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Elective Liver Transplantation for the Treatment of Classical Maple Syrup Urine Disease

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An 8.5-year-old girl with classical maple syrup urine disease (MSUD) required liver transplantation for hypervitaminosis A and was effectively cured of MSUD over an 8-year clinical follow-up period. We developed a collaborative multidisciplinary effort to evaluate the effects of elective liver transplantation in 10 additional children (age range 1.9–20.5 years) with classical MSUD. Patients were transplanted with whole cadaveric livers under a protocol designed to optimize safe pre- and post-transplant management of MSUD. All patients are alive and well with normal allograft function after 106 months of follow-up in the index patient and a median follow-up period of 14 months (range 4–18 months) in the 10 remaining patients. Leucine, isoleucine and valine levels stabilized within 6 hours post-transplant and remained so on an unrestricted protein intake in all patients. Metabolic cure was documented as a sustained increase in weight-adjusted leucine tolerance, normalization of plasma concentration relationships among branched-chain and other essential and nonessential amino acids, and metabolic and clinical stability during protein loading and intercurrent illnesses. Costs and risks associated with surgery and immune suppression were similar to other pediatric liver transplant populations.

Key words: Branched-chain ketoacid dehydrogenase, liver transplantation, maple syrup urine disease, metabolic disease, pediatric

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Introduction

Classical maple syrup urine disease (MSUD) is caused by mutations of mitochondrial branched-chain ketoacid dehydrogenase (BCKAD) and results in accumulation of branched-chain amino acids (BCAAs) and their corresponding branched-chain alpha-ketoacids (BCKAs) in tissues and plasma. Classical MSUD is a complex and volatile disorder. Acute metabolic decompensation can develop rapidly at any age. These episodes are associated with encephalopathy and brain swelling, and can culminate in stroke or sudden death (1–6). During such illnesses, restoration of metabolic control and treatment of brain edema require experienced physicians, costly pharmaceutical regimens and specialized hospital services.

Recently, we described uniformly good neurological outcomes in 36 young children with MSUD managed from the neonatal period (2). Nevertheless, we have become increasingly aware of an insidious mental health burden in our aging patient population. Neurological catastrophes are relatively rare in patients with MSUD, but prolonged essential amino acid imbalances are common (2,4). Even with rigorous laboratory monitoring and frequent dietary adjustments, chronic disturbances in plasma amino acid and ketoacid profiles are impossible to avoid, and are likely to result in structural and functional disturbances of the brain. Attention deficits, impulsivity and hyperactivity occur commonly in school-age children and mental illness is prevalent in adolescent and adult MSUD patients (4). Twenty-nine percent ($n = 21$) of our patients between 6 and 12 years of age require psychostimulant medication for core symptoms of attention deficit hyperactivity disorder (ADHD) and 37% ($n = 35$) of our patients over 12 years of age have been treated with psychotropic medications, singly or in combination, for symptoms of anxiety, panic or depression. Among drug classes, antidepressants were the most commonly used (47% of all treatment indications). Thus, while neonatal screening and sophisticated enteral and parenteral therapies have dramatically improved outcomes for MSUD patients, the risk of acute brain injury or death is always present and the long-term neuropsychiatric prognosis is at best guarded.

Our experience with liver transplantation for MSUD was serendipitous. In 1997, an 8.5-year-old MSUD patient under our care underwent orthotopic liver transplantation for hypervitaminosis A-associated liver failure (7). She had an

exceptional long-term metabolic and psychomotor outcome, suggesting that (i) liver transplantation is sufficient to establish long-term peripheral amino acid homeostasis on an unrestricted protein intake, (ii) allograft BCKAD activity appropriately adapts to the demands of dietary variation and illness and (iii) normalization of peripheral BCAA and BCKA metabolism is associated with normal long-term neurological development. Subsequently, several parents sought elective liver transplantation for their affected children. We developed a collaboration to optimize the safety of this procedure from both a metabolic and surgical perspective, and now report on its efficacy in this patient cohort.

