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Case Report

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Anesthetic Management of a Child With Propionic Acidemia Complicated by Bacteremia and Severe Acute Respiratory Syndrome Coronavirus 2

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Abstract

Propionic acidemia (PA) is a rare, multi-systemic inborn error of metabolism. PA results from an impaired activity of the mitochondrial enzyme, propionyl-CoA carboxylase (PCC). PCC holds an essential role in the catabolic pathways for odd-chain fatty acids, cholesterol side-chains and branched-chain amino acids. Errors in these pathways result in the accumulation of toxic metabolites that may advance into end-organ damage and dysfunction. Clinical manifestations of PA include relapsing courses of severe metabolic acidosis, concurrent viral or bacterial infection, episodic vomiting, gastroesophageal reflux disease (GERD), seizures, developmental delay, hypotonia, hyperammonemia, osteopenia, pancreatitis and cardiomyopathy. This case describes a 3-year-old boy with PA who presented with an acute metabolic crisis, precipitated by *Staphylococcus epidermidis* (*S. epidermidis*) bacteremia and severe acute respiratory syndrome due to coronavirus 2 (SARS-CoV-2) co-infection. He required anesthetic management for surgical removal of an infected central venous port. Anesthetic care for this patient presented the unique challenges of metabolic decompensation amidst infection with SARS-CoV-2. Options for anesthetic care for patients with PA have been elucidated in the literature. However, to our knowledge, this is the first case to describe anesthetic management in a PA patient with SARS-CoV-2.

Keywords: Propionic acidemia; Propionyl-CoA carboxylase deficiency; *Staphylococcus epidermidis*; SARS-CoV-2; COVID-19; Metabolic crisis; Anesthetic management; Pediatric anesthesia

Introduction

Propionic acidemia (PA) is an autosomal recessive disorder characterized by error in organic acid metabolism caused by mutations in the *PCCA* and *PCCB* genes that encode for the α- and β-subunits, respectively, of the tetrameric mitochondrial enzyme propionyl-CoA carboxylase (PCC) [1]. As a rare disease, it has an estimated incidence of approximately 1/60,000 to 1/280,000 individuals, depending on the region of the world [2]. PCC is an enzyme that is biochemically required for the catabolism of branched-chain amino acids (isoleucine, valine, threonine and methionine), cholesterol side-chains, odd-chain fatty acids, uracil and thymine [1, 3]. Derangements in these breakdown pathways lead to the toxic accumulation of metabolites in organs and can cause severe central nervous system impairment, seizures, hypotonia, cardiomyopathy, metabolic acidosis, osteoporosis, gastrointestinal symptoms (gastroesophageal reflux disease (GERD) and episodic vomiting), protein intolerance, hyperammonemia and pancreatitis [1]. PA can be identified at birth by measuring serum levels of metabolites of aforementioned compounds, particularly propionylcarnitine and methionine [1, 4]. Screening fetal DNA for pathogenic mutations in the *PCCA* and *PCCB* genes establishes a definitive diagnosis.

The main objective in the management of PA is the prevention of acute metabolic crises [5]. Acute metabolic decompensations can be triggered by fever, vomiting, prolonged fasting, gastroenteritis and infective syndromes [5, 6]. Acute episodes of PA are commonly treated with intravenous fluid therapy, appropriate nutritional intake (such as intravenous glucose, low-protein enteral feeding) with the avoidance of protracted fasting periods, administration of ammonia-scavenging medications, biotin (a cofactor for PCC), levocarnitine, carglumic acid, reduction of serum acid burden (with sodium bicarbonate) and management of precipitating events (including, but not limited to antibacterial or antiviral medications) [1, 7].

Severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) has caused significant morbidity and mortality around the world [8]. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus that enters the host cell through binding of its spike (S) protein to the host's angiotensin-converting enzyme 2 (ACE2) receptors in the lungs, intestinal epithelium, heart, vascular epithelium and kidneys, giving it a mechanism for potential multi-organ disease [9]. It is spread predominantly by respiratory droplets that have been shown to survive on certain surfaces for up to several weeks [10]. It has also been shown to remain stable in aerosolized

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form for as long as 3 days [10]. Clinical manifestations include fever, fatigue, chills, dry or productive cough, headache, nasal discharge and congestion, sore throat, dyspnea, anosmia, nausea, emesis, diarrhea and myalgias [9]. In severe cases, it can cause pneumonia (leading to respiratory failure or acute respiratory distress syndrome), thromboembolic events and cardiovascular compromise [9]. The case-fatality rate (CFR) has varied widely in different countries, but has been recorded to as high as 14.5% in Italy in the summer of 2020 [11]. The preferred diagnosis uses polymerase chain reaction (PCR) assay to detect the viral RNA from the upper respiratory tract, typically by way of nasopharyngeal swabbing [12]. Data and treatment recommendations regarding SARS-CoV-2 are rapidly evolving, but treatment plans among different institutions have included the use of dexamethasone (or other glucocorticoids), remdesivir (a new nucleotide analogue that has *in-vitro* activity against the virus), intravenous immunoglobulin (IVIG) and convalescent plasma [13-15].

