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Management of methylmalonic acidaemia by combined liver–kidney transplantation

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Summary: Methylmalonic acidaemia (MMA) is a rare autosomal recessive inborn error of metabolism that typically presents in infancy with recurrent episodes of metabolic acidosis, developmental delay and failure to thrive. The disease course is complicated by the development of chronic tubulointerstitial nephritis progressing to end-stage renal disease in adolescence. We describe two adolescents with cobalamin-nonresponsive MMA (mut^0) who developed polyuria, chronic tubulointerstitial nephritis, dystonia but normal synthetic liver function. Both patients received combined liver--kidney transplantation (CLKT), preceded by a single pretransplant haemodialysis for clearance of methylmalonic acid. Post CLKT there was 95--97% reduction in serum and urine methylmalonic acid, leading to significant liberalization of dietary protein intake and a consequent increase in body mass index, muscle strength and energy. In addition, renal function normalized and clinical neurological status stabilized. We propose that CLKT be considered as a therapeutic option early in the course of cobalamin-nonresponsive MMA. Progressive tubulointerstitial nephritis with disabling polyuria is a confounder in patient management even in the absence of end-stage renal disease. Successful CLKT restores methylmalonyl-CoA mutase enzyme levels in the liver and kidney, improves clearance of methylmalonic acid with resultant dietary protein liberalization, and offers excellent graft and patient outcomes with improvement in quality of life.

Methylmalonic acidaemia (MMA) (McKusick 251000) is an autosomal recessive inborn error of methylmalonate metabolism presenting with recurrent vomiting, lethargy, dehydration, failure to thrive, hypotonia, and metabolic ketoacidosis (Fenton and Rosenberg 2001). This is a rare disorder, estimated to affect 1:20 000 births (Illinois Department of Public Health 2004), caused by a complete (mut^0)

or partial (mut^-) deficiency of the enzyme methylmalonyl-CoA mutase (EC 5.4.99.2) or by defects in cobalamin metabolism (cb1A, cb1B). About 0–8% of mut^0, 0–10% of mut^- patients, 90% of cblA and 40% of cblB patients respond to cobalamin supplementation. Children with early-onset, cobalamin-nonresponsive MMA typically develop renal tubular dysfunction that often progresses to end-stage renal disease by early adolescence (Fenton and Rosenberg 2001). Therapeutic options include conservative management with dietary protein restriction, fluid and carnitine supplementation and antibiotics to eradicate gut flora, haemodialysis for clearance of methylmalonic acid and propionate (Leonard et al 2001), and organ transplantation. Only liver transplantation reduces generation of methylmalonic acid (Chakrapani et al 2001; Nyhan et al 2002), only kidney transplantation improves clearance of methylmalonic acid and may reduce its generation (Lubrano et al 2001; Van Calcar et al 1998), and combined liver–kidney transplantation (CLKT) reduces accumulation of methylmalonic acid by both reducing production and improving clearance (Van't Hoff et al 1998, 1999). In order to increase our understanding of CLKT as an early therapeutic option and the associated benefits and risks, we report two cases of cobalamin-nonresponsive MMA (mut^0) with chronic tubulointerstitial nephritis treated successfully with CLKT.

PATIENTS

Case 1: A male baby was born to a 31-year-old healthy primigravida following an uncomplicated pregnancy and delivery with a birth weight of 3.32 kg (75th centile). Over the first week of life, he developed significant jaundice, poor feeding, vomiting and lethargy and had a single seizure. Laboratory evaluations showed hyperbilirubinaemia, hyperammonaemia, severe metabolic acidosis but normal renal function, and he was placed on peritoneal dialysis for a few weeks for clearance of hyperammonaemia. He did not respond to a trial of intravenous vitamin B_{12}. At 3 weeks of age MMA (mut^0) was diagnosed by acylcarnitine differentiation in fibroblasts obtained from skin biopsy. He was started on a protein-restricted diet with restriction of branched-chain amino acids through a specially computed formula with essential amino acids, delivered by gastrostomy feedings, and intravenous carnitine supplementation. At age 6 years he had a serious episode of metabolic decompensation associated with a viral infection and magnetic resonance imaging (MRI) at this time showed lesions of the basal ganglia and periventricular white matter. He developed progressive neurological decompensation, with a shuffling gait, dystonia of his extremities, and mild difficulties with writing (impaired fine motor control) and spatial organization. At age 10 years he developed polyuria (>4 L urine per day), renal insufficiency (serum urea nitrogen 7.85 mmol/L (22 mg/dl); serum creatinine 123.76 μmol/L (2.3 mg/dl); calculated glomerular filtration rate (GFR) 38 ml/min per 1.73 m^2 (Schwartz et al 1976)) and requirement for magnesium, phosphate, bicarbonate, salt and fluid replacement. Interstitial nephritis was diagnosed on renal biopsy. On a 0.9 g/kg per day protein-restricted diet, his weight was at the 10th centile (down from 75th centile at birth) and his height was at

