Anesthetic Management of a Patient with Maple Syrup Urine Disease Undergoing Liver Transplantation from Living Related Donor

Mubarak Aldoseri, MD* Muhannad Alshahrani, MD** Plinio Sierra, MD***

ABSTRACT

Maple syrup disease is a rare metabolic condition affecting the pediatric population. It is related to reduction or deficiency of branched chain a-ketoacid dehydrogenase (BCKD). The mainstay of management is by strict dietary protein restriction with branch chain amino acid (BCAA) free diet along with supplementation of other essential amino acids and frequent monitoring of BCAA levels. However, the approach should be through multidisciplinary team addressing dietary requirement, growth and psychomotor development. This can be challenging due to compliance with such regimens as well as metabolic decompensations during physiological stress that can occur in fasting, surgery, infection and inflammation. Liver transplantation has been shown to enable MSUD patients to have unrestricted diet and normal BCAA post-operatively. Although MSUD is a rare disease, there is extensive literature published related to it from pediatrics, gastroenterology, hepatology and transplantation point of view. We describe a case report of peri-operative management of 4 years old MSUD patient undergoing living related liver transplantation (LRLT) with normal BCAA levels post-operatively as this type of surgery is relatively recent in addition to the limited data on the peri-operative management of MSUD patients undergoing surgical procedures.

Key words: Maple syrup urine disease, Liver transplant, Anesthetic management, Peri-operative

INTRODUCTION

Maple syrup urine disease (MSUD) has incidence about 1:200,000 children worldwide, but it has higher incidence among old order Mennonite families of about 1:200 children[1]. Patients with classical type of MSUD usually present early in life[2]. This condition progresses on to leucine encephalopathy, seizures and cerebral oedema especially if not diagnosed and treated promptly early on[3,4]. In MSUD, high levels of branched-chain amino acids (BCAA) has been found to induce dangerous protein turn over cycle with both protein synthesis and catabolism[5]. The mainstay treatment of the disorder is special diet with BCAA and it is very important as infants may become symptomatic before screening tests are available. Accumulation of BCAA in blood and BCKA in urine can occur within 3 days after loss of the normal enzyme from the mother's liver in the post-natal period[6]. If infants are not put on special diet, death can occur within 1-2 weeks as well as neurological damage which may be permanent during this developmental stage. Compliance with diet and frequent monitoring of protein levels in the serum does not prevent acute encephalopathic decompensation as it can occur with stress, surgery, fasting, starvation, and intercurrent illness[1].

Liver transplantation has been shown to enable MSUD patients to have unrestricted diet and normal BCAA post-operatively[7]. Domino liver transplantation and living related liver transplantation have been used as well to overcome shortage with organs and long waiting time. Living related liver transplantation was first described as another successful method to treat MSUD in 2014 by Feier et al[8]. When it comes to the recipients of MSUD livers, they do not exhibit the symptoms of maple syrup disease and remain functionally and metabolically well with no restrictions on diet. We describe a case report of peri-operative management of a 4 years old MSUD patient undergoing living related liver transplantation (LRLT) with normal BCAA levels post-operatively as this type of surgery is relatively recent in addition to the limited data on the peri-operative management of MSUD patients undergoing surgical procedures.

CASE

A 4-year-old baby girl was born on December 11, 2011, at King Abdullah Specialized Children's Hospital, Riyadh, Saudi Arabia. She was born as a product of spontaneous vaginal delivery (SVD) to consanguineous parents at full-term. She had a 6-year-old healthy sister with no known disease at the time of birth. However, her mother had a history of three previous miscarriages. Her family history was significant for her maternal cousins having been diagnosed with metabolic acidosis and spasticity.

At the time of birth, she was screened for plasma amino acids and was diagnosed with maple syrup urine disease (MSUD). Consequently, she stayed at the pediatric intensive care unit (PICU) for 7 days post-delivery. At the age of 2 months, she was admitted to the PICU with high leucine levels requiring hemodialysis. She was managed with special metabolic formula (Ketonex®-2), thiamine, isoleucine (90 mg OD) and valine (100 mg OD) with regular follow-up by a metabolic dietician and monitoring of their levels. The patient was genetically tested with a homozygous mutation in the BCKDHB gene (c 674 T > C p.L225P) nucleotide change in exon 6 of BCKDHB gene resulting in the replacement of the amino acid leucine with proline at position 225 (p.L225P). (Table 1) demonstrates the amino acid levels of the patient starting at birth in December 2011.

