CASE REPORT

Perioperative management of a patient with glutaric aciduria: A case report and literature review

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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. Progressive neurologic effects with spasticity and orthopedic deformities necessitate frequent surgical and anesthetic care. We present a 13-year-old girl with glutaric academia type-1 who required anesthetic care for posterior spinal fusion. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

Key words: Spinal fusion; Scoliosis; Glutaric aciduria type-1; Glutaryl-CoA dehydrogenase

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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 majority of the 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 glutaryl-CoA dehydrogenase, a mitochondrial enzyme involved in the metabolism of lysine, hydroxyl-lysine, and tryptophan.[8-11] This defect results in the accumulation of glutaric acid (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 academia type 1 who required anesthetic care for posterior spinal fusion. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

CASE REPORT

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, Ohio) for the presentation of single case reports. 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 type 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 co-morbid conditions included gastroesophageal reflux, dysphagia with chronic vomiting, osteoporosis, central nervous system 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 minutes,

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 hours), and

Ergocalciferol (1000 units via G-tube once a day).

Allergies included oxycarbazepine. 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 evaluation including electrolytes, renal function, coagulation function, blood glucose and hepatic function were normal. The hemoglobin was 10.2 gm/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* for 6 hours except for her usual medications and a peripheral intravenous infusion of 5% dextrose in ½ normal saline was started. The preoperative blood glucose was 79 mg/ml with oxygen saturation of 99% on room air. 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 IV. Neuromuscular blockade was provided with rocuronium (30 mg) and a 6.0 mm cuffed endotracheal tube was placed on the first attempt. After the induction of anesthesia, two additional 18G IV cannulas, an arterial and a central venous access were obtained using ultrasound guidance. Tranexamic acid 50 mg/kg IV followed by an infusion at 5 mg/kg/hr was administered for prevention of fibrinolysis and limit intraoperative blood loss. The patient was turned and positioned prone. Baseline neurophysiological monitoring including motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP's) were obtained. To allow 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 mmHg[12] to minimize intraoperative blood loss. Heart rates varied from 60-120 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 be decrease during placement of spinal instrumentation. A phenylephrine infusion was started to maintain the MAP $\geq$ 70 mmHg, 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 2007 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

Glutaric aciduria type 1 is an inherited metabolic disorder resulting from a deficiency of the mitochondrial enzyme, glutaryl CoA dehydrogenase. 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-hydroxyglutaric acid (3-OHGA) in urine. However, some patients may not excrete large amounts of 3-OHGA and therefore, direct measurement of glutaryl CoA dehydrogenase activity in fibroblasts and lymphocytes provides the most accurate diagnostic modality.[23]

Given the significant co-morbid sequelae of GA-1, there 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 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 neuromuscular blocking agents (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, suggamadex 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, remifentanil) may to 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 co-morbid 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 in the reports reviewed in Table 1 to be safe and effective in patients with GA.[35-39]

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.[40] This could predispose to propofol infusion syndrome and severe metabolic acidosis in patients with mitochondrial disorders, carnitine deficiency and inadequate carbohydrate intake.[41,42] Therefore, the use of propofol for prolonged anesthetic remains controversial in patients with mitochondrial disorders. 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.[43]

Given the progressive deterioration of CNS function, seizures are a frequent co-morbid 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 nil per os status with subsequent intraoperative dosing as needed.[44] Sodium valproate inhibits mitochondrial β-oxidation of fatty acids and should be avoided in patients with

Table 1: Previous reports of anesthetic care for patients with glutaric aciduria

Authors and reference	Patient demographics	Intraoperative management	Postoperative problems and management
Ituk US et al.[24]	23 year 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 hours postoperatively. She was discharged home on postoperative day 3.
Teng WN 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 hours after the procedure and was discharged uneventfully the next day.
Farag E 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.
JH Hernandez-Palazon et al.[27]	Two siblings: 17 and 30 month 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.
U Goktas et al.[28]	Two siblings: 12 and 16 (51 kg) years, presented with macrocephaly and psychomotor delay. Sedation for MR imaging.	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 hour after the procedure
Tsiotou AG et al.[29]	5 year 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 hours following the procedure. Water intake and a specific high carbohydrate solution were started at 2 and 4 hours respectively. Discharged home on postoperative day 2.

mitochondrial metabolic disorders.[45,46]

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.[47-49]

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.[50,51] 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, glutaryl-CoA dehydrogenase. Specific perioperative co-morbid 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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My most unforgettable experience

Sevo-odious paranoia: a blemish on the snow!