Reviews of SARS-CoV-2 infection in pediatric patients suggest that the clinical course of infection in children is milder and confers better prognosis compared to adult or elderly patients [16]. However, the impact of the virus on patients with inborn errors of metabolism is not well known [17]. A case report published by Cacioti et al identified SARS-CoV-2 infection as the precipitating factor for a metabolic crisis in a pediatric patient with PA; although, the patient did not require anesthetic management during hospital admission [18]. To date, anesthetic care for a patient diagnosed with PA and SARS-CoV-2 has not been described in the literature. We present a 3-year-old boy with PA who presented in acute metabolic crisis precipitated by *S. epidermidis* bacteremia and SARS-CoV-2. We present this because PA patients, as in our case, may require anesthetic management for surgical intervention, particularly for radiographic imaging (magnetic resonance imaging (MRI) or computed tomography (CT) scans), central venous cannulation and gastrostomy tube (G-tube) placement. The perioperative management of our patient focused on continuing supportive treatment for his metabolic crisis to avoid further decompensation, and ensuring that operating room (OR) personnel were protected from exposure to his SARS-CoV-2 infection.

Case Report

Investigations

The patient is a 3-year-old boy diagnosed with congenital PA, complicated by metabolic strokes with neurologic sequelae (seizures, developmental delay, non-verbal communication, non-ambulatory). He received tube feedings through a G-tube five times a day. He also had a left subclavian vein subcutaneous port that was placed 2 years ago. He presented to the emergency department with acute encephalopathy after experiencing cough, congestion and non-bloody, non-bilious post-tussive emesis in the previous 24 h. He was reported to be in his usual state of health prior to these symptoms. On examination, he was found to be markedly lethargic, hypotonic, normotensive, with a low-grade fever (38 °C), tachycardic (128 bpm) and tachypneic (34 breaths/min). Review of medical history and previous records revealed the patient had a recent hospital admission 3 months prior for status epilepticus, for which he was tracheally intubated for several days and discharged home with anti-seizure medications. Interview of his parents also revealed that both his mother and father, as well as his aunt, were diagnosed with SARS-CoV-2 infection 3 weeks prior. All of them completed self-quarantine and had since recovered.

Diagnosis

Laboratory workup in the emergency department showed results consistent with an episode of hyperammonemic metabolic acidotic crisis, including a pH of 6.95, bicarbonate level of 5 (hospital normal range: 18 - 27 mmol/L), glucose of 47 (range: 70 - 105 mg/mL), ammonia of 190 (range: 18 - 72 µmol/L) and white blood cell count of 16.7 (range: 4.5 - 14 × 10^9/L). Chest radiograph appeared normal. Blood cultures from his central port as well as from new venous sites were obtained, all of which grew gram-positive cocci that speciated into *S. epidermidis*. SARS-CoV-2 PCR assay was positive, while the remainder of his viral and bacterial respiratory panels were negative. A transthoracic echocardiogram was obtained revealing normal biventricular systolic function and no pathologic valve stenosis or regurgitation was seen.

Treatment and anesthetic management

The patient was admitted to the pediatric intensive care unit (PICU) and was treated with ammonia-scavenging drugs (a combination of sodium benzoate and sodium phenylacetate), carglumic acid, levocarnitine, biotin, serum acid buffering with sodium bicarbonate, glucose delivery and aggressive fluid hydration. Enteral feeding with low-protein formula was initiated through his G-tube. His anti-seizure medications (clonazepam and lamotrigine) were also continued. IVIG for SARS-CoV-2 infection and broad-spectrum intravenous antibiotics (vancomycin, clindamycin and piperacillin-tazobactam) were initiated per the infectious disease team recommendations.

The patient's metabolic crisis was attributed to a possible central venous port infection and co-infection with SARS-CoV-2. He was slated for the OR 2 days after his initial presentation and was scheduled for removal of his central port, as well as placement of a peripherally placed central catheter (PICC). A preoperative anesthetic evaluation revealed a 13.9-kg male with a blood pressure of 98/78 mm Hg, a heart rate of 120 bpm and respiratory rate of 35 breaths/min. Auscultation of the heart and lungs revealed no abnormalities. Laboratory values at this time were normalized from his treatments and were as follows: pH of 7.47, bicarbonate of 25 mmol/L, glucose of 75 mg/mL, ammonia of 55 µmol/L, white blood cell count of 11 × 10^9/L, in addition to normal serum creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), hemoglobin and platelet levels.