the 25th centile for age. He was unable to attend school regularly. He was referred to our institution for further management. Methylmalonic acid in serum was 2196 μmol/L (reference range 0.16–0.64) and in urine was 2195 mmol/mol creatinine (reference range 0–3.6). He underwent bilateral native nephrectomies for his polyuria and CLKT with anti-thymocyte globulin induction; maintenance immunosuppressive therapy consisted of low-dose prednisone (0.13 mg/kg per day) and tacrolimus (target range 5–7 ng/ml at 6 weeks post transplant). Post-transplantation complications at one month included mild reversible acute rejection of the liver and CMV gastritis, both treated successfully. His post-transplantation methylmalonic acid concentrations in serum fell dramatically to less than 100 μmol/L *L and in urine to less than 600 mmol/mol creatinine by 6 weeks post transplantation (Figure 1A), and his serum creatinine stabilized at 70.72 μmol/L (0.8 mg/dl), with a calculated GFR of 94.39 ml/min per 1.73 m^2 (Schwartz et al 1976). His body weight and height increased to the 50th centile by 4 months post transplantation. Based on his serum methylmalonic acid concentrations remaining stable at 300 μmol/L, his diet was gradually liberalized to normal protein intake of 1.5 mg/kg per day by 2 years post transplantation. He felt more energetic and began to attend school regularly. At current follow-up, 5 years post transplantation, his serum methylmalonic acid continues to remain stable at regular dietary protein intake (Figure 1A), his liver function and renal function are normal, and his neurological status is stable without progression of dystonia.*

Case 2: Following an uncomplicated pregnancy, a male baby was born at full term by normal vaginal delivery with a birth weight of 2.93 kg (10th centile). A week after birth he presented with persistent vomiting. Subsequent tests showed high methylmalonic acid concentrations in urine and MMA (mut^0) on skin biopsy. He did not respond to intravenous cobalamin therapy. He was placed on a low-protein diet with branched-chain amino acid restriction. At age 3 years, following a metabolic decompensation after a viral infection, he had regression of motor skills and needed special education classes. He was lost to follow-up after age 12 years and discontinued his dietary restrictions. At age 17 years, he presented with severe malnutrition (height and weight below the 5th centile for age), pancreatitis, two seizure episodes, deterioration of neurological status with dystonia, collapsing thoracolumbar kyphosis and muscular weakness, resulting in his being wheelchair-bound. MRI showed low-density areas in globus pallidus of basal ganglia and an old parietal haemorrhage. He had hypoalbuminaemia (serum albumin 18 g/L (1.8 mg/dl)), bone marrow suppression (haemoglobin 6.5 g/dl; leukopenia (3.7×10^3/μl); and thrombocytopenia (133×10^3/μl)) and high-output renal failure (serum creatinine 309.4 μmol/L (3.5 mg/dl), GFR 17 ml/min per 1.73 m^2 (Schwartz et al 1976)), hyperkalaemia and hypercalcaemia. He was placed on peritoneal dialysis for hyperkalaemia and referred to our institution. His methylmalonic acid in serum was 5554 μmol/L and in urine was 10 370 mmol/mol creatinine, nearly 10^6 time greater than normal levels in blood. A 4-litre right-sided pleural effusion was tapped and revealed to be dialysis fluid. Peritoneal dialysis was stopped and the patient was aggressively hydrated. Gradual return of renal function was observed, suggesting that much of