Index Case

Patient 1 was diagnosed with the classical Mennonite variant of MSUD after she presented with severe neonatal encephalopathy. Metabolic control was established with nutritional therapy. She made good developmental progress during infancy and early childhood, but exhibited some deficits in attention, concentration and impulse control. Unbeknownst to medical providers, she ingested 100,000–150,000 IUs vitamin A intermittently for several years as a component of a 'natural' vitamin supplement. She developed vitamin A toxicity, cirrhosis and hepatic failure. By the time of liver transplantation, she had intractable coagulopathy, severe portal hypertension, recurrent variceal bleeding and hypoxemia due to intrapulmonary arteriovenous shunting. Pre-transplant plasma amino acids were highly unstable due to advanced liver failure, poor appetite, malnutrition and intestinal bleeding (Figure 1). Neurological examination prior to transplantation was significant for stupor, irritability, inattention, ataxia, intermittent dystonia and spastic hyperreflexia of the lower extremities. These impairments reflected combined effects of hepatic encephalopathy and accompanying severe disturbances of plasma BCAA metabolism (Figure 1).

She received a whole cadaveric liver transplant at the age of 8.5 years (7). Within hours after allograft perfusion, BCAA levels and plasma essential amino concentration ratios normalized (Figure 1) and have remained so over an 8-year follow-up period on unrestricted protein intake. Amino acid homeostasis was stable through periods of prolonged fasting and several catabolic illnesses, including Epstein-Barr virus-associated lymphproliferative disease. Hepatopulmonary syndrome and spider angiomata resolved. Cognitive, behavioral and motor impairments improved slowly but completely. Her psychomotor examination is now normal. One notable clinical sign of BCKAD deficiency remains: the distinctive odor of maple syrup in cerumen.

Patients and Methods

Eleven children at a median age of 6.3 years (range 1.9–20.5 years) with classical MSUD were transplanted with whole cadaveric livers under tacrolimus and corticosteroids (n = 2) or rabbit anti-thymocyte globulin (rATG) preconditioning with post-transplant tacrolimus monotherapy (n = 9). Four patients

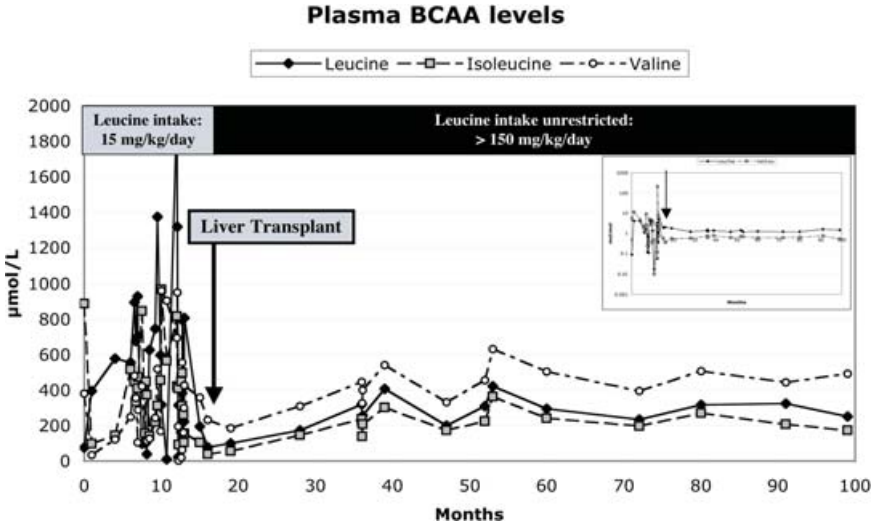

Figure 1: Long-term regulation of the amino acid profile in a transplanted Mennonite girl with classical MSUD. Both absolute amino acid values and ratios among them stabilize shortly after liver transplant at age 8.5 years, Plasma amino profile remains essentially normal on an unrestricted protein intake and through multiple infectious illnesses over 100 months of post-transplant follow-up. Pre-transplant, plasma molar ratios among the various BCAAs (inset, on a log 10 scale) were highly erratic. These concentration disturbances have an adverse impact on essential amino acid uptake by the brain. Molar ratios stabilized after transplant, demonstrating appropriate homeostatic regulation of amino acids oxidation by the liver and balanced transcellular amino acid transport. Overall neuropsychiatric function, particularly concentration, attention, memory and mood regulation improved in parallel (data from patient 1).

