

Perioperative management of an adult patient with heterozygous medium chain acyl CoA dehydrogenase deficiency: a case report

A Mitra, S Husaini, L John

Citation

A Mitra, S Husaini, L John. *Perioperative management of an adult patient with heterozygous medium chain acyl CoA dehydrogenase deficiency: a case report*. The Internet Journal of Anesthesiology. 2008 Volume 21 Number 1.

Abstract

Medium chain acyl CoA dehydrogenase (MCAD) deficiency is the most common disorder of beta-oxidation of fatty acids. The disease usually presents in childhood with episodes of hypoketotic hypoglycemic coma. Patients are particularly vulnerable during episodes of metabolic disruption, such as infection, surgery or starvation, which if left undetected can result in progressive multiple organ damage or even death. The enhanced recognition of heterozygous patients and the effective management of their metabolic milieu are likely to increase the prevalence of MCAD deficiency in the adult population, which will result in more adult patients with MCAD deficiency as a co-morbidity presenting for surgery. The disease has significant perioperative implications, and awareness about the condition and simple measures can significantly affect outcome. In this report, we describe uneventful anesthetic management during an emergent laparoscopic ovarian cystectomy in an adult female patient with compound heterozygous MCAD deficiency.

INTRODUCTION

Medium chain acyl CoA dehydrogenase (MCAD) deficiency is the most common disorder of beta-oxidation of fatty acids^{1,2,3}. The disease usually presents with repeated episodes of hypoketotic hypoglycemic coma during periods of stress or starvation^{1,2}. Failure to recognize and prevent these episodes leads to multiple organ damage. Its initial presentation is often fatal³. Increased recognition of the heterozygous state combined with the reduction in childhood mortality due to early intervention is likely to result in more adult patients who have MCAD deficiency as a co-morbidity presenting to surgical and anesthetic units. Although combined spinal-epidural anesthesia for labor in an adult patient has been reported, a Medline search did not reveal any reports of the general anesthetic management of adult patients with this disease. In this report, we describe the anesthetic management of an adult patient with heterozygous MCAD deficiency undergoing urgent laparoscopic ovarian cystectomy under general anesthesia.

CASE REPORT

A 16-year-old girl with MCAD deficiency was admitted for emergency ovarian cystectomy for a twisted ovarian cyst when she presented with a 1-day history of abdominal pain. She had been diagnosed with heterozygous MCAD

deficiency at the age of 10 months, following an episode of severe hypoglycemia. Genetic studies at that time revealed an A985G mutation in chromosome 1, and low MCAD enzyme activity in cultured fibroblasts which confirmed the diagnosis. When admitted for the emergency ovarian cystectomy, she had no recent history of hypoglycemic hypoketotic coma and denied any symptoms of syncope, exercise intolerance, or muscle weakness. She was adhering to a strict high-carbohydrate, low-fat dietary regime and was following advice to limit periods of starvation. She was hemodynamically stable on admission, and her clinical examination revealed only abdominal tenderness. Admission biochemistry was unremarkable. On the day of surgery, she was started on intravenous 5% dextrose supplementation with regular capillary glucose monitoring during the fasting period. She experienced one episode of hypoglycemia (blood glucose = 2.4 mmol/L) 3 hours into fasting, which was corrected by a bolus of 10% dextrose. Her preoperative blood glucose level was 6.7 mmol/L. A laparoscopic approach was planned for the ovarian cystectomy to minimize the metabolic disruption due to surgical stress.

