Treatment of Methylmalonic Acidemia by Liver or Combined Liver-Kidney Transplantation

Anna-Kaisa Niemi, MD, PhD[1], Irene K. Kim, MD[2], Casey E. Krueger, PhD[3], Tina M. Cowan, PhD[4], Nancy Baugh, MS, RD[5], Rachel Farrell, MS[1,6], Clark A. Bonham, MD[2], Waldo Concepcion, MD[2], Carlos O. Esquivel, MD, PhD[2], and Gregory M. Enns, MB, ChB[1]

Objective To assess biochemical, surgical, and long-term outcomes of liver (LT) or liver-kidney transplantation (LKT) for severe, early-onset methylmalonic acidemia/acid (MMA).

Study design A retrospective chart review (December 1997 to May 2012) of patients with MMA who underwent LT or LKT at Lucile Packard Children's Hospital at Stanford.

Results Fourteen patients underwent LT (n = 6) or LKT (n = 8) at mean age 8.2 years (range 0.8-20.7). Eleven (79%) were diagnosed during the neonatal period, including 6 by newborn screening. All underwent deceased donor transplantation; 12 (86%) received a whole liver graft. Postoperative survival was 100%. At a mean follow-up of 3.25 ± 4.2 years, patient survival was 100%, liver allograft survival 93%, and kidney allograft survival 100%. One patient underwent liver re-transplantation because of hepatic artery thrombosis. After transplantation, there were no episodes of hyperammonemia, acidosis, or metabolic decompensation. The mean serum MMA at the time of transplantation was 1648 ± 1492 μmol/L (normal <0.3, range 99-4420). By 3 days, post-transplantation levels fell on average by 87% (mean 210 ± 154 μmol/L), and at 4 months, they were 83% below pre-transplantation levels (mean 305 ± 108 μmol/L). Developmental delay was present in 12 patients (86%) before transplantation. All patients maintained neurodevelopmental abilities or exhibited improvements in motor skills, learning abilities, and social functioning.

Conclusions LT or LKT for MMA eradicates episodes of hyperammonemia, results in excellent long-term survival, and suggests stabilization of neurocognitive development. Long-term follow-up is underway to evaluate whether patients who undergo early LT need kidney transplantation later in life. *(J Pediatr 2015;166:1455-61)*.

See editorial, p 1346

Methylmalonic acidemia/acid (MMA) is an autosomal recessive disorder caused by complete (mut^0) or partial ($mut-$) deficiency of methylmalonyl-CoA mutase (*MUT*) or by defects in the synthesis of adenosylcobalamin (cblA, cblB, cblD variant 2). Severe MMA, most commonly the mut^0 subtype, is characterized by neonatal onset episodes of decompensation with metabolic acidosis and hyperammonemia, developmental delay, basal ganglia damage, and high morbidity and mortality.[1-6] Although newborn screening (NBS) has allowed early initiation of treatment, patients remain at risk for metabolic decompensation, and long-term complications. Despite medical and nutritional management, patients often suffer neurologic damage during catabolic stress,[5,6] and develop end-stage renal disease requiring kidney transplantation (KT) in adolescence.[4,7,8] Combined liver-kidney transplantation (LKT) or early liver transplantation (LT) has emerged as an intervention aimed at preventing episodes of decompensation and improving metabolic control. To our knowledge, 38 patients with severe MMA have been reported who have undergone transplantation.[9-33] Twenty-six received an isolated LT,[9-25] 7 LKT,[25-29] and 5 KT.[30-33] Most reports describe single cases and data on long-term outcomes after transplantation are lacking. We report long-term follow-up of 14 patients with MMA who received LKT or LT at a single institution to further the knowledge of long-term prognosis of MMA after organ transplantation.

CVVH	Continuous veno-venous hemofiltration
eGFR	Estimated glomerular filtration rate
GDD	Global developmental delay
HD	Hemodialysis
KT	Kidney transplantation
LKT	Liver-kidney transplantation
LT	Liver transplantation
MMA	Methylmalonic acidemia/acid
NBS	Newborn screening

From the [1]Division of Medical Genetics, Department of Pediatrics, [2]Division of Abdominal Transplantation, Department of Surgery, [3]Division of Neonatal and Developmental Medicine, Department of Pediatrics and [4]Department of Pathology, Stanford University; [5]Lucile Packard Children's Hospital at Stanford, Stanford, CA; and [6]Prenatal Diagnostics, Department of Obstetrics and Gynecology, University of California, San Francisco, San Francisco, CA

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Methods

We retrospectively reviewed charts between December 1997 and May 2012 of children with severe early onset MMA who underwent LT (n = 6) or LKT (n = 8) at Lucile Packard Children's Hospital at Stanford. The study was approved by the Institutional Review Board at Stanford University. Data reviewed included age of diagnosis, genetic (*MUT* gene), or enzyme analysis (fibroblast) data, NBS results, blood ammonia (NH_3) at the time of presentation, history of metabolic decompensations, indication for transplantation, age at the time of transplantation, allograft type, surgical complications, mode of immunosuppression, patient and allograft survival, neurodevelopmental data before and after transplantation (standardized testing utilizing the Bayley Scales of Infant and Toddler Development, Third Edition[34] or The Capute Scales,[35] special education evaluations, school reports, clinician observations, and parent report), estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) calculated based on age, race, sex, height, and serum creatinine (mg/dL) by using the appropriate formula for age,[36-39] protein intake (g/kg/d), and serum MMA levels before and after transplantation (maximum reported level, level at the time of admission for transplantation, and 3 days, 1 month, and 4 months after transplantation).

