Brief Communication and Review of the Literature

Anesthetic considerations in medium-chain acyl-CoA dehydrogenase deficiency

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Abstract

In the 1980's, medium-chain acyl-CoA dehydrogenase deficiency (MCADD) was first described in the literature as three children who presented with coma, hypoglycemia, hyperammonemia, and fatty liver while fasting. These symptoms while similar to Reye's Syndrome, were found to be due to an inability to metabolize medium chain fatty acids during fasting periods. Fatty acids are utilized by the body as essential fuel for skeletal and cardiac muscle, and as an important source of energy during fasting periods. Medium-chain acyl-CoA dehydrogenase is a mitochondrial enzyme required for the beta oxidation of medium chain fatty acids (C4-14), which is deficient in this syndrome. Anesthesiologists may come across these patients in their practice, as MCADD is the most common inhertited disorder of mitochondrial fatty acid oxidation. In addition to determining NPO timing and IV fluid selection, other preoperative issues anesthesiologists must consider are medication management to avoid metabolic decompensation. This manuscript will consider a pediatric patient with MCADD who presented to our pediatric hospital and received a general anesthetic following the guidelines created by our multidisciplinary perioperative team.

Keywords: Medium-chain acyl-CoA dehydrogenase deficiency, Perioperative Guidelines, Anesthetic management of Medium-chain acyl-CoA dehydrogenase deficiency

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Introduction

In 1983, Stanley published a paper in which he described three children who presented with coma, hypoglycemia, hyperammonemia, and fatty liver while fasting (1, 2). These symptoms while similar to Reye's Syndrome, were found to be due to an inability to metabolize medium chain fatty acids during fasting. As such, Stanley may be credited with first publishing medium-chain acyl-CoA dehydrogenase deficiency (MCADD) as a previously unrecognized metabolic disorder of fatty acid oxidation (1, 2). The body utilizes the oxidation of fatty acids not only to provide essential fuel for skeletal and cardiac muscle, but also as an important source of energy during fasting periods (1). While fasting, the brain converts fatty acids to energy in order to conserve glucose levels. The liver will oxidize fatty acids to ketones to servea dual purpose: to provide energy for gluconeogenesis, and generating

fat derived substrates to support the brain's metabolic requirements in lieu of glucose (1).

Medium-chain acyl-CoA dehydrogenase is a mitochondrial enzyme required for the beta oxidation of medium chain fatty acids (C4-14) (3, 4). During fasting, adipose tissue will mobilize fatty acids which are then absorbed by the liver and other tissues and converted to acyl-coA esters (3) intracellularily. These esters will then enter the mitochondria as carnitine esters and become re-esterified to acyl co-A esters. The beta oxidation of the esters will liberate electrons as the acyl chain is shortened by an enzymatic process (3). The catalysts are acyl-CoA dehydrogenases, each specific for very-long chain, long-chain, medium-chain, or short chain acyl-co-A esters. Figure 1 is a representation of fatty acid beta-oxidation; medium-chain acyl-CoA dehydrogenase is one of the enzymes responsible for the dehydrogenation of medium-chain fatty acids.

Fatty acids normally undergo β-oxidation during fasting periods to produce ketones. Those with MCADD will accumulate fatty acids during fasting, and not generate ketones. The systemic consequences of MCADD will result in a lack of ketones to meet tissue energy demands manifesting as severe hypoglycemia as well as toxicity of the liver, muscle, and central nervous system as fatty acids and their corresponding acylcarnitines accumulate. Hypoketotic hypoglycemia will develop in times of fasting because of the inability to utilize fat for fuel (2).

MCADD is the most common inherited disorder of mitochondrial fatty acid oxidation (5). It is inherited in an autosomal recessive fashion, occurring primarily in Caucasians with northern European ancestry (2, 3, 5–8). The prevalence has been reported to vary by population studied: 1:4,900 in Germany and 1:17,000 in Taiwan (9). MCADD occurs with a reported incidence of 1 in 12,000- 20,000 births (2, 5, 9).