Intraoperatively she received a 5% dextrose infusion at 100 ml/hour. Rapid-sequence induction of anesthesia was performed using thiopentone and suxamethonium. The

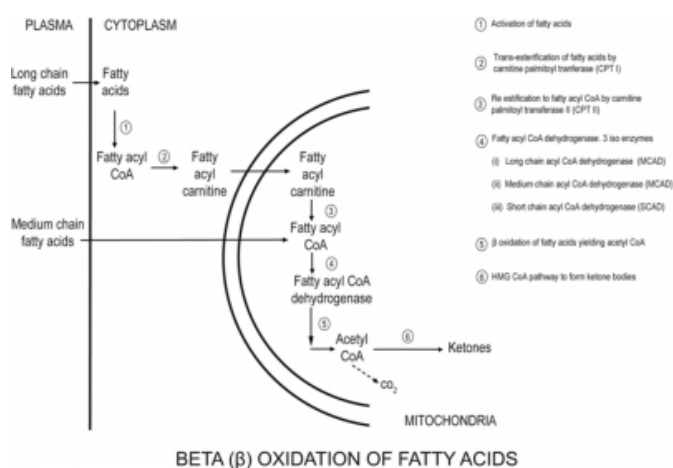
trachea was intubated, and her lungs were mechanically ventilated. Atracurium was used to facilitate neuromuscular blockade, and the depth of relaxation was monitored using peripheral nerve stimulators. Following induction of anesthesia, blood glucose levels dropped to 4.6 mmol/L without metabolic acidosis, and she was infused with a 100 ml bolus of 10% dextrose. She was given a prophylactic dose of intravenous ondansetron to prevent postoperative nausea and vomiting. Anesthesia was maintained with sevoflurane in air and oxygen, and she received morphine for pain relief. She had an uneventful laparoscopic left ovarian cystectomy and drainage of a right ovarian cyst, with successful extubation of the trachea after reversal of residual neuromuscular blockade. A 5% dextrose infusion was continued postoperatively. Feeding was restarted within 2 hours, and regular blood glucose monitoring continued until feeding was well established. Subsequent recovery was uneventful, and she was discharged the following day.

DISCUSSION

The most common fate of fatty acids is mitochondrial beta-oxidation leading to formation of acetyl CoA, which enters the tricarboxylic acid (TCA) cycle and generates energy. Acyl CoA dehydrogenases are a group of enzymes that facilitate the first step in the beta-oxidation of fatty acids in the mitochondria (Figure 1). The enzymes show chain length specificity with the medium chain variety being selective for fatty acyl CoA with 6 to 12 carbon atoms₃.

Figure 1

Figure 1: β -oxidation of fatty acids.



MCAD deficiency and indeed all other disorders of fatty acid oxidation lead to a failure to produce sufficient quantities of ketones despite rising levels of circulating free fatty acids during periods of stress or starvation. Ketones are

the body's prime source of energy following depletion of glycogen stores. When ketones are not produced in these circumstances, circulating free fatty acids are incorporated into triglycerides, leading to marked accumulation of fat in the liver during acute episodes. The lack of generation of acetyl CoA in the mitochondria results in reduced substrate availability for the TCA cycle, resulting in the nutritional deprivation of tissues. Gluconeogenesis is impaired due to impairment of the pyruvate carboxylase system secondary to the reduced availability of acetyl CoA. Additionally, there is accumulation of intermediate products that are potent neurotoxins, such as octanoyl CoA₁₃₄.

Diagnosis of MCAD deficiency is dependent on neonatal screening for the acyl-coenzyme A dehydrogenase, C-4 to C-12 straight chain (ACADM) gene. Fibroblast cultures demonstrate the reduced MCAD activity typical of the disease. The plasma acyl carnitine assay reveals accumulation of C6-10 species with elevated free and total fatty acids. Urinary organic acid analysis shows raised fatty acid excretion (C6>C8>C10) with inappropriately low ketone levels₁₃₄.

The onset of clinical features can occur as early as the perinatal period, manifesting as the sudden infant death syndrome₁₂₃₅ or as late as adulthood, when completely asymptomatic adults may present for the first time during an episode of stress or pregnancy₆₇. Children afflicted with the disease usually present between 3 months and 2 years of age with episodes of vomiting and lethargy. Hypoglycemia with reduced serum ketone levels, elevated blood ammonia, and raised liver enzymes are characteristic findings in these patients during acute episodes. Assessment for ketones is crucial as the differential diagnosis of hypoglycemia depends on the presence or absence of ketone production during acute episodes. Table 1 summarizes the causes of ketotic and non-ketotic hypoglycemia.

