Case report

Perioperative management of a child with very-long-chain acyl-coenzyme A dehydrogenase deficiency

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Summary

Very-long-chain acyl-coenzyme A dehydrogenase deficiency is an inborn error of fatty acid metabolism. The clinical presentation of this disease in children is either a severe form with onset of symptoms in the first months of life, cardiomyopathy, metabolic acidosis, myopathy and a high mortality, or a less severe form manifesting mainly with hypoglycaemia. Perioperative fasting and (even emotional) stress can trigger metabolic decompensation through the altered metabolism of endogenous fatty acids resulting in hypoglycaemia, acute cardiac and hepatic dysfunction and rhabdomyolysis. We report the perioperative management of a 9-year-old boy suffering from the severe form of this disease who underwent circumcision. Metabolism was kept stable in this child by using a glucose–electrolyte infusion throughout the perioperative period to avoid the biochemical consequences of fasting and a benzodiazepine–opioid technique combined with regional anaesthesia to minimize the stress response. Considering reports about a possible interference of propofol with fatty acid oxidation and to avoid the unnecessary administration of fatty acids, propofol should not be used in these patients.

Keywords: anaesthesia; child; lipid metabolism; inborn errors; fatty acids; propofol

Introduction

Mitochondrial fatty acid oxidation is the major source of energy during fasting and provides energy for gluconeogenesis in the liver, where fatty acids are also used to synthesize ketone bodies. Fatty acids are the preferred fuel of the heart and an essential source of energy for skeletal muscle during prolonged exercise. In the mitochondria, fatty acids are oxidized by a complex pathway involving multiple enzymes, which exhibit partially overlapping chain length specificity. More than 20 defects of fatty acid oxidation have been identified; among them short-chain, medium-chain, long-chain-3-hydroxy and very-long-chain acyl-coenzyme A dehydrogenase deficiency.
With the exception of medium-chain acyl-coenzyme A dehydrogenase deficiency (C4–C14 fatty acids), which has been reported as frequent as one in 10 000 births, these disorders are rare and the prevalence of most remains unknown. All these disorders present with multiple clinical phenotypes, possibly a consequence of varying degrees of residual enzyme activity and/or heterogeneity of the underlying genetic defect. However, the common feature of nearly all of these disorders is symptomatic hypoglycaemia after insufficient intake of carbohydrates and most of these defects can present in early infancy as acute life-threatening episodes of hypoketotic hypoglycaemic coma. The susceptibility to hypoglycaemia can be explained by excessive glucose utilization following failure of ketone body production and impaired gluconeogenesis. Because both the myocardium and skeletal muscle depend on long-chain fatty acid oxidation, many disorders involving long-chain fatty acid oxidation can present with acute and or chronic cardiomyopathy or acute exercise induced rhabdomyolysis, whereas these symptoms are extremely rare in the defects of short- and medium-chain fatty acid oxidation. Defects of long-chain fatty acid oxidation also tend to be more severe and present earlier in life; for a review, see (1).

Very-long-chain acyl-coenzyme A dehydrogenase (VLCAD) catalyses the first step of long-chain fatty acid oxidation (C14–C20 fatty acids). VLCAD deficiency is inherited as an autosomal recessive trait and was first described in 1993 (2,3). It can present with several clinical phenotypes. The characteristic manifestation in children is either a severe form with early, even neonatal, onset, hypertrophic cardiomyopathy, metabolic acidosis, myopathy and a high mortality, or a less severe form with later onset, hypoketotic hypoglycaemia, no cardiac involvement and a more favourable outcome (4). There are also adolescent and adult onset cases characterized by exercise- or fasting-induced muscle pain or rhabdomyolysis (5,6). In affected patients, the impaired metabolism of endogenous or exogenous long-chain fatty acids can lead to hypoglycaemia, lactic acidosis, acute cardiac and hepatic dysfunction and rhabdomyolysis. During decompensation, typical findings in the patient’s blood are elevated free fatty acids, characteristic acylcarnitines (C14–C18), absence of ketone bodies, elevated liver enzymes and elevated creatine kinase.

