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Case Report

Two consecutive partial liver transplants in a patient with Classic Maple Syrup Urine Disease☆,☆☆

H.L. Chin [a,*], M.M. Aw [a,b], S.H. Quak [a,b], J. Huang [a], C.E. Hart [c], K. Prabhakaran [d,e,f], D.L. Goh [a,b]

[a] Department of Paediatrics, National University Hospital, National University Health Systems, Singapore
[b] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[c] Biochemical Genetics and National Expanded Newborn Screening, Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore
[d] Department of Paediatric Surgery, National University Hospital, National University Health Systems, Singapore
[e] Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[f] Paediatric Solid Organ Transplantation, National University Hospital, National University Health Systems, Singapore

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ABSTRACT

Maple syrup urine disease is caused by a deficiency in the branched chain ketoacid dehydrogenase (BCKAD) complex. This results in the accumulation of branched chain amino acids (BCAA) and branched chain ketoacids in the body. Even when aggressively treated with dietary restriction of BCAA, patients experience long term cognitive, neurological and psychosocial problems. Liver transplantation from deceased donors has been shown to be an effective modality in introducing adequate BCKAD activity, attaining a metabolic cure for patients. Here, we report the clinical course of the first known patient with classic MSUD who received two consecutive partial liver grafts from two different living non-carrier donors and his five year outcome posttransplant. We also show that despite the failure of the first liver graft, and initial acute cellular rejection of the second liver graft in our patient, his metabolic control remained good without metabolic decompensation.

1. Introduction

Classic Maple Syrup Urine Disease (MSUD) is caused by a deficiency in the branched chain ketoacid dehydrogenase (BCKAD) complex. This results in the accumulation of branched chain amino acids and branched chain ketoacids in the body. The main stay of treatment of MSUD consists of restriction of branched chain amino acids and aggressive management of metabolic decompensations. If MSUD is untreated, the metabolic derangements result in neurological deficits and/or death. Even when treated, there often are long term cognitive, neurological and psychosocial sequelae in MSUD patients [1,2].

Whole liver transplantation from a deceased donor has been shown to be effective in introducing adequate BCKAD complex activity, resulting in metabolic cure for this condition [3]. In all but one of these transplanted patients, the metabolic control posttransplant was good despite complications. There is less experience with partial liver grafts from living donors. The first reported case was unsuccessful; the patient died from vascular complications [3]. The second reported case of partial liver graft involved a living donor (the mother) who was presumed to be an MSUD carrier [4]. Here, we report the clinical course of the first known patient with classic MSUD who received two consecutive partial liver grafts from two different living donors. We also show that despite the failure of the first transplanted liver graft, and initial acute cellular rejection of the second liver graft in our patient, his metabolic control remained good without metabolic decompensation.

2. Patient and methods

The patient was the second child of a consanguineous union. His parents were first cousins. He was presented within the first week of life with fluctuating consciousness, hypertonia and myoclonic jerks. He was transferred to our hospital in the second week of life. Metabolic workup done then was consistent with Classical MSUD. His plasma amino acid profile at day 15 of life showed elevated valine 271 μmol/L, isoleucine 234 μmol/L, leucine 2484 μmol/L, and alloisoleucine 186 μmol/L. His urine organic acid profile showed elevated excretions of 2-hydroxyisovaleric acid, 2-hydroxy caproic acid, 2-hydroxy isocaproic acid and the corresponding 2-keto acids. Subsequent genetic testing revealed that he was homozygous for a pathological mutation (c.1310_1311delAC, p.His437Leufs) in

Abbreviations: BCKAD, branched chain ketoacid dehydrogenase; MSUD, maple syrup urine disease.

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* Corresponding author at: Department of Paediatrics, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore.
E-mail address: hui-lin_chin@nuhs.edu.sg (H.L. Chin).

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the BCKDHA gene, and his parents were found to be heterozygous for this mutation. This mutation is predicted to result in a frameshift leading to a non-functional protein. No enzyme activity was done. The enzyme activity is predicted to be zero and his clinical picture is consistent with a child with severe deficiency.

