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CLINICAL REPORT

The child with glutaric aciduria type I: anesthetic and perioperative management

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Abstract Glutaric aciduria type I (GA-1) is an inborn error of metabolism caused by a deficiency of glutaryl-CoA dehydrogenase. It presents early in life, usually after an episode of fever, dehydration, infection or fasting, and results in metabolic decompensation and neurologic damage. We report the perioperative management of a 5-year-old boy admitted to the hospital for surgery because of neurogenic hip dislocation. Here we present the preoperative preparation, which focused on appropriate fluid administration and therapy intensification, as well as the safe anesthetic management with inhalation anesthesia and remifentanil, taking into consideration the mitochondrial basis of the disease. Furthermore, the role of postoperative care is emphasized in relation to stress response prophylaxis and the avoidance of complications related to the disorder.

Keywords Glutaric aciduria type I · Organic aciduria · Mitochondrial disorders · Propofol infusion syndrome · Inhalation anesthesia

Introduction

Glutaric aciduria type I (GA-1) is an autosomal recessive inborn error of lysine, hydroxylysine and tryptophan metabolism caused by a deficiency of glutaryl-CoA dehydrogenase [1]. The enzyme is located in the mitochondrial matrix and converts glutaryl-CoA to crotonyl-CoA. According to the classification of neurometabolic diseases, GA-1 is a mitochondrial metabolism disorder [2, 3].

The anesthetic management of mitochondrial disorders remains a confusing topic for many anesthesiologists dealing with children [2, 3]. Additionally, there are only a few reports about the anesthetic management of patients with GA-1, although they are vulnerable to metabolic decompensation and need careful monitoring in every aspect of their perioperative care.

The disease was first reported in 1975 by Goodman et al. [4], and is characterized by macrocephaly at birth or shortly thereafter, dystonia (which often resembles seizures), and degeneration of caudate and the putamen.

Case presentation

Having obtained consent, we report the case of our five-year-old patient suffering from GA-1, who was admitted to the hospital for aponeurotic lengthening of gracilis adductor longus and recession of the iliopsoas due to neurogenic hip dislocation. He was a healthy child until the age of 22 months, when a viral infection resulted in metabolic decompensation, seizures, degeneration of basal ganglia and consequently dystonia. He could not talk or walk independently, did not have macrocephaly, his cognition was normal, and he responded to commands. He was on a low protein diet, received vitamins B1 and B2, carnitine and tetrabenazine (a drug for hyperkinetic movement disorder). Clinical examination revealed no signs of respiratory compromise, although he was wheelchair bound. Routine laboratory results were normal.

Due to the predisposition of patients with GA-1 to vomiting and emesis, we recommended the avoidance of solid food for 8 h. An i.v. line was inserted afterwards,

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which provided a solution of D5 ¼ NS according to his hourly needs in order to maintain an appropriate balance between the preoperative fasting guidelines and the maintenance of dietary and fluid intake. To ensure metabolic stability during the perioperative stress period, an intensification of therapy was suggested by the neurologist, which consisted of carnitine 100 mg/kg/day starting the night before surgery and lasting two days. Additionally, diazepam 1 mg/kg every 8 h on the day of surgery was prescribed to alleviate anxiety and dystonia and to act prophylactically against seizures.

Intraoperatively, the main concern was to use anesthetic agents that do not increase the metabolic load. Induction of anesthesia was achieved with atropine 0.01 mg/kg, propofol 3 mg/kg, fentanyl 1 mcg/kg, and rocuronium 0.6 mg/kg. A continuous infusion of remifentanil 0.4 mcg/kg/min was started afterwards. Ondansetron 0.1 mg/kg was administered for antiemetic prophylaxis. Anesthesia was maintained with sevoflurane 1% and a continuous infusion of remifentanil. A mixture of oxygen and air was administered. Routine monitoring was continuously used during anesthesia. Body temperature was maintained between 36.8 and 37°C by a warming mattress. The patient was hemodynamically stable during the operation with an SpO_2 of 98–99% and an end-tidal carbon dioxide of 30–35 mmHg. Twenty minutes before the end of the operation, paracetamol 15 mg/kg i.v. was given for postoperative analgesia. D5 ¼ NS was the only solution used perioperatively. Glucose was 166 mg/dl 30 min after the start of surgery. Surgery was completed after 45 min. No prolongation of the muscle relaxation was noted clinically or through the neuromuscular monitoring device. The postoperative pain management protocol consisted of the administration of paracetamol 15 mg/kg i.v. every 6 h and nalbuphine 0.3 mg/kg i.v. 3 h after surgery.

Water intake and a specific high carbohydrate solution were started 2 and 4 h after the end of anesthesia, respectively. Glucose was always within acceptable limits. He had two episodes of vomiting in the next 24 h, resulting in a delay in postoperative feeding. Ondansetron was readministered. He was discharged on the second postoperative day.

Discussion

GA-1 is caused by heterogeneous mutations in the glutaryl-CoA dehydrogenase gene. The worldwide frequency of GA-1 is 1 in 100,000 infants [5]. It is very common (affecting up to 1 in 300) in the Old Order Amish community of Pennsylvania [6] and the North American Ojibway-Cree in Canada [7]. In Sweden, it affects 1 in 30,000 newborns [8] and about 1 in 50,000 in the USA [9].

Most patients have macrocephaly at birth or shortly thereafter [10]. Neurologic deterioration happens between 6 and 18 months of age after a febrile illness with some degree of dehydration, an infection or fasting. Children become acutely hypotonic, lose head control and have abnormal movements similar to seizures. Hypotonia is substituted by rigidity and dystonia. They remain severely disabled and are not able to walk, talk or eat, but they do have relatively normal cognition and respond to commands [1].

