

Anesthesia recommendations for Glutaric acidemia type 1

Disease name: Glutaric acidemia type 1

ICD 10: E72.3

ORPHAcode: 25

Synonyms: GA1, GCDHD, GDD, Glutaric aciduria type 1, Glutaryl-coenzyme A dehydrogenase deficiency

Brief disease summary: Glutaric acidemia type 1 (GA1) is a rare hereditary neurometabolic disorder with an autosomal recessive mode of inheritance [1]. GA1 has an estimated overall prevalence of 1 in 100,000 newborns and is caused by a deficiency of glutaryl-CoA dehydrogenase, a mitochondrial enzyme involved in the metabolism of lysine, hydroxylysine and tryptophan [2]. Untreated, approximately 90% of patients will develop an irreversible neurological disease during a finite period of brain development (age 3-36 months) following an acute encephalopathic crisis often triggered by gastroenteritis, intercurrent febrile illness, immunization or surgical intervention [3]. GA1 can also develop insidiously without clinically apparent crisis in 10-20% of patients [4,5].

Newborns are mainly asymptomatic. Macrocephaly at birth or shortly thereafter may be present. Symptoms that may develop include psychomotor delay, muscular hypotonia, dystonia, convulsions, and, later, spastic quadriparesis if patients remain untreated [1,6]. Patients generally appear to have relatively preserved cognitive function and respond to commands but have trouble talking or performing tasks due to poor muscle coordination and severe spasticity [7]. Mild cases causing only slight neurological complaints and/or fatigue have also been described.

Brain imaging performed shortly after birth usually shows frontoparietal atrophy with widening of Sylvian fissures and arachnoid cysts. The brain is more vulnerable to head trauma, which can lead to acute subdural or retinal hemorrhage. The cerebral damage seen in GA1 is caused by the direct effect of glutaric acid or related metabolites such as 3-hydroxyglutaric acid and glutaconic acid, which accumulate in the brain and lead to glial proliferation and atrophy of striatal neurons due to lymphocyte infiltration, elevated concentrations of inflammatory cytokines and nitric oxide [2,6].

The diagnosis is confirmed by genetic analysis or by measuring elevated levels of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid and glutarylcarnitine in blood or urine samples. Many countries perform these tests as part of routine newborn screening.

Metabolic therapy consists of a low-lysine diet, carnitine supplementation and intensified emergency treatment in situations of catabolism. After the age of six years dietary treatment can be less strict. If treatment is started early, normal neurological development can be achieved [1].

Diagnosis may be incorrect; if uncertainty exists, the diagnosis should be re-evaluated.

Every patient is unique; individual circumstances must always guide clinical care.

Medicine is in progress; new clinical knowledge may not be yet reflected in this recommendation.



Recommendations are not rules or laws; they provide a framework to support clinical decision-making. Although this recommendation has passed a structured review process, it does not meet the formal criteria of a guideline.

Translations may not always reflect the most recent updates of the English version.



Find more information on the disease, its centers of reference and patient organizations on Orphanet: www.orpha.net

Emergency information

A	AIRWAY / ANESTHETIC TECHNIQUE	Increased risk of aspiration, difficulty in positioning, prefer video-assisted device. Avoid prolonged fasting. Minimize stress and catabolism. Start an intravenous infusion containing glucose during the fasting and perioperative period.
B	BLOOD PRODUCTS (COAGULATION)	None.
C	CIRCULATION	None.
D	DRUGS	Avoid propofol for continuous infusion. Avoid succinylcholine. Avoid drugs with extrapyramidal effects. Inhalational anesthetics appear to be safe. Cautious use of Ringer's lactate, consider saline solution with dextrose instead. Continue home medications such as carnitine, anticonvulsant agents and riboflavin perioperatively.
E	EQUIPMENT	Consider arterial catheterization for serial measurements of glucose, lactate, and electrolytes. Neuromuscular junction and temperature monitoring. Careful positioning in case of spasticity.

Additional disease information

None.