He was *nil per os* (NPO) for 6 h for enteral feedings. At least one functioning intravenous cannula was verified. To avoid worsening of his metabolic crisis due to catabolic processes, maintenance with intravenous fluid consisting of D5 ½ NS with 20 mEq KCl/L and 27 mEq $NaHCO_3$/L was initiated immediately after the discontinuation of enteral feeds. Because of the patient's positive SARS-CoV-2 status, he was taken to a negative-pressure OR for his procedure. Routine monitors were used, including pulse-oximetry, electrocardiography, non-invasive blood pressure, end-tidal CO_2 and skin temperature. An attending anesthesiologist and a resident anesthesiologist both donned controlled air-purifying respirators (CAPRs) while the rest of the OR personnel wore N95 masks. Rapid sequence induction and intubation were performed without difficulty using indirect visualization with a video-laryngoscope. To limit the exposure of OR personnel to respiratory droplets and aerosols that may carry SARS-CoV-2, non-anesthesiology staff were asked to leave for the induction and intubation period. The patient was given 2 mg of intravenous midazolam. A bolus dose of propofol (1.5 mg/kg), fentanyl (1 µg/kg) and rocuronium (1.2 mg/kg) were given on induction, and anesthesia was maintained with 1.8-2.2% sevoflurane in 50% oxygen. Before the start of the procedure, another intravenous line was placed, as well as an arterial line for continuous blood pressure monitoring.

Follow-up and outcome

Upon removal of the port, significant bleeding occurred where the previous catheter entered the venous system, at the junction of the subclavian and internal jugular veins. About 350 mL of blood was lost before hemostasis of the venotomy was achieved. The patient was rapidly transfused 120 mL of packed red blood cells (PRBCs). Vital signs remained normal throughout the procedure, however. Upon the completion of the procedure, he was transported back to the PICU and was extubated there without issues. The patient remained hemodynamically stable throughout the remainder of his stay in the PICU, and was discharged home 3 days after his procedure with instructions to continue intravenous vancomycin (following *S. epidermidis* susceptibility results) for 6 weeks. Another SARS-Co-V-2 PCR test was obtained 2 weeks after he was discharged, which resulted negative.

Discussion

PA is a rare, autosomal recessive inborn error of metabolism, resulting from a deficiency in the activity of the mitochondrial enzyme PCC [1]. PCC is a tetrameric protein with two protein subunits encoded by the genes *PCCA* and *PCCB* located on the long arm of chromosome 3 and on chromosome 13, and mutations in either or both of the two genes result in PA [19]. PCC plays a chief role in the catabolism of branched-chain amino acids (isoleucine, valine, threonine and methionine), cholesterol side-chains, odd-chain fatty acids, uracil and thymine [3]. A normally functioning PCC catalyzes the conversion of the enzyme propionyl-CoA to methylmalonyl-CoA with biotin as a cofactor [3]. Methylmalonyl-CoA is eventually transformed into succinyl-CoA, which functions as a substrate in the citric acid or tricarboxylic acid cycle (TCA) [3]. In PA, the deficient conversion of propionyl-CoA to methylmalonyl-CoA leads to the intracellular buildup of propionyl-CoA and damaging metabolites, such as 3-OH-isopropionate, propionic acid, 2-methylcitrate, propionylglycine, propionylcarnitine and fatty acids [3]. In addition, the decreased levels of succinyl-CoA results in TCA and oxidative phosphorylation dysfunction, which subsequently leads to impaired mitochondrial adenosine triphosphate (ATP) production [3]. Aggregation of these toxic metabolites and insufficient ATP production result in multi-systemic chronic disease, particularly affecting organs with high energy requirements, such as the brain, the heart and muscles (particularly muscles of respiration).

PA is often diagnosed in the neonatal period by increases in serum propionylcarnitine and methioinine levels. Confirmatory diagnosis is made by molecular genetic testing for *PCCA* and *PCCB* mutations [1, 6]. Acute metabolic crises related to PA can be triggered by fever, prolonged fasting, gastroenteritis, vomiting and other viral or bacterial infections [5, 6]. In this case, concurrent bacteremia and SARS-CoV-2 infection was the trigger. It is believed that SARS-CoV-2 may produce a dysregulated immune response, particularly through a disordered production of proinflammatory cytokines, which could lead to an immunocompromised state [19, 20]. Since the patient had had the central venous port for 2 years, it is possible that his SARS-CoV-2 infection allowed for the development of an immunocompromised state which resulted in a bloodstream bacterial infection.

