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BRIEF REPORT

Renal transplant in methylmalonic acidemia: could it be the best option?

Report on a case at 10 years and review of the literature

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Abstract Methylmalonic acidemia (MMA) is an inborn error of organic acid metabolism. Patients with severe disease develop many complications despite treatment; often, the disease progresses to severe damage of the central nervous system or to end-stage renal disease (ESRD). When medical treatment is ineffective, liver, kidney, or combined liver and kidney transplantation is advocated. At present, there are no definite guidelines as for the organ to be transplanted, and results are inconsistent. We report on a 27-year-old woman with MMA MUT^0. The clinical symptoms developed at age 4 months. She progressed to ESRD and received a kidney transplant in November 1996 at age 17 years. One hundred and twenty months after transplant, renal function is normal; although urinary levels of methylmalonic acid are above normal limits, no episodes of metabolic decompensation have been observed after transplantation. Although liver is the major site of methylmalonyl-CoA mutase activity, this case and similar ones in the literature suggest that the smaller mutase activity present in the transplanted kidney may be sufficient to ensure partial correction of the metabolism of organic acids sufficient to prevent the onset of episodes of metabolic decompensation. It is worth investigating whether kidney transplant can be a safer and more satisfactory alternative to liver transplantation in cases of MMA unresponsive to medical treatment although urine MMA excretion remains significantly elevated.

Keywords Methylmalonic acidemia · Kidney transplant · Liver transplant · Kidney–liver transplant

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Introduction

Methylmalonic acidemia (MMA) is a heterogeneous group of inborn errors of metabolism characterized by accumulation of methylmalonic acid in serum. Its underlying causes are a partial (mut^-) or complete (mut^0) defect of the mitochondrial enzyme methylmalonyl CoA mutase (MCM, EC 5.4.99.2) or a faulty synthesis of 5-deoxyadenosylcobalamin, cofactor of MCM. The outcome is a defective metabolism of branched chain amino acids (isoleucine, valine, methionine, and threonine), of fatty acids with an odd number of carbon atoms, and the side chain of cholesterol [1]. Treatment is aimed at controlling protein

catabolism, both in muscle and liver, and to increase renal clearance of organic acids [2]. Protein intake is restricted, and high parenteral glucose intake is instituted; in case of metabolic crisis, the triggering cause should be treated [3]. The clearance of organic acids may be improved by hydration and control of acidosis, but extracorporeal dialysis may be necessary [2–5]. Patients with MCM cofactor deficit sometimes benefit from administration of hydroxocobalamin.

Due to improved survival and optimization of medical treatment, we have witnessed an increased incidence of long-term complications of the disease [6–9], such as neurological impairment [10], cardiomyopathy [11], and chronic progressive loss of renal function [12–17]. Some degree of neurological impairment and mental retardation is found mostly in children with early onset of MMA; on the contrary, children with late onset are more likely to have normal neurological development [18]. If medical treatment fails, liver or combined liver and kidney transplantation is considered an effective alternative [19]. So far, the real benefits of transplantation in MMA have not been assessed: the data on long-term follow up are scanty and are contradictory in some cases. Complications following transplant or incomplete correction of enzyme deficiency reported in a number of cases make it difficult to make decisions for individual patients.

We report on a solo kidney transplant performed on a girl with MMA MUT^0 complicated by end-stage renal failure. We had previously reported on the case 4 years after transplant [20]. Presently, at 10-year follow-up, her renal function and her clinical state is satisfactory. We also compare our findings with data available in the literature on organ transplantation in children with MMA.