Typical surgery and procedures

Neurosurgery (cerebral spinal fluid shunting procedures for hydrocephalus and subdural fluid collections) [7,8]; muscle biopsy, general surgery [9]; neuroradiological imaging procedures, obstetric procedures [4,5,10], dental procedures [11], orthopedic procedures [12].

Type of anesthesia

No clear recommendation for either general or regional anesthesia can be given.

For general anesthesia, there are no definite reports on the superiority of one anesthetic drug over another. Both inhalational and total intravenous anesthesia with propofol have been administered without complication despite safety concerns regarding use in mitochondrial disease [15].

There are no known contraindications to sedation or analgesia. Consider risk of aspiration.

Patient cooperation during regional anesthesia may be limited due to dystonia.

Necessary additional preoperative testing (beside standard care)

If surgical intervention is planned, the responsible metabolic center/specialist should be informed. This would enable all staff involved to discuss specific risks and to establish a protocol for perioperative metabolic management and monitoring. Management of these patients involves providing nutritional support in order to prevent catabolism as well as treating complications such as metabolic decompensation and encephalopathic crises. Therefore, standard care should be implemented by a multiprofessional team [7]. According to the latest guidelines, regular follow-up monitoring should be performed in patients with GA1, by an interdisciplinary team in a specialized metabolic center [1,3]. Metabolic management should be optimized preoperatively, and a treatment protocol should be available to the anesthetic team. L-carnitine levels should be controlled preoperatively, as carnitine is supplemented lifelong aiming to maintain a normal plasma concentration of free L-carnitine [1]. Further preoperative laboratory evaluations should include blood glucose, acid-base balance, lactate, electrolytes, and renal and liver function parameters [15].

An emergency treatment protocol should be established, as perioperative patients are at a high risk of increased catabolism, a fact that can trigger an acute encephalopathic crisis. [1,13].

A preoperative neurological examination and evaluation should be performed.

Particular preparation for airway management

Patients with severe dystonia may be at a greater risk for aspiration of gastric contents during general anesthesia. Appropriate measures to avoid aspiration including the use of proton-

pump inhibitors/H₂-blockers and rapid sequence induction of anesthesia should be considered. In case of severe dystonia, be prepared for difficult airway management.

At the end of the surgical procedure, tracheal extubation must be carried out when the patient is awake and when protective reflexes are present.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilization

Positioning for airway management and for surgery may be challenging if contractures due to spasticity are present.

Interactions of chronic disease and anesthesia medications

Patients are usually treated with a low-protein (lysine and tryptophan restriction) diet, riboflavin and carnitine supplementation. Carnitine dosage should be doubled during the perioperative period. Intravenous administration may be considered if oral intake is not reliable [1,3].

Patients with a history of epilepsy may be on anticonvulsant therapy. A lower seizure threshold should be considered if local anesthetics are used.

Anesthetic procedure

Limit the preoperative fasting period to prevent hypoglycemia, dehydration and mild metabolic acidosis caused by an overnight fast [1,3]. Start a maintenance intravenous infusion containing glucose during the fasting period.

The literature suggests avoiding Ringer's lactate solution while surgery is in progress as it contains lactic acid and recommends dextrose dissolved in normal saline instead. However, a case series of 11 surgical patients with well-controlled organic acidurias between 2000 and 2013 showed no metabolic complications from intraoperative fluid replacement with Ringer's lactate solution, provided that the duration of surgery was less than 2 hours [16].

Regarding volatile anesthetics, sevoflurane seems to be safe, although anecdotal reports ruled out episodes of malignant hyperthermia and other intraoperative events attributable to the general anesthesia with sevoflurane in pediatric patients with mitochondrial disease [7,15].

Propofol can provide lipid overload and inhibit oxidative phosphorylation, carnitine palmitoyltransferase transport of long-chain fatty acids, and β -oxidation of fatty acids in mitochondria. These reports raise concerns about a potential occurrence of propofol infusion syndrome and severe metabolic acidosis [7,9,12]. Long procedures involving total intravenous anesthesia with propofol are probably not advisable.

There are also reports of thiopental or ketamine use for a safe induction without complications [15].

