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ORIGINAL ARTICLE

Renal transplantation in a boy with methylmalonic acidaemia

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Abstract We present the first reported case of B_{12} non-responsive methylmalonic acidaemia due to *MMAB* mutation to undergo an isolated renal transplant for renal failure. At 8 years of age he was listed for a combined liver and kidney transplant following progressive renal impairment. His metabolic control deteriorated with declining renal function and he was commenced on haemodialysis, leading to marked symptomatic and biochemical improvement. He was therefore relisted for isolated cadaveric renal transplant instead. He underwent successful renal transplantation at 12 years of age and now 6 years post transplant he is enjoying a more normal lifestyle with a marked reduction in plasma methylmalonate.

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Introduction

Methylmalonic acidaemias (MMA) comprise a heterogenous group of inborn errors of organic acid metabolism that are inherited in an autosomal recessive manner. Successful metabolism of branched chain amino acids is dependent upon activity of several mitochondrial enzymes; methylmalonyl-CoA racemase, methylmalonyl-CoA mutase and the methylmalonyl-CoA mutase cofactor 5'-deoxyadenosylcobalamin. Many different genetic defects are known to cause isolated MMA: Methylmalonyl-CoA mutase deficiency (defect of the *MUT* gene), Methylmalonyl-CoA racemase deficiency (*MCEE*), and several defects of cobalamin metabolism cblA (*MMAA*), cblB (*MMAB*) and cblD (*MMADHC*). Enzyme deficiency leads to the accumulation of methylmalonic acid in the plasma, urine and other bodily fluids (Ogier de Baulny and Saudubray 2002, Fowler et al. 2008).

Vitamin B_{12} non-responsive MMA variants are the most severe, characterised by recurrent episodes of decompensation, mostly precipitated by intercurrent febrile illness. At present there is no satisfactory method for monitoring metabolic status in these patients. Treatment with an isocaloric low protein diet and supplemented amino acids (which are not methylmalonate precursors) is advised. With improved recognition and treatment, survival is increasing and longer term complications including pancreatitis, chronic neurological and renal impairment are becoming more apparent (Baumgarter and Viardot 1995, Ogier de Baulny et al. 2005).

Renal failure is a recognised complication of MMA not seen in other organic acidurias (Hörster and Hoffmann 2004). Long term studies have found the highest incidence occurs in those with *mut* ^{0} and *cblB* forms of the disease with 61 and 66% developing chronic renal impairment (Hörster et al. 2007). Renal impairment is found more commonly in those presenting early with MMA, and in patients with higher urinary excretion of methylmalonic acid. Progressive renal failure usually develops in adolescence or early adulthood in these groups (Baumgarter and Viardot 1995, Ogier de Baulny et al. 2005, Hörster and Hoffmann 2004) but the youngest described patient was 2 years old (Hörster et al. 2007).

We present the successful management of an 8-year boy with MMA due to *MMAB* mutations who developed end-stage renal failure with concomitant metabolic instability requiring haemodialysis and subsequent renal transplantation.

Case report

A six month old boy presented with vomiting, failure to thrive, hypotonia and metabolic acidosis. He was the third child of a consanguineous relationship, the older siblings were both well. He was born at term weighing 3.2 kg. He had experienced frequent vomiting since birth and was noted to have reduced tone with delayed motor milestones at 4 months of age.

A diagnosis of MMA was suspected on the basis of elevated urinary methylmalonic acid levels on organic acid analysis; plasma homocysteine levels were normal. A skin biopsy showed fibroblast methylmalonyl-CoA mutase activity was normal, 1049pmol/min per mg (control range 207-1730pmol/min per mg) and there was no evidence of in vitro stimulation with vitamin B_{12}. He was subsequently found to harbour a previously described intronic mutation c. 197-1 G>T in the *MMAB* gene. (Dobson et al. 2002). Plasma creatinine at presentation was 69 μmol/l, settling to 34 μmol/l after four days.