Acute management of metabolic acidotic crises and hyperammonemia in PA focuses on the pathophysiological processes characterizing the disease, particularly with quick initiation or continuation of enteral feeding with a low-protein formula that is devoid of the aforementioned proteinogenic amino acids methionine, isoleucine, threonine and valine [1, 7]. Fasting is avoided not only to minimize hypoglycemic episodes, but also to prevent the catabolism of protein that may worsen metabolite accumulation and hinder ATP production [21]. Hyperammonemia is treated with ammonia-scavenging drugs, biotin and carglumic acid [21]. Levocarnitine is given to promote the renal excretion of organic metabolites [21]. Metabolic acidosis is attenuated with sodium bicarbonate administration in addition to nutritional support [21]. Supportive treatment for precipitating factors, such as bacterial or viral infections, is established [21]. With our patient, we limited NPO time to the strict 6-h minimum for enteral feeds and immediately started dextrose-containing intravenous fluids.

Preoperative evaluation of a patient with PA should focus on acid-base homeostasis, nutritional state, muscular tone, severity of central nervous system involvement and gastrointestinal function [22]. Ammonia, pH, bicarbonate and glucose levels should be included in the preoperative laboratory tests [22]. End-organ involvement that may affect perioperative care should be assessed, such as obtaining an electrocardiogram or an echocardiogram for possible cardiac disease that may increase perioperative mortality [22]. Severity of hypotonia or psychomotor dysfunction should also be evaluated

as they may confer weakness in respiratory muscles that may make tracheal extubation difficult [22].

Guidelines for tracheal intubation of patients with SARS-CoV-2 vary among healthcare institutions. However, commonly used strategies are listed here, all of which were followed in our case. Personal protection with proper use of appropriate personal protective equipment (PPE) is the main priority [23]. If possible, intubation should be performed in a negative-pressure room. The number of healthcare providers in the OR should be limited during the intubation period, and the most experienced anesthetist available should perform the procedure [23]. Finally, rapid sequence induction and intubation with a video-laryngoscope should be performed with the intent to limit bag-mask ventilation and decrease the potential aerosolization of the virus from the airway.

Intraoperatively, rapid sequence induction and intubation should be considered because PA patients typically present with gastrointestinal reflux and vomiting. We elected to perform rapid sequence induction and intubation because our patient presented with vomiting, and we intended to limit aerosolized particle formation that may potentially carry SARS-CoV-2. Neuromuscular blocking medications that are processed by ester hydrolysis, such as mivacurium and succinylcholine, should be avoided because their metabolites include odd-chain compounds [22]. Propofol was used for induction in our case, but should have been avoided because it is prepared as an emulsion that consists of soybean oil, high in odd-chain fatty acids. Non-steroidal anti-inflammatory drugs (NSAIDs) that are derivatives of propionic acid, such as ibuprofen, ketorolac and naproxen, should also be avoided [22]. Because hypotonia and lethargy are not uncommon clinical findings in PA patients, they are particularly sensitive to the central nervous system depressant effects of volatile anesthetics and opioid medications. Accordingly, their dosages should be carefully titrated [22]. In addition to the aforementioned triggers of acidotic crises in PA, surgical stress, hypoxia and hypotension can also precipitate metabolic acidosis [22]. Limiting the occurrence of these states is crucial in preventing intraoperative decompensation. Our patient in particular sustained blood loss that was rapidly replaced with PRBCs. In addition to standard American Society of Anesthesiologist (ASA) monitoring requirements, we were able to continuously monitor his blood pressure with an arterial line, and ensuing hypotension or hypoxia was not observed.

During the post-operative period, PA patients may be prone to develop respiratory distress secondary to upper airway obstruction or muscular fatigue [21]. Airway complications can be minimized if tracheal extubation is deferred until the patient has fully regained baseline strength [22].

Learning points

PA is a rare, inborn error of metabolism, resulting from a defective PCC enzyme. Perioperative management of patients focuses on proper preoperative evaluation of end-organ involvement, avoiding catabolic and acidotic states by continuing appropriate nutrition, and vigilance in the use of anesthetics. Postoperatively, PA patients should be observed for clinical signs of respiratory insufficiency or deterioration. Co-infection with SARS-CoV-2 presents a particularly unique situation, but of utmost importance are the proper use of appropriate PPE, limiting aerosol-generation and limiting the number of health care providers in the room where the patient is to be intubated.

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Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

Informed Consent

Informed consent was obtained from the parents of the individual participant included in this case report. The patient was also appropriately de-identified for this manuscript.

Author Contributions

LS initiated the case report idea. LS, WK and LL treated this patient. LS, WK, LL, SS, JM and AM contributed to data collection, analysis, interpretation, and paper elaboration.

Data Availability

Any inquiries regarding data supporting findings of this case report should be directed to the corresponding author.

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