* Senior Resident
Anesthesia & ICU Department; Bahrain Defence Force Hospital
Bahrain, E-mail: dr.mubarak.aldoseri@gmail.com
** Resident
Anesthesia Department; King Abdulaziz medical City, Riyadh
*** Consultant
Pediatric Anesthesia and Pain Medicine, King Abdullah Specialized Children's hospital

Table 1: Amino acid levels of the patient since birth

Date	Leucine	Isoleucine	Valine
27-2-2016	1222	497	707
1-2-2016	1599	331	507
28-12-2015	900	371	608
15-11-2015	1478	221	407
9-5-2015	263	420	766
2-1-2012	49	563	695
12-2011	2080	453	558

The patient's MRI was conducted demonstrating abnormal low T1 and high T2 signal intensity representing edema involving periirolandic cortex, posterior limb of the internal capsule, corticospinal tracts, cerebellar peduncle, dorsal aspect of the brainstem down to involve right cerebellar white matter with these areas showing restricted diffusion. The isolated involvement of myelinated white matter was visible showing low T1, high T2 signal density and restricted diffusion suggestive of MSUD. An ultrasound liver was conducted at the age of 3 years for the patient demonstrating normal liver Doppler ultrasound with increased echogenicity and heterogeneity of the liver. Her renal ultrasound and Doppler were unremarkable.

At the age of 5 years, the patient was offered orthotropic liver transplantation after a discussion with parents on many occasions and as effective treatment for maple syrup urine disease due to frequent metabolic decompensations of the patient. On March 2, 2017, the patient received clearance for general anesthesia (GA). On March 15, 2017, the patient was admitted for her surgery. Her pre-operative findings are demonstrated in (Table 2).

Table 2: Pre-operative findings of the patient

Vitals	**Results**
weight	16.6 Kg 50th percentile
Height	106 cm 75th percentile
Head circumference	47.5 5-10th percentile
HR	111
BP	109/77
RR	26
T	36.4
SpO2	97 RA
Physical Examination	**Results**
Head/ neck	Normal
ENT	Normal
Chest	Normal breath sounds
Cardiac	Normal heart sounds with no murmur
Musculoskeletal	Normal
Neurological	Conscious, mild hypotonia, normal gait, no motor/sensory deficits
Investigations	**Results**
Bilirubin total	18.3 mg/dL
Albumin	33 g/L
ALT	33 IU/L
Alkaline phosphatase	181 U/L
Calcium	2.21 mmol/L
Total protein	56 g/dL
PO4	1.34 mmol/L
Mg 2+	0.59 mmol/L
Na	137 mmol/L
K	4.5 mmol/L
CL	106 mmol/L
Random glucose	3.8 mmol/L
BUN	4.6 mg/dL
Cr	36 mg/dL
CO2	22 mmol/L

The patient was operated for living donor liver transplantation (LDLT) on April 17, 2017. The patient was induced with fentanyl (2.5 mcq/kg), propofol (2 mg/kg), midazolam 0.05 mg/kg and cistacurium (0.25 mg/kg). She was intubated with ETT size 5 cuffed. Anaesthesia was maintained with remifentanil infusion (0.2 mcq/Kg/min to 0.25 mcq/kg/min) and sevoflurane 2% in O2/air 50% along with cistracurium infusion (3 mcq/Kg/min). A 5.5 triple lumen central line catheter inserted in left internal jugular under US guidance. Two arterial lines inserted G22 left radial and left femoral G20. Regarding fluids management, patient was continued with infusion of plasmalyte 200 ml/hr, Dextrose 5% in NS 0.45 at 70 ml/hr (which average as 3.5 mg/Kg/min, 1.5 maintenance fluid for her weight) as well as lipid emulsion SMOF 30 g in 55 NS at 7.5 ml/hr (3.75 g/hr, around 5.5 g/kg/day if infusion continued for 24 hours). The dextrose and intra-lipid infusions started from midnight when fasting started as per metabolic specialist/dietician to prevent catabolism and metabolic decompensation. She received intra-operative tranexamic acid as a bolus of 10 mg/kg, then infusion intra-operatively with 10 mg/kg/hr methylprednisolone 240 mg IV after receiving the liver graft. She remained vitally stable yet required electrolytes replacement in the intra-operative period. She received 160 mg Calcium gluconate, and a total of 35 mEq sodium bicarbonate. At the end of surgery, the patient was transferred intubated to PICU to continue her post-op care.