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A 38-year-old male, ASA PS- I, diagnosed with prolapsed intervertebral disc (PIVD) at L5-S1 level, was posted for discectomy under GA. He had strong predictors of difficult intubation [thyromental distance was 5.5 cm, sternomental distance 9 cm, upper lip bite test grade III and severe limitation in neck extension]. He was premedicated with glycopyrrolate 0.2 mg, midazolam 1 mg, and fentanyl 100 μg and preoxygenated with 100% oxygen for 3 minutes. In anticipation of difficult airway, inhalational induction with 6% sevoflurane was planned. Tracheal intubation was successfully accomplished on first attempt with the aid of Glidescope® (Verathon Inc. Bothell, WA, USA). Anesthesia was maintained with 70% nitrous oxide in oxygen and 1.5-2% sevoflurane to maintain bispectral index (BIS) between 40-60 and neuromuscular blockade was achieved with intermittent doses of vecuronium bromide. The surgical intervention underwent uneventful. At the end of surgery, anesthesia was reversed with IV neostigmine 2.5 mg and glycopyrrolate 50 μg. The patient was hemodynamically stable with return of all protective reflexes.

In post anesthesia care unit (PACU), suddenly patient displayed severe agitated behavior and was trying to pull the intravenous (IV) line and get down from the bed. He even screamed repeatedly that "*I am dying. Don't kill me. I am dying*". This agitated and inconsolable behavior continued for nearly 20 minutes. He abused the health caregivers and attendants and even tried to physically harm them. In view of this perilous situation, we sedated him with titrated dose of fentanyl and midazolam resulting in nearly complete resolution of his intense paranoid delusions. Afterwards, we observed that patient had a complete recall of his action and he thought that he would be taken for surgery again and will be harmed. He apologized for his agitated behavior and denied of any pain during that period. No further medications were required and rest of the period passed uneventfully.

Sevoflurane induced emergence agitation (EA) is a short-lived phenomenon, which generally occurs during immediate postoperative period and is usually self-limiting. There is no relation between the presence and severity of EA and duration of anesthesia or postoperative pain. Many theories have been suggested to explain this unusual behavioural pattern due to the neuro-pshyco-pharmacological properties of sevoflurane and its metabolites. Some authors explain it to be due to the difference in recovery speed within the nervous system, which increases the sensitivity to stimulation from the surrounding environment, thus causing a state of functional dissociation.[1] While others believe it to be due to changes and relationship of gamma-aminobutyric acid (GABA) in the central nervous system, decreased inhibitory signals from the globus pallidus interna and substantia nigra, and the inability to suppress thalamocortical neurons and brain stem neurons due to disorder in the nervous system.[1] Although sevoflurane induced EA is well documented in pediatric patients[2] but data in adult patients are relatively sparse.[1,3] It has been shown in literature that the co-administration of drugs along with sevoflurane anesthesia, such as propofol, midazolam, dexmedetomidine, clonidine, ketamine, fentanyl, sufentanil and remifentanil may reduce the incidence and severity of EA.[4] The occurrence of EA in adults may result in more injury to patient and it is an onerous task for caregivers to physically restrain them from causing self-harm by this behavior.

By undergoing this sevoflurane-induced odious experience of intense paranoid delusion, we re-emphasised that though sevoflurane causes more EA in pediatric patients, it is indeed more troublesome if seen in adult population, and one must keep this in mind, while maintaining anesthesia with sevoflurane as a sole anesthetic agent.

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