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Perioperative Management of a Patient With Glutaric Aciduria

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Abstract

Glutaric aciduria type-1 (GA-1) is an autosomal recessive metabolic disorder due to the deficiency of the enzyme, glutaryl-CoA dehydrogenase. The enzymatic defect leads to secondary damage to the central nervous system due to the accumulation of glutaric acid. Due to the progressive neurologic effects with spasticity and orthopedic deformities, surgical and anesthetic cares are frequently required. We present a 13-year-old girl with glutaric acidemia type 1 who required anesthetic care for posterior spinal fusion. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement is discussed, and options for anesthetic care are presented.

Keywords: Posterior spinal fusion; Scoliosis; Glutaric aciduria type-1

Introduction

Glutaric aciduria type-1 (GA-1) is an uncommon, severe autosomal recessive metabolic disorder due to the deficiency of the enzyme, glutaryl-CoA dehydrogenase (GCDH) within the mitochondria [1]. It is one of several genetic/metabolic disorders in the category of organic acidurias. The disorder generally presents in early childhood with the majority of children having no measurable enzyme activity. The estimated prevalence varies from 1 in 30,000 newborns in one Scandinavian study to 1 in 30,000 - 100,000 newborns in other studies [2-5]. The prevalence may be much higher in isolated populations in the Middle East countries due to higher rates of consanguinity [6, 7]. GA-1 was described first by Goodman et al in 1975 [8]. Mutations in the mitochondrial GCDH gene located on chromosome 19 (19p13.2) lead to a deficiency of GCDH, a mitochondrial enzyme involved in the metabolism of lysine, hydroxyl-lysine, and tryptophan [8-11]. This defect results in the accumulation of GA and 3-hydroxyglutaric acid (3-OHGA) with secondary carnitine depletion. The progressive neurologic effects of the disorder frequently lead to spasticity and orthopedic deformities requiring surgical and anesthetic care. We present a 13-year-old girl with glutaric acidemia type 1 who required anesthetic care for posterior spinal fusion. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement is discussed, and options for anesthetic care are presented.

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Case Report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, OH) for the presentation of single case report. The patient was a 13-year-old, 31.75 kg, girl who presented for posterior spinal fusion for the treatment of progressive scoliosis. Her past history was significant for GA-1 which was diagnosed at 5 months of age. Her past surgical history included Nissen fundoplication with gastrostomy tube (G-tube) placement due to aspiration problems, umbilical hernia repair, bilateral tympanostomy with tube placement, left hip joint surgery, and botulinum toxin injections to treat spasticity. Associated comorbid conditions included gastroesophageal reflux, dysphagia with chronic vomiting, osteoporosis, central nervous system (CNS) involvement with spasticity, osteoporosis, developmental delay, asthma, bowel and urinary incontinence. Current home medications included levocarnitine (500 mg via G-tube once daily), riboflavin (100 mg via G-tube every night), clonazepam (0.5 mg via G-tube TID), diazepam (5 mg via G-tube), diazepam rectal gel as needed for seizures lasting more than 5 min, lamotrigine (75 mg in the morning and 100 mg at night), lansoprazole (30 mg once a day), sucralfate (500 mg via G-tube TID), ondansetron (3 mg via G-tube QID), albuterol (high-flow nebulizer every 4 h), and ergocalciferol (1,000 units via G-tube once a day). Allergies included oxcarbazepine. Preoperative physical examination revealed an adolescent in no acute distress with moderate