He was encephalopathic and comatose for 1 week at presentation. He required a double volume exchange transfusion on the second day of admission and intubation for 7 days. He was not thiamine responsive. He was managed with a BCAA restricted diet. The target was to achieve leucine level of 200–400 μmol/L, adequate caloric intake and adequate total protein intake. His dietary prescription was as follows: isoleucine 52–90 mg/kg/day, valine 44–68 mg/kg/day, and leucine 68–90 mg/kg/day with total protein intake of 2.5–3 g/kg/day. His leucine levels in the first two years of life hovered between 40 and 200 μmol/L when he was well, and between 500 and 900 μmol/L when he had metabolic decompensations. He had frequent metabolic decompensations despite compliance to dietary restriction with 7 requiring hospital admissions in 3 years. These decompensations were usually triggered by mild viral illnesses, and were treated by managing the triggers, providing sufficient calories, adjusting protein and leucine intake as well as preventing cerebral edema.

He had comorbidities of myoclonic jerks, gastroesophageal reflux disease, hyperactive airway disease and global developmental delay. These were managed medically. He was prescribed oral phenobarbitone for his myoclonic jerks with improvement and this was stopped at 18 months of age. His gastroesophageal reflux was treated by giving him frequent small feeds, positioning, and the use of anti-acids and a prokinetic agent. He required inhaled bronchodilators when he was wheezing.

His global developmental delay was evident within the first year of life. He was delayed in achieving his milestones, and he had evidence of mild spastic diplegia. These were likely secondary to the initial leucine encephalopathy.

At the age of 2 years 4 months, his developmental level was assessed to be approximately 20 months (using the Bayley Scales of Infant and Toddler Development, Third edition) with a composite score of 75 (95% CI 74–90) on the cognitive scale. This meant that his general developmental ability as reflected on the Cognitive scale was in the "borderline" range. Based on parental report, the result of the Vineland Adaptive Behavior Scale (2nd edition) showed that his overall adaptive functioning was at a "low" level compared to his age, and at the 2nd percentile of the population at his age level. He participated in the Early Intervention Program which consists of physiotherapy, speech therapy and occupational therapy two to three times per week to optimize his learning and development. With this, at the age of 3 years 1 month, after approximately 9 months of participation in this program, a repeat assessment showed that his cognitive developmental level was in the "average" range compared to similarly aged peers, with an equivalent developmental age of 32 months. His composite score improved to 95 (95% CI 87–109). His overall adaptive functioning based on the Vineland Adaptive Behavior Scale (2nd edition) was classified as "moderately low" and at the 16th percentile of the population at his age.

Despite great vigilance and very good compliance to the metabolic treatment plan, the patient had frequent metabolic decompensations. Liver transplantation was considered as a curative option for his condition. This was with the hope of preventing further cognitive decline in him as well. The patient was placed on the deceased donor list, whilst the search for a suitable living donor commenced.

In 2009, in Singapore, even though many of the pediatric patients were placed on the deceased liver transplant waiting list, grafts from deceased donors were not frequently available to them. Of 74 liver transplants done between 1991 and 2009, 25 (31.6%) were from deceased donors, but only 3 of these went to pediatric patients. This was because adults were by default prioritized over children (size-matched grafts), we did not have an active split-liver program, and there were relatively few pediatric-age deceased donors. The majority of the pediatric liver transplant recipients received liver grafts from living-related donors.

The patient was on the deceased liver donor wait list for several months without being successful in receiving a liver allograft. As such, he underwent a living donor liver transplant in the first half of 2009, at the age of 3 years 4 months. He did not undergo an auxiliary transplant. His first cousin (a blood relative in his early 20s who was tested and found not to be a carrier of the family's deletion) was the donor. The patient received a left lateral liver graft (340.6 g, graft recipient ratio of 1.7:1) with a single hepatic artery, bile duct, hepatic vein and a sizeable portal vein. The warm ischemic time was 47 min and anhepatic phase was 1 h 37 min. This surgery was complicated by hepatic artery thrombosis at the site of the anastomosis, extending proximally to the native artery. This was discovered via on-table ultrasound Doppler. For this, he underwent a thrombectomy with re-do of the anastomosis.

During the pre- and intra-operative phase, his metabolic control was good. Leucine levels were 96–284 μmol/L (See Fig. 1). Immediately postperfusion of the new liver, his metabolic control improved. By day 3, he had normal branched chain amino acid (BCAA) levels. During the post-operative period, he had an upper gastrointestinal bleed and a biloma that required drainage. Despite these events which were considered to be metabolic stressors, his leucine levels remained within the normal range. He was discharged on postoperative day 33.

