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CLINICAL REPORT

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Management of COVID-19 infection in organic acidemias

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Abstract

The COVID-19 pandemic has affected the health and healthcare of individuals of all ages worldwide. There have been multiple reports and reviews documenting a milder effect and decreased morbidity and mortality in the pediatric population, but there have only been a small number of reports discussing the SARS-CoV-2 infection in the setting of an inborn error of metabolism (IEM). Here, we report two patients with underlying metabolic disorders, propionic acidemia and glutaric aciduria type 1, and discuss their clinical presentation, as well as their infectious and metabolic management. Our report demonstrates that individuals with an underlying IEM are at risk of metabolic decompensation in the setting of a COVID-19 infection. The SARS-CoV-2 virus does not appear to cause a more severe metabolic deterioration than is typical.

KEYWORDS
COVID-19, glutaric acidemia type 1, pediatric, propionic acidemia, SARS-CoV-2

1 | INTRODUCTION

To date, there have been very few published reports of COVID-19 infection in patients with a known inborn error of metabolism (IEM). Patients with IEMs are at a high risk for metabolic decompensation in the setting of any infection due to catabolic shift in the body's metabolism. The Centers for Disease Control and Prevention (CDC) suggests that this patient population may be at a high risk for severe illness due to COVID-19, and therefore should take extra precautions. Most families with a child with an IEM have been advised to take precautions to avoid exposure, and to respond to an acute illness per usual with an emergency room (ER) protocol. It was not known whether pediatric patients with inborn errors of metabolism would have mild symptomatology similar to the general pediatric population, or if they could have more severe symptoms due to their underlying IEM in addition to metabolic decompensation. Here, we report our center's first known patients with an established diagnosis of an IEM and an acute illness due to COVID-19.

2 | CASE REPORTS

2.1 | Patient 1

We report an 8-month old female with a known diagnosis of propionic acidemia who presented with a dry cough of 2 days duration, fever for 1 day with a TMax of 38.9°C for 1 day, difficulty breathing and two episodes of diarrhea on the day of presentation. She was tolerating her gastrojejunal (GJ) tube feeds (Anamix Early Years + Prophree + Enfamil) with no episodes of vomiting. There was no reported exposure to contacts with COVID-19.

She was identified to have propionic acidemia via newborn screening, which was confirmed with an elevated C3 and 3-OH propionic acid and propionylglycine in the urine. Ammonia at presentation was 163. Molecular testing revealed a homozygous likely pathogenic variant in *PCCA* (c.425 G>A /p.Gly142Asp). She was on chronic treatment with carglumic acid (Carbaglu), carnitine, bicitra, and monthly metronidazole with good compliance. Since her diagnosis, she has been admitted five times (four of which were intensive care admissions) due to metabolic decompensation with hyperammonemia attributed to frequent viral infections. She required hemodialysis on one occasion, when she was 1 month old, and her ammonia was elevated to the 400s. She required GJ tube placement due to poor feeding, and port placement due to difficult access during her multiple admissions. Her growth is age appropriate, but she has global developmental delay, and was being evaluated for liver transplant due to the frequency and severity of her metabolic decompensations.

She was febrile on presentation to the emergency department. SARS-CoV-2 infection was suspected due to symptomatology, so PCR testing was obtained and was positive. She was treated per her

propionic acidemia ER protocol, and was immediately started on dextrose 10% fluids at 1.5 times maintenance fluid rate. Her initial lab work is shown in Table 1 and was significant for an anion gap metabolic acidosis, ketonuria, mild elevation of ammonia, pancytopenia, a prolonged PTT, elevated ferritin, elevated D-dimer, and normal CRP. She was started on ceftriaxone, in the setting of an indwelling port and febrile neutropenia. She had prolonged capillary refill and was hypotensive to 40/20 mmHg, which was concerning for septic shock. A normal saline bolus was given and she was started on a dopamine drip. She received respiratory support with high flow oxygen via nasal cannula. Her GJ-tube feeds were adjusted to have 50% reduced natural protein, while providing a total of 140% of her calculated weight based daily caloric needs. Her home metabolic medications were continued. She was admitted to the pediatric intensive care unit (PICU) for further care. Antibiotics were escalated to cefepime and vancomycin, but discontinued after blood cultures were negative for 48 hours and symptoms were attributed to her SARS-CoV-2 infection. Final results for cultures were also negative. Blood pressures improved after fluid resuscitation and the dopamine drip was discontinued. Oxygen support was also weaned off within 24 hours. While receiving fluids with a high glucose infusion rate, she developed hyperglycemia with lactic acidosis. An insulin drip was started, but she developed insulin resistance, which has occurred with some of her previous decompensations, so the caloric source was transitioned to full feeds and intravenous (IV) intralipids.