Although this disease is rare, it has important implications for anaesthetists because perioperative fasting, infection and even emotional stress (5) can trigger severe metabolic decompensation. The hazardous nature of VLCAD deficiency is highlighted by the case of a child whose diagnosis was unknown at the time of a dental procedure and whose subsequent death was considered to have been elicited by perioperative fasting (7). We report the perioperative management of a 9-year-old boy with the severe neonatal onset form of VLCAD deficiency who presented for surgery for phimosis.

Case report

This child presented 40 h after birth with cardiorespiratory arrest requiring prolonged resuscitation. He subsequently had dysrhythmias, signs of ischaemia on electrocardiogram (ECG), elevated liver enzymes, elevated creatine kinase including MB isoenzyme, severe lactic acidosis, and myoglobinuria. The boy recovered on intravenous fluids and frequent breast-feeding. Two months later, his failure to thrive and hypertrophic cardiomyopathy led to the diagnosis of a defect in fatty acid oxidation. The specific diagnosis of VLCAD deficiency was made 1 year later. Since the age of 3 months, he has been on a carbohydrate-rich diet, low in long-chain triglycerides with supplemental medium-chain triglycerides and seven or more meals per day. With this regimen, the cardiomyopathy resolved and his somatic and psychomotor development was normal except for a mild neuropsychological deficit, possibly as a consequence of the prolonged postnatal resuscitation.

Mild metabolic decompensation, usually caused by fever or gastroenteritis and the subsequent inadequate intake of food leading to mobilization and metabolism of endogenous fatty acids, has been experienced by us several times per year, requiring hospitalization and feeding via a nasogastric tube. Several episodes of severe decompensation, presenting with myocardial and hepatic dysfunction and once encephalopathy secondary to severe hypoglycaemia, required treatment in the intensive care unit.

The 9-year-old boy, weighing 27 kg, had never been operated on and was scheduled for resection of a phimosis causing recurrent balanitis. Results from echocardiography performed a week before the planned procedure were normal. The boy received
extensive counselling about the intended operation from doctors, nurses and his parents. Despite this, he was emotionally stressed by the imminent procedure and this caused mild metabolic decompensation manifested by elevated free fatty acids at admission (2608 μmol·l⁻¹, 4 h after his last meal; normal values for the patient’s age group after a 15-h fast are 200–1100 μmol·l⁻¹). Other reasons for this metabolic decompensation, such as infection or inadequate diet, were ruled out. The operation was cancelled and rescheduled 1 month later.

A second attempt at surgery was attempted using an unorthodox approach in order to minimize emotional stress. The boy entered hospital 1.5 h after his regular breakfast, which consisted only of fluids. He had only been told that a blood sample needed to be taken. His parents had proposed this extraordinary lack of information. Local anaesthetic cream was applied to the back of both hands and an infusion was started 1 h later. The boy was familiar with this procedure. The infusion had been prepared by the metabolic unit and contained glucose (120 g·l⁻¹), sodium (21 mmol·l⁻¹), chloride (43 mmol·l⁻¹) and potassium (22 mmol·l⁻¹) and was adjusted to deliver glucose at 8 mg·kg⁻¹·min⁻¹. Laboratory values (free fatty acids, creatine kinase, acylcarnitines) were normal at admission. In the preoperative waiting area, 4 h after his last meal with his mother present, the patient received supplemental oxygen and intravenous midazolam was titrated until a deep level of anaesthesia was achieved. A total of 15 mg were injected over several min. The sleeping child was taken to the operating theatre where after an injection of 40 mg of thiopental a laryngeal mask airway™ was inserted and, after another 40 mg of thiopental plus 1 mg of alfentanil, a penile block (without circumpenile infiltration) using a mixture of lidocaine 1% and bupivacaine 0.5% was performed. Anaesthesia was maintained with midazolam and alfentanil. The intraoperative course was uneventful. Postoperative analgesia was provided with a single dose of intravenous nalbuphine prior to removal of the laryngeal mask and later rectal paracetamol. The boy slowly awoke 3 h postoperatively in the presence of his mother. He did not seem to be distressed by the fact that an operation had been performed rather than having only blood drawn. The glucose–electrolyte infusion was continued overnight. Oral feeding was started after 8 h of fasting. Shortly after the operation and the next morning, free fatty acids, creatine kinase and acylcarnitine levels did not rise. Despite the considerable dose of glucose that was administered, serum glucose never exceeded 9.3 mmol·l⁻¹ and no insulin was given. The child was discharged 24 h after the operation.