Case history

GD underwent renal transplant 10 years ago at the age of 17. Born after an uneventful pregnancy, beginning at age 4 months, she suffered from occasional vomiting. Soon thereafter, vomiting became a regular occurrence following each feeding. A diagnosis of vitamin B_{12}-unresponsive MMA MUT^0 type was made at age 9 months during a crisis of metabolic acidosis. From then on, the child was fed a low-protein diet (≅0.6 g/kg per day) and given carnitine and sodium bicarbonate. Later, she developed chronic interstitial nephritis and progressive renal failure. During these years, her general conditions were satisfactory and her neurological development was normal. Her weight and height were slightly below the third centile; however, this was consistent with her parents' heights (father=165 cm; mother=157 cm). Cardiac studies revealed a concentric-hypertrophic cardiomyopathy with an ejection fraction within normal limits. Her blood pressure was kept below the 90th centile for age and height with amlodipine 2.5 mg qd. At age 16 years and six months, her chronic interstitial nephritis reached end stage. She was started on hemodialysis, and 6 months later, at age 17, she received a kidney transplant.

The postoperative course was uneventful except for an allergic reaction to the antilymphocyte serum. On the fourth day posttransplantation, her renal function tests had returned to normal (serum creatinine=50.4 μmol/l). At present, the patient age is 26 years and 7 months. She is 120 months after transplant and receives standard immunosuppression with prednisone (5 mg/die), mycophenolate (500 mg b.i.d.), and cyclosporine A (3.33 mg/kg/die) with no side effects. Serum levels of cyclosporine are the following: before taking the daily dose (C0) ≅122 ng/ml; 2 h after taking the daily dose (C2) ≅653.8 ng/ml.

Immediately following transplantation, she was kept on an amino-acid-free diet for 7 days to prevent possible acute metabolic decompensation. To monitor her urinary concentration of methylmalonic acid, we used a photometric method [21]. At the time of transplant, her urinary concentration of methylmalonic acid was 8.16 mmol/24 h (≅14.844 mmol/mmol of creatinine) and after transplant it decreased consistently. She was then started on a high-calorie, low-protein diet (0.5 g protein/kg/die), and the protein intake was gradually increased to 1.0 g/kg/die in the first month posttransplant. Two months following transplant, the urine concentration of methylmalonic acid decreased below measurable levels. From then on, she was on an unrestricted diet. Only 36 months after transplant, at age 20 years, the urinary concentration of MMA unexpectedly increased to 1.36 mmol/mmol of creatinine with no plausible explanation. The protein intake was temporarily reduced to 0.7 g/kg/die. Urinary excretion of MMA went back to 0.48 mmol/mmol of creatinine in 6 months and remained stable thereafter on an unrestricted protein intake.

During the 120 months of posttransplant follow-up, there have been no acute rejection episodes. No metabolic crises have been recorded, and the metabolic parameters have remained stable (Fig. 1). Also, renal function assessed by serum creatinine, creatinine clearance, proteinuria, and indices of tubular function has remained stable at all times (Table 1). Annual renal scintigraphy with 99mTc-diethylenetriamine pentaacetic acid (DTPA) has never revealed changes in the function of the transplanted kidney (Table 1).

At age 21, 4 years after transplantation, a graft biopsy showed mild to moderate (20% of the renal cortex) focal tubular atrophy with focal interstitial fibrosis and infiltrating mononuclear cells and was classified as chronic allograft nephropathy (CAN) grade Ia. At age 26 years