Diagnosis of MCADD can be accomplished by DNA analysis for mutations or tissue testing of heart, liver, or skeletal muscle for enzyme activity (2, 9). Those affected by MCADD are predominantly homozygous for a single mutation of an A to G nucleotide; the remaining 20% are either carriers of the single gene mutation or compound heterozygotes (2, 10). As of 2009, the United Kingdom performs neonatal screening for MCADD (5). While the Discretionary Advisory Council on Heritable Disorders in Newborns and Children recommends screening for MCADD as a part of the newborn screening panel, conditions tested for in the United States vary by state (11).

Typically those affected with MCADD will exhibit symptoms between 3 months to 2 years of age (mean age 13 months), however neonatal and adult presentations have been reported (5, 9, 10). Roughly 1/3 of affected individuals are asymptomatic throughout life, but will remain at risk for metabolic decompensation in times of fasting (10). Symptoms of MCADD typically manifest after 12-16 hours of fasting when glycogen storesare depleted with no generation of ketones in times of increased energy demands such as: fasting, stress due to surgery, pregnancy, illness, or alcohol binge drinking (5, 8). Although there is no diagnostic stigmata of MCADD, those in acute decompensation may present to physicians with hypoketotic hypoglycemia, encephalopathy, hepatomegaly, vomiting, seizures, coma, or causedeath (5, 9). Table 1 lists the systemic consequences of MCADD. Patients with MCADD are placed at potential risk for aphasia, loss of developmental milestones, and attention deficit disorder attributed to brain damage acquired during metabolic decompensation (8).

There is no specific medical therapy to treat MCADD. Patients are advised to limit exacerbations by limiting nil per os (NPO) times or fasting, which varies by age:

1) 6-12 months: No more than 8 hours
2) 1-2 years: No more than 10 hours
3) 2 years and beyond: No more than 12 hours (8, 9).

During times of stress such as fever, illness, or fasting those with MCADD should ingest additional glucose sources such orange juice or dissolving glucose tablets (9). In a preoperative environment intravenous (IV) fluids with dextrose should be administered until the patient resumes adequate PO intake; point of care glucose testing is not sufficient to assess the energy reserves for those with MCADD (9). The use of carnitine supplementation is controversial though recommended for patients that have a low serum carnitine level (9, 12).

In addition, to determining NPO timing and IV fluid selection, other preoperative issues anesthesiologists must consider are medication management to avoid metabolic decompensation.While inhalational agents, propofol, andneuromuscular blocking agents are not contraindicated in MCADD, they certainly present some controversy (2, 5). Some datasuggests an impairment of fatty acid metabolism associated with anesthetic vapors such as enflurane, thus posing a theoretical increased risk during anesthesia (5, 13).

Cautions in using both depolarizing and non-depolarizing neuromuscular blockers preoperatively have been made. Patients with MCADD may have hypotonia and impaired hepatic metabolism (5, 8); as such may have prolonged effects of certain non-depolarizing agents. Some authors urge caution in the use of succinylcholine in the presence of a potential myopathy (2).

Propofol infusion syndrome (PRIS) is defined by acute bradycardia progressing to asystole during propofol infusion associated with lipoemic plasma, fatty liver enlargement, metabolic acidosis, rhabdomyolysis, and a base excess > -10 mmol (14). PRIS carries an estimated mortality rate of 20%, and is thought to be due to impaired fatty acid metabolism inhibiting the mitochondrial respiratory chain (5). It has been suggested to avoid propofol in patients with MCADD and other mitochondrial disorders, due to the extra fatty acid contents of the soy bean oil and impairment of fatty acid oxidation (4, 5, 15).

Careful multidisciplinary preoperative planning is highly advisable for MCADD patients requiring anesthesia. Ideally they should be the first case of the day, and preoperative dextrose containing IV fluids started to avoid metabolic decompensation. This can be especially challenging in pediatric patients due to cooperation or perhaps difficult IV access. The anesthesiologist should consider risk: benefit of utilizing such anesthetic agents such as volatile anesthetics, neuromuscular blocking agents, and propofol. This manuscript will consider a pediatric patient with MCADD who presented to our pediatric hospital and received a general anesthetic following the guidelines created by a multidisciplinary team consisting of anesthesiology, genetics, and pediatric surgery.