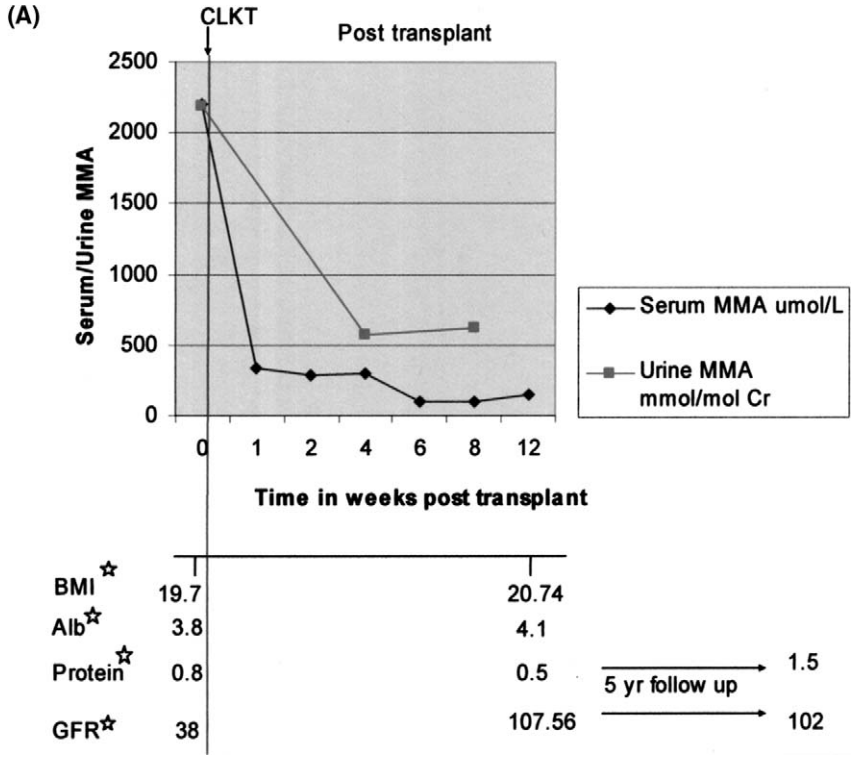

Figure 1 Serum and urine methylmalonic acid (MMA), nutrition status and renal function before and after combined liver–kidney transplantation (CLKT) in case 1 (A) and case 2 (B). BMI, body mass index (kg/m^2); Alb, serum albumin (mg/dl); Protein, protein intake (mg/kg per day); GFR, glomerular filtration rate (ml/min per 1.73 m^2)

his renal failure was prerenal from chronic dehydration. Aggressive nutritional support was instituted, with restricted dietary protein (0.5 mg/kg per day), increased delivery of essential amino acids by G-tube and intravenous carnitine. Over 4 months, his weight improved to the 10th centile (weight increase from 33 kg to 48 kg), his muscular strength improved to allow ambulation with a wheelchair, his serum albumin normalized, and his renal function improved with resolution of chronic dehydration (serum creatinine recovered from 309.4 μmol/L (3.5 mg/dl) to 70.72 μmol/L (0.8 mg/dl)). Over the following 2 years, renal insufficiency gradually progressed (serum creatinine 176.8 μmol/L (2 mg/dl), GFR 42.49 ml/min per 1.73 m^2 (Schwartz et al 1976)), and fluid intake and delivery became difficult, as his polyuria worsened to over 6 L/day. At 21 years of age, he underwent bilateral native nephrectomies and CLKT, preceded by a single preoperative haemodialysis session for 4 h for clearance of methylmalonic acid. He was maintained on an immunosuppression regimen of low-dose tacrolimus (target levels 5–7 ng/ml), sirolimus (target levels 5–8 ng/ml) and prednisone (0.05 mg/kg per day). Given

