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Heterozygote to homozygote related living donor liver transplantation in maple syrup urine disease: A case report

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Abstract: Liver transplantation is an accepted treatment modality in the management of MSUD. To our knowledge, ours is only the second successful case to date of a patient with MSUD receiving an allograft from an RLD who is a heterozygous carrier for the disease. In view of the worldwide shortage of available organs for transplantation, heterozygote to homozygote transplantation in the setting of MSUD may provide a viable alternative for those awaiting transplantation. We report on the case of a two-yr-old infant with MSUD, who received a left lateral segment (segments II and III) liver transplant from his mother, a heterozygote carrier of one of the three abnormal genes implicated in MSUD. Post-operative BCAA levels normalized in our patient and remained so on an unrestricted protein diet and during times of physiological stress. To date, this is only the second case of a successful RLD liver transplant in a child with MSUD. Preliminary results indicate that RLD liver transplants are at least equivalent to deceased donor liver transplants in the treatment of MSUD, although longer term follow-up is required. Heterozygote to homozygote RLD transplant in patients with MSUD presents a new pool of potential liver donors.

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Background

MSUD is an autosomal recessive condition caused by dysfunctional oxidative decarboxylation of BCKA (1). MSUD is a rare inborn error of metabolism with an incidence of <1 in 180 000 and may be found in all racial and ethnic groups throughout the world (2). In certain populations with high rates of consanguinity, the incidence of MSUD approaches one in 50 000 (3).

MSUD results in significant mental and physical morbidity and may result in death in the neonatal period (2). Morbidity and mortality from MSUD are the result of the affected individual's inability to catabolize the BCAA leucine, valine, and isoleucine (2,4). Leucine, valine, and isoleucine are essential amino acids that accumulate in the body due to abnormal functioning of the BCKDH (2), an enzyme complex present in all cells in the human body (2). Leucine and its transamination product 2-ketoisocaproate are believed to exert the strongest neurotoxic effects of the amino acids implicated in MSUD, resulting in acute and chronic brain dysfunction (4). Long-term intellectual outcome is indirectly related to the duration of ketoacidosis during periods of illness and long-term plasma BCAA levels (4, 5). The nucleotide alterations that impair BCKDH activity may occur in any of the catalytic components of the enzyme complex, but both alleles at a single locus must demonstrate nucleotide changes for MSUD to manifest clinically (3). The failure of this regulatory process results in excess levels of BCAA and their corresponding BCKAs in body tissues and plasma (6).

Abbreviations: BCAA, branched-chain amino acid; BCKA, branched-chain α-ketoacids; BCKDH, branched-chain α-ketoacid dehydrogenase complex; DLT, domino liver transplant; MSUD, maple syrup urine disease; RLD, related living donor.

Individuals affected by MSUD are protein intolerant and must have strictly regulated intake of leucine, valine, and isoleucine (2). During times of stress or unregulated protein intake, disturbances in plasma and tissue amino acid levels result in reduced glutamate, glutamine, and γ-aminobutyrate concentrations in the brains of patients with MSUD (6–8). The neurological sequelae of these disturbances are dependent on a number of interrelated factors, including frequency of amino acid monitoring, genetic background, quality of long-term metabolic control, prevention of disastrous brain injury, and frequency and duration of hyperleucinemia (6). In the severe classical form of MSUD, structural and functional disorders of the brain resulting from dysregulation of leucine, isoleucine, and valine metabolism may manifest in seizures, spasticity, encephalopathy, and uncal herniation. In milder forms of the disease, these abnormalities manifest more subtly with delayed presentation of impulsivity, hyperactivity, and attention deficits (8, 9). In adult patients, the social consequences of MSUD are significant and present in patients with poor professional and educational development, declining cognitive function, an inability to live independently, maintain relationships, and raise children (6, 9, 10).

