities, we suspected a genetic syndrome predisposing him to both type 1 diabetes and aHUS. However, despite initial neonatal testing revealing numerous areas of homozygosity, whole-exome sequencing did not reveal any known genetic defects.

This presentation of COVID-19 with new-onset DKA was particularly notable for extraordinary insulin resistance, which developed days after resolution of his ketoacidosis. This patient’s total daily insulin dose peaked twice, first during DKA treatment and again on hospital days 11 to 12 before aHUS diagnosis. Although it is clear that diabetes is a risk factor for mortality with COVID-19, the virus also may cause significant hyperglycemia, above what would be expected with stress hyperglycemia. Because a hyperinflammatory state is a hallmark of COVID-19, this hyperglycemia may result from insulin resistance in the context of inflammation. Many inflammatory markers, including interleukin-6, interleukin-1β, TNF-α, monocyte chemoattractant protein-1, inducible protein 10, and C3, have been linked with insulin resistance.

This patient was also found to have a TMA characterized by hemolytic anemia and thrombocytopenia. Although there is a previous report of autoimmune hemolytic anemia triggered by COVID-19, this patient’s Coombs testing was negative. Initially, TTP was high on the differential diagnosis given the patient’s history of postnatal stroke, which is a known complication of congenital TTP. However, his normal ADAMTS13 activity and complement functional panel ruled out TTP, making a diagnosis of aHUS more likely. There have been numerous reports of infectious triggers for aHUS and TMA, including H1N1 influenza virus. Given the timing of aHUS after SARS-CoV-2 infection and negative genetic evaluation, it is likely that COVID-19 was an infectious trigger for this patient’s condition, although an idiopathic etiology is still possible.

The patient in this case report did not receive anticoagulation and did not develop thrombosis. The use of combined dipyridamole and therapeutic dosing of unfractionated heparin in HUS has been studied and is associated with mild bleeding that did not require anticoagulation discontinuation. Patients with COVID-19, a high sepsis-induced coagulopathy score, and elevated D-dimer display decreased overall mortality when treated with prophylactic anticoagulation. Given the benefits of prophylactic anticoagulation in COVID-19 and the lack of a significant increase in bleeding events in anticoagulated HUS patients, the benefits of low molecular weight heparin would have outweighed the risks for this patient.

The association between aHUS and COVID-19 described in this article are unclear at this time. There is evidence that COVID-19 causes a prothrombotic state, and there are case reports suggesting complement-mediated inflammation and thrombotic microangiopathic processes may play a larger role in COVID-19. Campbell et al describe autopsy findings which reveal diffuse microvascular thrombi without viral infiltrates. Additionally, mouse models deficient in C3 revealed reduced respiratory distress and pulmonary inflammation when infected with severe acute respiratory syndrome coronavirus (SARS-CoV) (related virus to novel SARS-CoV-2), suggesting the complement system is instrumental in the hyperinflammatory response in SARS-CoV. In another mouse model with Middle East respiratory syndrome coronavirus infection, elevated levels of C5a and C5a–9 complex were reported, providing further evidence of the role of complement. Furthermore, with the SARS-CoV 2009 outbreak, complement activation, particularly C3 and C5a, was directly involved with the development of acute lung injury.

ACKNOWLEDGMENTS

We acknowledge Drs Matthew Heeney and Jeremi Carswell for their support in the clinical care of this patient and in article preparation.

ABBREVIATIONS

aHUS: Atypical hemolytic-uremic syndrome
COVID-19: coronavirus disease
DKA: diabetic ketoacidosis
SARS-CoV: severe acute respiratory syndrome coronavirus
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
TMA: Thrombotic microangiopathy
TTP: Thrombotic thrombocytopenic purpura
REFERENCES


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Pediatrics 2021;147;
DOI: 10.1542/peds.2020-016774 originally published online October 9, 2020;

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*Pediatrics* 2021;147;
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