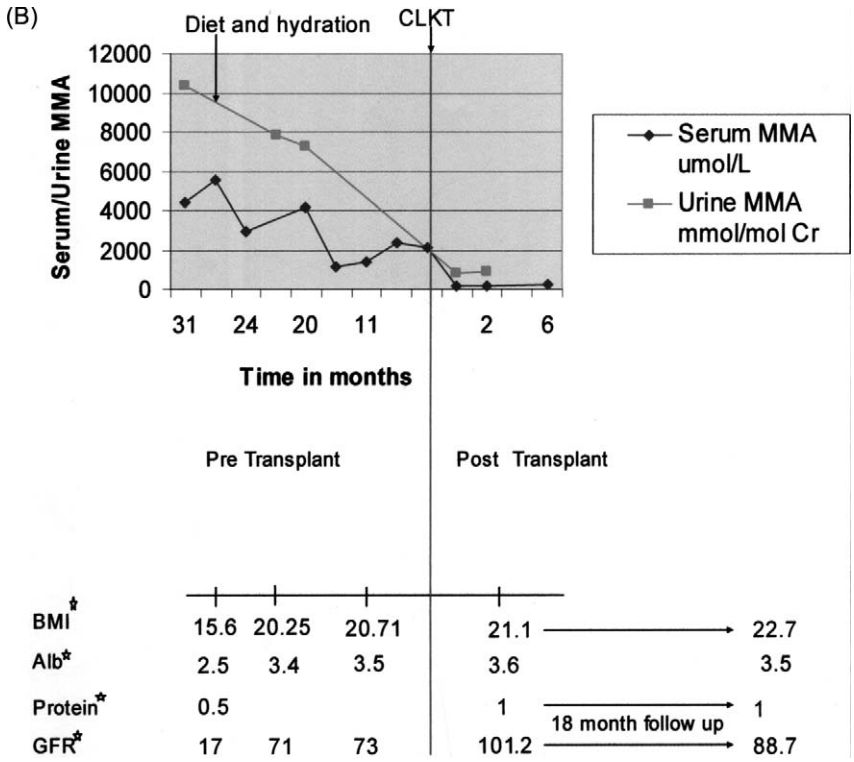

Figure 1 (Continued)

his baseline neurological dysfunction, he was sensitive to tacrolimus, developing mental status changes and tremors, which resolved with reduction of the dose of tacrolimus.

After transplantation, his serum methylmalonic acid decreased dramatically to below 200 μmol/L and urine methylmalonic acid to below 900 mmol/mol creatinine by one month (Figure 1B); his bone marrow indices, liver and renal functions normalized (serum creatinine 79.56 μmol/L (0.9 mg/dl); GFR 101.2 ml/min per 1.73 m^2 (Schwartz et al 1976)); and he gained 6 kg in weight within 3 months post transplantation. He developed mild glucose intolerance at 3 months post transplantation (fasting blood glucose 180–250 mg/dl) and he is currently maintained on low-dose insulin. His diet was liberalized to allow 1.5 g/kg per day of protein by 6 months post transplantation, with stabilization of his serum methylmalonic acid at less than 300 μmol/L. His energy levels, muscle tone and strength improved further and he ambulated increasingly with his walker. At follow-up 18 months post transplantation, he continues to have good renal and liver function, stable serum methylmalonic acid concentrations and no further deterioration of dystonia.

DISCUSSION

Management of cobalamin-nonresponsive MMA includes highly protein-restricted diet (0.5–1 g/kg per day protein), with attention to restriction of branched-chain amino acids threonine, methionine, isoleucine and valine, which are metabolized to propionate and methylmalonic acid. Provision of sufficient protein and energy is necessary to ensure natural growth in children afflicted by this disorder and these are provided by synthetic formulas devoid of the offending amino acids. In addition, carnitine and metronidazole or other antibiotics are given to decrease propionate production by gut flora (Leonard et al 2001). Despite conservative management, patients develop recurrent metabolic crises and are at risk for long-term neurological complications including developmental delay, hypotonia, basal ganglia lesions, brain infarcts and renal complications such as decreased GFR, tubular concentrating defects, chronic tubulointerstitial nephritis, azotaemia and renal tubular acidosis (Rutledge et al 1993). Synthetic liver function remains normal, although hyperammonaemia is exacerbated during the metabolic crises. The patients in this case report presented with all the mentioned symptoms including renal dysfunction. High serum concentrations of methylmalonate appear to be important in the pathogenesis of chronic renal disease as chronic administration of methylmalonate in rats has been shown to be nephrotoxic, particularly to renal tubular epithelial cells (Kashtan et al 1998). Haemodialysis is used in the management of MMA patients in end-stage renal failure waiting for organ transplantation. Chronic haemodialysis treatment is a cumbersome option for the patient and results in only periodic clearance of methylmalonic acid from the body. Haemodialysis is desirable a few hours prior to transplantation surgery to reduce serum methylmalonic acid concentrations and avoid immediate toxicity to the transplanted kidney.