Approximately 75% of all MSUD patients are affected by the classical form of the disease that appears in the neonatal period with poor feeding, lethargy, seizures, coma, and death (3, 11). This form of MSUD was first reported by Menke et al. in 1954 (12). The remainder of MSUD patients are affected by alternate forms of the disease with later onset, episodic nature, and/or the absence of cerebral symptoms (13). These patients are classified into intermediate, intermittent, thiamine responsive, and asymptomatic groups based on their clinical presentation and biochemical response to thiamine administration (2, 3). Intermediate MSUD manifests with advancing developmental delay and mental retardation in the absence of severe metabolic stressors. Intermittent MSUD patients have normal plasma BCAA levels and develop normally until stressors (such as infection or dehydration) precipitate metabolic decompensation and ketoacidosis. Thiamine responsive MSUD is clinically similar to intermediate and intermittent MSUD but responds to pharmacological doses of thiamine through normalization of plasma BCAA levels (11). Three molecular genotypes of MSUD are recognized based on the affected locus of the BCKDH complex: subtype Ia for mutations of the E1α (BCKDHA) gene, subtype Ib for mutations of the E1β (BCKDHB) gene, and subtype II for mutations of the E2 (DBT) gene (3, 4). Classical, intermediate, and intermittent MSUD may manifest from mutations in all subtypes of MSUD (2, 13).

The BCKDH is a mitochondrial multi-enzyme complex encoded by nuclear genes that program for four proteins that facilitate catalytic function and two other proteins that regulate BCKDH activity in the different body tissues (2). This regulatory function is essential to prevent the depletion of BCAA stores, as the BCKDH complex is present in all body tissues, most notably, skeletal and smooth muscle (54–60%), brain (9–20%), liver (9–13%), and kidney (9–13%) (6, 7). It is this high relative activity of the BCKDH complex in muscle that protects recipients without MSUD from accumulation of BCAA in domino grafts (6). Liver transplantation in patients with classical MSUD results in full or partial correction of the disease phenotype (5). Strauss et al. and Mazariegos et al. report that restoring 9–13% of the body's BCKDH complex activity by means of liver transplantation is adequate to control BCAA metabolism in the majority of patients due to the graft livers ability to adapt to changes in metabolic demand by changes in enzyme expression and phosphorylation (6, 8).

In spite of early diagnosis and adequate care, long-standing imbalances in plasma amino acid and ketoacid profiles in conjunction with periods of metabolic decompensation precipitated by physiological stressors are associated with significant cognitive, behavioral, and psychosocial consequences in patients with MSUD (8, 10, 13). Management of these periods of decompensation requires experienced physicians and highly specialized and costly medical services (6, 8). In addition to aggressive management of the precipitants of ketoacidosis, liver transplantation for MSUD affords sufficient control of BCAA levels to allow for protein unrestricted diets and neuroprotection during periods of illness (2, 9). Cure of MSUD through liver transplantation has been associated with improvements in brain function (9). According to Shellmer et al., those patients transplanted early in life may benefit most from the neuroprotective effects of liver transplantation (6, 10). In adults, even under ideal circumstances, existing conservative modalities for the treatment of MSUD do not appear to benefit brain nutrition and function as much as liver transplantation (6, 9). With a better understanding of the neurological effects of liver transplantation in patients with MSUD, these effects may become an indication for transplantation in teenagers and adults (9).

DLT is an emerging strategy to increase the total number of donor livers available (14). Apart from the production of abnormal proteins, the livers of patients with rare metabolic diseases such as MSUD are morphologically and functionally normal. Recipients of DLTs usually remain asymptomatic for the particular metabolic disease of the donor for many years of post-transplantation (14). In general, those patients receiving DLTs are those whose underlying pathology affords them a low priority on the waiting list for liver transplantation, and with a life expectancy shorter than the time required to develop symptoms of the domino donor's underlying metabolic disease (14, 15). DLT may also be utilized as a "tiding-over" option for neonates, allowing them to grow until they can receive a size compatible and normal liver (14). Regarding MSUD, Mazariegos et al. reported a series of five patients receiving DLT from patients with MSUD. In all cases, the recipients maintained close to normal plasma BCAA levels on an unrestricted protein diet due to extrahepatic oxidation of leucine (14, 15). These findings are supported by Feier et al. (16) in their experience with DLT in the context of MSUD. Thus, DLT with livers of patients with MSUD may offer a viable option and significant resource for well-selected patients awaiting liver transplantation who meet the criteria for DLT (14, 15). This said, further studies with larger number of patients and longer term follow-up are required to establish metabolic disorders such as MSUD as indications for DLT (14).