The patient stayed for 1 week in the PICU and intubated for 1 day. She was managed in the hepatic ward for 5 days, and then to general pediatrics ward for 6 days. The patient faced difficulties feeding orally and was managed by NGT for feeding and medications. She received Tacrolimus and prednisolone post-operatively as immunosuppressant. On April 23, 2017, the patient had liver transplant Doppler which was within normal range. All her blood cultures were negative, and she was discharged on May 7, 2017.

DISCUSSION

Our patient was diagnosed early with metabolic screening and started on proper treatment, but liver transplantation was offered due to frequent metabolic decompensations and developmental delay as per metabolic physicians. It is essential to evaluate patients with MSUD in the perioperative period to provide safe anesthetic management as done in our patient. Various case reports mention the use of dextrose and intra-lipid infusions starting from fasting time to avoid catabolism, buildup of toxic metabolites, and metabolic complications. These infusions are stopped once patients resume their usual metabolic diet[9-12]. The use of tranaxemic acid as antifibrinolytic agent was based on multiple systematic reviews on adult liver cases and major pediatric operations. However, in the field of pediatric liver transplantation, there has not been randomized trials and further research is required[13-17]. In literature, there are few case reports describing the anesthetic management for different type of procedures and it is mainly individualized to patients factors as well as surgical procedure considerations.

When reviewing reports similar to our case, most of these articles describe the outcomes of liver transplant as treatment for MSUD and not from anesthetic point of view. Regarding the anesthetic approach for patients with MSUD, Pal et al. reported a similar case whereby an 11-month-old boy had three decompensations with high leucine levels[9]. The boy was induced with fentanyl, propfol and atracurium with maintenance by isoflurane and atracurium infusion. Intrapipid

20% was administered as infusion and NGT 10 G MSUD formula at 10 ml were transfused intraoperatively. He had uneventful course and was having unrestricted diet for 2 years. Another case report by Karahan et al. described anesthetic management for a 3-month-old patient undergoing peritoneal dialysis[18]. The patient was induced with 8% sevoflurane and intubated with ET size 3 and had remifentanil maintenance at 0.5 µg kg-1and sevoflurane 3% in N2O/O2 50%. An uneventful intraoperative and postoperative course was reported apart from pre-op metabolic acidosis that remained intra-op and post-op as well.

Riviello et al. highlighted the importance of preoperative optimization of hydration status, acidosis and supplementing nutritional needs to avoid over-hydration as it can lead to increased intracranial pressure and cerebral oedema[4]. No specific anesthetic agent is preferred in such conditions as it should be individualized according to patients' conditions and surgical considerations and it is necessary to avoid medications that can cause convulsions (4). It is also pertinent to avoid metabolic deterioration by decreasing fasting time along with correcting dehydration and acidosis[10]. Other considerations include infusing lipids to provide a stable caloric intake and avoiding catabolic states to avoid over-hydration. Garcia et al. also identified the importance of optimization in the preoperative period when considering fluid status and acidosis by using hypertonic dextrose[11]. Such measures are necessary in preoperative metabolic acidosis to avoid hypoglycemia and over-hydration leading to cerebral oedema. Avoiding hypoglycemia is possible by reducing fasting hours through frequent monitoring of glucose, intraoperative acidosis status, and maintenance of high calorie intake[12]. While there is no consensus regarding the anesthetic choice, patient and surgical factors are important considerations. In cases where there are no neurological complications, ketamine has been used safely. However, in patients with a history of seizures and neurological abnormalities, propofol has been preferred[12].