Figure 2

Table 1: Causes of ketotic and non-ketotic hypoglycemia

Ketotic hypoglycemia	Non-Ketotic hypoglycemia
<ol style="list-style-type: none"> 1. Metabolic disorders <ul style="list-style-type: none"> Organic acidurias Inborn errors of glycogenolysis Inborn errors of gluconeogenesis 2. Cortisol deficiency 3. Growth hormone deficiency 4. Starvation 5. Alcohol overdose 	<ol style="list-style-type: none"> 1. Metabolic disorders <ul style="list-style-type: none"> Disorders of beta-oxidation of fatty acids 2. Insulinoma 3. Sulphonylurea or insulin overdose 4. Insulin receptor antibodies 5. Sarcoma, hepatoma and other solid tumors

A quarter of acutely presenting children are at risk of dying ¹²⁷. Survivors remain asymptomatic between episodes but may have delayed achievement of developmental milestones and are more likely to have reduced exercise tolerance, fatigue, myalgia, neuro-psychiatric symptoms, and weight gain ⁸. Severity of the disease is influenced by the zygosity of the patient, with the compound heterozygous variety—as in our patient—demonstrating a less severe course ¹²³. Phenotypic heterogeneity with variable clinical severity, even within the same family, is well documented ¹. Early diagnosis and intervention can lead to asymptomatic survival to adulthood with reduced morbidity, at least in those heterozygous for the disease ⁸. The mainstay of treatment of acute episodes is intravenous dextrose therapy to supply an alternative fuel source. Carnitine therapy is reserved for poor responders. The rationale for its use lies in its ability to conjugate toxic intermediate metabolites, facilitating their removal in urine ¹²³. Effective prevention of acute episodes depends on maintaining a high carbohydrate, low-fat diet and avoiding starvation. Dextrose supplementation during anticipated periods of stress or fasting can help to prevent the triggering of an acute episode.

In the peri-anaesthetic setting, the main considerations are the accompanying starvation state, the deranged metabolic responses to surgical stress, the morbidity of pre-existing multisystem involvement by the disease, and the safety of pharmacological agents employed during anesthesia. Preoperative assessment of a patient with MCAD deficiency should include a detailed medical history as well as a thorough neurological assessment ². Baseline investigations should include a coagulation profile, particularly if regional anesthetic techniques are being considered. Liver function tests including blood ammonia levels are relevant, as impaired hepatic function may affect drug metabolism and hyperammonemia can reduce sedation requirements and

minimal alveolar concentration (MAC) values. Although the involvement in MCAD deficiency is predominantly hepatic, extra-hepatic involvement with underlying cardiomyopathy or generalized myopathy may occur, as in long chain acyl CoA dehydrogenase (LCAD) deficiency, and should be ruled out, since some patients may have multiple enzyme deficiencies ¹.

Every effort must be made to minimize the duration of fasting with intensive perioperative monitoring of glycemia and prompt management of hypoglycemia if it occurs. Although our patient had the compound heterozygous disease, believed to be less severe, she experienced two episodes of hypoglycemia, despite a 5% dextrose maintenance infusion. Both of these episodes of hypoglycemia responded to supplementary glucose. Carnitine supplementation should be considered in the event of refractory hypoglycemia or worsening neurological symptoms. Regional anesthesia should be selected whenever possible, to minimize the stress response. Laparoscopic surgery as opposed to open surgery may be a better choice for the same reason. Arterial blood gas analysis to closely monitor the acid base status may be required in patients with clinically severe disease. The effect of neuromuscular blocking agents in myopathic patients is poorly understood. Close monitoring of neuromuscular function is indicated, as patients with multiple acyl CoA dehydrogenase deficiency may demonstrate hypotonia, with the potential for prolongation of drug action due to concomitant hepatic impairment if present. In our patient, standard doses of suxamethonium and atracurium produced predictable clinical responses and were monitored using train of four (TOF) response and double burst suppression (DBS). The response to volatile anesthetics and thiopentone was predictable. Although total intravenous anesthesia using propofol should probably be avoided due to the potential for development of the propofol infusion syndrome with mitochondrial fatty acid disorders, a single dose of propofol is probably not contraindicated ⁹. However, we used thiopentone for the induction of anesthesia. Postoperative nausea and vomiting can delay restarting of oral feeds and increase the risk of hypoglycemia. Prophylactic anti-emetics with intravenous glucose supplements and close monitoring of capillary glucose values well into the postoperative period is crucial until oral feeding is effectively established.