Expect prolonged responses to non-depolarizing muscle relaxants and hyperkalemic responses to succinylcholine. Antagonism of neuromuscular blockade with pyridostigmine or neostigmine seems to be possible. Sugammadex to antagonize any residual neuromuscular blockade might be a good option.

Patients with GA1 are vulnerable to postoperative emesis. Antiemetic prophylaxis is advisable. Medications with extrapyramidal side effects such as metoclopramide and droperidol should be avoided.

Particular or additional monitoring

Neuromuscular blockade monitoring is strongly recommended if a neuromuscular blocking agent is used [7,12].

Monitor body temperature to avoid hypothermia, shivering and an increased oxygen demand [5,7,9].

Consider serial intraoperative arterial blood-gas analysis for closely monitoring pH status, electrolytes, lactate and glucose [14].

Possible complications

Encephalopathic crisis and acute metabolic decompensation may occur during surgery and in the postsurgical period, especially in patients aged 0 to 6 years. With increasing age, in particular after the age of 6 years, the risk of acute neurological insult appears to be much reduced [1].

Conditions accelerating catabolism, such as repeated vomiting and diarrhea (with or without fever), and the manifestation of severe neurological symptoms (i.e., hypotonia, irritability, rigor, dystonia, reduced consciousness) should be considered as alarming symptoms [1,3,6].

Emergency treatment should be started before the onset of alarming neurological symptoms:

- (1) Prevention or reversal of a catabolic state by administration of a high-energy intake (plus insulin to control for hyperglycemia, if required);
- (2) Reduction of glutaric acid or reduced production of related metabolites by transient reduction or total deprivation of natural protein for 24 to 48 hours;
- (3) Amplification of physiological detoxification mechanisms and prevention of secondary carnitine depletion by L-carnitine supplementation;

(4) Maintenance of normal fluid, electrolytes and pH status via enteral or IV fluids [1,3].

Non-adherence to previously described emergency treatment recommendations has been associated with a high probability of developing striatal injury.

Postoperative care

If possible, the postsurgical metabolic management should be performed in a metabolic center.

Consider emergency treatment as described above.

Consider risk of perioperative respiratory insufficiency due to poor upper airway control and sensitivity to anesthetics in patients with associated cerebral damage.

Disease-related acute problems and effect on anesthesia and recovery

Repeated vomiting and diarrhea (with or without fever), and the manifestation of severe neurological symptoms (i.e., hypotonia, irritability, rigor, dystonia, reduced consciousness) should be considered as alarming symptoms of an encephalopathic crisis in the postoperative period and might indicate an acute metabolic decompensation.

Ambulatory anesthesia

Ambulatory anesthesia should probably be considered only for older patients (over 6 years of age) and only in cases of low-risk procedures and surgery.

Obstetrical anesthesia

Management of pregnancy in women with GA1 remains largely experience-based, with a lack of standardized protocols. Physiological changes of pregnancy and the catabolism associated with labor and delivery may impose a risk of a neurological 'crisis'. Women with GA1 should be optimized before attempting pregnancy [4]. Early monitoring by a multidisciplinary team, consisting of metabolic, dietetic and obstetrics' care providers, should be implemented to avoid any decompensation [4,5,10]. Parturients should continue their regular therapy, including a protein-restricted diet. A metabolic team should actively implement disease-specific protocols including individualized nutritional planning and serial biochemical monitoring throughout pregnancy. The goal is to maintain adequate caloric support and minimize catabolic stress throughout pregnancy and during both elective and emergency obstetric procedures [4,5,10].

There are case reports on both vaginal delivery with labor epidural [4] and cesarean delivery with spinal anesthesia [5,10] without any adverse reactions or decompensation of the patients. As in nonobstetric cases, careful examination of the cardiovascular and neuromuscular system should be done preoperatively [10]. Preoperative fasting should be minimized. Neuraxial anesthesia is the technique of choice. The team should aim to reduce peripartum stress, keep the patient normothermic, avoid hypoglycemia and lactate-containing fluids, and administer early antiemetic prophylaxis [10].

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