Brief Report

A 19 month old 11.7kg male with a history of MCADD was admitted for possible bilateral orchiopexy for undescended testes. He was diagnosed with MCADD by a newborn screen completed in the state of his birth. He was seen in our pre-operative clinic where a clear note was written in the patient's record including recommendations by the genetics team for management, guided by our institution's metabolic protocol.

The patient was admitted the day before by the genetics service and had an IV placed with D10 ½ normal saline running at 45ml/hr (glucose infusion rate (GIR) of 6.4). He was given 250 mg of levocarnitine intravenously the morning of surgery. Other preoperative considerations for this patient included avoiding muscle relaxants and propofol; the genetics team recommended avoidance of benzodiazepines, barbiturates, and neuromuscular blocking agents. Standard American Society of Anesthesiologists (ASA) monitors (16) were used which included: 3 lead electrocardiogram, noninvasive blood pressure monitor, pulse oximetry, and capnography. Intravenous induction of anesthesia was completed with ketamine 50 mg and fentanyl 20 mcg. He was easily intubated with a 4.0 endotracheal tube without the use of paralytics. Sevoflurane was used for anesthesia maintenance. The patient was extubated deep after no true testes were found, and the procedure was terminated. He was brought to the post anesthesia care unit (PACU) with continued D10 fluid. After an uneventful PACU stay, he was discharged to the floor with D10 fluid until he was able to tolerate solid food. He was discharged by the genetics team later that day with no complications noted in the electronic medical record.

Discussion

In 2013 a multidisciplinary team was assembled at our institution to create preoperative guidelines and best practice recommendations for children with inborn errors of metabolism. The team consisted of pediatric anesthesiologists, geneticists, and pediatric surgeons. They identified best preoperative practices with the dual aim to prevent procedural cancellations or metabolic crises.