In summary, we have described a patient with compound heterozygous MCAD deficiency who underwent surgical

intervention under general anesthesia. As the disease has an approximate incidence of 1.4 per 10,000 and is now a part of the UK neonatal screening programme¹⁰, the number of such patients presenting in non-tertiary centers and requiring routine anesthesia is likely to increase. Early recognition and improved metabolic management of the heterozygous patients is likely to increase the survival of patients with MCAD deficiency into adulthood. Our case-report illustrates that relatively simple measures—such as preoperative evaluation of hepatic, neurological, muscular, and cardiac function, with diligent monitoring of glycemia—can prevent catastrophic episodes and lead to a successful anesthetic outcome.

ACKNOWLEDGEMENTS

Department of Medical illustration.

Diana Princess of Wales Hospital Grimsby

References

1. Roe CR, Coates PM. Mitochondrial fatty acid oxidation disorder. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. 7th ED. New York: McGraw-Hill, 1995: 1515-22.
2. Wang SY, Kannan S, Shay D, Segal S, Datta S, MD, Tsen L. Anaesthetic considerations for a patient with compound heterozygous medium-chain acyl-CoA dehydrogenase deficiency. *Anaesthesia Analgesia* 2002; 94: 1595-7.
3. Roth KS. Medium –Chain Acyl CoA Dehydrogenase Deficiency www.emedicine.co.uk (accessed 12/01/2009).
4. Matern D, Rinaldo P. Medium-Chain Acyl Coenzyme A Dehydrogenase Deficiency. www.genetests.org (accessed 08/02/2009).
5. Bennett MJ, Rinaldo PR. The metabolic autopsy comes of age. *Clinical Chemistry* 2001; 47: 1145-6.
6. Santos L, Patterson A, Moreea SM, Lippiatt CM, Walters J, Henderson M. Acute liver failure in pregnancy associated with maternal MCAD deficiency. *Journal of Inherited Metabolic Diseases* 2007; 30: 103.
7. Feillet F, Steinmann G, Vianey-Saban C, de Chillou C, et al. Adult presentation of MCAD deficiency revealed by coma and severe arrhythmias. *Intensive Care Medicine* 2003; 29:1594-7.
8. Derks JK, Dirh-Jan R, Waterham HR, et al. The natural history of medium chain acyl CoA dehydrogenase deficiency in the Netherlands: Clinical presentation and outcome. *Journal of Paediatrics* 2006; 148: 665-70.
9. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty oxidation in propofol infusion syndrome. *Lancet* 2001; 357: 606-7.
10. Dezateux C, Oerton J, Khalid JM, Cole T, Stanford B, Phillips P. The UK Collaborative Study of Newborn Screening for medium chain acyl coA dehydrogenase deficiency (UKCSNS-MCADD): Overview and early findings. www.newbornbloodspot.screening.nhs.uk (accessed 15/04/2009).

Author Information

A. Mitra, MD, FRCA

Specialist registrar in Anaesthesia, Diana Princess of Wales Hospital

S. Husaini, FRCA

Consultant in Anaesthesia, Diana Princess of Wales Hospital

L. John, MRCP

Consultant Physician, Diabetes and Endocrinology, Diana Princess of Wales Hospital