Table 1: Characteristics of eleven MSUD patients

Patient no.	Age at transplant (years)	Genotype			Pre-existing psychomotor disability	Current follow-up (months)	Current total bilirubin (mg/dL)
			Sequence variant(s)	Trivial name(s)			
1	8.5	BCKDHA	1312T→A/1312T→A	Y438N/Y438N	Yes	106	0.3
2	4.3	BCKDHB	1A→T/410C→T	1A→T/A137V		17.5	0.4
3	3.0	BCKDHA	IVS5–1G→C/IVS5–1G→C	IVS5–1G→C/IVS5–1G→C		16.6	0.1
4	1.9	BCKDHB	75delG/75delG	75delG/75delG		15.8	0.2
5	2.7	DBT	75_76delAT/75_76delAT	75_76delAT/75_76delAT		15.5	0.3
6	8.1	BCKDHA	647C→T/1312T→A	A216V/Y438N	Yes	13.8	0.4
7	2.0	DBT	828_829insGATACCTCATTTT/?	828_829insGATACCTCATTTT/?		10.6	0.2
8	8.7	BCKDHB	326delG/831G→C	326delG/W277C	Yes	7.9	0.6
9	9.8	BCKDHA	IVS7+1G→A/940C→T	IVS7+1G→A/R314X		4.5	0.3
10	20.5	DBT	75_76delAT/[555delT; IVS5+1delG]	75_76delAT/[555delT; IVS5+1delG]	Yes	4	0.4
11	6.3	BCKDHA	117delC/1312T→A	117delC/Y438N		4	0.7

had significant pre-existing psychomotor disabilities related to MSUD and the remaining patients were neurologically healthy at the time of surgery (Table 1). Patient 1, the index case, was transplanted emergently at Children's Hospital of Philadelphia, while patients 2–11 were transplanted electively under our protocol at Children's Hospital of Pittsburgh. The protocol included: (i) minimization of pre-transplant fasting, (ii) initiation of a dextrose infusion $\geq$7 mg/kg/min upon hospital arrival, (iii) strict attention to perioperative sodium and water homeostasis, (iv) 24-h analytical capability for plasma amino acid profiles (AAPs) and (v) in-hospital availability of an extemporaneous 10% branched-chain-free parenteral amino acid solution and individual BCAA solutions (1% leucine, isoleucine or valine in normal saline). AAPs were done at preoperative, anhepatic and reperfusion stages, postoperative days 1 and 2 and approximately once monthly throughout the follow-up period. Parents kept a record of *ad libitum* protein intake, which was assumed to be 10% leucine by weight. In six children, AAPs were obtained during at least one infectious illness. For patient 1, serial AAPs were available for 15 months pre- (n = 23) and 85 months post-transplant (n = 14) as shown in Figure 1. For patients 2–11, there were 112 pre- and 94 post-transplant AAPs pooled for analysis.

Two parameters were used to characterize *in vivo* amino acid homeostasis before and after transplant: leucine tolerance and plasma amino acid concentration ratios. Leucine tolerance is defined as the weight-adjusted daily leucine intake sufficient for normal growth that also allows maintenance of steady-state plasma leucine within the normal range (8,9). Urinary losses of BCAAs are negligible (10,11) and in patients with classical MSUD, the leucine oxidation rate is close to zero. Thus leucine tolerance reflects the sum of insensible protein loss and net accretion rate of body protein, which in turn is dependent on the growth rate. For patients with classical MSUD leucine tolerance is typically 50–70 mg of leucine/kg/day during infancy, decreasing to 15–40 mg/kg/day by age 2 years and 5–15 mg/kg/day by adolescence. Tolerance in excess of the leucine accretion rate is definitive evidence of *in vivo* leucine oxidation (O) and provides an estimate of the oxidation rate (4). Regulation of the oxidation rate is necessary to maintain constancy of plasma BCAAs when dietary protein intake varies over a wide range or when free amino acids are liberated during net protein catabolism.

Disturbed plasma concentration relationships among BCAAs and between branched-chain and other essential and nonessential amino acid species are characteristic of MSUD (2). These ratios are normally maintained within a narrow range by balanced transport of branched-chain and other essential amino acids across common carriers (LAT1/2; see Figure 2), intracellular transamination equilibria and coordinated activity of multiple catabolic pathways (12–16). As representative markers of amino acid regulation, we chose plasma ratios of leucine:isoleucine, valine:leucine, leucine:tyrosine, leucine:phenylalanine and leucine:alanine (μmol:μmol).