Discussion

In view of the episode of mild decompensation caused by emotional stress, we based our perioperative management not only on the concept that catabolism (i.e. mobilization and metabolism of endogenous fatty acids) must be avoided, but also that emotional stress must be minimized. To avoid the biochemical consequences of fasting and to stimulate insulin secretion to suppress fatty acid oxidation and to block lipolysis, we administered a large dose of glucose throughout the perioperative period. In our opinion, the time interval between the last meal and the start of the glucose infusion should not exceed 3 h. We decided that, in this child, an intravenous anaesthetic technique was preferable to the use of inhalational anaesthetic agents in order to avoid a possibly unpleasant inhalational induction and, more importantly, an emergence delirium. An additional reason was that elevated free fatty acids have been reported during minor procedures under inhalational anaesthesia (8). To avoid accumulation of exogenous long-chain fatty acids and the following build-up of long-chain acyl carnitines that are both known to promote dysrhythmias (9), we did not use propofol. The preparation we currently use (Disoprivan™, AstraZeneca AG, Zug, Switzerland) contains 100 mg of fat per ml, mainly C18 fatty acids with only 1% of these fatty acids being shorter than C16 (personal communication; B. Bürgi, AstraZeneca AG, Zug, Switzerland). Interestingly, the propofol infusion syndrome presents with symptoms similar to VLCAD deficiency: bradydysrhythmias, acidosis, and rhabdomyolysis. Indeed, the recent case of a child who developed this syndrome after infusion of 5.2 mg·kg⁻¹·h⁻¹ of propofol over 72 h has been presented where it was possible to demonstrate a reversible impairment of mitochondrial entry of long-chain fatty acids and an inhibition of the respiratory chain at several points, leading to a lack of substrates and accumulation of intermediaries of
short, medium and long-chain fatty acid metabolism (10). In our opinion, this suggests that propofol should not be used in patients with any disorder of fatty acid oxidation because a propofol-induced disturbance of multiple steps in fatty acid metabolism potentially increases the risk of metabolic decompensation. We chose midazolam for induction of anaesthesia because it allowed the induction of anaesthesia with maintained spontaneous respiration in the presence of the mother, which facilitated separation from her. The large dose that was administered also contributed to a slow and controllable emergence. Alfentanil was chosen because of its duration of action. In addition, thiopental was administered to further increase depth of anaesthesia during stressful manipulations. We performed a penile block to reduce postoperative pain and to avoid the prolonged use of opioids, thus reducing the risk of postoperative nausea or vomiting that would have delayed oral feeding. Skeletal muscle is clearly involved in this disease and it can be speculated that the effects of neuromuscular blocking drugs are altered in these patients. To our knowledge, there are no reports concerning this issue and we decided not to paralyse this patient.

Management of a patient with a severe form of VLCAD deficiency presenting for emergency surgery would most probably be complicated by metabolic decompensation. Ringer’s lactate should be avoided in this situation because lactic acidosis must be expected. There should be monitoring for any signs of hepatic dysfunction (elevated liver enzymes and, in severe cases, elevated ammonia) and myocardial involvement (dysrhythmias and ECG or laboratory signs of ischaemia). The most important element of emergency treatment is intravenous administration of glucose; 8–12 mg·kg⁻¹·min⁻¹ are generally recommended. In addition, insulin can be used to stop catabolism and the metabolic acidosis should be corrected.

When providing anaesthesia for patients with VLCAD deficiency presenting for elective or emergency surgery, it is reasonable to perform preoperative echocardiography. The reversibility of the hypertrophic cardiomyopathy under appropriate nutritional treatment, as in our patient, has been reported (11). It is unclear whether the cardiomyopathy is caused by accumulation of tissue long-chain acylcarnitines (12) or by inhibition of long-chain fatty acid oxidation and the associated reduced energy production (13).

To the best of our knowledge, this is the first report on the anaesthetic management of VLCAD deficiency. To provide effective perioperative management of patients with this rare metabolic disorder, both catabolism and emotional stress must be avoided. In our opinion, propofol should be not be used in order to avoid the unnecessary administration of long-chain fatty acids and because of its possible interference with fatty acid oxidation. Using a glucose–electrolyte infusion, a benzodiazepine–opioid combination and regional analgesia, we maintained stable metabolism in this child throughout the perioperative period.

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References


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