scoliosis, normal systemic examination, and a G-tube in place. Airway examination revealed a Mallampati grade I view. Preoperative laboratory evaluations including electrolytes, renal function, coagulation function, blood glucose and hepatic function were normal. The hemoglobin was 10.2 g/dL with a hematocrit of 32.2%. The patient was admitted the day before surgery to manage her preoperative comorbid conditions. She was held nil per os (NPO) for 6 h except for her usual medications and a peripheral intravenous infusion of 5% dextrose in 1/2 normal saline was started at 1.5 times maintenance. The preoperative blood glucose was 79 mg/mL with a room air oxygen saturation of 99%. The patient was transported to the operating room and routine American Society of Anesthesiologists' monitors were applied. Anesthesia was induced with propofol (50 mg) and fentanyl (25 µg) which were administered intravenously through a pre-existing peripheral intravenous line. Bag-valve-mask ventilation was provided without difficulty. Neuromuscular blockade was provided with rocuronium (30 mg) and direct laryngoscopy was performed with a Miller 2 blade. Laryngoscopy revealed a Cormack-Lehane grade I view and a 6.0 mm cuffed endotracheal tube was placed on the first attempt. After the induction of anesthesia, arterial and central venous accesses were obtained using ultrasound guidance. Additionally, using ultrasound guidance two additional 18-gauge intravenous cannulas were placed in the right and left saphenous veins. Tranexamic acid was administered for prevention of fibrinolysis and limit intraoperative blood loss (50 mg/kg followed by an infusion at 5 mg/kg/h). The patient was turned and positioned prone. Baseline neurophysiological monitoring including motor evoked potentials (MEP) and somatosensory evoked potentials (SSEPs) was obtained. Per our usual practice to allow for neurophysiological monitoring during spinal surgery, anesthesia was maintained with desflurane titrated to maintain the bispectral index (BIS) at 50 - 60 and a remifentanil infusion of 0.1 - 0.3 µg/kg/min to maintain the mean arterial pressure at 55 - 65 mm Hg [12]. Intraoperative antibiotics included cefazolin and gentamicin. The MAP was maintained at 55 - 65 mm Hg for controlled hypotension to minimize intraoperative blood loss. Heart rates varied from 60 to 120 beats per minute with a normal sinus rhythm. No bradycardia or arrhythmias were noted. During the procedure, the amplitude of the MEP was noted to decrease during placement of spinal instrumentation. A phenylephrine infusion was started to maintain the MAP $\geq$ 70 mm Hg, which resulted in the return of the MEP to baseline. Intraoperative fluids included 1 unit of packed red blood cells, 125 mL of cell saver autologous blood, 250 mL of 5% albumin and 2,007 mL of isotonic crystalloid solution. The estimated blood loss was 600 mL. During wound closure, the remifentanil and tranexamic acid infusions were discontinued. Acetaminophen (15 mg/kg) was administered intravenously along with incremental doses of hydromorphone to provide postoperative analgesia. Following completion of the surgical procedure, the patient was turned supine and her trachea was extubated when awake. The patient was transferred to the post-anesthesia care unit (PACU) followed by the pediatric intensive care unit (PICU) for observation of hemodynamic and respiratory function. Postoperative pain control was provided with hydromorphone delivered via nurse-controlled analgesia. The remainder of her postoperative course was uncomplicated and she was discharged home on postoperative day 5.

Discussion

GA-1 is an inherited metabolic disorder resulting from a deficiency of the mitochondrial enzyme, GCDH. This enzyme is involved in the degradation of several amino acids (lysine, hydroxyl-lysine, and tryptophan) with their eventual conversion to acetyl-CoA and entry into the Kreb's cycle as citric acid. The absence of this enzyme results in increased levels of glutaric acid and a related metabolite (quinolinic acid) with reduced levels of γ-amino-butyric acid (GABA) within the brain and cerebrospinal fluid. These alterations result in progressive damage to the CNS, especially in the basal ganglia (caudate nucleus and putamen) resulting in extrapyramidal symptoms and seizures. Routine newborn screening has allowed early diagnosis with the institution of dietary restriction, carnitine and riboflavin supplementation, and treatment of acute encephalopathic crisis, thereby allowing for more normal development [11, 13, 14]. Despite these therapies, acute exacerbations of the disorder (encephalopathic crisis) may be triggered by infections, stress, fever, or surgery. These crises may result in progressive CNS damage.