For patient 1, pre- and post-transplant leucine intake and amino acid homeostasis were analyzed longitudinally. For patients 2–11, we compared leucine intake and AAPs over a 2-year period preceding transplant to similar parameters obtained approximately monthly during the postoperative follow-up period. These values were pooled and analyzed using a 2-tailed Welch-corrected *t*-test (which does not assume equal variances) to detect differences between pre- and post-transplant mean metabolic parameters. An F test was used to compare variances. Given the large number of *t*-tests peformed (n = 18 calculations), p-values $<$0.002 were considered significant.

For all patients in the cohort, parents provided written consent for molecular testing and the use of clinical data for purposes of analysis and publication. The study was approved by the University of Pittsburgh Institutional Review Board.

Results

Metabolic and clinical response

All 11 patients are alive after a median follow-up period of 13.8 months (4 months to 8.6 years). In all cases, BCAAs normalized within 6–12 hours of allograft perfusion and remained so on unrestricted protein intake. Steady-state leucine levels and leucine variability were significantly lower post-transplant (165.4 $\pm$ 52.4 μmol/L vs. 300.1 $\pm$ 197.2 μmol/L, $p < 0.0001$ for mean and variance, Table 2, Figures 1 and 3) as weight-adjusted leucine tolerance increased from 15–37 mg/kg/day to greater than 140 mg/kg/day. The range of *ad libitum* leucine intakes after surgery was 145–350 mg/kg/day, reflecting *in vivo* leucine oxidation rates exceeding 125 mg/kg/day. We did not observe an apparent limit to tolerance. Indeed, young children ingesting over 20 g of protein (approximately 2000 mg leucine) in one meal remained asymptomatic. Following transplantation, plasma amino acid concentration ratios were less variable and remained appropriately regulated through periods of dietary fluctuation, fasting

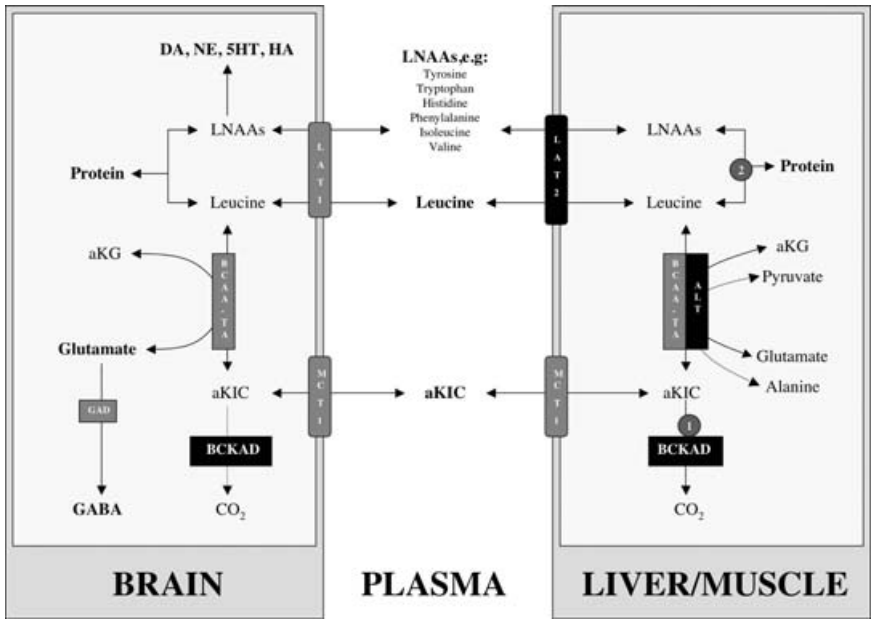

Figure 2: Pathophysiological model of maple syrup disease. Plasma leucine and other large zwitterionic amino acids (LNAAs: isoleucine, valine, phenylalanine, tyrosine, tryptophan, histidine, threonine, methionine) enter cells through a common sodium-independent hetero-exchanger, LAT1 (brain) or LAT2 (peripheral tissues). Alpha-ketoisocaproic acid (aKIC) is likely to be carried by the monocarboxylate transporter (MCT) shared by 3-hydroxybutyric acid. In brain and other tissues, leucine and aKIC equilibrate through reversible transamination reactions (BCAA-TA). In patients with classical MSUD, the leucine oxidation rate (reaction 1) by BCKAD is negligible, and the amount of leucine tolerated in the diet reflects its net deposition into body protein (reaction 2) and insensible protein losses (e.g. enteral mucus, sloughed skin and hair). Plasma BCAAs can increase rapidly during periods of net protein catabolism that occur during infectious illness, dehydration, injury or psychological stress. Elevated and/or unbalanced plasma BCAA, essential amino acids and ketoacids disrupt cerebral protein turnover, monoamine transmitter production (DA, dopamine; NE, norepinephrine; 5HT, serotonin and HA, histamine) and the 'fast' neurotransmitter pools (glutamate, GABA, aspartate). There are both acute and chronic consequences for growth and function of the brain. Liver transplantation introduces regulated BCKAD activity into the body sufficient to maintain plasma BCAA and aKIC levels through a range of dietary and physiological challenges, and restores normal molar relationships among essential amino acid competing for transport. Neurological improvements occur despite persistent BCKAD deficiency in the brain.