Not unexpectedly, he developed biliary strictures, a known consequence of hepatic artery thrombosis. Over the following 3 months after the transplant, he had 3 episodes of bacterial cholangitis, each requiring prolonged antibiotic treatment. He subsequently became icteric (conjugated bilirubin rose to the 400 s μmol/L), with mildly elevated liver transaminases. He developed evidence of liver synthetic dysfunction, (lowest serum albumin of 24 g/L) and coagulopathy (Prothrombin time 46.5 s, Activated partial thromboplastin time 51.2 s). Even in the face of these events, he did not revert back to being an MSUD patient. He continued to have normal BCAA levels and undetectable alloisoleucine levels while on an unrestricted diet (estimated protein intake was 2 g/kg/day).

As a result of his frequent episodes of cholangitis and deteriorating graft function, it was decided that the patient required a re-transplant. He underwent a second living donor liver transplant in late 2009, 6 months after his first transplant. His donor was his maternal aunt, who was tested and found not to be a carrier of the family's pathological mutation. The patient received a liver graft consisting of the left lateral segment with a sliver of segment 4. The warm ischemic time was 51 min, and cold ischemic time was 3 h and 3 min, with an anhepatic phase of 4 h 12 min. A bile duct was anastomosed to a roux loop with a size 6 feeding tube spanning the biliary enteric anastomosis with externalization to the anterior abdominal wall via the roux loop. The previous roux en y anastomosis was refashioned to a hepaticojejunostomy. He had an intra-operative complication of stomach perforation along the greater curve, requiring direct closure.

Acute cellular rejection (confirmed on histology) occurred on post-operative day 7 while on adequate tacrolimus immunosuppression (tacrolimus trough levels were maintained around 10 ng/mL). The patient responded to 3 doses of intravenous pulsed methylprednisolone (10 mg/kg/dose), and a tapering dose of oral prednisolone. He also experienced wound dehiscence and underwent repair on postoperative day 9. Throughout these events, his BCAA levels remained within the normal range. His alloisoleucine levels reappeared immediately posttransplant with the highest levels of 231 μmol/L on postoperative day 1, but was subsequently undetectable from postoperative day 6 onwards (Fig. 1). He was kept fasted for two weeks after the surgery in view of the stomach perforation, and was on total parenteral nutrition. The protein component of his total parenteral nutrition was initially BCAA restricted, but by postoperative day 10, he had transitioned to a full normal protein diet. He demonstrated good catch-up growth in his post-transplant course with regard to his height (Fig. 2).

One year posttransplant, at age 5 years and 3 months, he underwent a repeat IQ assessment. Based on the Wechsler Preschool and Primary Scale of Intelligence — Third edition (WPPSI-III), his overall cognitive

