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Case Report

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Anesthetic Management of a Patient With Carnitine-Acylcarnitine Translocase Deficiency

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Abstract

Carnitine-acylcarnitine translocase (CACT) deficiency is a rare disorder of mitochondrial fatty acid metabolism that results in an acute encephalopathic and/or myopathic disorder. Carnitine and CACT play an essential role in the transport of fatty acids into the mitochondria. The deficiency leads to the reduced transport of long-chain fatty acids into the mitochondria, thereby limiting the use of fatty acids for energy production especially during prolonged fasting, febrile illnesses, increased muscular activity, and other periods of systemic stress. We present the anesthetic management of a 10-year-old girl, diagnosed with CACT deficiency at birth, who presented for multiple osteotomies. The preoperative evaluation of such patients is presented, previous reports of anesthetic care are reviewed, and options for intraoperative care are discussed.

Keywords: Carnitine-acylcarnitine translocase deficiency; Mitochondrial disorders; Fatty acid metabolism

Introduction

Carnitine-acylcarnitine translocase (CACT) is one of 10 closely related mitochondrial-membrane carrier proteins that shuttle substrates including fatty acids between the cytosol and the intra-mitochondrial matrix space across the external and internal mitochondrial membranes [1, 2]. With CACT and the carrier protein, carnitine, fatty acids are able to cross the mitochondrial membrane to undergo beta-oxidation. A rare mitochondrial fatty acid oxidation disorder, CACT deficiency, is acquired as an autosomal recessive condition due to mutations of the SLC25A20 gene on chromosome 3p21.31 [3, 4]. The clinical signs and symptoms of CACT deficiency result from a combination of energy depletion and endogenous toxicity. The metabolic consequences of defective or deficient CACT include hypoketotic hypoglycemia during fasting, hyperammonemia, elevated creatinine phosphokinase and hepatic transaminases, dicarboxylic aciduria, a low free carnitine plasma concentration, and a marked elevation of long-chain acylcarnitines. The predominantly affected organs include the brain, heart, skeletal muscle, and liver, leading to neurological abnormalities with seizures and developmental delay, cardiomyopathy and arrhythmias, skeletal muscle weakness with hypotonia, and in severe cases hepatic failure. The majority of patients become symptomatic in the neonatal period with a rapidly progressive metabolic deterioration with a high mortality rate, mostly due to hepatic and cardiac failure. However, presentations at a later age or survival beyond infancy with a milder phenotype have also been reported. We present the anesthetic management of a 10-year-old girl, diagnosed with CACT deficiency at birth, who presented for multiple osteotomies to correct orthopedic deformities. The preoperative evaluation of such patients is presented, previous reports of anesthetic care are reviewed, and options for intraoperative care are discussed.

Case Report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, OH) for the presentation of single case reports. The patient was a 10-year-old, 28.8 kg girl who presented for anesthetic care for left pelvic osteotomy, bilateral varus derotational osteotomies, and adductor releases. Co-morbid conditions included CACT deficiency with quadriplegic cerebral palsy, epilepsy, cortical blindness, developmental delay, and gastroesophageal reflux disease. She had undergone multiple surgeries in the past including corpus callotomy resection, multiple endoscopies for severe gastroesophageal reflux, Nissen fundoplication, and adenotonsillectomy. Preoperative physical examination revealed a small girl with failure to thrive and multiple joint contractures. There were no abnormal airway, craniofacial, cardiovascular or pulmonary findings. Abdominal examination revealed a midline scar with a G-tube. Preoperative laboratory evaluations including electrolytes, coagulation profile, liver function tests, and