He was treated with a protein-restricted diet, bicarbonate and carnitine. Urine methylmalonic acid levels did not significantly change with intramuscular B_{12} and he was deemed vitamin B_{12} unresponsive.

Throughout his early years he had a very poor appetite and suffered from frequent vomiting episodes requiring the use of an emergency protein free regime at least once per month. His dietary management provided a protein intake of around 1.5 g/kg/day and net energy of only 66 kcal/kg/day. Growth remained poor with height and weight persistently around the 3rd centile. His development and education were limited due to his ill-health. His progress was also hindered by unexplained fractures to his clavicle and right tibia at 3 years of age; at this time his plasma creatinine, alkaline phosphatase 350 IU/l (range 250-850 IU/l) and parathyroid hormone levels 26 ng/l (11-35 ng/l) were within normal range for his age.

At the age of 7 he was found to have a rising plasma creatinine. Inulin clearance studies suggested a glomerular filtration rate of 27 ml/min/1.73m^2, with a plasma creatinine of 95 μmol/l. During the course of the following year his creatinine rose significantly; this was accompanied by frequent episodes of metabolic decompensation and hospitalization. At the age of 8 years he was listed for a combined liver and kidney transplant; the indications for combined transplantation were to improve metabolic control in addition to treating renal failure and to decrease the risk of recurrent renal disease.

Whist awaiting transplantation, his renal function and metabolic instability deteriorated further and by age 9 he was having monthly admissions with metabolic decompensation, rendering him unfit for transplantation most of the time. His weight gain remained poor and his height dropped further away from the 3rd centile. Feed tolerance was poor and he required continuous tube feeding and was failing to attend school. In an attempt to improve his metabolic control he was commenced on haemodialysis three times a week.

His clinical status improved immediately and he required no further hospital admissions for metabolic decompensation; additionally, his vomiting and appetite improved. He started to tolerate bolus feeds, his emergency regime was rarely needed and his school attendance and general quality of life improved. His protein intake was increased to 1.3 g/kg/day with 66 kcal/kg/day. Haemodialysis resulted in rapid reduction in plasma methylmalonic acid levels (mean pre-dialysis 5932 μmol/l; mean 1765 μmol/l immediately post dialysis); concentrations increased rapidly between haemodialysis sessions but this was not associated with metabolic instability. Haemodialysis was continued for 3 years between the ages of 9 and 12. Despite his improved metabolic control he experienced recurrent episodes of abdominal pain due to chronic pancreatitis. A MRI revealed an atrophic pancreas and magnetic resonance cholangiopancreatography revealed no anatomical abnormality. Symptomatic improvement was achieved with vitamin C, E and creon treatment. He had no cardiovascular problems at any stage and an echocardiogram at 11 years of age showed no evidence of cardiomyopathy.

Due to the dramatic improvement in his general well being and metabolic control with haemodialysis a decision was made to list him for isolated renal transplant rather than a combined liver/kidney transplant, which was considered much riskier.

A cadaveric renal transplant was carried out successfully at the age of 12 years; he was dialysed immediately prior to

the transplant and tolerated the surgical procedure well. His initial immunosuppressive regime consisted of tacrolimus, azathioprine and steroids. He did not tolerate azathioprine and was managed on mycophenolate mofetil and low dose tacrolimus in an attempt to minimise calcineurin toxicity.

Following the transplant his plasma creatinine fell to 62 μmol/l day 5, and increased to 90-100 μmol/l by 3 weeks post transplant with estimated GFR 50 ml/min/1.73m^2. A biopsy of the transplanted kidney showed patchy inflammatory infiltrate with occasional early inflammation of a small number of tubules with no evidence of rejection. A further biopsy was performed 7 months following transplant due to concern that the transplanted kidney would undergo further MMA-related damage and that a liver transplant might be considered. This second biopsy showed mild chronic damage with a moderate patchy inflammatory infiltrate of lymphocytes within the interstitium, around the tubules, glomeruli and small arteries. The interstitial fibrosis was focal and very mild (Fig.1).