Depending on the age of diagnosis, there can be a wide spectrum of clinical features in patients with GA-1 including severe and progressive CNS involvement with severe psychomotor retardation [15]. Macrocephaly is generally present at birth; however, progressive CNS damage can lead to microcephaly [16]. Without routine newborn screening, early diagnosis is difficult as there are no pathognomonic signs or symptoms. Without clinical treatment including dietary therapy, the majority of patients manifest clinical signs and symptoms by 6 - 12 months of age including psychomotor delay, dystonia, and seizures [17, 18]. Hypotonia may be present early, progressing to spastic quadriparesis with progressive CNS involvement. An encephalopathic crisis with necrosis of the basal ganglia can result in dystonic dyskinetic movement disorders such as dysarthria and choreoathetosis, which may be misdiagnosed as athetoid cerebral palsy, attributed to perioperative birth asphyxia. Although there are no specific radiologic findings, CNS imaging may reveal suggestive clinical features including hydrocephalus, brain atrophy, structural changes of basal ganglia, and demyelization. In the majority of patients, basal ganglia abnormalities, the incomplete opercularization of the insular cortex with widening of the Sylvian fissures and CSF spaces can be seen. Additionally, subdural collections of fluid over the convexities with bilateral temporal arachnoid cysts have been reported [19, 20]. Subdural hematomas suggestive of non-accidental trauma have been reported, making it mandatory to rule out GA-1 in cases of suspected non-accidental trauma [21, 22]. If not identified during routine newborn screening, the diagnosis can be confirmed by quantification of 3-OHGA in urine. However, some patients may not excrete large amounts of 3-OHGA and therefore, direct measurement of GCDH activity in fibroblasts and lymphocytes provides the most accurate diagnostic modality [23].

Given the significant comorbid sequelae of GA-1, there

Table 1. Previous Reports of Anesthetic Care for Patients With Glutaric Aciduria

Authors and reference	Patient demographics	Intraoperative management	Postoperative problems and management
Ituk et al [24]	23 years for a scheduled cesarean section at 36 weeks' gestation for marginal placenta previa.	Intravenous infusion of carnitine in 10% dextrose was started to prevent excess protein metabolism. Spinal anesthesia was performed for the cesarean delivery using hyperbaric bupivacaine. A prophylactic phenylephrine infusion was started along with volume loading to maintain blood pressure.	The carnitine and 10% dextrose infusion was continued perioperatively until a regular diet was resumed. No perioperative hemodynamic issues were noted. Male infant delivered without complications. The patient's plasma carnitine, lactate, and electrolytes were within normal limits 24 h postoperatively. She was discharged home on postoperative day 3.
Teng et al [25]	37-month-old, 19 kg girl with macrocephaly and hypotonia for comprehensive dental surgery for treatment of multiple dental caries.	Anesthesia was induced with atropine, thiamylal (5 mg/kg), and fentanyl (2 µg/kg). Neuromuscular blockade with cis-atracuium (0.2 mg/kg). Maintenance anesthesia with sevoflurane. Blood levels of glucose and lactate, and arterial blood gas were monitored and maintained within normal range. Ketorolac was administered for postoperative analgesia. Neuromuscular blockade was reversed with neostigmine and the patient's trachea was extubated.	The patient resumed a normal diet 8 h after the procedure and was discharged uneventfully the next day.
Farag et al [26]	11-year-old, 50 kg patient for closure of a perimembranous ventricular septal defect (VSD).	Anesthesia was induced with ketamine and fentanyl. Neuromuscular blockade with rocuronium. Maintenance anesthesia with isoflurane and nitrous oxide. During cardiopulmonary bypass, anesthesia was maintained with intermittent doses of ketamine. Remifentanil infusion throughout and morphine for postoperative analgesia.	During recovery, insulin was administered to maintain normoglycemia and sodium nitroprusside was administered to control blood pressure. The postoperative course was uneventful and the patient was discharged from the hospital on the postoperative day 3.
Hernandez-Palazon et al [27]	Two siblings: 17 and 30 months old sisters for VP shunt placement.	Perioperative dextrose and fluids were administered. Anesthesia was induced with atropine, propofol, and remifentanil. Neuromuscular blockade with rocuronium. Maintenance anesthesia with propofol and remifentanil. Dextrose infusion intraoperatively to prevent hypoglycemia.	The postoperative course was satisfactory and the patients were discharged home 7 days after the procedure.
Goktas et al [28]	Two siblings: 12 and 16 (51 kg) years, presented with macrocephaly and psychomotor delay. Sedation for MRI.	Peripheral intravenous infusion of glucose in normal saline started. Sedation achieved with propofol bolus dosing followed by an infusion. Spontaneous ventilation maintained with supplemental oxygen delivery via a facemask.	The procedures were completed uneventfully. No hemodynamic or respiratory problems were noted. The patients were discharged home 1 h after the procedure.
Tsiotou AG et al [29]	5 years old boy posted for surgery for neurogenic hip dislocation.	Induction of anesthesia with atropine, propofol, and fentanyl. Rocuronium for neuromuscular blockade. Maintenance anesthesia with sevoflurane and a remifentanil infusion. Intravenous paracetamol to supplement postoperative analgesia. D5¼NS was administered throughout the case.	Intravenous paracetamol continued every 6 h following the procedure. Water intake and a specific high carbohydrate solution were started at 2 and 4 h respectively. Discharged home on postoperative day 2.