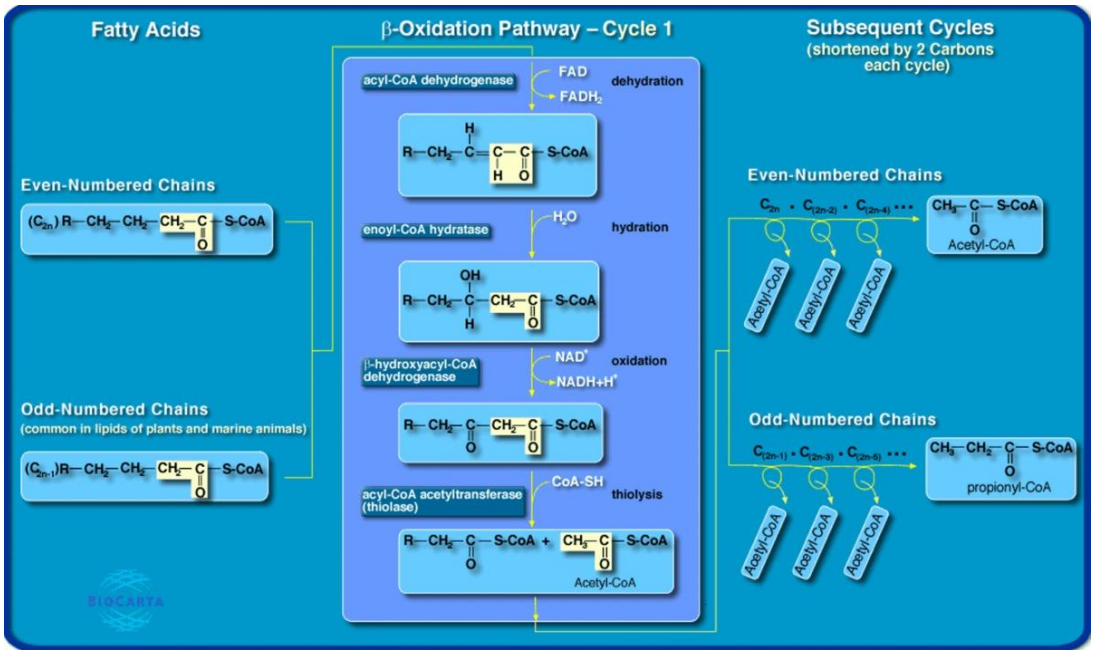

Figure 1. Medium-chain acyl-CoA dehydrogenase (MCAD) is one of the enzymes responsible for dehydrogenation of fatty acids as they cycle through the beta-oxidation spiral.By Modre-Osprian, Robert; Osprian Ingrid; Tilg, Bernhard; Schreier, Gunter; Weinberger, Klaus; and Graner, Armin.
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Per our institutional protocol, if a child with MCADD needs a procedure requiring an anesthetic, he/she is referred to our preoperative evaluation clinic for a pre-anesthetic evaluation. Part of this evaluation consists of direct communication with the genetics team for their specific recommendations, i.e. unique preoperative labs, medications and IV fluid management. The day before surgery, if indicated, the patient will be admitted to the hospital and an IV placed prior to becoming NPO. Ideally, to minimize prolonged NPO times due to changes in the schedule, the patient will be the first case in the room.

The NPO policy for our institution follows the ASA NPO guidelines which is 2 hours for clear liquids; 4 hours for breast milk; 6 hours for formula; and 6-8 hours for solid food depending on the fat contents (17). For IV fluids, D10 (or D12.5) ½ NS + 2mEQ/100mL KCl to run with glucose infusion rate (GIR) 8-9 (mg/kg/min). Glucose infusion rate is derived from factors such as the IV fluid infusion rate, the patient's weight, and % of dextrose in the solution. A GIR of 5-8 is considered an average rate to maintain euglycemia (18). If additional fluids are required to replace losses, normal saline or Plasma-Lyte is preferred over Ringer's Lactate since this may theoretically increase acidosis as well as metabolic load on dysfunctional mitochondria.

Our institutional metabolic disorders guidelines also include recommendations for intraoperative anesthetic management. With regards to medications, drugs that are metabolized into odd chain fatty acids should be used cautiously in patients with MCADD which include: succinylcholine, atracurium, mivacurium, and propofol (as it is high in polyunsaturated fats) (19, 20). Some patients may be more sensitive and show prolonged effects to central nervous system depressants, and therefore it is recommended to delay extubation until complete muscle strength as returned. Specific MCADD preoperative fluid recommendations advocate the use of carnitine if it is currently prescribed.

Table 1: Systemic consequences of medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

Organ System	Symptom
Central Nervous System	• Coma • Encephalopathy • Lethargy • Seizures • Sudden death
Cardiac	• Arrhythmia • Cardiovascular arrest
Gastrointestinal	• Abnormal liver function tests • Hepatomegaly • Peripheral lobular fatty liver • Vomiting
Metabolic	• Hyperammonemia • Impaired ketogenesis with hypoketotic hypoglycemia • Metabolic acidosis • Secondary carnitine deficiency

Authors agree that the preoperative management of MCADD requires strategic planning to limit NPO times thus avoid depleting glucose stores with resulting metabolic decompensation (2, 5–7, 12). Table 2 provides a side by side comparison of anesthetic recommendations for MCADD. While these recommendations advocate for glucose containing IV fluids to start preoperatively and continue into the preoperative period, there is no overall consensus of the specific type of fluid nor the GIR (2, 5–7, 12). Our recommendations include guidelines on a specific GIR, as it provides a measure of how quickly a patient receives carbohydrates. While caution has been issued regarding the use of propofol, volatile anesthetics, and muscle relaxants in the context of MCADD, there are case reports of uneventful anesthetics (2, 6, 7).

Our case report considers an uneventful anesthetic utilizing our institution's evidenced based metabolic guidelines which are supported by others in the literature. The British Inherited Metabolic Disease Group provides specific preoperative guidelines for MCADD patients which include recommendations on NPO times and IV/oral glucose replacement (12). Created in 2013, the BIMDG guidelines formalized practices in the United Kingdom which included the preoperative use of 10% glucose solutions (5, 12). Like the BIMDG guidelines, our institutional recommendations share multidisciplinary preoperative planning, limiting NPO times, pre/intra/postoperative use of 10% glucose solutions, and the resumption of a normal diet as soon as feasibly possible.