At 6 years post renal transplantation he had a serum creatinine of 120 μmol/l, with an estimated GFR of 45 ml/min/1.73m^2 on an immunosuppressive regimen of sirolimus and mycophenolate mofetil.

Plasma methylmalonic acid levels fell from 8000 μmol/l prior to renal transplantation to 2460 μmol/l immediately after and are currently 1132 μmol/l (Fig. 2). His urinary excretion of methylmalonic acid remains markedly elevated at 9–10,000 μmol/mmolCr, with no appreciable change in levels following transplantation. He has had no further admissions for metabolic decompensation. He remains on a protein restricted diet of 1–1.2 g/kg/day and carnitine supplementation.

He is being educated in a mainstream school and is functioning approximately 2 years behind his peers. His gait is mildly abnormal with distal muscle atrophy; nerve conduction studies show him to have a generalised sensory motor peripheral neuropathy. MRI scans of his brain at ages 14 and 16 revealed long-standing bilateral changes in the globus pallid and no other significant abnormalities.

His growth remained poor in the first year following transplantation and his height moved further away from the 3rd centile. An x-ray estimated his bone age to be 2 years behind his chronological age. At 16 years his height and growth were on the 3rd centile and he has undergone puberty normally.

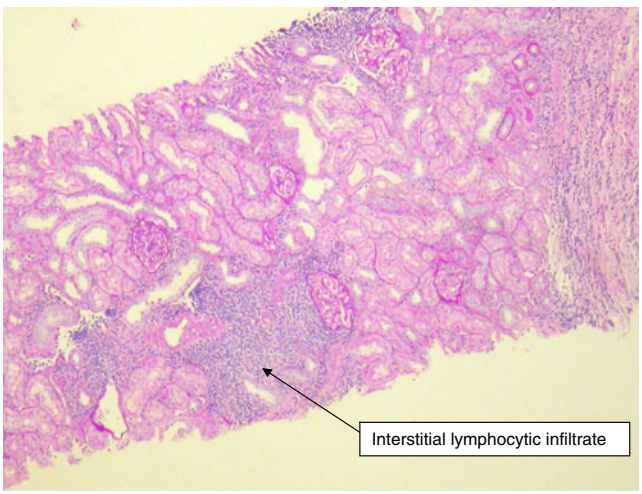

Fig. 1 Renal transplant biopsy 7 months following transplant showing evidence of mild patchy chronic damage

Discussion

We present here the first reported case with B_{12} non-responsive MMA and confirmed cblB defect, to undergo an isolated renal transplant for renal failure. Isolated kidney transplants have been described previously in a 17 year old female with vitamin B_{12} unresponsive MMA, (Lubrano et al. 2001, Lubrano et al. 2007) a child with vitamin B_{12} responsive MMA (Coman et al. 2006) and 24 year old with mut$^-$ MMA (Van Calcar et al. 1998).

Screening for renal impairment in MMA patients is complicated by their low muscle mass and low protein intake, making plasma creatinine a poor test of renal function. The clinical manifestations of renal involvement in MMA include proximal and distal tubular dysfunction and renal tubular acidosis type 4. Renal histology demonstrates progressive tubulo-interstial nephritis with mononuclear infiltration, interstitial fibrosis and tubular atrophy (Walter et al. 1989, Rutledge et al. 1993). The decreased renal function is believed to be secondary to tubular damage caused by tubulo-interstitial nephritis. Metabolic deterioration can be expected with worsening renal failure as methylmalonic acid is usually removed from the body by renal excretion.