Patients were admitted for transplantation in stable clinical condition. They were maintained on their regular dietary regimen until 6 hours before estimated time of surgery, after which they received intravenous fluids with dextrose (typically 10%) and electrolytes and intravenous lipid solution (typically 2 g/kg/d) pre- and intraoperatively. Levocarnitine was also given intravenously when patients were not provided enteral nutrition. Postoperatively, intravenous amino acids were added at 0.5 g/kg/d on the first postoperative day, increasing to 1.0 g/kg/d by the third postoperative day (or slightly less if protein intake was less than 1.0 g/kg/d prior to transplantation). Once patients tolerated enteral nutrition, preoperative outpatient diet and oral levocarnitine were reinstituted.

Results

Fourteen patients with MMA underwent LT (n = 6) or LKT (n = 8) at Lucile Packard Children's Hospital at Stanford from December 1997 to May 2012 (**Table I**). Eleven (79%) were diagnosed during the neonatal period. Three (23%) were diagnosed after neonatal period (ages 3 months, 9 months, and 2 years) but had been symptomatic as neonates. Six (43%) were ascertained by NBS, and all were exhibiting symptoms when the screening results were returned; the remaining 8 were born before the introduction of expanded NBS by tandem-mass spectrometry and were, therefore, ascertained clinically. Results of *MUT* gene analysis were available for 10 (71%) (**Table I**). One additional patient had abnormal *MUT* gene analysis according to the medical records, but original results were not available for review. In 2 patients the diagnosis was confirmed by fibroblast assay. One patient (patient 1, **Table I**) had no original diagnostic testing results available; however, he presented as a neonate and was not responsive to vitamin B_{12}.

The indication for transplantation was chronic kidney disease (stage III or IV) in patients who received LKT. In those who received LT, the indication was a difficult clinical course with multiple admissions per year for hyperammonemia and metabolic acidosis. Mean age of transplantation was 8.75 ± 7 years (range 0.8-20.7 years) for all, 13.3 ± 4.9 years (range 5.9-20.7 years) for patients with LKT, and 1.5 ± 0.9 years (range 0.8-3.3 years) for those with LT. Two patients underwent LT at less than 1 year of age (10 months and 11 months). These patients had a severe early-onset course with multiple hospitalizations because of hyperammonemia.

All patients underwent a deceased donor transplantation; 12 (86%) received a whole liver graft and 2 (14%) a reduced-size graft. Postoperative survival was 100%. At a mean follow-up of 3.25 ± 4.2 years (range 0.25-14 years), patient survival was 100%, kidney allograft survival 100%, and liver allograft survival 93%. One patient (patient 11, **Table I**) successfully underwent re-transplantation after losing the first graft because of hepatic artery thrombosis 5 days after transplantation. Other postoperative complications were bleeding requiring re-exploration (n = 2), drainage of subphrenic abscess (n = 1), 1 patient had a seizure on 12th postoperative day that was attributed to a high blood tacrolimus level, and 1 patient developed diabetes mellitus (**Table I**).

Of the patients who received LKT, 7 (88%) underwent preoperative hemodialysis (HD), and 1 intraoperative continuous veno-venous hemofiltration (CVVH) because of lack of time for preoperative HD. The first patient at our institution to receive an LT underwent intraoperative CVVH (patient 5, **Table I**). All subsequent patients with LT have had transplantation without preoperative HD.

Immunosuppression regimens immediately following transplantation were determined by standard protocols in place at the time of transplantation. Five (36%) undergoing LKT received antithymocyte globulin for induction. All patients received steroids and tacrolimus at the time of transplantation, followed by tapering of the steroid dose. Patients with LT only have remained on tacrolimus maintenance therapy for long-term immunosuppression with the exception of one (patient 5, **Table I**) who had an acute rejection four weeks post-transplantation and received three doses of methylprednisolone.

Mean blood ammonia at the time of diagnosis was 611 ± 404 μmol/L in those in whom the level was available (n = 6, range 197-1200). This includes patients who were ascertained by NBS, but were nevertheless symptomatic at the time of positive NBS. All patients had frequent hospitalizations (several/y) pre-transplantation because of hyperammonemia, metabolic acidosis, or both. After transplantation, there were no episodes of hyperammonemia or metabolic