Pancytopenia was noted, which is known to be a feature of PA, but could also be secondary to the acute SARS-CoV-2 infection (Baumgartner et al., 2014). She required two platelet transfusions and one packed red cell transfusion. A head ultrasound was obtained due to thrombocytopenia and concern for hemorrhage. It showed increased echotexture in the bilateral thalami and caudate nuclei. These were new findings compared to her last head ultrasound 6 months prior. Findings were to be followed on a brain MRI at a future date.

The infectious disease team was consulted due to concern for Multisystem Inflammatory Syndrome in Children (MIS-C) in the setting of a COVID-19 positive status with lactic acidosis, elevated inflammatory markers, and labile blood pressures. It was unclear if these abnormalities were caused solely by her underlying propionic acidemia or if she was also developing MIS-C due to a COVID-19 infection. IV immunoglobulin and aspirin were to be considered if cardiac abnormalities were detected; however, an echocardiogram was obtained and was unremarkable with no signs of coronary vessel involvement. IV remdesivir was also under consideration, to be used if there was respiratory decompensation, but was not required.

With increased caloric intake, the metabolic derangements resolved, and her clinical condition improved. She was eventually transitioned back to her outpatient feeds and medications, and discharged home with no known long-term sequelae from this acute decompensation secondary to COVID-19. Prior to discharge, all of her laboratory abnormalities resolved with the exception of persistent anemia, which was thought to be iatrogenic. She had an 8-day hospital course, seven of which were spent in the PICU.

She did follow-up with cardiology 2 months after discharge, at which time her cardiac exam, electrocardiogram, and echocardiogram were unremarkable.

TABLE 1 Laboratory markers of metabolic decompensation and SARS-CoV-2 infection in patients with COVID-19 with an underlying IEM

Test (normal range)	Patient 1 at presentation	Patient 2 at presentation	Caciotti et al.
Ammonia (16–53 μmol/L)	103	34	145
Lactic Acid (0.4–2.0 mMol/L)	2.3	4.0	2.3
Bicarbonate (21–31 μmol/L)	12	16	23.8
Anion gap (5–15 μmol/L)	26	16	Not reported
ALT (7–52 U/L)	25	17	Not reported
AST (13–39 U/L)	33	37	Not reported
LDH (140–271 U/L)	475	N/A	Not reported
Ferritin (11–306.8 ng/mL)	240.9	N/A	Not reported
BNP (<101 pg/mL)	128	N/A	Not reported
Troponin (3–17 ng/L)	11	N/A	Not reported
WBC (5–20 K/CUMM)	2.5	6.2	5.65
Lymphocytes (3.5–14 K/CUMM)	2.0	2.4	37.3% (2.1)
APTT (23.1–33.1 s)	108.1	N/A	Not reported
PT (9.4–11.7 s)	11.5	N/A	Not reported
INR (0.9–1.13)	1.11	N/A	Not reported
D-dimer (<0.5 mg/L)	3.19	N/A	Not reported
Fibrinogen (186–466 mg/dL)	204	N/A	Not reported
Urine ketones	3+	Negative	Not reported

