Published in final edited form as:

Mol Genet Metab. 2008 January ; 93(1): 22–29. doi:10.1016/j.ymgme.2007.08.119.

Combined liver–kidney transplant for the management of methylmalonic aciduria: A case report and review of the literature

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Abstract

Over 27 cases of liver transplant, kidney transplant and combined liver–kidney transplant have been reported for the treatment of methylmalonic aciduria. We describe a case of a 5-year-old boy who underwent combined liver–kidney transplant (CLKT) for phenotypic *mut0* disease. His history was notable for more than 30 hospitalizations for severe acidosis, metabolic strokes, liver disease, pancreatic disease, chronic renal insufficiency with interstitial nephritis, and decreased quality of life. Post-CLKT, there was a marked reduction in serum (80%) and urine MMA levels (90%) as well as a cessation of metabolic decompensations. Neurologic deterioration continued post-CLKT manifested as a cerebellar stroke. The clinical details and therapeutic implications of solid organ transplant for methylmalonic aciduria are discussed.

Keywords

Methylmalonic aciduria; Liver transplantation; Kidney transplantation; Immunosuppression; Neurologic complications; Metabolic stroke

Introduction

Methylmalonic aciduria (MMA, OMIM 251000) is a rare autosomal recessive disorder that results from derangements in the catabolic pathway of several essential amino acids, odd chain fatty acids and cholesterol. This organic aciduria causes significant morbidity in affected patients, including recurrent bouts of potentially life-threatening ketoacidosis and neurologic, hematologic, and renal impairment [1,2]. There are several different biochemical abnormalities involving methylmalonyl CoA mutase and its cofactor, cobalamin (vitamin B12), that can result in methylmalonic aciduria [2]. Methylmalonyl CoA mutase can be completely deficient (*mut0*) or partially deficient (*mut-*). Abnormalities in the activation of cobalamin can result in elevations of methylmalonic acid and homocysteine in all body fluids. The clinical presentation of MMA is characterized by lethargy, vomiting, hyperammonemia, and metabolic acidosis. Progression to coma is not uncommon. If the patient does not succumb to the initial metabolic decompensation, failure to thrive, developmental retardation, renal failure and metabolic strokes follow [1,3–14].

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The management of methylmalonic aciduria includes a low protein diet avoiding an excess of isoleucine, methionine, threonine, valine, cholesterol, odd chain fatty acids, and an avoidance of long fasts. Hydroxycobalamin is used in B12 responsive variants. Levocarnitine aids in the excretion of carnitine esters and repletes a relative deficiency. Organ transplantation in MMA may be thought of as gene therapy on a limited scale. To date, 27 cases of liver transplantation, kidney transplantation and combined liver–kidney transplantation have been reported for the management of these complex patients with mixed results (Table 2) [15–35].

Here we report a case of combined liver–kidney transplantation in a 5-year-old boy with methylmalonic aciduria. The details of his clinical presentation and biochemical findings are presented here followed by a discussion of his clinical management.

Patient

The patient, a 5-year-old male of Ecuadorean descent, has been followed by the Program for Inherited Metabolic Diseases at our institution since infancy. He was the product of a nonconsanguineous union, born full term via normal spontaneous vaginal delivery with a birth weight of 3.5 kg. There was no evidence of hypoxic ischaemic encephalopathy and the newborn course was normal. His early clinical course was marked by multiple admissions before the age of 3 months for vomiting. Subsequent workup for infectious etiologies was negative. At 3 months of age, the patient was admitted to a local community hospital for tachypnea, vomiting and metabolic acidosis refractory to fluid and sodium bicarbonate resuscitation. He progressed to coma and was transferred to our institution for further management. Plasma amino acids showed elevated glycine and alanine, and normal homocysteine and methionine. Serum methylmalonic acid was also elevated at 511 $\mu\text{mol/L}$. An evaluation of urine organic acids by GC–MS showed a large peak of methylmalonic acid (2222 mmol/mmol Cr), consistent with the diagnosis of methylmalonic aciduria. A metabolic diet was instituted and maintained with a protein restriction that varied between ~ 2.0 and 2.5 g/kg/day using natural protein ($\sim 33\%$ of total protein) and proprietary formula ($\sim 66\%$ of total protein). Levocarnitine ($100\text{--}300$ mg/kg/day) was added to enhance the elimination of organic acids. A 3-month trial of hydroxycobalamin ($1\text{--}3$ mg/d) did not result in a reduction of plasma and urine methylmalonic acid. Serum bicarbonate was maintained >17 mEq/L utilizing oral bicarbonate (Bicitra). Several trials of metronidazole (20 mg/kg/day for 5 days) were instituted to decrease bacterial production of organic acids. These initial findings, in conjunction with the clinical history presented hereafter, led to a presumptive *mut0* diagnosis. After several months of feeding difficulties including oral aversion, a gastrostomy tube was placed for feeding and weight gain.

