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Living related versus deceased donor liver transplantation for maple syrup urine disease

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ABSTRACT

Maple syrup urine disease (MSUD) is an inherited disorder of branched chain ketoacid (BCKA) oxidation associated with episodic and chronic brain disease. Transplantation of liver from an unrelated deceased donor restores 9–13% whole-body BCKA oxidation capacity and stabilizes MSUD. Recent reports document encouraging short-term outcomes for MSUD patients who received a liver segment from mutation heterozygous living related donors (LRDT). To investigate effects of living related versus deceased unrelated grafts, we studied four Brazilian MSUD patients treated with LRDT who were followed for a mean 19 ± 12 postoperative months, and compared metabolic and clinical outcomes to 37 classical MSUD patients treated with deceased donor transplant. Patient and graft survival for LRDT were 100%. Three of 4 MSUD livers were successfully domino transplanted into non-MSUD subjects. Following LRDT, all subjects resumed a protein-unrestricted diet as mean plasma leucine decreased from 224 ± 306 μM to 143 ± 44 μM and allo-isoleucine decreased 91%. We observed no episodes of hyperleucinemia during 80 aggregate postoperative patient-months. Mean plasma leucine:isoleucine:valine concentration ratios were ~2:1:4 after deceased donor transplant compared to ~1:1:1.5 following LRDT, resulting in differences of predicted cerebral amino acid uptake. Mutant heterozygous liver segments effectively maintain steady-state BCAA and BCKA homeostasis on an unrestricted diet and during most catabolic states, but might have different metabolic effects than grafts from unrelated deceased donors. Neither living related nor deceased donor transplant affords complete protection from metabolic intoxication, but both strategies represent viable alternatives to nutritional management.

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1. Introduction

Maple syrup urine disease (MSUD) is caused by mutations of *BCKDHA*, *BCKDHB*, or *DBT* that abrogate function of branched chain ketoacid dehydrogenase (BCKDH), a multiunit complex that mediates oxidative degradation of branched-chain ketoacids (BCKAs) derived from leucine, isoleucine, and valine [1,2]. In BCKDH-deficient subjects, protein catabolism entrained by infection or physiologic stress leads to accumulation of branched-chain amino acids (BCAAs) and BCKAs in tissues and plasma [3]. Supraphysiologic concentrations of leucine and alpha-ketoisocaproic acid (aKIC) are neurotoxic, causing encephalopathy and brain swelling that can culminate in cerebral herniation and death [4–7]. Recurrent encephalopathy and chronic BCAA imbalances characteristic of MSUD are associated with reduced synaptic complexity [8], impaired executive function, and affective illness [9].

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Despite major advances in dietary management over the last two decades [1,6,10,11], MSUD remains a volatile and dangerous disease [9]. This fact has prompted investigation of novel treatment strategies, including liver transplantation [12]. Transplantation of liver tissue from a deceased unrelated donor—presumed wild type for *BCKDHA*, *BCKDHB*, and *DBT*—replaces 9–13% of BCKDH activity on a whole body basis [13](Fig. 1) and has proven effective for treatment of severe (i.e. 'classical') MSUD [12,14]. Although steady state plasma leucine concentrations are 2-fold elevated after deceased donor transplant, they remain stable in the face of unregulated dietary protein intake and catabolic challenges, and post-transplant concentration relationships among the BCAAs are maintained across physiologic states [14], affording the brain a balanced supply of essential amino acids [15].

Despite the success of deceased donor transplant [12,14,16,17], access to deceased donor livers is limited in many clinical settings and unfortunately, these same settings are often marked by poor access to dietary therapies and biochemical monitoring [18–21]. Parents and clinicians who care for MSUD patients under such conditions are moved by humane and practical imperatives, and have pushed the paradigm of MSUD transplant to include related (i.e. obligate mutation heterozygous) tissue donors [22,23]. Hepatocytes from an obligate heterozygote parent express only ~50% of BCKDH activity and can thus theoretically restore only ~4–7% whole body enzyme activity in the recipient (Fig. 1). This might be too narrow a margin to insure good metabolic outcome, particularly in younger children, who can exhibit very high rates of net endogenous protein catabolism during illness [3,11,24]. Indeed, Mazariegos et al. [14] reported a toddler with MSUD who presented with gastroenteritis and severe dehydration 55 months after deceased donor transplant and was found to have transient hyperleucinemia without neurologic manifestations (plasma leucine 2170 μM; reference value 119 ± 38 μM) that resolved with rehydration and supportive care. Thus even patients who receive tissue from a deceased unrelated donor (and should express 9–13% whole body BCKDH activity) can suffer metabolic decompensation under sufficient catabolic pressure (Fig. 1) [14].

Initial case reports of living related donor transplantation (LRDT) for MSUD showed evidence of efficacy [22,23,25]. To more rigorously document the metabolic effects and clinical durability of LRDT, we conducted an intermediate term follow up study of four Brazilian children with classical MSUD who underwent LRDT between 19 and 39 months of age and were followed for 12–37 post-operative months. Heterozygous liver transplant proved effective for controlling the principal metabolic derangement of MSUD (i.e. leucine homeostasis) in the face of an unrestricted diet, but may result in a different homeostatic outcome than deceased donor transplant. Although we observed no episodes of post-transplant hyperleucinemia during 80 aggregate patient-months of follow up, this does not supplant the need for continued monitoring of amino acids following LRDT, particularly during illness [14]. Our observations have important implications for the management of MSUD among underserved populations throughout the world [26].