2.2 | Patient 2

Our second patient was an 8-month old female with glutaric acidemia type 1 detected on newborn screen, and confirmed with an elevated C5DC and 3-OH glutaric acid in the urine. A homozygous pathogenic variant in *GCDH* (c.368A>G/p.Tyr123Cys) was identified. She had no previous hospitalizations for metabolic decompensation. She had normal growth and was developmentally on track. She presented on the first day of illness with a fever of 38.9°C, increased crying, rhinorrhea, nasal congestion, decreased intake of formula, and no intake of solid food. One of her parents had been symptomatic for 7 days with fever, chills, sore throat, and muscle aches, with a COVID-19 test pending. She was taken to the emergency department, where she was started on Dextrose 10% IV fluids at 1.5 times maintenance. A SARS-CoV-2 PCR swab was obtained and was positive. Initial lab work showed an anion gap metabolic acidosis with a bicarbonate of 16, with elevated lactic acid, possibly secondary to hypoperfusion. Ammonia was normal. CBC was normal. On examination she was breathing comfortably on room air with normal oxygen saturation. She was started on IV lipids, her home carnitine was switched to IV, and she was admitted to the floor. She was also diagnosed with left otitis externa, treated with ciprodex drops, and left otitis media, treated with amoxicillin. A sick day formula regimen consisting of just Anamix Early Years was prepared with no natural protein. The next day, repeat labs revealed resolution of her metabolic acidosis, with normal bicarbonate and lactic acid levels. Her IV lipids were then discontinued and her natural protein intake was increased to half her typical protein intake. However, she continued to have poor oral intake and fevers, and remained on Dextrose 10% IV fluids at 1.5 times maintenance until her oral intake improved on Day 3 of her hospitalization. On Day 6, her protein intake was increased to the amount in her home regimen. She was discharged on Day 7 of admission.

3 | DISCUSSION

Patients with IEMs are considered to be part of the high risk population for the global pandemic caused by the SARS-CoV-2 virus. A large number of these patients are still in infancy and childhood, so it is uncertain whether they are at increased risk for decompensation compared to the general pediatric population. The pediatric population in general has been less severely affected compared to the adult population. In fact, despite infants being more susceptible to severe infection than older children, 90% of COVID-19 cases in infants are reported to be asymptomatic, mild or moderate (Dong et al., 2020). This has been theorized to be due to the different state of ACE II receptor maturity and binding ability in children (Dong et al., 2020). Another hypothesis is the presence of antibodies to other coronavirus strains may have cross reactivity to the current strain. High-risk pediatric populations have been classified as those with underlying pulmonary pathology or immunocompromise similar to high risk classifications in adults (Ogimi et al., 2019). Patients with IEMs have been considered to be part of the high risk population, and therefore have been advised to be more cautious with isolation measures and to take more precautions to prevent viral transmission. Patients with IEMs such as PA or MMA may have hematopoietic dysfunction and cytopenias leading to immunodeficiency, but in the absence of leukopenia, patients with IEM should not be more susceptible to contracting an infection. Transmission was initially reported as contact, feco-oral, droplet, and airborne, but now it appears that transmission is most likely limited to droplet, unless there is aerosolization of the virus leading to airborne transmission.

There is also another condition associated with COVID-19 that has been reported in the pediatric population, known as Multisystem Inflammatory Syndrome in Children (MIS-C), typically associated with elevations of inflammatory markers such as ferritin, LDH, and CPK. Myocarditis, coagulopathy and end organ damage have all been reported in association with MIS-C. As of October 30, 2020 there have been 1163 MIS-C cases reported in the USA (Centers for Disease Control and Prevention, 2020).