Renal failure in our patient became apparent with an elevated serum creatinine and poor metabolic stability. As creatinine is known to be a poor indicator of renal function, we would recommend formal assessment of renal function be performed regularly from an early age. His general condition deteriorated rapidly with the decline in his renal function, reflecting a reduction in the clearance of methylmalonic acid by the kidneys. Haemodialysis is well documented as a means of treating acute metabolic decompensation (Ogier de Baulny et al. 2005) and has been described as effective in clearing methylmalonic acid prior to transplantation (Van Calcar et al. 1998, Nagarajan et al. 2005, Van't Hoff et al. 1998). In end stage renal failure haemodialysis results in periodic clearance of methylmalonic acid from the body (Van't Hoff et al. 1998, 1999), associated with a reduction of hospitalizations due to metabolic decompensation. Both peritoneal

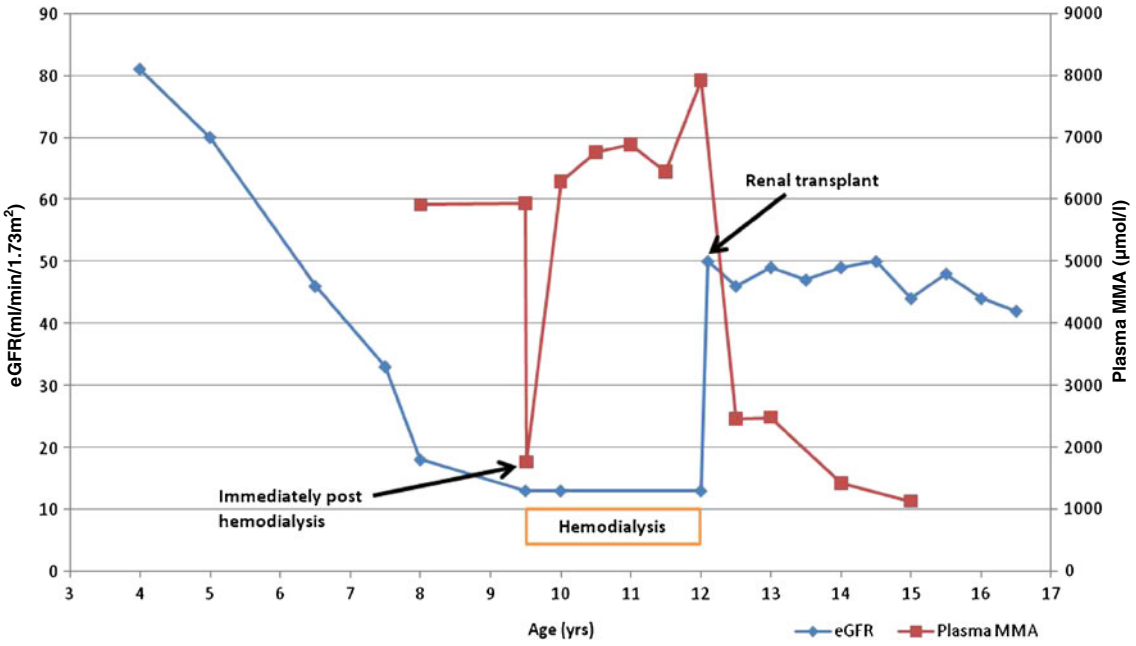

Fig. 2 Serum methylmalonate concentrations and eGFR pre-dialysis, during hemodialysis and after renal transplantation

and haemodialysis are effective in reducing methylmalonic acid levels if only temporarily and have been successfully used in a child with poor metabolic control and normal renal function (Paik et al. 2004). In patients with MMA who are metabolically very brittle, a trial of renal replacement therapy should be considered, even in the absence of frank renal failure. The long term options available to treat these patients include dialysis or transplantation either with an isolated kidney transplant or combined liver-kidney transplant.

As the liver is a major site of methylmalonyl-CoA mutase activity, liver transplantation for early onset of MMA has been suggested to prevent recurrent metabolic decompensation and hopefully avoid subsequent neurodevelopmental complications (Van't Hoff et al. 1999, Morioka et al. 2007). Successful liver transplantation requires careful perioperative management but offers consistent protection from metabolic decompensation and dietary de-restriction in the majority of patients. Longer term outcomes following transplantation have been varied, with several case reports describing acute and chronic neurological complications and progressive renal failure despite successful grafting (Leonard et al. 2001, Chakrapani et al. 2002, Kaplan et al. 2006, Nyhan et al. 2002).