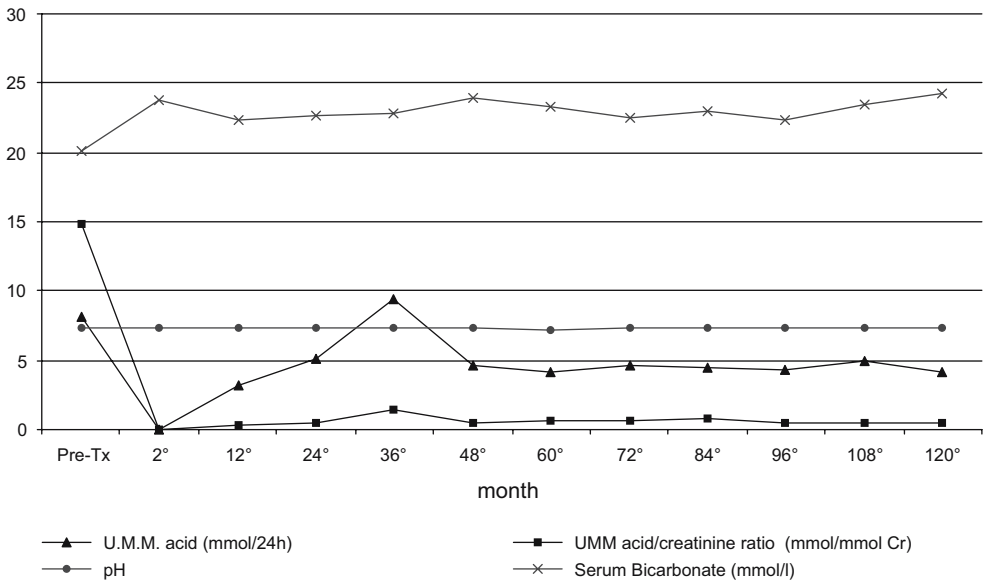

Fig. 1 Urinary excretion of methylmalonic acid (mmol/24 h), urinary methylmalonic acid/creatinine ratio (mmol/mmol creatinine-normal values <0.004), pH and serum bicarbonate (mmol/l) before (*PreTx*) and after (*PostTx*) kidney transplant (*U.M.M. acid* urinary methylmalonic acid, *Cr* serum creatinine)

and 6 months, a second biopsy showed a slight progression (to 30% of the renal cortex) of tubulointerstitial disease with a few obsolescent glomeruli and mild arteriolosclerosis and was classified as CAN grade IIa. No signs of allograft rejection or significant alterations of tubular epithelial cells were seen. At present, 10 years after transplant, at age 27, the patient is in good general condition. She complies well with the immunosuppressive therapy. The concentric-hypertrophic cardiomyopathy is stable at sonogram and blood pressure is at the 50th–75th percentile with no changes in her antihypertensive treatment.

Discussion

Conservative treatment in pediatric patients with vitamin B_{12}-unresponsive MMA cannot always attain an optimal control of metabolism. Secondary organ damage remains one of the most significant problems for long-term survivors of this disease, even when the disease seems under satisfactory control both clinically and biochemically. Neurological and renal deficits are among the most severe complications of MMA [8, 9]. Permanent clinical neurological signs, mostly acquired during episodes of acute metabolic decompensation, are hypertonia, developmental retardation, dystonic posture, and dysphagia [22]. Renal damage is the most common complication in long-term survivors and consists of a slowly progressive tubulointerstitial nephritis [12]. Histological changes are detected in the basal ganglia in the central nervous system [23] and in the renal tubuli [15], tissues both requiring high amounts of energy [24]. The cellular insult is believed to stem from an altered energy metabolism: the high concentrations of MMA and its metabolites (malonate and methyl citrate) [25] in the brain (at striatum and hippocampus) [26] inhibit complexes II and III of the respiratory chain and in the

Table 1 Parameters of renal function before (PreTx) and after (PostTx) renal transplantation

	PreTx						PostTx					
Months		2	12	24	36	48	60	72	84	96	108	120
Cr	397.8	88.4	70.72	79.56	97.24	88.4	106.08	106.08	97.24	114.92	114.92	114.92
BUN	20.35	3.57	3.57	3.21	3.93	5.00	3.21	5.00	6.43	6.07	5.71	6.07
GFR creatinine		50	75	80	58	67	39.8	45.3	67.2	53.8	52.2	50.0
GFR 99TcDTPA			65	64	63	62	83.4	76.2	77.6	70.1	62.1	62.4
Proteinuria		90	111	90	85	37	55	54	99	50	53	62.4
RTP		92.8	92.4	91.0	69.4	97	83.5	91.4	90.3	90.8	99.3	86.2
FENa		0.55	1.10	1.61	1.07	0.27	0.9	1.0	1.49	1.36	1.05	1.27

Cr serum creatinine (μmol/l), *BUN* blood urea nitrogen (mmol/l), *GFR* glomerular filtration rate $_{(Creatinine)}$ (ml/min/1.73 m^2), GFR $_{[99Tc\ diethylenetriamine\ pentaacetic\ acid\ (DTPA)]}$ (ml/min/1.73 m^2), Proteinuria (mg/24 h), *RTP* renal threshold phosphate concentration (%), *FeNa* fractional excretion of sodium (%)

renal tubular cells inhibit complexes I and III [7]. The resulting cellular damage is similar to that observed in cellular pathology of mitochondrial origin [27, 28]. In experimental studies on rats, administration of MMA can induce proteinuria and tubular damage [29], and in children with methylmalonic acidemia, optimal diet control induces improvement and even recovery of renal function [17].