Allen et al performed a retrospective chart review of 14 patients with MCADD who received a total of 20 general anesthetics over a 17 year period (5). The small number reflects that although MCADD may be the most common inherited form of error in fatty acid oxidation, it is not a disease process that requires multiple procedures for satisfactory quality of life. A majority of these children received glucose containing fluids preoperative hydration per BIMDG recommendations, with 5 reported cases of hyperglycemia (no hypoglycemia or decompensation). Propofol and volatile anesthetics were given, often in combination for these procedures, uneventfully. There was, however, 1 reported case of delayed offset of atracurium; and the authors urge the use of twitch monitoring if neuromuscular blocking agents are used. Allen et al strongly advocate preoperative glucose supplementation following BIMDG, without making specific recommendations on medications to absolutely avoid. Our case report reflects similar results, no incidence of metabolic decompensation when glucose supplementation was given, and the safe use of volatile anesthetics for a brief procedure.

The three decades following Stanley's description of MCADD has greatly expanded the medical communities understanding of this disease.

Table 2: Comparison of anesthetic recommendations for MCADD

	NPO	IV Fluids	Anesthetic Recommendations
Texas Children's Hospital	• Minimum pre-operative fasting interval • Patient admitted the night before surgery to commence IV fluid therapy	• D10 (or D12.5) ½ NS + 2mEQ/100mL KCl to run with GIR 8-9 (weight x GIR x 0.6); • If extra fluids are to be required to replace losses, NS is preferred over Ringer's Lactate	Recommend avoiding benzodiazepines, barbiturates, neuromuscular blocking agents, and propofol.
British Inherited Metabolic Disease Group (BIMDG)	• Minimum pre-operative fasting interval • Feed the child at the time you would feed any other child following an equivalent procedure • Discontinue the intravenous infusion ONLY after the child tolerates food	• IVF to start at time operations starts • 10% glucose 0.45% saline • Fluid/24 hours = 100ml/kg for 1st10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter. Potassium should be added to this solution 10 mmol in 500 ml • Replete carnitine only if deficient	
Allen et al.	Recommends following BIMDG guidelines	Recommends following BIMDG guidelines	• May be safest to avoid propofol; or use 2% formulation to limit fatty acid load • High dose opiate with low dose volatile anesthetic • Recommends antiemetics to control post op nausea vomiting • Cautions use of volatile anesthetics and propofol
Dearlove et al.	Recommend that children for the afternoon operating lists should have a light breakfast and a glucose drink at 1100 h	10% glucose infusion	Reported using thiopental and local anesthetic uneventfully
Justiz et al.	• Limit NPO status to 2–4 h • Close perioperative blood glucose monitoring	• Preoperative intravenous catheter placement • 5% dextrose in lactated Ringer's • Consider adding carnitine	Reported using midazolam, propofol, sevoflurane uneventfully
Wang et al.	• Limit NPO status to 12 hours max	• 10% glucose to start preoperatively • Considering giving carnitine if neurologic status changes	• Preop: assess medical history, neurologic status, coagulations profile, and blood glucose levels • Recommends avoiding succinylcholine • Reported using intrathecal0.25% bupivacaine, fentanyl uneventfully

Apart from dietary management, future treatment may include gene therapy as trials are promising using fiberblast cultures using in vitro studies (21). Anesthetic medications, preoperative guidelines, and

glycemic control would benefit from future prospective studies to optimize recommendations (5). Currently, an IRB has been submitted at our institution to prospectively study the impact of these metabolic guidelines and safety with anesthesia.

Conclusion

MCADD is the most common inherited disorder of mitochondrial fatty acid oxidation. Roughly 1/3 of affected individuals are asymptomatic throughout life, but will remain at risk for metabolic decompensation in times of of increased energy demands such as: fasting, stress due to surgery, pregnancy, or illness. Although there is no diagnostic stigmata of MCADD, those in acute decompensation can exhibit hypoketotic hypoglycemia, encephalopathy, hepatomegaly, vomiting, seizures, coma, or cause death. Multidisciplinary preoperative planning is highly advisable for MCADD patients requiring anesthesia. Ideally they should be the first case of the day, and preoperative dextrose containing IV fluids started to avoid metabolic decompensation. This can be especially challenging in pediatric patients due to cooperation or perhaps difficult IV access. The anesthesiologist should consider risk: benefit of utilizing such anesthetic agents such as volatile anesthetics, neuromuscular blocking agents, and propofol.

