Prevention of metabolic decompensation in an infant with mutase deficient methylmalonic aciduria undergoing cardiopulmonary bypass

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Background: **Effects of circulatory arrest upon an inborn error of metabolism patient are unknown.**

Methods: **A retrospective chart review was performed of outcome and biochemical parameters obtained during palliative cardiac surgery for a mutase-deficient methylmalonic aciduria patient with Ebstein's cardiac anomaly was performed.**

Results: **The levels of ammonia, methylmalonic acid, free carnitine, and propionylcarnitine of the patient were improved. The patient survived surgery following institution of four metabolic treatment principles: 1) restriction of toxic substrate; 2) promotion of anabolism via administration of carbohydrate and lipid calories; 3) administration of detoxifying levocarnitine and sodium benzoate; and 4) cobalamin enzymatic co-factor administration. The patient died from post-operative dysrhythmia and was posthumously determined to have compound heterozygosity for mutations predicting severe, cobalamin non-responsive disease: c.322C>T/c.1233del3 (p.R108C/p.ΔI412).**

Conclusion: **Metabolic decompensation is preventable during cardiopulmonary bypass and cardioplegia using four principles of metabolic treatment.**

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Case report

Introduction

Methylmalonic aciduria due to methylmalonyl-coenzyme-A (CoA) mutase deficiency (mut-MMA, OMIM#251000) results in deficient breakdown of methylmalonyl-CoA from valine, methionine, isoleucine, threonine, and odd-chain fatty acyl-CoAs, to succinyl-CoA. Catabolic patients develop metabolic decompensation with lethargy, anorexia, vomiting, and potentially death. Biochemically, elevated methylmalonic acid (MMA) body fluid levels and secondary hyperammonemia, carnitine depletion, hypoglycemia, and metabolic acidosis are observed.[1]

Attention must be paid to prevent metabolic decompensation during catabolic circumstances, such as surgery. Patients with metabolic disorders can decompensate from fasting required for anesthesia and stresses induced by surgery.[2] However, effects of cardioplegia, hypothermia, and cardiopulmonary bypass in *mut*-MMA patients are unknown. While hypothermia reduces cellular metabolism, cardiac arrest creates energy-deficient conditions from reduced tissue perfusion.

A neonate referred to our institution with cyanotic congenital heart disease from Ebstein's anomly with pulmonary atresia was found to have mut^0-MMA via newborn screening and underwent cardiopulmonary bypass for a Starnes palliative procedure.[3] The clinical outcome and results of pre- and intra-operative metabolic monitoring were reported herein.

Case report

This study was approved by the CHOC Children's Institutional Review Board.

The neonate was the third child of nonconsanguineous hispanic parents without a family history of congenital heart disease or recurrent miscarriages. He demonstrated cyanosis refractory to supplemental oxygen and was evaluated for congenital heart disease. Physical examination noted a reactive newborn with a harsh holosystolic murmur, palpable precordial thrill, acrocyanosis, and palpable liver 2 centimeters below the right costal margin. Echocardiogram demonstrated

Ebstein's anomaly with thickened, inferiorly displaced and regurgitant tricuspid valve, severely dilated right atrium, pulmonary atresia, and secundum atrial septal defect. Surgical palliation with the Starnes procedure was elected.

The patient received 3.5 g/kg parenteral protein per day until newborn screening demonstrated an elevated propionylcarnitine level of 19.3 micromolar (normal <6.5 μmol/L) and a propionylcarnitine:acetylcarnitine ratio of 0.74 (normal <0.25). Confirmatory testing showed high levels of urine MMA, with normal plasma homocysteine. Other biochemical results are summarized in Table 1. Genetic sequencing of the *MUT* gene demonstrated compound heterozygous mutations predicting severe, cobalamin-nonresponsive (mut^0) disease: c.322C>T and c.1233del3 (p.R108C/p.ΔI412).[4]

Following treatment, secondary carnitine deficiency corrected; blood levels of MMA, propionylcarnitine, and ammonia improved (Table 1). Specific management principles included the following: 1) protein intake to 1 g/kg per day was given to reduce toxic substrate (60 mg/kg per day each of isoleucine and valine). The infant's unstable clinical status precluded enteral feeding and necessitated parenteral nutrition. Plasma amino acid measurements were performed to ensure target amino acid levels at a lower limit of reference ranges; 2) promotion of anabolism was effected by administration of dextrose, 13 mg/kg per minute (18.72 g dextrose/day) and fat emulsion, 3 g/kg per day, while adhering to fluid restrictions imposed by the cardiac defects. Total caloric intake was 72 kcal/kg per day; 65% from carbohydrate and 31% from fat; 3) detoxification agents were given in the form of intravenous levocarnitine, 200 mg/kg per day, and enteral sodium benzoate 250 mg/kg per day to treat hyperammonemia (initial 111 μmol/L, increasing to 160 μmol/L in twelve hours; normal <80 μmol/L); 4) prior to knowledge of the cobalamin non-responsive phenotype, intramuscular hydroxocobalamin injections, 1000 μg daily, were administered to attempt enhancing enzymatic activity of mutase.

Similar management was employed throughout surgery. Core temperature was lowered to 35 ºC to reduce metabolic rate. Protein-free intravenous dextrose was provided at 13 mg/kg per minute, lipid infusion discontinued; levocarnitine and hydroxocobalamin were given prior to surgery. Arterial blood gas, blood glucose, ammonia, lactic acid, and acylcarnitines were measured regularly throughout the perioperative period.