One of our patients presented with cough, fever, difficulty breathing, and diarrhea which are all well-known symptoms of the COVID-19. Both patients tested positive for the COVID PCR, and were managed with close monitoring and supportive care. Neither patient met the clinical criteria in use at the time for MIS-C. Although Patient 1's elevated inflammatory markers were concerning for MIS-C, the diagnosis was thought to be less likely due to a normal CRP. The definition of MIS-C has evolved since this admission, and Patient 1 meets the current diagnostic criteria for MIS-C. The patient in our first case has had a history of multiple decompensations since her metabolic diagnosis, attributed to viral infections. During this presentation, she again had metabolic decompensation with elevation of her ammonia levels above her baseline and metabolic acidosis. She was managed as usual, given caloric support until her infection (the inciting factor) resolved. The metabolic decompensation did not seem to be more severe or more prolonged than usual. She had no apparent residual effects from COVID-19. Our second patient presented early in her clinical course with fever and decreased oral intake, and was immediately treated with aggressive caloric support. Her lab abnormalities were less severe, with a normal ammonia, and a metabolic acidosis that resolved by Day 2 of illness. Caloric support was continued in order to prevent metabolic decompensation, including the risk for metabolic stroke, and she likewise had no apparent residual effects from COVID-19.

Caciotti et al. (2020) recently reported a 14-month old male with propionic acidemia who presented with a metabolic decompensation and later tested positive for SARS-CoV-2, suggesting that the decompensation was secondary to the SARS-CoV-2 infection. He presented with symptoms of decompensation (vomiting, drowsiness, and dyspnea), was hypoxemic on presentation and was treated per the center's protocol for managing an acute metabolic decompensation. He was tested for SARS-CoV-2, as he developed fever and diarrhea on Day 3 of admission. The report does not discuss whether alternative therapy due to the diagnosis of COVID-19 was considered. This case also supports the hypothesis that metabolic decompensations secondary to a COVID-19 infection are not significantly more severe than any other metabolic decompensation.

Our center is the largest metabolic management center in the state of Michigan. We follow approximately 873 pediatric patients with a confirmed IEM. We have only had two reported patients with a diagnosis of a SARS-CoV-2 infection 8 months into the pandemic, and both required hospitalization. Our center's general recommendation has been to pursue testing in the presence of any symptoms consistent with COVID-19 or exposure to sick contacts. However, there is likely an underrepresentation of total COVID-19 positive patients in our cohort due to a combination of parental reporting bias, infrequent testing, or possible asymptomatic presentation.

As of November 2, 2020, the pediatric population (age 0–17) accounted for 9.1% of the total COVID-19 cases in the United States (Centers for Disease Control and Prevention, 2020). As of November 7, 2020, pediatric (age 0–19) COVID-19 cases accounted for about 10% of the total cases in the State of Michigan (MDHHS, 2020). Per a recent joint report from the American Academy of Pediatrics and the Children's Hospital Association, there are approximately 1134.1 cases of COVID-19 per 100,000 children in the United States and 949.4 cases of COVID-19 per 100,000 children in the state of Michigan (American Academy of Pediatrics, 2020). The above statistics for COVID-19 cases demonstrates that pediatric COVID-19 rates are low. There have been 391,814 cases of COVID-19 in the <21 age group in the United States between February 12 and July 31, 2020 with 121 deaths reported. Five of the decedents reportedly had an underlying metabolic disorder, although the total number of individuals with IEMs infected with SARS-CoV-2 are not reported (Bixler et al., 2020). Despite the apparently high percentage of deaths in children with an underlying IEM, our center's experience suggests that individuals with an underlying IEM are not at a higher risk than the general pediatric population of being severely symptomatic from COVID-19.

4 | CONCLUSION

This report demonstrates that an infection with SARS-CoV-2 in a patient with a metabolic disorder may present as a typical metabolic crisis. The metabolic crisis should be managed as usual with provision of increased calories and dietary management. A hospitalist or intensivist, depending on acuity of presentation, and the infectious disease team should be involved in managing COVID-19 or MIS-C and any associated complications. As COVID-19 has rarely been reported in pediatric patients with IEMs, it can be hypothesized that increased measures to isolate them have been successful or they may have a mild or asymptomatic presentation, but are at risk of metabolic decompensation as with any other infection. Standard hygienic precautions should be taken as children of all ages are susceptible to a symptomatic infection. Children with metabolic disorders are a high risk population due to the risk of metabolic decompensation that may lead to a more complicated course, as they would be with most other infectious diseases. To our knowledge, there have been no reports of patients with inborn errors of metabolism being diagnosed with MIS-C secondary to COVID-19.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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