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.5,6 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, 1-22 years) also completed cognitive and adaptive testing 1 year after liver transplantation, and results were analyzed qualitatively in a separate report. For the present work, we analyzed pretransplantation and posttransplantation scores using the paired t-test.

## 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 who underwent transplantation 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 complications 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...
both posterior cerebral arteries, causing massive ischemic injury to thalami, sensorimotor areas, and visual cortices. She is now confined to a wheelchair, mentally retarded (IQ 47; adaptive 43), and blind. Transplantation has not allowed any patients to stop treatment for inattention, hyperactivity, or mental illness; 4 posttransplantation patients (11%) are receiving psychostimulant medication, and 6 (16%) are being treated for anxiety, panic, or depression.

Adding 17 cases from the UNOS registry, a total of 54 liver transplantations for MSUD were performed in the United States between January 2004 and February 2010. In this group, patient and graft survival were 98% and 96%, respectively; 1 child died in the immediate postoperative period due to vascular complications in the graft, and 1 other child required retransplantation. Fifty-three patients received a liver from a deceased donor (51 whole livers, 2 split), and the child who died after transplantation received a partial liver from a living donor. Among 17 patients who underwent transplantation at other centers, half were under age 5, one-quarter were aged 6-10, and the remainder were aged 11-34.

Discussion

The largest relative activity of BCKDH is in muscle (54%-66%), with equal contributions by liver and kidney (9%-13% each) and a considerable amount in brain (9%-20%).6 This has several important ramifications. First, it suggests that kidney transplantation might be equally effective in controlling BCAA metabolism; we prefer liver based on superior long-term posttransplantation outcomes and its central role in adaptive intermediary metabolism. Second, the high BCKDH activity of muscle “protects” recipients without MSUD from BCKDH deficiency in domino grafts. Finally, BCKDH deficiency within the brain might cause neurologic sequelae independent of peripheral disturbances of BCAA and branched-chain ketoacid metabolism. A longitudinal study of patients who underwent transplantation early in life is a crucial way to explore this possibility.

The protection afforded by liver transplantation has limits. Our experience with 1 patient demonstrates that catabolic stress and dehydration can temporarily overwhelm the capacity of the grafted liver to oxidize BCAAs. Severe dehydration may transiently reduce hepatic blood flow such that total body enzyme activity is insufficient to keep pace with a large catabolic efflux of BCAAs from muscle tissue. This observation reveals quantitative relationships among in vivo BCKDH activity, endogenous protein catabolic rate, and the demand for BCAA oxidation. There are 4 important clinical implications: (1) Clinicians should continue to monitor amino acids in posttransplantation patients, particularly those who develop serious catabolic illness or unexplained encephalopathy; (2) Visceral ischemia, hepatic vascular compromise, dehydration, or anything that restricts hepatic blood flow can compromise BCAA clearance by the graft; (3) Centers that perform transplantation in patients with MSUD should be prepared to contend with metabolic crisis if the procedure fails. At minimum, this requires on-demand amino acid monitoring, extemporaneous MSUD hyperalimentation solution, and a capable inpatient metabolic service; and (4) Despite encouraging results in
In 33 pretransplantation patients, there was a strong correlation between IQ (x-axis) and adaptive function (y-axis). Only 3 patients had IQ scores at or above the mean (100; dotted line). One-third had IQ scores in the deficient range (≤ 70). Shaded areas represent the mean ± 2 SD in normal subjects. Gray circles represent Old Order Mennonite subjects and indicate that different cultural background did not bias toward lower test scores. Open circles indicate non-Old Order Mennonite patients.

Figure 2. In 33 pretransplantation patients, there was a strong correlation between IQ (x-axis) and adaptive function (y-axis). Only 3 patients had IQ scores at or above the mean (100; dotted line). One-third had IQ scores in the deficient range (≤ 70). Shaded areas represent the mean ± 2 SD in normal subjects. Gray circles represent Old Order Mennonite subjects and indicate that different cultural background did not bias toward lower test scores. Open circles indicate non-Old Order Mennonite patients.
and speed of amino acid monitoring, and access to emergency metabolic care. The up-front cost of transplantation also will affect the treatment decision in some cases, especially in uninsured patients. Although frequent hospitalization for encephalopathic crises would support transplantation, a history of “good metabolic control” in a patient with a classical phenotype is no guarantee of future stability and should not be considered a contraindication to the procedure. Metabolic crises can arise at any time and without warning; each such episode is a risk for brain swelling and death.