are several specific perioperative implications which may significantly impact the risk for perioperative morbidity and mortality. 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. Previous reports regarding the perioperative care of patients with GA-1 syndrome are summarized in Table 1 [24-29]. Perioperative care focuses on the maintenance of normal homeostasis with provision of fluid and glucose during fasting to prevent catabolism and the release of endogenous amino acids. During NPO times, given the potential impact of catabolism and the risks of hypoglycemia, intravenous fluids and dextrose should be provided to meet maintenance needs. Perioperatively, routine medications including anticonvulsant agents, carnitine, and riboflavin should be continued.

When considering the case reports listed in Table 1, they demonstrate several features which should be considered when anesthetizing patients with GA. Most chose to start a peripheral intravenous infusion of glucose to avoid catabolism when the children were placed NPO. The glucose infusion was continued intraoperatively and postoperatively in many patients with ongoing systemic glucose monitoring. In general, they noted no problems with airway management either by bag-valve-mask ventilation or direct laryngoscopy and endotracheal intubation. Several chose to use cricoid pressure or a modified rapid sequence intubation given the potential issues of gastroesophageal reflux in children with chronic debilitating CNS disorders. These case reports demonstrate the safe use of both volatile anesthetic agents and propofol. Intermediate acting neuromuscular blocking agents (NMBAs) such as cis-atracurium or rocuronium were used with no reports of the use of succinylcholine. In one report, brief CNS imaging was accomplished as an outpatient procedure with intravenous propofol sedation while the other patients were admitted at least overnight for monitoring.

One of the primary concerns in children with GA-1 or any chronic debilitating CNS disorder with loss of function relate to the possibility of pulmonary aspiration during anesthetic induction, prolonged responses to non-depolarizing NMBAs, and a hyperkalemic response to succinylcholine. Dysphagia is often seen in these cases, especially with severe dystonia which results in repeated chocking and regurgitation, increasing the risk for aspiration of gastric contents during general anesthesia. Precautions to prevent such problems may include the preoperative administration of H_2-antagonists blockers and the use of cricoid pressure with modified rapid-sequence induction. Medications with extrapyramidal side effects such as metoclopramide and droperidol, although sometimes used to facilitate gastric emptying or treat nausea, should be avoided given their extrapyramidal effects in a patient with underlying involvement of the basal ganglia.

For airway management, a rapidly acting NMBA may be required. Although higher doses of rocuronium (1 mg/kg) may speed the onset and allow earlier tracheal intubation, an exaggerated and prolonged response may be seen in patients with CNS disorders with hypotonia. Given the associated involvement of the CNS, the use of succinylcholine is controversial because of possible hyperkalemia [30]. However, the associated hypotonia may lead to an exaggerated response to NMBAs, making precise dosing with train-of-four monitoring a prerequisite 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. Although not available in the United States, sugammadex may offer an advantage in patients with pre-existing hypotonia who require reversal from profound blockade.