CONCLUSION

MSUD is a rare disorder with patients presenting to pediatric anesthetists to facilitate surgery. The key to providing safe peri-operative anesthesia is by understanding the pathophysiology of MSUD and its implications clinically. Surgical anesthesia has been provided by different methods including GA and regional/ neuroaxial techniques. The technique or agent used is tailored based on patient and surgical considerations with no agent seeming to be superior to others in relation to MSUD. A multi-disciplinary approach between surgeons, anesthetists, metabolic physicians and metabolic dietician is important to prevent metabolic decompensations, ensure good caloric intake and optimize fluid/acidosis status peri-operatively. MSUD patients who are recipients of LDLT and on unrestricted diet may be at risk of metabolic decompensation under stress in the future. Care and early consultation with metabolic physicians is required when such patients present before surgery.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflict of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 09 April 2021

REFERENCES

1. Strauss, Kevin A, Robinson D, et al. Classical maple syrup urine disease and brain development: principles of management and formula design. Mol Genet Metab 2010; 99(4):333-45.
2. Blackburn, Patrick R, Vairo FPE, et al. Maple syrup urine disease: mechanisms and management. Appl Clin Genet 2017; 10:57-66.
3. Wei F, Jia J, Guan H, et al. Case report: maple syrup urine disease with a novel DBT gene mutation. BMC pediatrics 2019;19(1):494.
4. Riviello Jr, James J, DiGeorge AM, et al. Cerebral edema causing death in children with maple syrup urine disease. J pediatr 1991;119(1):42-5.
5. Holeček M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab 2018; 15:33.
6. Menkes JH, Hurst PL, Craig JM. A new syndrome: progressive familial infantile cerebral dysfunction associated with an unusual urinary substance. Pediatrics 1954;14(5):462-7.
7. Mazariegos George V, Morton DH, Sindhi R, et al. Liver transplantation for classical maple syrup urine disease: long-term follow-up in 37 patients and comparative United Network for Organ Sharing experience. J Pediatr 2012; 160(1):116-21.
8. Feier FH, Miura IK, Fonseca EA, et al. Successful domino liver transplantation in maple syrup urine disease using a related living donor. Braz J Med Biol Res 2014; 47(6): 522-6.
9. Pal A, Chatterji C, Rana DS, et al. Perioperative management of living donor related liver transplantation in an infant for Maple syrup urine disease. Indian J Anaesth 2018; 62(10): 820-2.
10. McCarron E, McCormack O, Cronin T, et al. Management of maple syrup urine disease in the peri-operative period. Ir Med J 2013;106(9):277-8.
11. Fuentes-Garcia D, Falcon-Arana L. Perioperative assessment of supracondylar fracture in a patient affected with maple syrup urine disease. BJA Br J Anaesth 2008;101(eLetters Supplement).
12. Kahraman S, Ercan M, Akkuş, Ö, et al. Anaesthetic management in maple syrup urine disease. Anaesthesia 1996; 51(6):575-8.
13. Molenaar IQ, Warnaar N, Groen H, et al. Efficacy and safety of antifibrinolytic drugs in liver transplantation: A systematic review and meta-analysis. Am J Transplant 2007; 7(1):185-94.
14. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; 19(1):CD001886.
15. Schouten ES, Van De Pol AC, Schouten ANJ, et.al. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr Crit Care Med 2009;10(2):182-90.
16. Faraoni D, Goobie SM. The efficacy of antifibrinolytic drugs in children undergoing noncardiac surgery: a systematic review of the literature. Anesth Analg 2014; 118(3):628-36.
17. Ortmann E, Besser MW, Klein AA. Antifibrinolytic agents in current anaesthetic practice. Br J Anaesth 2013; 111(4):549-63.
18. Karahan MA, Sert H, Havlioğlu I, et al. The Anaesthetic Management of a Patient with Maple Syrup Urine Disease. Turk J Anaesthesiol Reanim 2014; 42(6): 355-7.