Neurologic deterioration reflects the damage that the accumulation of glutaric acid and 3-OH glutaric acid (due to the deficiency of glutaryl-CoA dehydrogenase) causes to basal ganglia at times of sepsis or fever. Neuronal loss happens during an acute event and does not progress over time [11]. The diagnostic metabolite is 3-OH-glutaric acid in urine analysis. Glutaric acid can be very elevated or completely normal. Carnitine deficiency is present. Metabolic acidosis and hypoglycemia predominate during metabolic stress [3]. A low-protein diet, a diet restricted in lysine/tryptophan, supplementation with carnitine/riboflavin, and chronic anticonvulsant medication are usual treatment protocols [12]. In emergencies (persistent fever, poor feeding, trauma), the goal is to reverse the catabolic state by giving intravenous fluids containing glucose 10%, maintenance fluids to replace fluid deficits promptly, intralipids to enhance anabolism, sodium bicarbonate in metabolic acidosis, carnitine i.v., and anticonvulsant drugs. Glucose should be tightly controlled at levels of 80–120 mg/dl [1].

When dealing with children with GA-1 in the operating room, it is essential to realize that the disorder is located in the mitochondrium [2, 3]. Mitochondrial disorders include many subgroups, such as defects in pyruvate metabolism, in fatty acid oxidation, in the oxidative phosphorylation electron transport chain, etc. GA-1 is an organic acidemia belonging to the group of mitochondrial disorders [2, 3]. Sometimes there is overlap between these subgroups. In children with GA-1 and other mitochondrial disorders, limiting the preoperative fasting period is important since it prevents hypoglycemia, dehydration and mild metabolic acidosis caused by an overnight fast. This is not feasible sometimes though, due to a tendency to vomit, swallowing difficulties, etc. Starting a maintenance intravenous infusion containing glucose during the fasting period is an alternative [13]. Communication with the attending neurologist is useful in order to provide intensification of therapy that perioperatively protects the patient from metabolic complications during stressful surgery and anesthesia. Efficient pain management reduces the response to surgical stimuli, postoperative anxiety and dystonia.

Regarding anesthetic management, the use of inhalation anesthetics is considered to be safe since there is no association between mitochondrial disorders and malignant

hyperthermia [14–16]. The publication of a few cases connecting malignant hyperthermia with mitochondrial disorders provoked confusion about this subject for some time [17, 18]. Footit et al. retrospectively studied 38 mitochondrial patients who had undergone 58 anesthesias using various induction and maintenance anesthetic agents in a seven-year period in an effort to demonstrate the standard practice and perioperative adverse events. No episodes of malignant hyperthermia or rhabdomyolysis were noted, although, in 54 of the 58 anesthesias, inhalation anesthesia and in two cases suxamethonium was used [19]. The use of TIVA with propofol in mitochondrial disorders is probably not advisable, since it increases the metabolic load and in some types of mitochondrial disorders (mitochondrial myopathy) is associated with propofol infusion syndrome and severe metabolic acidosis [20–23].

Propofol has been used in patients with GA-1 for procedures of short duration, such as CSF shunting and routine MRI. Two siblings who underwent CSF shunting for hydrocephalus received propofol 2.5 mg/kg for induction and 2.5 μgr/ml TCI for maintenance, along with continuous infusion of remifentanil [24]. Similarly, patients who underwent MRI for follow-up received propofol 1 mg/kg for induction and 0.5 mg/kg when necessary for a total procedure duration of 10 min [25]. Although the procedures ended uneventfully, we cannot suggest propofol as the anesthetic agent of choice for those children. The satisfactory outcomes in those cases may have been related to the small doses of propofol, which did not increase the metabolic loads of those children. The reason for choosing TIVA also appears to have been the purported relationship of mitochondrial diseases such as GA-1 to malignant hyperthermia, a fact that is not supported by the recent literature, as already mentioned [14–16].

In our patient we considered it relatively unsafe to increase the metabolic load of an organelle that is metabolically defective by administering propofol for a considerable period, since a very safe alternative, such as sevoflurane, is available. Regarding the use of nondepolarising neuromuscular blocking agents, the avoidance of excessive doses is a prudent approach, while it is always necessary to monitor the neuromuscular blockade. In modern anesthetic practice there is usually no need for additional administration of muscle relaxants when sufficient anesthesia and analgesia with sevoflurane and continuous infusion of remifentanil are provided. Patients with GA-1 are susceptible to cyclic vomiting, a fact that makes them vulnerable to postoperative emesis. Antiemetic prophylaxis with ondansetron given during anesthesia and for at least 24 h postoperatively is therefore necessary. The omission of postoperative ondansetron administration in the case of our patient resulted in a delay to normal feeding of 12 h, although fluid intake was almost normal. Maintenance of the i.v. line postoperatively is as important as it is preoperatively.

The rarity of GA-1 and the lack of reports about anesthetic management in lengthy operations motivated us to present the anesthetic management of patients with GA-1, focusing on the perioperative as well as the intraoperative period, and based on the pathophysiologic origin of the disease and the vulnerability of the patient when their balance is tested.

Decreased morbidity of the disease due to proper diagnosis and treatment by pediatricians, neurologists and metabolism specialists will result in an increase in the number of patients appearing in the OR for elective or urgent operations. Protection from metabolic decompensation perioperatively is the responsibility of the anesthesiologist. Clinical evaluation, communication with the patient's health care providers and family, and a review of the literature will simplify the anesthesiologist's task and reduce the anxiety of the child and his/her family.

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