Issues related to poor upper airway control and defective control of ventilation with the associated CNS damage may lead to perioperative respiratory insufficiency. Such problems may be exacerbated by the residual effects of anesthetic agents, the surgical procedure, poor cough effort, and the use of postoperative opioids for pain management. As noted in the previous reports of anesthetic care in patients with GA, short acting anesthetic agents (desflurane, sevoflurane, and remifentanil) may be chosen to eliminate concerns of their effects on postoperative respiratory function. In our patient, the choice of maintenance anesthetic agents including desflurane and remifentanil was based on not only the comorbid conditions, but also the intraoperative requirements mandated by the surgical procedure and neurophysiological monitoring [12]. Given the variable response to anesthetic agents and the need to maintain an acceptable level of anesthesia in a patient with CNS damage, we chose to use bispectral index monitoring to gauge the depth of anesthesia while using remifentanil to provide analgesia and control the hemodynamic response [31, 32]. Postoperative monitoring of respiratory function is suggested especially when opioids are required for postoperative analgesia. The use of adjunctive agents (acetaminophen or non-steroidal anti-inflammatory agents) is suggested as a means of decreasing opioid needs and their associated adverse effects. Non-invasive techniques of respiratory support such as BiPAP may be used to facilitate postoperative tracheal extubation in these patients and avoid postoperative respiratory insufficiency [33, 34].

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 and as demonstrated in the reports reviewed in Table 1 has been shown to be safe and effective in patients with GA [35-38]. Of note, carnitine deficiency is a frequent secondary finding in patients with GA. As carnitine is an essential cofactor in the transport of long-chain fatty acids into the mitochondria and has a pivotal role in fatty acid oxidation, it has been suggested that propofol should be avoided in this condition. Propofol not only can provide excessive lipid, in select patients, it also may impair mitochondrial electron transport with inhibition of oxidative phosphorylation, carnitine palmitoyltransferase transport of long-chain fatty acids, and β-oxidation of fatty acids in the mitochondria [39]. This could predispose to propofol infusion syndrome and severe metabolic acidosis in patients with mitochondrial disorders, carnitine deficiency and inadequate carbohydrate intake [40, 41]. Therefore, the use of propofol for prolonged anesthetic care remains controversial in patients with mitochondrial disorders. Although its use as a single dose for anesthetic induction has not been questioned, the safety of more prolonged infusions remains questionable with some au-

thors cautioning against its 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 [42].

Given the progressive deterioration of CNS function, seizures are a frequent comorbid condition in patients with GA-1. 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 [43]. Alternative routes of delivery (intravenous or rectal) may be required when enteral administration is not feasible. Consultation with the neurology or pharmacology service may be helpful to determine dosing conversion from enteral to intravenous administration or to guide intraoperative redosing. Sodium valproate inhibits mitochondrial β-oxidation of fatty acids and should be avoided in patients with mitochondrial metabolic disorders [44, 45].

Although it has known that specific agents such as etomidate may activate the EEG and even stimulate seizure activity, the inhalational anesthetic agents, propofol, and the barbiturates have potent anticonvulsant properties. Many of these agents have been used to treat status epilepticus that is refractory to conventional therapy [46]. Although motor movements resembling seizure activity and even occasional spike and wave activity on the EEG have been reported with sevoflurane, these effects generally occur only when the inspired concentration is rapidly increased during anesthetic induction when there is accompanying hypocarbia [47, 48]. In general clinical practice, there does not appear to be any contraindication to the use of sevoflurane in this population and other patients with underlying seizure disorders.

Patients with progressive and deteriorating neurologic disorders such as GA-1 frequently have multiple joint contractures. Limited range of motion (flexion and extension) of the limbs can make insertion of invasive arterial cannulae and intravenous access difficult. These difficulties may be compounded by anatomical malposition of the vessels. As was noted with our patient, the use of ultrasound guidance may be invaluable to aid in gaining adequate vascular access for major surgical procedures [49, 50]. The muscle wasting and joint contractures also mandate close attention to surgical positioning.

In summary, GA-1 is an autosomal recessive metabolic mitochondrial disorder due to the deficiency of the enzyme, GCDH. Specific perioperative comorbid concerns include the associated underlying seizure disorder and the potential for perioperative respiratory compromise related to respiratory or upper airway involvement. Prolonged fasting may lead to hypoglycemia and increased catabolism resulting in worsening of physiologic homeostasis. 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 neuromuscular blocking agents. 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.

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