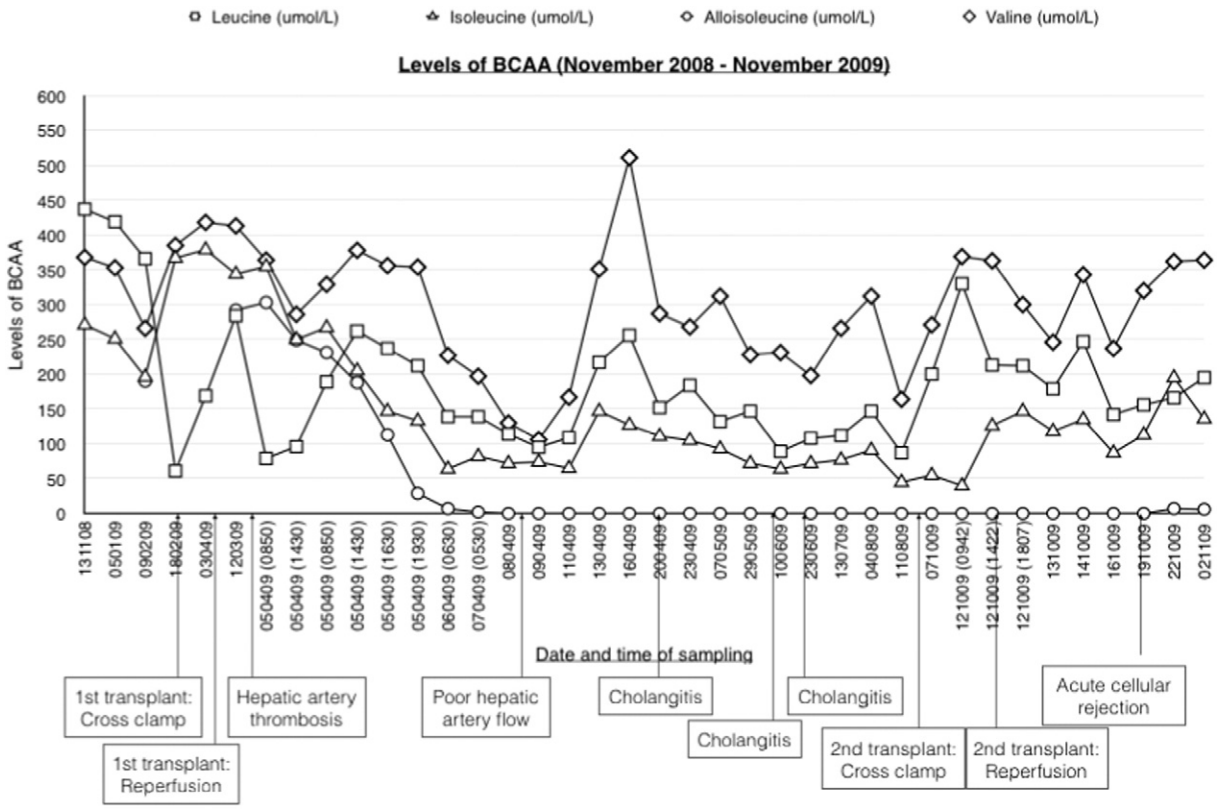

Fig. 1. BCAA and alloisoleucine levels in the peri-operative period of both liver transplants in 2009.

ability was in the low average range (FSIQ 80), his verbal abilities were in the borderline range (Verbal Intelligence Quotient 77) and general performance abilities in the low average range (Performance Intelligence Quotient 82). At the time of this report, he was 5 years postliver transplant. He had remains metabolically stable with no incidences of decompensation despite inter current illnesses. He has normal graft function and his immunosuppression consists of tacrolimus monotherapy. He is attending mainstream education. He has some difficulty in academics especially in Mathematics and English. There is some impairment in executive functioning but no problems with social functioning.

3. Discussion

This is the first report of a Classic MSUD patient who had received two consecutive partial liver grafts from two different living donors.

MSUD is a chronic metabolic illness that was traditionally treated by manipulating the diet. Metabolic control becomes more difficult with increasing age because leucine tolerance decreases with age [5]. In addition, classic MSUD patients are predisposed to have frequent metabolic decompensation. Even with adequate treatment, the long term outlook for classic MSUD is guarded, with potential for neurological and psychosocial burdens [1,2].

Whole liver transplantation has been shown to attain metabolic cure for patients with MSUD [3]. The donors tend to be non-relative deceased donors who are assumed to be non-MSUD carriers. The patient survival ranged from 87.5% to 98%. The graft survival ranged from 75% to 96%. The transplants are shown to arrest the brain damage but did not reverse it. Transient elevation in leucine occurred in 1 patient during an episode of gastroenteritis with severe dehydration [3].

There is much less experience with partial liver grafts from living donors. The first reported case was unsuccessful; the patient died from vascular complications [3]. There is no information available on the carrier status of the donor. The second reported case involved a living donor (the mother) who was presumed to be an MSUD carrier [4]. The recipient had acute cellular rejection and cytomegalovirus infection but did not have any metabolic decompensation.

The choice of the living donor in this case took into consideration several factors. The first factor was the distribution of the BCKAD complex activity. Most of the body's BCKAD complex activity lies within the muscle; only 9–13% of the body's BCKAD complex is in the liver [6]. Previous reports showed that a whole liver graft could replace sufficient BCKAD activity and could ameliorate MSUD [7]. What we did not know, in 2009, was whether a partial graft from a living MSUD-carrier donor (i.e. a carrier will only have half the enzyme activity compared to a non-carrier) would provide sufficient enzyme activity to ameliorate MSUD. In addition, in the event of a graft dysfunction, it was uncertain if the partial MSUD-carrier graft would ameliorate the MSUD. Hence, the decision was made to use a non-carrier donor if a living donor was to be considered. Several family members were screened and several potential non-carrier donors were identified, including his first cousin and maternal aunt who were donors.

Our patient's experience suggested that partial grafts from living non-MSUD-carrier donors were adequate to achieve and maintain good long-term metabolic control while on an unrestricted leucine rotein intake even in the face of sepsis, biliary complications, graft dysfunction and acute cellular rejection. Five years posttransplant, our patient continued to remain metabolically stable, effectively achieving metabolic cure. The transplant in our patient did not reverse previous cognitive and neurological deficits that were present prior to the transplant. This is also consistent with what is reported for whole liver transplants [7].