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blood glucose were normal. Preoperative medications included cetirizine (5 mg once a day), clobazam (20 mg every morning), baclofen (TID), lansoprazole (15 mg BID), melatonin (10 mg at night), glycopyrrolate (1 mg twice a day), zonisamide (150 mg twice a day), and lacosamide (10 mg twice a day). Given the CACT deficiency, she was admitted the day prior to surgery for placement of a double lumen (4 Fr) peripheral intravenous central catheter (PICC) in the left brachial vein for perioperative access and the administration of glucose and intravenous fluids while she was *nil per os* (NPO). Routine G-tube feeds were administered until 2 am and then an infusion of 5% glucose in lactated Ringer's was started while she was NPO. Anesthesia was planned with specific concerns for difficult vascular access, the administration of blood products, and invasive monitoring. Anesthesia was induced with propofol (4 mg/kg) and fentanyl (2 µg/kg). Neuromuscular blockade was provided by rocuronium (1.2 mg/kg) followed by endotracheal intubation with a 6.0 mm cuffed endotracheal tube. Anesthesia was maintained with isoflurane (exhaled concentration 0.6-1.2%) in air and oxygen and supplemental intravenous fentanyl. A second peripheral intravenous catheter and an arterial catheter were placed. For postoperative analgesia, an epidural catheter was placed in lumbar region (L_{1-2}). No significant intraoperative hemodynamic concerns were noted. To limit intraoperative blood loss, tranexamic acid was administered (loading dose of 50 mg/kg followed by an infusion of 5 mg/kg/h). Serial intraoperative arterial blood gas analyses including sodium, potassium and ionized calcium level were normal. Serial glucose measurements were 258, 261, 247 and 221 mg/dL. Due to the slightly elevated blood glucose values, the maintenance intravenous (IV) fluids were changed from 5% dextrose in lactated Ringer's to lactated Ringer's. The surgical procedure lasted 8 h with an estimated blood loss of 150 mL. Intraoperative fluids included 600 mL 0.9% NS and 250 mL 5% albumin. Intraoperative hemoglobin decreased from a starting value of 12.9 to 8.8 g/dL. Postoperative nausea and vomiting prophylaxis was provided by dexamethasone (4 mg) and ondansetron (3 mg). At the completion of the surgical procedure, dexmedetomidine (0.3 µg/kg) and acetaminophen (15 mg/kg) were administered. Residual neuromuscular blockade was reversed with sugammadex (4 mg/kg) and the patient's trachea was extubated. The patient was transported to the post-anesthesia care unit (PACU). Postoperative analgesia was provided by an epidural infusion of 0.1% ropivacaine 0.1% with hydromorphone at 6 mL/h. The patient's PACU stay was uneventful and she was trasnferred to pediatric intensive care unit (PICU) for overnight observation. She was discharged to the inpatient ward the next day and home on postoperative day 7.

Discussion

Carnitine plays an essential role in the enzymatic transport of long-chain fatty acids into the mitochondria for beta-oxidation [3]. During prolonged fasting, the primary energy source shifts to the catabolism of fatty acids via beta-oxidation occur in the mitochondria. Through this process, fatty acids are broken down into two carbon fragments which can then enter the Kreb's cycle to generate ATP or serve as a substrate for gluconeogenesis. However, the movement of fatty acids into the mitochondria across their inner and outer membranes depends on the normal functioning of carnitine and its associated enzymes including CACT [5]. For transport through the mitochondrial membranes, the fatty acid is bound to carnitine, forming acylcarnitine which crosses the external mitochondrial membrane. CACT is responsible for transporting the carnitine-fatty acid complex (acylcarnitine) across the inner mitochondrial membrane. During the process, the acylcarnitine is degraded to acyl-CoA and carnitine via the enzyme, carnitine palmitoyltransferase type II (CPT II), releasing carnitine inside the mitochondria. Deficiencies of any of the enzymes (CPT I, CPT II, or CACT) or the substrates (carnitine) needed for the process result in the ineffective movement of the fatty acids into the mitochondria, thereby limiting their availability for catabolism.