The ability to treat MSUD and other serious metabolic conditions with liver transplantation expands the list of indications for this procedure. However, deceased donor organs are in short supply, and we acknowledge objections to “elective” transplantation for metabolic disorders when more than 1500 people die each year on the liver waitlist. Although an in-depth analysis of the ethics of transplantation for MSUD is beyond the scope of this article, this published experience addresses several concerns that have been expressed by Ross. First, decision making for patients with metabolic disease requires the type of longer-term data on both graft- and nongraft-related outcomes, such as the neuropsychological outcomes considered here. Successful elimination of sustained BCAA dysregulation and preliminary evidence of the stabilization of neurocognitive function are important elements that will aid clinical and community decision making. Although matched controlled subjects not undergoing transplantation were not included in the present analysis, the collective published experience by us and others supports the long-term benefits of transplantation. In addition, the success of domino transplantation reported here and in additional cases also may mitigate some of these concerns.

Finally, it is also important to remember that MSUD, even if detected early, is still a lethal condition in many countries. As of 1988, before we established a local metabolic service in Lancaster County, 14 of 36 (39%) Mennonite patients with MSUD died of brain herniation by age 6 years. In 2006, Vietnam began using tandem mass spectrometry to screen newborns for MSUD. Fourteen cases were diagnosed during the first 3 years of the program. Among 12 patients diagnosed as newborns, 11 are dead, and the sole survivor is disabled. Two remaining patients, diagnosed at 6 months and 2.5 years, have brain damage (Vu Chi Dung, personal communication, April 14, 2011). In Vietnam as elsewhere, liver transplantation potentially may be more readily available than medical foods and inpatient services to manage MSUD.

Similar clinical circumstances exist throughout the world. Our cohort included 2 children from India and Brazil who had no consistent medical care and would have died or been crippled without liver transplantation. Even within the United States, metabolic services for MSUD are inconsistent. Some families travel long distances to see a specialist once or twice yearly and cannot find appropriate care during emergencies. Monitoring practices vary from region to region, and families sometimes wait up to days or weeks for amino acid results. For most patients, fragmented and unreliable subspecialty services disintegrate further as they pass into adulthood. Even under ideal clinical circumstances, classical MSUD is a volatile and dangerous condition that hangs like a sword of Damocles over the child and family. Cases of serious brain disease reported in this cohort are a stark reminder of the fear and anxiety that families live with daily; a consistent effect of transplantation is to relieve families of this psychological burden. Indeed, the recommendation for liver transplantation during the multidisciplinary evaluation of the child with significant neurologic injury was based on the overall assessment that her medical care could be facilitated and further neurologic injury potentially abrogated by successful transplantation. Although ongoing study of both long-term transplantation and nontransplantation outcomes is needed, this report provides important support for liver transplantation for MSUD as a sound ethical and medical practice.

Liver transplantation substitutes one set of problems for another. It sets the risks of surgery and immune suppression against those of acute and chronic brain injury. Parents and young adults who elect transplantation understand the trade-off and place their priority on neurologic health. Ongoing

Figure 3. There was no correlation between age at transplantation and IQ (upper panel) or adaptive scores (lower panel). No correlations were found between test scores and age at diagnosis, number of hospitalizations, number of metabolic crises, or age at transplantation.
clinical investigation is needed to determine whether neurologic protection is sustained over the long term and at acceptable costs.

We thank the children and families who continue to inspire our work. Many clinicians, nurses, physician assistants, nurse practitioners, and students made important contributions to their care. We especially wish to acknowledge the contributions of Dr Nicholas L. Rider, Donna Robinson, and Christine Hendrickson (Clinic for Special Children); Lynn Seward, Kim Haberman, JoAnne Blice, Tammy Fazzolare PA-C, Lisa Remaley PA-C, and Lorna Cropcho (Children’s Hospital of Pittsburgh of UPMC). Dr. Vũ Chí Dũng, Head of the Department of Medical Genetics, Metabolism, and Endocrinology at the National Hospital of Pediatrics in Hanoi, graciously shared newborn screening and follow-up data.

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References

Table. Perioperative and postoperative complications in 37 patients

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<td>Posttransplantation lymphoproliferative disease†</td>
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*At previous gastrostomy tube sites.
†Antibody therapy for steroid-resistant rejection in 3/15 (8% of all patients).
‡Intestinal posttransplantation lymphoproliferative disease developed in 1 patient who underwent transplantation at another center; it resolved with transient withdrawal of immunosuppression, and the patient has been disease-free for 12 years.

Figure 4. A, Change in test scores for a subgroup of 14 patients. Pretransplantation IQ (78 ± 14) and adaptive (81 ± 20) scores were no different at 1 year after transplantation (posttransplantation IQ, 83 ± 15; adaptive, 82 ± 22). Gray shaded areas show the normal mean (dotted line) ± 2 SD. B, Mean percentage change (dotted line) and 95% CI (gray shaded area). IQ increased by an average of 6.2% (95% CI, –1.0% to 12.6%; range, –13% to 30%) at 1 year after transplantation, but the difference was not statistically significant (P = .059).