During the years following diagnosis, the patient has been hospitalized more than 30 times for metabolic acidosis. Ongoing medical problems in this patient highlighted the sequelae of methylmalonic aciduria, including significant involvement of the renal, gastrointestinal and neurologic systems (Table 1). Anthropometric parameters reflect failure to thrive and the difficulties of metabolic management (Fig. 1a and b). The dashed line represents the age at transplantation. Metabolic control was difficult to maintain with dietary and pharmaceutical modifications as illustrated in Figs. 2–4. Fig. 2 demonstrates bicarbonate measurements prior to and following transplantation. There is a downward trend of serum bicarbonate levels with increasing supplementation with oral bicarbonate. The upper dashed line indicates the level at which bicarbonate correction was instituted acutely. The lower dashed line indicates the lower limit of detection for serum bicarbonate in the hospital clinical laboratory. Samples processed >2 h after acquisition were not included in Fig. 2. The patient had a significant number of clinical decompensations as reflected in Fig. 2. The increasing number of bicarbonate measurements <17 meq/L reflects the number of hospitalizations and worsening of clinical status. Several decompensations were characterized by bicarbonate concentrations below the detectable limit. Aside from a single decompensation post-transplant (Fig. 2, arrow), three

additional bicarbonate levels below the correction limit did not correlate with clinical decompensation. Furthermore, these low bicarbonate levels corrected without intervention.

As part of the standard of clinical care for patients with MMA, serum and urine MMA were measured during hospitalizations and clinic visits. Fig. 3a and b demonstrates pre-CKLT plasma and urine methylmalonic acid levels. Despite protein restriction, the patient maintained levels of serum methylmalonic acid between ~350 and 500 $\mu\text{mol/L}$ and urine methylmalonic acid between ~2500 and 11,000 mmol/mmol Cr . Renal function progressed to renal insufficiency with the serum creatinine slowly rising over many years (Fig. 4).

Clinical decompensations became progressively more severe culminating in necessitated intubation for respiratory support. After eventually being weaned from the ventilator the patient became aphasic and had difficulty ambulating due to weakness and tremors. An MRI of the brain was performed which showed restricted diffusion of the lenticular nuclei bilaterally, compatible with infarcts (Fig. 5a). The patient underwent intensive physical, occupational and speech therapy with partial recovery of neurologic function.

Given the decreased quality of life and the multiple medical conditions associated with the disease, the decision was made to offer combined liver–kidney transplantation to the family. A splenectomy was considered, as a potential source of methylmalonic acid post-transplant, but was decided against due to the risk of infection with encapsulated organisms. At 5 years of age, an orthotopic cadaveric split-liver and kidney transplant procedure was performed.