Table 2: Measurements of metabolic homeostasis

Variable	Pre-transplant N = 112, mean (SD)	Post-transplant N = 94, mean (SD)	p-value mean[2]	p-value variance
Leucine tolerance, *ad libitum* (mg/kg/day)	15–37	145–350	*<0.0001*	*<0.0001*
Plasma amino acids (μmol/L)				
Leucine	300.1 (197.2)	165.4 (52.4)	*<0.0001*	*<0.0001*
Isoleucine	237.5 (96.6)	108.9 (57.3)	*<0.0001*	*<0.0001*
Valine	450.7 (170.6)	273.9 (129.7)	*<0.0001*	0.0067
Plasma leucine standard score[1]	4.4 (5.2)	0.9 (1.4)		
Amino acid concentration ratios (μmol:μmol)				
Valine/Leucine	2.3 (2.0)	1.6 (0.4)	*0.0007*	*<0.0001*
Leucine/Isoleucine	1.4 (1.0)	1.9 (1.2)	*0.0019*	0.0265
Leucine/Phenylalanine	4.1 (3.7)	2.7 (0.9)	*<0.0001*	*<0.0001*
Leucine/Tyrosine	3.8 (4.8)	3.3 (0.9)	0.288	*<0.0001*
Leucine/Alanine	1.1 (1.4)	1.0 (0.4)	0.4107	*<0.0001*

[1]Leucine values are subject to normal variation in healthy individuals. To capture the effect of liver transplant relative to this variation, all leucine concentrations were converted to standard score (normal +3 to –3) against a reference population of healthy Mennonite and Amish children (plasma leucine 133 ± 38 μmol/L).

[2]Given the large number of *t*-tests performed (18), a low p-value of <0.002 was accepted as significant for individual parameters, to maintain a p-value of <0.05 for the overall data set. Significant results are in italics.