There have been no reported auxiliary transplants done for MSUD. Neither has human heterologous liver cell infusion been reported to be successful in MSUD patients. Domino liver transplants, where MSUD patients donated their explanted livers to consenting recipients without MSUD have been carried out. The recipients have normal liver function and normal BCAA homeostasis while on unrestricted protein intake. A domino liver transplant was not carried out in our patient.

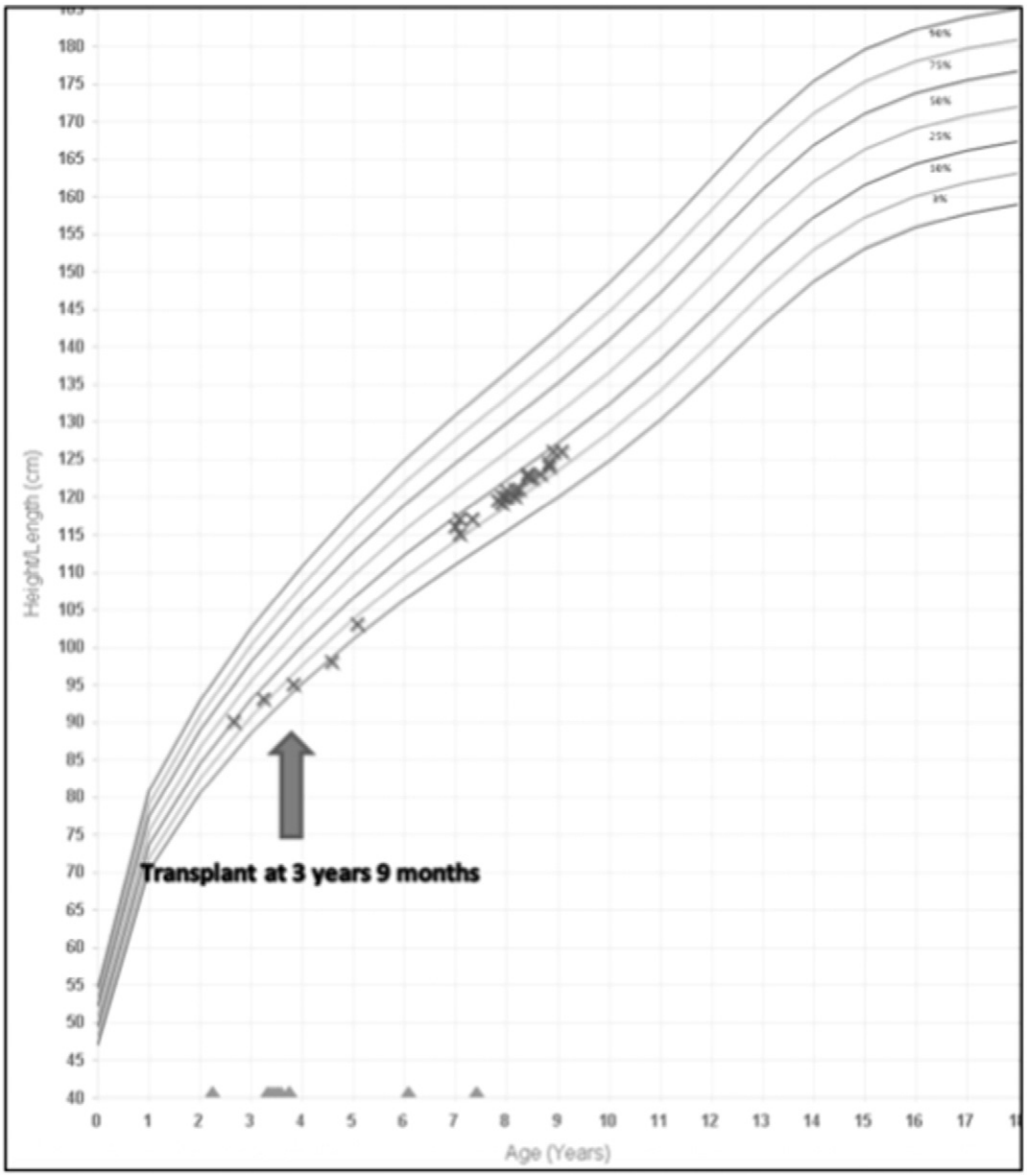

Fig. 2. Pre- and posttransplant growth centiles.

In conclusion, partial liver grafts from living non-MSUD-carrier donors appear to have sufficient enzyme activity to ameliorate MSUD even in the face of biliary complications, infections, graft dysfunction and acute cellular rejection.

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