Liver Transplantation for Classical Maple Syrup Urine Disease: Long-Term Follow-Up in 37 Patients and Comparative United Network for Organ Sharing Experience

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Objective To assess clinical and neurocognitive function in children who have undergone liver transplantation for classical maple syrup urine disease (MSUD).

Study design A total of 35 patients with classical MSUD (age 9.9 ± 7.9 years) underwent liver transplantation between 2004 and 2009. Six patients donated their liver to recipients without MSUD ("domino" transplant). We analyzed clinical outcomes for our cohort and 17 additional cases from the national United Network for Organ Sharing registry; 33 patients completed IQ and adaptive testing before transplantation, and 14 completed testing 1 year later.

Results Patient and graft survival were 100% at 4.5 ± 2.2 years of follow-up. Liver function was normal in all patients. Branched-chain amino acid levels were corrected within hours after surgery and remained stable, with leucine tolerance increasing more than 10-fold. All domino transplant recipients were alive and well with normal branched-chain amino acid homeostasis at the time of this report. Patient and graft survival for all 54 patients with MSUD undergoing liver transplantation in the United States during this period were 98% and 96%, respectively. One-third of our patients were mentally impaired (IQ ≤ 70) before transplantation, with no statistically significant change 1 year later.

Conclusion Liver transplantation is an effective long-term treatment for classical MSUD and may arrest brain damage, but will not reverse it. *(J Pediatr 2012;160:116-21)*.

Despite progress in nutritional and medical management, classical maple syrup urine disease (MSUD) poses a risk of serious neurologic disability and untimely death.[1,2] Acute metabolic intoxication causes cerebral edema that can culminate in brain herniation and cardiorespiratory arrest.[3,4] Chronic disturbances of branched-chain amino acid (BCAA) and ketoacid homeostasis alter cerebral amino acid uptake and neurotransmitter metabolism and can result in chronic cognitive impairment and mental illness.[2,5] The liver expresses 9%-13% of the body's total branched-chain ketoacid dehydrogenase complex (BCKDH) activity.[6] In 2006, we presented evidence that liver transplantation controlled BCAA metabolism in 11 children with MSUD.[7] Here we extend our observations to 37 patients followed for a mean of 4.5 years and also review 17 additional cases from the United Network for Organ Sharing (UNOS) registry.

Methods

Between May 2004 and December 2009, 35 patients with classical MSUD (22 males, 13 females) underwent transplantation with deceased-donor livers under an elective protocol at Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center.[7] Two additional patients who underwent transplantation 13.2 and 5.8 years ago at other centers were also followed at Children's Hospital of Pittsburgh. IRB approval was obtained for this report.

Mean age at transplantation was 9.9 ± 7.9 years (range, 1.7-32.1 years). Immunosuppression was achieved with methylprednisolone (2 mg/kg) premedication, perioperative rabbit antithymocyte globulin (5 mg /kg) intravenous induction, and long-term tacrolimus monotherapy. All patients who underwent transplantation were afebrile, metabolically stable, and selected according to the UNOS match run list. Six patients consented to donate their explanted liver to consenting recipients without MSUD ("domino" transplantation). To manage any metabolic complications, plasma amino acid monitoring was available around the clock, and MSUD hyperalimentation solution could be prepared on demand.[7]

BCAA	Branched-chain amino acid
BCKDH	Branched-chain ketoacid dehydrogenase complex
MSUD	Maple syrup urine disease
UNOS	United Network for Organ Sharing

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BCAA homeostasis, weight-adjusted leucine tolerance, and metabolic control during illness were used to assess the efficacy of transplantation. Plasma BCAA levels for 3 MSUD groups (pretransplantation, 1-11 months posttransplantation, and ≥1 year posttransplantation) were compared with a pediatric reference population of 51 children without disorders of amino acid or organic acid metabolism. Groups were studied using ANOVA and the Tukey posttest for pairwise comparisons (with $P < .05$ indicating significance). Our outcome data were supplemented with information on 17 additional UNOS-registered patients with MSUD who underwent liver transplantation at other US centers during the same time period.