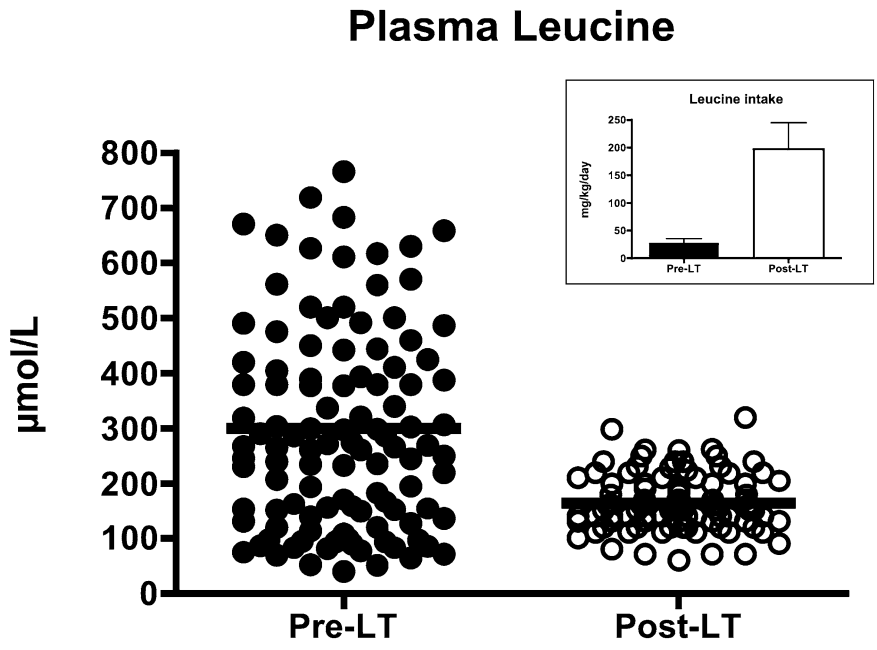

Figure 3: Pooled plasma amino acid data from patients 2–11 collected 2 years pre- (n = 112) and at regular intervals post- (n = 94) liver transplantation. Plasma leucine was significantly lower ($p < 0.0001$) and less variable ($p < 0.0001$) following liver transplantation (LT), despite an increase in *ad lib* leucine intake from 15–37 mg/kg/day to 145–350 mg/kg/day (inset). Several post-transplantation values were obtained during intercurrent illness, during which protein was not restricted.

Table 3: Complications following liver transplantation

Complication	Total number
Surgical revisions	
Hepatic arterial repair	2
Arterial graft revision	1
Delayed abdominal closure	2
Acute cellular rejection	4[1]
Asymptomatic viremia	
Ebstein-Barr virus	3
Cytomegalovirus	1
EBV-associated PTLD	1[2]
Electrolyte disturbances	
Hypokalemia	4
Hypomagnesemia	3

[1]Managed with corticosteroids in three cases. One case required monoclonal antibody therapy.
[2]PTLD occurred 3 years post-transplant, and resolved with temporary withdrawal of immunosuppression.

and illness (Table 2, Figure 1). Following transplantation, allo-isoleucine (17) was still detectable at very low levels (1–10 µmol/L) in patient's plasma.

Similar to our experience with patient 1, patients 6 and 8 had significant psychomotor improvements evident within weeks after surgery that continued throughout the follow-up period. Parents of the additional five children volunteered unsolicited reports of stable improvements in mood, concentration and attention span in their children following transplantation. We are conducting prospective evaluations to formally assess these claims.

Peritransplant management and Peri- and postoperative complications

Following rATG preconditioning, the majority of electively transplanted patients could be managed with tacrolimus alone throughout the follow-up period (18). Oral or intravenous corticosteroids were only used perioperatively for the two patients that did not receive rATG and in four instances of postoperative acute cellular rejection (Table 3). All patients are currently on tacrolimus monotherapy with the exception of the index patient, who was transplanted under an older protocol.

Transplant-related complications are listed in Table 3. Only patient 3 received MSUD 10% parenteral amino solution immediately prior to transplant due to an elevated leucine level and an extended period of fasting. Two patients had early successful re-exploration for hepatic arterial revision and two patients required delayed closure of abdominal fascia. Biliary complications did not occur. Four acute rejection episodes (patients 4, 5 and 10) were easily managed with corticosteroid therapy and did not alter amino acid homeostasis. Patient 8 required a brief course of monoclonal antibody therapy to reverse an episode of steroid-resistant rejection. Three patients had asymptomatic viremias, which were treated with reduction of immunosuppression. Patient 1 developed Ebstein-Barr virus-associated lymphoproliferative disease (PTLD) 3 years after transplantation, which resolved with temporary withdrawal of immunosuppression. None of the 10 electively transplanted patients developed clinical CMV or EBV disease or PTLD. All patients are presently well and have normal liver function.