Case

We present the case of a two-yr and seven-month-old-male child (at time of transplant) diagnosed with MSUD as a neonate, who underwent RLD liver transplant. In this case, the RLD was his mother, a heterozygote for MSUD. Specific studies to demonstrate the mutation in mother and child were not performed prior to transplantation. To the best of our knowledge, this is the second successful described case of a homozygote individual with MSUD receiving the liver of a heterozygote RLD.

The patient presented at 11 days of life for routine neonatal checkup with a history of poor feeding and excessive sleepiness. On examination, he was found to be jaundiced, bradycardic, tachypneic, floppy, and dehydrated, with absent Moro and poor suck reflexes. On day 20 of life, the diagnosis of MSUD was confirmed on the basis of plasma amino acid levels. He was started on medical therapy to manage his MSUD. Pretransplant protein intake was restricted to 0.9–1.2 g/kg/day. Over the subsequent two yr, the child experienced repeated hospital admissions for the treatment of various ailments that aggravated his underlying metabolic dysfunction. During this time, he also experienced poor growth (below the third centile) and developmental delay, as documented by the family physician.

Table 1. Pretransplantation plasma isoleucine, leucine, and valine levels

Date	BCAA	Level (μmol/L)	Reference (μmol/L)	Ailment
10/12/2012	Isoleucine	417	(31–86) Elevated	Required admission for treatment of lower respiratory tract infection (LRTI), treated with intravenous antibiotics and discharged
	Leucine	1445	(47–155) Elevated	
	Valine	755	(64–294) Elevated	
12/02/2013	Isoleucine	119.98	(0–122) High Normal	Nil
	Leucine	218.84	(30–246) High Normal	
	Valine	188.46	(132–480) Normal	
16/09/2013	Isoleucine	132.16	(6–122) Elevated	Nil
	Leucine	241.66	(30–246) Normal	
	Valine	130.40	(132–480) Low normal	

Table 1 presents an example of the patient's plasma leucine, isoleucine, and valine levels prior to his liver transplantation. As evident, even during periods when he was well and free of illnesses that aggravate existing abnormalities in BCAA homeostasis, the patient experienced persistently high levels of at least one of the three BCAAs involved in MSUD.

Table 2. Post operative plasma levels of the BCAA involved in MSUD

Date	BCAA	Level (μmol/L)	Reference (μmol/L)	Ailment
20/11/2013	Isoleucine	103.58	(6–122) Normal	Within 1/52 post op
	Leucine	194.2	(30–246) Normal	
	Valine	232.38	(132–480) Normal	
20/02/2014	Isoleucine	122.00	(6–122) Normal	Admitted for treatment of rhinovirus pneumonia
	Leucine	203.48	(30–246) Normal	
	Valine	206.10	(132–480) Normal	

The child was found to be a suitable candidate for liver transplantation and listed accordingly. He underwent an RLD liver transplant on November 5, 2013. His immediate post-operative recovery was complicated by acute graft rejection that was successfully managed medically. Immediately post-transplantation, the patient's protein tolerance increased to 1.5 g/kg/day, and he is now on a protein unrestricted diet. He has been admitted to hospital on three occasions of post-transplantation, with the first instance being for acute graft rejection, the second for weight loss and a lower respiratory tract infection, and the third for a lower respiratory tract infection. Notably, plasma BCAA levels have remained normal even at times of metabolic stress post-transplantation. Further, the child has experienced some catch-up toward his normal milestones with some improvement in his speech, socialization, and gross motor skills, although he is still unable to walk, due to the possibility of a spastic diplegia present prior to liver transplantation (Table 2).

Conclusion

Early results from this case would suggest that liver allografts from RLDs are comparable to those from deceased donors in the treatment of MSUD. This said, longer term follow-up and a greater pool of patients are required before definitive conclusions can be drawn. The treatment of MSUD with RLD liver allografts opens avenues for further research into specific subtypes and genetic mutations in MSUD, and which may be best treated with RLD liver grafts. In conjunction with DLT when utilizing a deceased donor organ for the MSUD transplant, when feasible, RLD liver transplants may offer a valuable and necessary potential new source of donor livers in these patients.

Authors' contributions

N. Patel, J. Loveland, M. Zuckerman, P. Moshesh, R. Britz and J. Botha: Participated in concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics, and data collection.

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