The initial post-operative period showed a marked reduction in plasma and urine MMA levels (Fig. 3a and b). Serum MMA levels were reduced by 80% while urine MMA levels were reduced 90%. In addition, there was a cessation of metabolic decompensations in the following months. Immunosuppression was instituted with tacrolimus (FK506) and steroids. Tacrolimus levels were maintained in the therapeutic range $<5 \text{ ng/ml}$ after the initial post-operative period. Weeks following the institution of immunosuppression, the patient developed tremors, seizures, hallucinations, hemiplegia/hemiparesis, speech disturbances, altered mental status, and fever of unknown origin. A presumptive diagnosis of tacrolimus toxicity was made and the patient's immunosuppressive drug was changed to cyclosporine (CsA). This intervention was followed by a resolution of the tremors, seizures, and fevers, but hemiplegia, truncal ataxia and speech dyspraxia persisted. An MRI/MRS demonstrated post-ischaemic changes in the pons, old infarcts in the globus pallidus, as well as possible lactate peak in anterior left insular region. These findings were consistent with damage during the previous clinical decompensation requiring intubation, but also indicated ongoing metabolic derangements in the CNS. A subsequent MRI brain showed a cerebellar infarct consistent with the clinical findings (Fig. 5b). Ten months post-transplantation, an iatrogenic metabolic decompensation occurred. Prior to a genitourinary procedure for renal calculi, the patient was deprived of glucose-containing fluids for approximately 12 h. Intraoperatively, the patient developed metabolic acidosis with a bicarbonate of 12 meq/L . A high glucose infusion rate (10–12 mg/kg/min), intralipids (2 g/kg/day) and bicarbonate administration reversed catabolism and the patient returned to baseline without sequelae.

Currently, the patient continues to receive physical, occupational and speech therapies with some improvement in neurologic status. The patient's dietary regimen has also been modified. Prior to transplantation his most recent regimen consisted of 10 g of natural protein, 21 g of protein from proprietary formula for a total of 31 g/d (1.95 g/kg/day). Proprietary formula had been discontinued following transplantation and total protein was maintained at ~30 g (~1.9 g/kg/day). Proprietary formula (50% of total protein) was reinstituted with natural protein (50% of total protein) due to elevations in serum and urine methylmalonic acid. The patient's current

regimen consists of ~30% of total protein from natural protein and ~70% from proprietary formula to maintain low serum and urine methylmalonic acid levels.

Discussion

Solid organ transplantation for the treatment of inborn errors of metabolism has been viewed as gene therapy on a targeted basis. By replacing large organs such as the liver and kidney, enzyme deficiencies may be overcome by these functioning organs. To date, 27 cases in the form of case reports and abstracts, including the case mentioned here, have been reported of solid organ transplantation in the treatment of methylmalonic aciduria (Table 2). Treatment modalities have varied: 6 (22%) kidney transplants, 15 (55%) liver transplants and 6 (22%) combined liver–kidney transplants. The majority of known diagnoses were *mut0* (14/17, 82%) followed by *mut-* (2/17, 12%). A single case of *CblA* disease was also noted. Ten diagnoses were not known and represent a major gap in the literature. Indeed, our own case may represent *mut0* or *CblB* disease. All diagnoses were made within the first 4 months of life. The average age of transplant was 9.2 years of age. The clinical characteristics of the patient presented here are similar to those described previously.

Complications following transplantation have also been varied. Five deaths occurred post-transplantation, four from infection and one due to metabolic decompensation. Enzymatic activity data, serum or urine methylmalonic levels were not available for this latter patient. Common post-operative sequelae included infection (7/27, 26%), acute rejection (6/27, 22%), immunosuppressive medication toxicity (3/27, 11%) and continued neurologic deterioration (5/27, 19%).

Regarding immunosuppressive toxicity, cyclosporine A and tacrolimus induced leukoencephalopathy is a significant complication which occurs at therapeutic levels [36]. Clinical findings include seizures, altered mental status, visual abnormalities, hemiplegia/hemiparesis, and fever of unknown origin. Resolution of neurologic symptoms and MRI findings occurs 4 days and 20 days, respectively, post-cessation of the offending medication.