CACT deficiency is a life-threatening, inherited disorder of fatty acid beta-oxidation, which usually presents in the neonatal period with severe hypoketotic hypoglycemia, hyperammonemia, cardiac involvement with cardiomyopathy and arrhythmia, hepatic dysfunction, skeletal muscle weakness, and encephalopathy. CACT deficiency was first reported by Stanley et al in 1992 in a newborn who presented with seizures, severe apnea and bradycardia after 36 h of life [6]. The clinical presentation was thought to be provoked by fasting secondary to limited breast output from the mother. Treatment was initiated with intravenous fluids, mechanical ventilation, and cardiovascular support with vasoactive agents. Arrhythmias including recurrent premature ventricular contractions and ventricular tachycardia were treated with lidocaine. During the first 3 months of life, the patient was hospitalized twice for vomiting, lethargy, and coma. Associated hepatomegaly resolved when reduced in size when the patient was fed a high carbohydrate and low fat formula. Persistently elevated plasma ammonia levels were also noted. Oral carnitine administration did improve the patient's clinical state. Fasting provoked episodes of coma that responded to intravenous glucose administration. By 30 months of age, the patient developed generalized weakness which increased over the ensuing months along with the development of feeding intolerance and hepatomegaly. The patient subsequently expired a month later due to aspiration pneumonia and respiratory failure.

The preoperative evaluation of patients with CACT deficiency is similar to patients with other mitochondrial defects of fatty acid metabolism [5, 7]. End-organ involvement related to the deficient enzyme function may include the central nervous system (developmental delay and seizures), skeletal muscle (myopathy), cardiovascular system (cardiomyopathy and arrhythmias), hepatic dysfunction, and alterations in blood glucose levels with hypoglycemia. A hallmark of this and other disorders of fatty acid catabolism is non-ketotic hypoglycemia. During fasting, as the fatty acids are unable to enter the mitochondria and as such as not available for catabolism (production of glucose and ketone bodies), hypoglycemia without the presence of ketone bodies (non-ketotic) is noted.

As with the anesthetic care of all patients, the focus of effective perioperative care begins with the preoperative examination and the identification of end-organ involvement by

the primary disease process. Cardiac involvement should be evaluated with a preoperative echocardiogram and 12-lead ECG. Although our patient had no evidence of myocardial involvement, the anesthetic technique may need to be modified in patients with depressed myocardial function with attention to the potential negative inotropic effects of anesthetic agents used for induction and maintenance. Invasive hemodynamic monitoring may be indicated based on the presence of co-morbid cardiac diseases. The preoperative evaluation of serum electrolytes, blood urea nitrogen, creatinine, hepatic enzymes, and coagulation function is suggested given the potential for hepatic or renal involvement.

Involvement of the central nervous system (CNS) is an invariable component of CACT deficiency including developmental delay, mental retardation, and seizures. Preoperative management to limit the potential for perioperative seizures includes optimizing and confirming therapeutic anticonvulsant levels prior to the surgical procedure. Routine anticonvulsant medications should be administered the morning of the procedure despite concerns of the patient's NPO status with subsequent intraoperative dosing as needed [8]. Alternative routes of delivery (IV or rectal) should be considered when enteral administration is not feasible. Consultation with the neurology or pharmacology service may be helpful to determine dosing conversion from enteral to IV administration or to guide intraoperative redosing. Sodium valproate inhibits mitochondrial beta-oxidation of fatty acids and should be avoided in patients with mitochondrial metabolic disorders [9, 10].

Several factors may predispose these patients to perioperative respiratory insufficiency including co-morbid involvement of the CNS with poor airway control and altered central control of ventilation, and skeletal muscle involvement with hypotonia and poor cough effort. Such problems may be exacerbated by the residual effects of anesthetic agents, the surgical procedure, and the use of postoperative opioids for pain management. To limit the perioperative need for IV opioids in our patient and their effects on respiratory function, an epidural catheter was placed for postoperative analgesia. Postoperative monitoring of respiratory function with early institution of pulmonary toilet is suggested, preferably in an ICU setting given the potential for perioperative respiratory insufficiency. The use of adjunctive agents (acetaminophen or non-steroidal anti-inflammatory agents) may also be effective to decrease opioid needs and their associated adverse effects. Non-invasive techniques of respiratory support such as BiPAP may be used to avoid or treat postoperative respiratory insufficiency without the need for endotracheal intubation [11, 12].