In those with renal failure, combined liver-kidney transplantation offers the potential of reducing plasma methylmalonic acid by up to 95-97% with improved urinary excretion (Nagarajan et al. 2005, Van't Hoff et al. 1998). Combined transplantation allows reduction in immunosuppression as a result of immunological privilege conferred by the transplanted liver. Unfortunately, despite combined transplantation significantly reducing methylmalonic acid levels, these levels are not normalised and ongoing neurological damage has been reported, (McGuire et al. 2008) and morbidity and mortality may be high (Leonard et al. 2001). As our patient showed considerable improvement in his metabolic status following commencement of haemodialysis, the lower risk of isolated renal transplantation was favourable. The kidney is estimated to have only 18% of the methylmalonyl-CoA mutase activity of the liver (Van Calcar et al. 1998) but despite this, offers a useful partial correction, with a significant fall in plasma methylmalonate and improved metabolic control (Lubrano et al. 2001, Lubrano et al. 2007 Coman et al. 2006, Van Calcar et al. 1998). Maintaining strict protein restriction together with a lower incidence of infection in older children may further improve metabolic control and reduce the risk of progressive damage to the transplanted kidney.

The major concerns regarding isolated renal transplantation lie with the ongoing systemic metabolic defect damaging the transplant and the risk of neurological deterioration. Our patient developed a generalised sensory motor peripheral neuropathy following transplantation assumed to be secondary to immunosuppression rather than his underlying MMA. His renal function and creatinine levels have remained stable over a period of 6 years with an estimated glomerular filtration rate of 45 ml/min/1.73m^2. The question remains as to whether liver transplant could prolong the survival of the kidney graft from ongoing damage from methylmalonic acid. The long term outcome of combined kidney-liver and solo kidney transplants

remains unclear and it is not possible to say if a combined transplant prolongs the transplanted kidney survival. Only one patient in the literature has been followed to 10 years post isolated kidney transplant and continues to have good graft function (Lubrano et al. 2007).

Dysfunction of the respiratory chain and the tricarboxylic acid (TCA) cycle as well as oxidative stress have been implicated in the pathogenesis of organ damage in MMA (Chandler et al. 2009, Mirandola et al. 2008, Morath et al. 2008). Methylmalonyl-CoA mutase and ATP: cob(I)alamin adenosyltransferase are mitochondrial matrix enzymes, and it is possible that intramitochondrial accumulation of methylmalonic acid and related metabolites (such as methylcitrate and propionyl-CoA) within renal tissues is important in the pathogenesis of renal pathology. As the ATP: cob(I)alamin adenosyltransferase enzyme activity in the transplanted kidney is normal, intramitochondrial metabolism of methylmalonyl-CoA should be normal. Intramitochondrial accumulation of methylmalonic acid and related metabolites, therefore, would be expected to be significantly lower than in the native kidney, with comparatively less secondary effects on energy metabolism. This may partly explain the relative long-term preservation of renal function in patients who have undergone transplantation for renal failure in MMA. Nevertheless, excess exogenous methylmalonic acid is also believed to have a pathogenic role by inhibiting the transport of anaplerotic TCA intermediates into renal tubular cells through the Na+ dependent dicarboxylate transporters hNAC1 and hNAC3 (Morath et al. 2008) and the transplanted kidney may still be vulnerable to damage in the longer term.

Chronic renal impairment remains a serious long term complication of MMA. Although experience is limited, isolated renal transplantation can be a viable alternative to liver or combined liver-kidney transplantation as it appears to have similar salutary effects on metabolic stability with a lower risk of morbidity and mortality. Transplantation offers palliation until gene or enzyme replacement therapy becomes a therapeutic option. International collaboration with long term outcome data for the different transplant options will help guide the optimal transplant strategy for this heterogeneous group of patients.

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