Neurologic deterioration post-transplant in methylmalonic aciduria is well documented [17, 19,23,32,37]. Of the four patients with neurologic disability (Table 2), two were confirmed *mut0*, while the remaining two cases were undefined [19,23,32,37]. In our case, the initial neurologic presentation of tremors, seizures, altered mental status and fever was consistent with tacrolimus toxicity. The clinical signs of toxicity improved after change in immunosuppressive medications consistent with previous reports [36]. The persistence of cerebellar signs prompted a MRI brain study which demonstrated a cerebellar infarction (Fig. 5b). Our case closely paralleled one recent case reported by Kaplan et al. [32]. CSF studies in that case provided some information on the pathophysiologic processes contributing to the adverse clinical outcome. CSF methylmalonic levels remained >1000-fold higher than normal post-liver transplantation despite a significant reduction in serum levels. MMA is poorly transported across the blood–brain barrier, so the *de novo* synthesis of cerebral propionic acid leading to methylmalonate accumulation could account for the continued neurologic deterioration in the face of reduced serum levels [32]. In all of the transplanted patients with neurologic complications, protein restriction was still required despite significant post-operative reductions in methylmalonate levels. With the liberalization of natural protein in our patient's diet, we found an increase in serum and urine methylmalonic acid levels. The amount of natural protein (~30% of total protein) remains similar to pre-transplant dietary regimen. Importantly, the post-transplant decompensation and recorded low bicarbonate levels experienced by our patient proved that despite the presence of normal enzyme activity in both liver and kidney, he was still susceptible to metabolic derangements under conditions of stress.

To date, the criteria for solid organ transplantation in MMA have not been well-established. The decision to undertake a transplantation is a complicated one and involves: (1) a comprehensive understanding of the disease and the risks and benefits of transplantation; (2) consideration of the natural history of the disease, current therapeutic alternatives, potential future developments, and quality of life [38]. The role of transplantation in MMA was addressed by a workshop at an international meeting on inborn errors of metabolism [22]. It was concluded that children with organic acidemias appear to be at higher risk of complications from transplantation than other metabolic disorders. While quality of life may be improved, transplantation does not cure patients who remain at risk for complications. To develop clinical guidelines, a registry of all MMA patients who have been or are being considered for transplantation has been suggested [22]. The clinical decision-making process in our case involved a multidisciplinary discussion regarding combined liver–kidney transplantation. A splenectomy was proposed in addition to CLKT to further decrease methylmalonate levels due to the ubiquitous nature of the enzyme. The risk of infection with encapsulated organisms was thought to contraindicate splenectomy. Although, CKLT in our patient was not curative and had a post-operative clinical course similar to that described in previous reports [19,23,32, 37], we conclude that the patient has benefited from an improved quality of life based on the dramatic decrease in time spent in hospital or in chronic care facilities during recovery from decompensations. Besides the single episode of iatrogenic decompensation, he has not been hospitalized for metabolic acidosis since the transplantation, reflecting the beneficial effect of the CKLT. Based on our difficulty in deciding on the proper course of action for this patient, given the suboptimal clinical details and outcomes described in the literature, we believe that a registry of transplantation candidates in keeping with the recommendations of the Workshop: Management of Organic Acidemias and the establishment of guidelines regarding solid organ transplantation in organic acidurias by a multinational collaborative group would be of great benefit to clinicians who will need to decide on the relative benefits of such an intervention for future patients.

Acknowledgments

The authors thank Drs. Edwin Kirk and Felicity Collins for their contribution to this manuscript.

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Fig. 1. Anthropometric parameters from CDC growth charts in patient with MMA: (a) weight; (b) height.

Fig. 2.
Serum bicarbonate levels pre- and post-CKLT.

Fig. 3. Serum (a) and urine (b) methylmalonic acid pre- and post-CKLT.

Fig. 4.
Serum creatinine levels pre- and post-CKLT.

Fig. 5. MRI brain studies of patient with MMA. (a) Axial flair demonstrating infraction of the lenticular nuclei bilaterally. (b) Axial T2 image demonstrating a right cerebellar infarct.

Table 1

Ongoing medical problems in a patient with methylmalonic aciduria

Metabolic	MMA, diffuse osteopenia
Ophthalmologic	Optic nerve atrophy
Gastrointestinal	Hepatomegaly, liver disease, pancreatic disease, gastrostomy tube, oral aversion
Renal	Chronic renal insufficiency
Hematologic	Chronic anemia, indwelling central venous catheter
Dermatologic	Dermatitis (Ile deficiency), mucositis, hair loss
Neurologic	Lenticular nuclei infarct, extrapyramidal signs
Development	ht/wt <3rd percentile, PT/OT/speech

Table 2

Clinical details of 27 cases reported to date of solid organ transplantation for methylmalonic aciduria