The invariable involvement of the skeletal muscle system with hypotonia and contractures may impact the choice of neuromuscular blocking agent (NMBA). Given the potential for gastroesophageal reflux and poor airway control, a rapidly acting non-depolarizing NMBA with a rapid sequence induction may be chosen for airway management. With the associated involvement of the skeletal musculature, the use of succinylcholine is relatively contraindicated [13]. Although not tested specifically in patients with CACT deficiency, associated hypotonia may predispose to an exaggerated and prolonged effect from NMBAs. Dosing based on monitoring may be helpful to avoid prolonged recovery times. Residual neuromuscular blockade should be reversed at the completion of the procedure and full recovery documented prior to tracheal extubation. In our patient, we chose to reverse neuromuscular blockade with sugammadex given its limited adverse effect profile and superior efficacy when compared to cholinesterase inhibitors [14].

Patients with debilitating neurologic disorders such as CACT deficiency frequently have multiple joint contractures with limited range of motion. Restricted flexion and extension of the limbs can make insertion of invasive arterial cannulae and IV access difficult. Ultrasound guidance may be invaluable in gaining adequate vascular access for major surgical procedures [15]. The muscle wasting and joint contractures also mandate close attention to surgical positioning.

A key component of the perioperative care of patients with disorders of fatty acid metabolism includes avoidance of prolonged periods of fasting. In our patient, we chose to admit the patient the evening before the procedure to allow for the institution of an IV infusion of glucose when the patient was held NPO. Alternatively, it may be feasible to allow day of surgery admission provided that clear liquids are strictly administered up to 2 h prior to the surgical procedure. Intraoperatively and postoperatively, IV glucose is administered and blood glucose is maintained in the normal range to avoid to maximally inhibit lipolysis and the need for fatty acid beta-oxidation to avoid acute deteriorations in the patient's metabolic status. Long-term strategies include avoidance of fasting with frequent meals and a special diet with restriction of long-chain fatty acids. Due to the extremely low plasma free carnitine concentrations, carnitine supplementation is often used although its efficacy in CACT deficiency has not been proven in rigorous clinical trials. As noted above, carnitine is an essential transport substrate for the movement of fatty acids across mitochondrial membranes. Furthermore, carnitine binds to excessive metabolites generated in fatty acid oxidation disorders, and facilitates their excretion. Carnitine along with a dextrose infusion should be considered if there is any deterioration in the neurologic status during the postoperative period (vomiting, lethargy, or change in mental status).

Although there have been anecdotal reports of malignant hyperthermia in patients with enzymatic defects involving the mitochondria, the association is not universal and the use of volatile agents has been demonstrated to be safe in this population [16, 17]. Theoretical biochemical concerns have been expressed with the use of propofol in patients with mitochondrial disorders of fatty acid metabolism. Propofol not only can provide a large lipid load given its preparation, it also may impair mitochondrial electron transport in select patients through inhibition of oxidative phosphorylation, carnitine palmitoyltransferase transport of long-chain fatty acids, and beta-oxidation of fatty acids [18]. These effects may lead to an exacerbation of the mitochondrial defect with the development of propofol infusion syndrome and severe metabolic acidosis [19, 20]. Given these concerns, we limited the use of propofol in our patient to a single dose for anesthetic induction and then used a volatile agent for the maintenance of anesthesia. The safety of more prolonged propofol infusions remains questionable with some authors cautioning against it uses. Given the potential for inhibition of mitochondrial function, it may be

appropriate to monitor acid-base status and plasma lactic acid when prolonged infusions are used and to immediately discontinue the infusion should chemical abnormalities be noted.

In summary, CACT deficiency is a rare disorder of mitochondrial fatty acid metabolism (mitochondrial myopathy). Carnitine and the enzyme, CACT, play an essential role in the transport of fatty acids into the mitochondria. The deficiency leads to multi-system involvement including the cardiac, hepatic, skeletal muscle, and CNS. The preoperative assessment of end-organ impairment by the primary disease process and close postoperative monitoring are mandatory for the effective perioperative care of these patients. Prolonged fasting may lead to hypoglycemia and acute metabolic decompensation. Anesthetic concerns include the potential for metabolic derangements from the effects of prolonged propofol infusions on mitochondrial fatty acid metabolism and the potential for prolonged effects of noon-depolarizing NMBAs.

Disclosures

None.

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