Cardiopulmonary bypass time was 94 minutes; arrest time was 28 minutes. Table 2 demonstrates the results of intraoperative biochemical monitoring; hypoglycemia and hyperammonemia never developed during surgery. A dextrose bolus was given in the first hour, when glucose dropped from 161 mg/dL to 103 mg/dL. Post-bolus hyperglycemia (Table 2) was treated with insulin 0.45 units/kg per hour. The Starnes procedure was successful, but junctional tachyarrhythmia developed during cardiac re-animation requiring multiple attempts to cardiovert to sinus rhythm.

Six hours afterwards, the infant displayed poor peripheral perfusion secondary to ventricular tachycardia, degenerating to ventricular fibrillation and sinus bradycardia resistant to anti-arrhythmics and cardioversion. The etiology was a right intra-ventricular thrombus impairing cardiac output. Twelve hours later, the patient died from refractory hypoxemia after the thrombus extended into the Blalock-Taussig shunt.

Table 1. Biochemical parameters before and after institution of metabolic treatment

Parameters	Normal values (μmol/L)	Pre-treatment (μmol/L)	Post-treatment (μmol/L)
Methylmalonic acid	<0.40	167.23 (H)	60.00 (H)
Propionylcarnitine	<3.15	25.80 (H)	13.25 (H)
Free carnitine	>12	0.90 (L)	279.00 (H)
Ammonia	<35	132 (H)	46 (H)
Methylmalonic acid-producing amino acid levels			
Valine	80-246	279 (H)	63 (L)
Isoleucine	27-53	84 (H)	26 (L)
Methionine	9-41	49 (H)	24
Threonine	114-335	218	164

H: high; L: low.

Table 2. Biochemical parameters in the perioperative period

Parameters	pH	Bicarbonate	Base excess	Glucose	Ammonia	Lactate	Propionylcarnitine
Normal	7.30-7.45	20-28 mEq/L	-5 to +5 mEq/L	60-150 mg/dL	<80 μM	<2.2 μM	<3.15 μM
120 min prior to incision	7.33	29.7	+3.1	122	39	**5.7 (H)**	**21.5 (H)**
30 min prior to incision	**7.27 (L)**	32.0	+3.7	**161 (H)**	45	-	**21.0 (H)**
26 min post incision	7.45	22.2	-0.9	103	-	-	**14.8 (H)**
50 min post incision	7.30	27.2	-0.2	**599 (H)**	34	-	-
68 min post incision	7.40	**18.9 (L)**	-4.7	**488 (H)**	36	-	**16.3 (H)**
103 min post incision	7.42	26.2	+1.5	**381 (H)**	40	-	**14.1 (H)**
131 min post incision	7.30	20.8	**-5.5 (L)**	**306 (H)**	49	-	**19.8 (H)**
147 min post incision	7.30	**33.2 (H)**	+4.7	**310 (H)**	-	-	-
155 min post incision	7.30	**28.4 (H)**	+0.7	**288 (H)**	-	-	**15.1 (H)**
3.5 h post incision	7.34	**18.8 (L)**	**-6.2 (L)**	**229 (H)**	30	**10.1 (H)**	-
6.3 h post incision	**7.05 (L)**	**12.5 (L)**	**-17.7 (L)**	**302 (H)**	**93 (H)**	**12.2 (H)**	-
23.5 h post incision	**7.27 (L)**	27.7	-0.6	**221 (H)**	-	**4.4 (H)**	-

Abnormal values are marked in bold. H: high; L: low; "-": not measured.

Discussion

Successful intra-cardiac surgery has been reported, without detailing intra-operative biochemical markers, in two patients with cobalamin C/D-deficient methylmalonic aciduria who successfully underwent passive hypothermia and cardiopulmonary bypass for ventricular septal defect repair.[5,6] To our knowledge, our case represents the first report of cyanotic congenital heart disease or Ebstein's anomaly in *mut*^{0}-MMA.

Biochemical data sampled throughout the patient's surgical cardiac palliation indicate pre-operative optimization of metabolic control, and peri-operative prevention of decompensation. This was enabled by restricting methylmalonic acid precursors via reduction of parenteral amino acid intake. Provision of dextrose stimulated insulin production, preventing catabolism and allowing safe tolerance of 1 g/kg of protein per day. Detoxification agents were administered to reduce deleterious ammonia, methylmalonic and propionic acid levels. Finally, because the patient was critically ill and cobalamin-responsiveness was unknown, *mut* enzyme enhancement was attempted via hydroxocobalamin. Since mutations were posthumously identified as cobalamin-nonresponsive, most likely the first three principles accounted for the metabolic control.

Transient metabolic acidosis following discontinuation of bypass (Table 2, +131 minutes) may have reflected reperfusion and release of ischemic metabolites into the circulation, or resulted from intra-operative hyperglycemia. However, the pro-anabolic effects of insulin should have mitigated any lactic acidosis arising from hyperglycemia. Significant metabolic acidosis and hyperammonemia (Table 2, +6.3 hours) developed only after prolonged, hemodynamically significant ventricular tachycardia and poor systemic perfusion. At death, the patient had intact metabolic control, with bicarbonate and lactic acid at pre-operative levels.

Patients with Ebstein's anomaly are at high risk of developing tachyarrhythmias, a common cause of their mortality.[7] The infant had intra-operative difficulty maintaining sinus rhythm because of the arrhythmogenic, severely dilated right atrium, so death occurred likely from complications associated with Ebstein's anomaly. However, ventricular tachycardias have been reported in *mut*-MMA patients. One experienced the dysrhythmia in the context of peri-anesthetic hyperkalemia (serum potassium: 5.8-7.4 mmol/L, normal: less than 5.5 mmol/L) and the other following worsening cardiomyopathy with ejection fraction of 18%.[8,9]

With adherence to basic principles of metabolic management, metabolic control can be successfully maintained even for a patient with a severe metabolic disorder and cyanotic congenital heart defects experiencing profound catabolic stress induced by cardiopulmonary bypass and cardioplegia.

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