Before transplantation, 33 subjects completed IQ testing using the Routing Test of the Stanford-Binet Intelligence Scales or the Wechsler Abbreviated Scale of Intelligence. Thirty-one subjects were tested for adaptive skills using the Vineland Adaptive Behavior Scale II or Adaptive Behavior Assessment System Second Edition. Associations among pretransplantation test scores and various clinical variables were explored using Spearman correlations (r_s). Ten males and 4 females (mean age, 11.5 ± 7.1 years; range, 2-22 years) also completed cognitive and adaptive testing 1 year after liver transplantation, and results were analyzed qualitatively in a separate report.[8] For the present work, we analyzed pretransplantation and posttransplantation scores using the paired *t*-test.[9,10]

Results

Patient and graft survival were 100% with satisfactory liver function (mean bilirubin level, 0.6 ± 0.5 mg/dL; mean γ-glutamyl transpeptidase level, 31.8 ± 60.4 IU/L) in all 37 patients under our care at a mean posttransplantation follow-up period of 4.5 ± 2.2 years. The longest follow-up period was 13.2 years. All 6 domino transplantation recipients were alive and well, with normal liver function and BCAA homeostasis on unrestricted protein intake, at the time of this report.

In all of the patients with MSUD who underwent liver transplantation, BCAA metabolism was stable soon after surgery and remained so as leucine tolerance increased from 10-25 mg/kg/day to >150 mg/kg/day (natural protein intake >1.5 g/kg/day). Compared with control subjects (mean leucine level, 119 ± 38 μM), patients with MSUD had 2-fold higher mean plasma leucine values before transplantation (253 ± 185 μM), 1-11 months after transplantation (202 ± 51 μM), and ≥1 year after transplantation (233 ± 71 μM). Although leucine levels were similar before and after transplantation, posttransplantation values were much less variable (F test; $P < .0001$) and remained tightly regulated relative to isoleucine and valine levels (**Figure 1**).

Enzyme activity of the transplanted liver prevented BCAA elevations during illness, with one important exception. One child developed transient leucinosis at 55 months posttransplantation during an episode of gastroenteritis and severe dehydration (leucine, 2170 μM; isoleucine, 1009 μM; valine, 1483 μM; reference ranges, leucine, 119 ± 38 μM; isoleucine, 81 ± 29 μM, valine, 275 ± 57 μM). With routine intravenous hydration therapy, his BCAA levels normalized within a few days (leucine, 110 μM; isoleucine, 70 μM; valine, 219 μM), and no specific metabolic treatment was required.

The **Table** (available at www.jpeds.com) lists major medical and surgical complications in our cohort. The median length of hospital stay after liver transplantation was 17 days (range, 8-39 days). The most common perioperative problems were organ rejection within 90 days (40%), delayed wound closure (27%), and ventral hernia repair (11%). Two patients underwent successful hepatic arterial revascularization for arterial thrombosis, and 3 patients underwent arterial revisions for ultrasound findings of arterial stenosis. There were no biliary complications. Most patients (78%) are currently receiving low-dose tacrolimus monotherapy (mean, 0.09 mg/kg/day); 9 patients also are receiving low-dose prednisone (mean, 0.17 mg/kg/day). Renal function and glucose homeostasis remained normal after surgery, and only 1 patient developed hypertension. As expected, asymptomatic viremia was common, but cytomegalovirus (n = 1) and Epstein-Barr virus (n = 2) disease were rare. The first patient, who underwent transplantation elsewhere, developed Epstein-Barr virus–induced intestinal posttransplantation lymphoproliferative disease before being transferred to our center. Transient withdrawal of immune suppression resolved lymphomatous changes in her gastrointestinal tract and did not compromise her graft. She did not experience recurrence during 12 years of follow-up.

Mean scaled IQ and adaptive scores for 33 pretransplantation patients were 81 ± 15 (range, 47-103) and 82 ± 21 (range, 33-120), respectively (normal scores, 100 ± 15). Eleven patients (33%) had an IQ score in the deficient range (≤70), and only 3 patients were of average or better intelligence (≥100). Twelve patients had an adaptive score <70; only 8 scored average or higher. Scaled IQ was correlated to adaptive function ($r_s = 0.74$; $P < .0001$) (**Figure 2**), but there were no significant correlations between IQ or adaptive test scores and age at diagnosis, number of preceding metabolic crises, number of hospitalizations, or age at transplantation (**Figure 3**). In the subgroup of patients who completed testing 1 year after transplantation,[8] scaled IQ and adaptive scores increased by an average of 6.2% (95% CI, −1 to 12.6%; $P = .059$) and 1.6% (95% CI, −9.3 to 10.7%; $P = .779$), respectively. These changes were not statistically significant, but the sample size had limited power to detect real differences of this magnitude (**Figure 4**; available at www.jpeds.com).

Four children sustained serious brain injury before transplantation. All 4 of these children had spastic diplegia, in 1 case requiring prolonged posttransplantation rehabilitation and multilevel corrective orthopedic surgery. One child was physically and neurologically healthy until age 6, when she developed severe cerebral edema during a metabolic crisis. This child sustained bilateral uncal herniation that occluded