Acknowledgment

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Stanley CA, Hale DE, Coates PM, et al. Medium-chain acyl-CoA dehydrogenase deficiency in children with non-ketotic hypoglycemia and low carnitine levels. Pediatr Res. 1983;17(11):877-84.
2. Wang SY, Kannan S, Shay D, Segal S, Datta S, Tsen L. Anesthetic considerations for a patient with compound heterozygous medium-chain Acyl-CoA dehydrogenase deficiency. Anesth Analg. 2002;94(6):1595-1597.
3. MD VCB, MPH JEOM. Anesthesia for Genetic, Metabolic, and Dysmorphic Syndromes of Childhood. Second edition. Philadelphia, PA: LWW; 2006.
4. Steiner LA, Studer W, Baumgartner ER, Frei FJ. Preoperative management of a child with very-long-chain acyl-coenzyme A dehydrogenase deficiency. Paediatr Anaesth. 2002;12(2):187-91.
5. Allen C, Perkins R, Schwahn B. A retrospective review of anesthesia and preoperative care in children with medium-chain acyl-CoA dehydrogenase deficiency. Paediatr Anaesth. November 2016.
6. Dearlove OR, Perkins R. MCAD deficiency and anaesthesia. Anaesthesia. 1995;50(3):265.
7. Justiz AC, Mayhew JF. Anesthesia in a child with medium-chain Acyl-CoA dehydrogenase deficiency. Paediatr Anaesth. 2006;16(12):1293-4.
8. Matern D, Rinaldo P. Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews(®). Seattle (WA): University of Washington, Seattle; 1993. http://www.ncbi.nlm.nih.gov/books/NBK1424/. Accessed December 8, 2016.
9. Gartner V, McGuire PJ, Lee PR. Child Neurology: medium-chain acyl-coenzyme A dehydrogenase deficiency. Neurology. 2015;85(4):37-40.
10. Loughrey C, Bennett MJ. Screening for MCAD deficiency in newborns. BMJ. 2009;338:b971.
11. Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2005;6(3 Suppl):S3-5.
12. British Inherited Metabolic Diseases Group. Management of surgery in children with fat oxidation disorders. 2013. Available at: http://www.bimdg.org.uk/store/guidelines/ Management-of-surgery-in-children-with-fatoxidation- disordersv4-619512-22-05-.
13. Kleemann PP, Jantzen JP, Fenner R, Wiegand UW. [Preoperative increase in the plasma concentration of free fatty acids during minor elective interventions using a conventional anesthesia technic with enflurane]. Anaesthesist. 1986;35(10):604–608.
14. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. Minerva Anestesiol. 2009;75(5):339-44.
15. Farag E, Deboer G, Cohen BH, Niezgoda J. Metabolic acidosis due to propofol infusion. Anesthesiology. 2005;102(3):697-698-699.
16. American Society of Anesthesiology House of Delegates Committee on Standard and Practice. Standards for basic anesthetic monitoring. 2010.
17. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology.

2011;114(3):495-511.
18. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther JPPT Off J PPAG. 2013;18(3):199-208.
19. Harker HE, Emhardt JD, Hainline BE. Propionic acidemia in a four-month-old male: a case study and anesthetic implications. Anesth Analg. 2000;91(2):309-311.
20. Karagoz AH, Uzümcügil F, Celebi N, Canbay O, Ozgen S. Anesthetic management of a 2-year-old male with propionic acidemia. Paediatr Anaesth. 2006;16(12):1290-1.
21. Schowalter DB, Matern D, Vockley J. In vitro correction of medium chain acyl CoA dehydrogenase deficiency with a recombinant adenoviral vector. Mol Genet Metab. 2005;85(2):88-95.