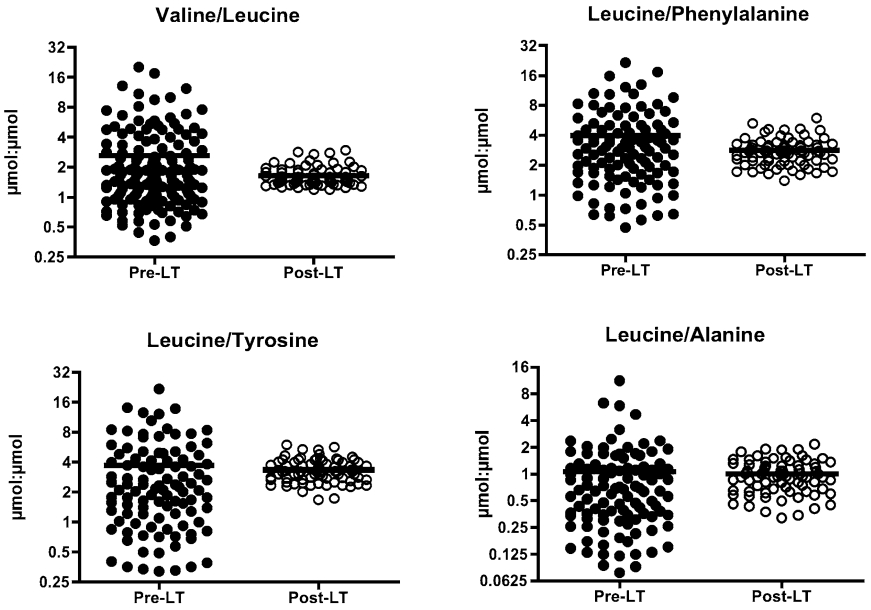

Figure 4: Plasma amino acid concentration ratios for patients 2–11 before (n = 112) and after (n = 94) liver transplantation (LT). The overall plasma amino acid profile normalizes following transplant, as shown here by stable concentration ratios among the BCAAs (valine:leucine), and between BCAAs and other essential amino acids (leucine:phenylalanine), neurotransmitter substrates (leucine:tyrosine), and nonessential amino acids leucine:alanine). Note: y-axes on log 2 scale.

Discussion

Metabolic effects of liver transplantation in MSUD

BCKAD is expressed and metabolically active in liver, muscle, heart, brain and other tissues (19). The efficacy of orthotopic liver transplantation for MSUD indicates that introducing about 10% of normal BCKAD enzyme on a whole body basis is sufficient to maintain peripheral amino acid homeostasis in the face of unrestricted protein intake (Figure 2) (19). The transplanted enzyme is subject to regulation, allowing it to adapt oxidation rates to prevailing physiologic conditions and maintain molar constancy of the plasma AAP despite large nitrogen fluxes that accompany protein loading, fasting and infectious illness (Figures 1 and 3). While transplantation of a single kidney would introduce a similar whole-body fraction of BCKAD (9–12%), it may not afford the same degree of metabolic control. The anatomical position of the transplanted enzyme may be relevant to its physiological effect; the liver is normally a major site of regulatory oxidation of surplus amino acids that result from both dietary excess and muscle proteolysis (8,9,16,20). Figures 1, 3 and 4 show that liver transplantation not only eliminates high and variable BCAA levels, but also protects children from essential amino acid deficiencies, which may be of equal importance for optimizing physical and neurological development (4,21–26).

In previous work (2,4), we hypothesized that two major mechanisms account for the acute and chronic neurological manifestations of MSUD: (i) unbalanced transport of LAT1 substrates across the blood-brain barrier alters cerebral protein turnover and monoamine neurotransmitter metabolism (23,27–29) and (ii) intermittent and chronic elevations of BCKAs disturb cerebral transamination fluxes that normally maintain 'fast' neurotransmitter pools (Figure 2) (26,30–32). Based on the present experience, we expect that such ongoing neurochemical disturbances cause cognitive, motor and psychiatric morbidities, which can improve after surgery despite persistence of *cerebral* BCKAD deficiency in all transplanted patients (Figure 2).

Weighing risks, costs and benefits

At the Clinic for Special Children, the average annual cost of nutritional and medical care for a patient with MSUD was $7000–$9000 per patient per year (U.S. dollars, surveyed in 2002) or about $80,000 per 10 years of follow-up. Thus for most individuals with classical MSUD, the lifetime costs of nutritional management will greatly exceed those associated with transplantation. Importantly, cost averaging does not capture the extraordinary monetary and human costs experienced by individual patients. Acute metabolic decompensation with attendant cerebral crisis can strike at any age and culminate in neurological catastrophe (1,3–6). Before 1988, 14 of 36 (44%) Mennonite infants with MSUD died before 10 years of age from sudden brain herniation. Over a 16-year period, we have managed MSUD patients through over 170 hospitalizations for acute metabolic decompensations and have not witnessed a single death. Nevertheless, approximately 10% of these admissions were protracted and generated single-hospitalization costs greater than $100 000; single hospital bills have exceeded $450 000. Patient 8 suffered a nonlethal brain herniation that resulted in hospital costs in excess of $600 000 and left her with right-sided paraplegia, cognitive impairment and cortical blindness. This tragic clinical outcome is compounded by a lifetime requirement for costly supportive services and underscores a fear all MSUD families live with on a daily basis.