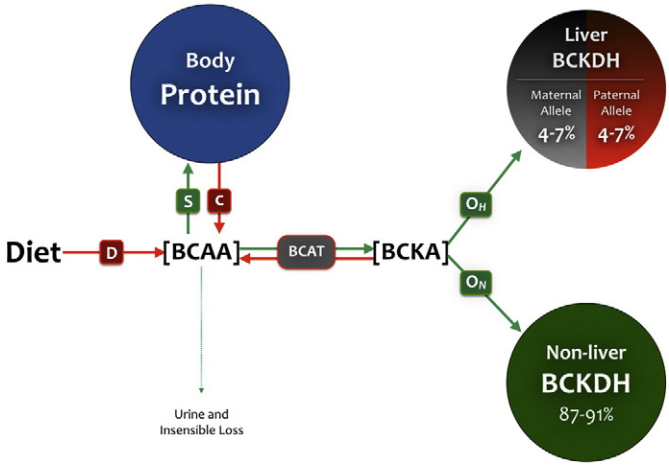

Fig. 1. Appearance of branched chain amino acids (BCAA)—leucine, isoleucine, valine—in the circulation represents the sum of dietary intake (D), endogenous protein catabolism (C), and reverse flux through tissue branched chain amino acid transaminases (BCAT). The BCAAs leave the circulation via protein synthesis (S) and transamination (BCAT) followed by oxidation of BCKA derivatives by hepatic (O_H; 9–13% whole body) and non-hepatic (O_N; 87–91% whole body) branched chain ketoacid dehydrogenase (BCKDH) enzyme activity. Urine and insensible losses of BCAAs are negligible. Transplantation of a parent (obligate heterozygous) liver graft is predicted to restore only 4–7% whole body BCKDH capacity.

2. Methods

2.1. Patients and methods

Four children with MSUD (current ages 2.7–5.2 years, 2 females) received a liver segment between ages 19 and 39 months from a parent who was heterozygous for a pathogenic MSUD variant (Table 1). Liver transplants were performed at Hospital Sirio Libanes in São Paulo, SP ($n = 3$), and Hospital de Clinicas de Porto Alegre, RS ($n = 1$) between October 2012 and December 2014. Preliminary data for the first transplanted subject was published by Feier et al. [22] and three-year follow-up data for this patient are included herein. Three additional patients were studied prospectively following careful selection for the procedure. This report includes all children with MSUD who received a live donor liver transplant in Brazil during the study period. In each case, we confirmed segregation of compound heterozygous ($n = 3$) or homozygous ($n = 1$) pathogenic variants in either *BCKDHB* ($n = 1$) or *BCKDHA* ($n = 3$); the genotype of each mutation heterozygous liver graft was inferred from the parent of origin (Table 1).

Pre-transplantation diets consisted of 10–50 mg/kg/day of leucine from a natural protein source supplemented with ≥70% of caloric intake from a BCAA-free medical formula. Following transplantation, all subjects were switched to an unrestricted natural protein intake (dietary leucine tolerance ≥100 mg/kg/day) and stopped consuming BCAA-free formula. Pre- and post-transplantation metabolic control was assessed by measuring *o*-phthaldialdehyde-derivatized amino acid concentrations from plasma or dried filter paper blood spots using high performance liquid chromatography (Agilent Technologies).

Blood sampling was unbalanced due to logistical constraints; we pooled 55 pre-transplantation (Pre-Tx: 1, 40, 8, and 6 samples per subject) and 28 post-transplantation (LRDT: 2, 6, 6, and 14 samples per subject) amino acid profiles from 4 MSUD patients and compared these with amino acid data from 51 healthy children (control group) and a cohort of 37 MSUD patients who received liver grafts from deceased unrelated donors and were the subject of previous publications [12,14].

2.2. Gene sequencing

We isolated peripheral blood DNA from each proband and his or her biological parents. Coding exons of *BCKDHA*, *BCKDHB*, and *DBT* were amplified by polymerase chain reaction (PCR) with specific oligonucleotide primers. PCR products were sequenced using a fluorescence-based cycle sequencing protocol and extension products were subsequently size-fractionated on an ABI 3130 Genetic Analyzer (Applied Biosystems). To identify genetic variants, sample sequences were compared to sequences from GenBank (http://www.ncbi.nlm.nih.gov/genbank/). We interrogated exonic sequence from initiator codon to termination codon as well as splice donor, splice acceptor, and branch point sites, but did not screen for mutations in the promoter region, 3′ untranslated region, or introns (except as described above). Most pathogenic variations occur within coding regions or consensus splice and branch sites, and thus our approach can detect most but not all mutations. This method does not detect large genomic deletions or deletions involving oligonucleotide primer sequences.

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