Significant correction of the metabolic defect can be achieved with organ transplantation. There are reports of a 77% reduction in urine methylmalonic acid and elimination of metabolic decompensation with liver transplantation alone. However, liver transplantation alone does not prevent the progressive renal and neurological deterioration post transplantation, even when intervention by this method occurs very early in life (Chakrapani et al 2002; Nyhan et al 2002). Methylmalonic acid concentrations in cerebrospinal fluid continue to remain high following transplantation and could cause an abrupt metabolic stroke (Kaplan et al 1999). Of adolescents with cobalamin-nonresponsive MMA, 20–60% develop chronic renal failure, and these patients have been treated with only kidney transplantation. Kidney transplantation alone has been reported to reduce urine methylmalonic acid concentrations by 97%, with good renal and metabolic function at 3–4 years follow-up (Lubrano et al 2001; Van Calcar et al 1998).

CLKT is an option for inherited metabolic diseases. Significant improvement in quality of life has been documented with CLKT for metabolic diseases (Kayler et al 2002). Davis and colleagues (2002) analysed the United Network of Organ Sharing (UNOS) data (United Network for Organ Sharing 2000) and reported a 5-year patient survival of 76% for CLKT performed for metabolic diseases and a low acute renal rejection rate of 10% compared to 30–50% rejection rate for cadaveric kidney trans-

plantation alone. Complications encountered with CLKT include toxicity related to the drugs used, such as calcineurin inhibitor renal toxicity, diabetes (Van Calcar et al 1998), sepsis, CMV/EBV infections, surgical complications such as bleeding (Kayler et al 2002), late renal allograft loss due to immunological and nonimmunological processes (Davis et al 2002) and hepatic artery thrombosis (Kayler et al 2002; Margreiter et al 2002). Successful CLKT has been reported previously in two patients with MMA (Van't Hoff et al 1998, 1999). Van't Hoff and colleagues (1998) reported the successful treatment of a MMA (mut^0) patient in end-stage renal failure with preoperative haemodialysis for 6 months followed by CLKT. In comparison, our patients had sufficient renal reserve to be dialysis-independent at the time of transplantation, yet their quality of life was poor owing to the requirement of obligate fluid intake, and metabolic decompensation when unable to meet this requirement. CLKT is an effective management option early in the course of renal injury in patients with high serum methylmalonic acid and disabling polyuria, as it serves to restore normal renal function and increases the transplanted tissue load containing the normal enzyme. Prevention of delayed graft function is important to avoid post-operative haemodialysis, which is a confounder in immunosuppression management. CLKT in our patients resulted in an improvement in overall metabolic control and a 95–97% reduction in serum methylmalonic acid (Figure 1A and B).

Post-operative management of CLKT for MMA includes continued attention to diet and hydration. Oral hydration is encouraged to improve perfusion of the transplanted kidney. Dietary protein restriction can be considerably liberalized post CLKT. We titrated the dietary protein liberalization by the resultant increase in serum and urine methylmalonic acid, our target being to keep serum methylmalonic acid below 300 μmol/L. Serum and urine methylmalonic acid concentrations are followed up as indicators of metabolic disease control and have remained stable at current follow-up in both of our patients, despite liberalization to normal dietary protein intake (1.5 mg/kg per day) post transplantation. A combination of improved clearance of methylmalonic acid by the transplanted kidney and decreased generation due to a new source of enzyme from both kidney and liver may have contributed to this. With attention to nutrition, serum albumin and body mass indices normalize (case 1 had a BMI increase of 1.1 and case 2 had a more dramatic increase of 5.5). Immunosuppressant dosing can be minimized, owing to the immunological privilege conferred by the concomitant liver transplantation and the relatively lower risk of rejection in CLKT (Kayler et al 2002). Significant improvement in quality of life is achieved. Our patients relish eating regular foods that had been restricted prior to transplantation, enjoy increased muscle strength, greater mobility and the ability to attend school, and are able to better interact socially with their peer group.

In our experience, CLKT is a relatively safe and highly effective treatment for MMA. We recommend that CLKT be considered as a therapeutic option when significant interstitial nephritis and polyuria confound patient management, without using end-stage renal disease as a sole criterion for the transplantation.

In summary, CLKT offers improved outcomes for patients with severe MMA and renal disease. The combined transplantation corrects the renal impairment and prevents damage to the newly transplanted kidney by reducing generation of methylmalonic acid. The patient gains dietary protein liberalization from severely restricted to normal, improved growth, muscular strength and wellbeing, and freedom from metabolic and renal crises. Further follow-up is required to study the long-term outcomes of CLKT and its effect on neurological disability and quality of life in patients with severe MMA disease.

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