MSUD patients entering adulthood face daunting challenges on various fronts. First, metabolic control tends to deteriorate with age. This likely results from the combined

effects of decreasing weight-adjusted leucine tolerance, decreased metabolic monitoring and waning parental and physician control over nutritional therapy. Leucine tolerance becomes very low (about 10 mg/kg/day) once the adult lean body mass has accrued. For practical purposes, this means that the adolescent and adult MSUD patient will only tolerate about 7–9 g of natural protein daily and be 90% dependent on synthetic medical foods for life. Social stigmata and serious health hazards accompany such a diet. We have documented widespread severe omega-3 fatty acid and zinc deficiencies in our patients (4), and surely they are at high risk for other iatrogenic nutritional deficiencies over the life span. Second, appropriate medical services for older patients do not exist. The large majority of adult MSUD patients in the United States and abroad are cared for by pediatricians. After such patients pass age 18 or 21 years, pediatric medical centers and insurance providers can stop providing specialized care, but the disease becomes neither less costly nor less dangerous. Third, the older MSUD patient population suffers from substantial neuropsychiatric morbidities that require treatment with psychoactive medications and impact work competency, earning potential, and the quality of cognitive and emotional life. This, in turn, can adversely affect dietary control. Many adult MSUD patients cannot maintain jobs that require sustained concentration, organization or memory and they are uniformly discouraged by long-term dietary constraints. Even under optimal circumstances, few classical MSUD patients can achieve full independence. The aforementioned arguments extend to a much larger aging population of individuals with phenylketonuria, partial ornithine transcarbamylase deficieny and other inborn metabolic errors, which similarly can be corrected with transplantation. The experience with MSUD may create new treatment opportunities for such patients.

Data presented here indicate that in terms of overall efficacy and protection from disease progression, liver transplantation is a reasonable treatment option for classical MSUD, similar in principle to its use in disorders such as familial hypercholesterolemia, primary hyperammonemia and Crigler-Najjar disease type 1 (33–36). However, donor livers are in short supply. Only 32% of 18 000 patients listed annually receive a graft, and the use of cadaveric livers to treat patients without primary liver failure engenders ethical judgments about a limited resource. However, young classical MSUD patients, like those with urea cycle disorders, qualify for high prioritization due to the neurological burden of their disease. Furthermore, liver transplantation was considered reasonable treatment by four state Medicaid agencies, five independent insurance carriers and the U.S. Military, all of whom reimbursed fully for the procedure. Finally, Khanna et al.[†] recently demonstrated that the liver of a classical MSUD patient can be successfully 'domino' transplanted into a recipient with no adverse consequences for peripheral amino acid homeostasis. It is possible that in the future, directed utilization of MSUD explants may help to resolve the controversy over allograft distribution.

The emergence of lymphoproliferative disease in patient 1, although successfully treated, underscores the fact that there are no easy solutions for patients living with MSUD. Nevertheless, the risks of perioperative mortality and postoperative complications were reviewed explicitly with families during the pre-transplant evaluation. Such knowledge did not dissuade parents during the decision phase, nor did it weaken their resolve when complications occurred during or after transplantation. Furthermore, long-term survival and quality of life post-transplant should continue to improve due to improved monitoring for EBV- and CMV-related complications (37), elimination of corticosteroids from immunosuppressive regimens and efforts to minimize immunosuppressive medication for individual patients (18,37).

The decision about medical versus surgical treatment for classical MSUD is a complicated one, and factors contributing to the decision will vary with each individual case. In our view, the parents of a child with such a dangerous and difficult problem are best informed to make comparative judgments about quality of life, health risk and financial burden, provided they receive accurate information regarding the risks and prognostic implications of various treatment options (38). If an individual with classical MSUD is to undergo the procedure, surgical planning should take into account the unpredictable nature of the disease. Pre- and post-transplantation complications occur (Table 3) and cannot be anticipated in an individual case. Thus, to optimize safety the procedure should be performed under protocol at a hospital with experienced surgical and metabolic specialists, and pharmacy and laboratory services ready to respond to contingencies in a timely manner.

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[†]Khanna A et al., 2005, Domino liver transplantation in maple syrup urine disease. This manuscript in press by Dr. Ajai Khanna and colleagues describes a domino transplant from a 25-year-old MSUD patient into a 53-year-old man with hepatitis C and hepatocellular carcinoma. After transplantation, both patients had normal AAPs, unrestricted protein tolerance and *in vivo* leucine oxidation rates of approximately 45% control.

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