Source	Dx	Age Dx	Age Tx	Tx type	Complications	MMA pre-Tx P; μ mol/L U; μ mol/mmol Cr	MMA post-Tx P; μ mol/L U; μ mol/mmol Cr	Protein g/kg/d
Kirk, Collins (2007, personal communication) Goyens (1997) Van Calcar (1998) van't Hoff (1998), van't Hoff (1999)	NA	NA	18 y	Kidney	Died of overwhelming fungal infection	P: 5000–10000	P: 4000–5000	1.0
	Mut0	37 days	17 months	Liver	Progressive renal failure	NA	U: decreased	1.5
	Mut- (5% residual)	3 months	24 y	Kidney (LRKT)	Lymphocele, CsA toxicity, diabetes	P: 6825 U; 4.31 mmol/24 h	P: 148 U; 1.58 mmol/24 h	0.6
	Mut0	9 months	13.5 y	Liver–kidney	Kidney rejection responsive to prednisone	P: 3500 U; 8700–11200	P: 1000 U; 660	NA
Ho (2000) Lubrano (2001) Leonard (2001) Nyhan, 2002	NA	6 wks	18 y	Liver–kidney	Retransplant due to polyuria in native kidneys	NA	NA	NA
	NA	Prenatal	6 months	Liver	Died in acidosis	NA	NA	1.0
	NA	Birth	9 months	Liver	Movement disorder, renal dysfunction, rejection $\times$ 1, varices	NA	P:300–400 U; 800–3600	NA
	Mut0	Neonatal	20 months	Liver	Graft rejection treated w/steroids	P: 475	P: 167	NA
Kayler (2002)	NA	9 months	17 y	Kidney	None	U: 14.8	U: 0.5	0.7
	NA	4 months	17 y	Kidney	Died from infection	NA	NA	NA
	Mut0	1 wk	22 y	Liver	Progressive neurologic disability, progressive renal failure	P: 4490	P: 300–681	Restrict
	Mut-	Neonatal	16 months	Liver (whole)		NA	NA	NA
Hsui (2003) Shinkai (2003) Morioka (2005), Morioka (2005) Huang (2005)	Mut0	Neonatal	13 y	Liver–kidney (heterotopic)	Retransplant due to hepatic artery thrombosis	NA	NA	NA
	NA	Neonatal	11 months	Liver	Bronchiolitis	NA	NA	NA
	Mut0	1 day	4 months	Liver	NA	NA	NA	NA
	NA	NA	13 months	Liver	Died from infection	NA	NA	NA
Nagarajan (2005)	NA	NA	12 y	Liver	Died from infection	NA	NA	NA
	Mut0	NA	8 months	Liver	EBV infection	NA	NA	NA
	Mut0	NA	11 months	Liver	CMV infection	NA	NA	NA
	Mut0	1 wk	10 y	Liver–kidney	Acute liver rejection and CMV gastritis	P: 2196 U; 2195	P: <100 U; <600	1.5
Manzoni (2006) Kaplan (2006)	Mut0	1 wk	21 y	Liver–kidney	Tacrolimus toxicity	P: 5554 U; 10,370	P: <200 U; <900	1.5
	Mut0	10 days	11 months	Liver	Acute rejection, cholangitis	NA	NA	NA
	Mut0	2 wks	19 months	Liver	Metabolic acidosis, basal ganglia infarct	P: 273–1666 U; 1475–28,261	P: 75–402 U; 998–8816	2.0
	cbIA	14 y	14 y	Kidney	Metabolic acidosis	NA	P: 30–4000 U; 250–17,400	No restriction
Coman (2006) ^d Kasahara (2006) Lubrano (2007) This report (2007)	Mut0	1 day	4 y	Liver	None	None	NA	NA
	Mut0	4 months	27 y	Kidney	Chronic allograft nephropathy	U: 14844	U: 480	No restriction
	NA	3 months	5 y	Liver–kidney	Tacrolimus toxicity, cerebellar infarction	P: 20–2591 U; 1101–13,962P: 25–525 U; 116–1895		2.3

^aCase diagnosed post-kidney transplantation for renal deterioration.