At present, when medical treatment is ineffective, even in the absence of end-stage renal disease (ESRD), extracorporeal hemodialysis offers satisfactory control of metabolic disequilibria [5] but at a cost in terms of quality of life [5, 14]. Therefore, in case of medical treatment failure, before renal failure ensues and particularly when there is progressive neurological deficit, some authors suggest liver transplant [18, 30–37]; however, when MMA has progressed to ESRD, combined transplant of liver and kidney [32, 38, 39] or kidney only [20, 40, 41] is usually undertaken (Table 2).

Further to our case, a total of 13 transplants for MMA have been reported in the literature with various length of follow-up: three solo kidney, five solo liver, and five combined liver and kidney (Table 2). Examining the reported outcomes, it is immediately apparent that renal transplant, either alone [20, 40, 41] or in combination [32, 38, 39], attains better results: all patients are alive, and in all but one the metabolic status has improved. On the contrary, of the ten solo liver transplants [18, 30–37], only two are reported uneventful, whereas two have suffered from severe metabolic disorders, one has manifested progressive neurological deficit after transplantation, one is alive with neurological deficits, two died in the postoperative period due to sepsis, and of the remaining two cases, there are no outcome data available. All patients with severe posttransplant metabolic disorders were less than 1 year old, and this could add to the unsatisfactory results. However, it is impressive that after kidney transplant, not only was renal function restored, even the metabolic disorder improved, with significant reduction of urinary excretion of methylmalonic acid, although it is believed that kidney contributes only 18% of the mutase enzyme activity normally provided by the liver [42]. As in our laboratory we have been using a colorimetric method, we have now double-checked urinary excretion of methylmalonic acid with the more reliable mass spectrometry [43]. At mass spectrometry, urinary excretion of methylmalonic acid in our patient is presently 0.906 mol urinary MMA/mol of urinary creatinine (n.v.<0.004 mol urinary MMA/mol urinary creatinine) vs. 0.85 mol urinary MMA/mol of urinary creatinine with the colorimetric method. These levels are to be considered significantly higher than normal. However, although urinary concentrations of methylmalonic acid did not return completely to normal, our patient has remained clinically stable during the 10-year follow-up of the transplant.

Liver transplant supposedly provides a much larger mutase enzyme activity and on this basis has been advocated as the cure for MMA. However, it is a major undertaking, much more so than kidney transplant, and we might ask ourselves if it is really what a patient suffering from MMA needs. Recently, Kaplan et al. [37] severely criticized the benefits of liver transplantation in the treatment of MMA, and Kasahara et al. [36], referring to the main rationale of liver transplantation—i.e., to supply

Table 2 Transplant for methylmalonic acidemia (MMA) in children: literature review

Graft	Author	Age at transplant	Follow-up (months)	Outcome
Kidney	[41]	24 years	36	Alive
	[40]	14 years	48	Alive
	[20]	17 years	120	Alive
Liver	[18]	6 months	–	Death, metabolic complications
	[30]	9 months	60	Metabolic stroke
	[31]	22 years	24	Alive, progression of the neurological damage
	[32]	16 years	13	Alive
	[33]	11 months	53	–
	[34]	8 months	25	–
	[35]	13 months	0.5	Death (sepsis)
	[35]	12.2 years	2.2	Death (sepsis)
	[36]	4 years	9	Alive
	[37]	19 months	96	Alive, with some neurologic disabilities
Kidney and liver	[18]	13.5 years	36	Alive
	[38]	18.3 years	3	Alive, posttransplant problems and retransplant
	[39]	10 years	60	Alive
	[39]	21 years	18	Alive
	[32]	13 years	48	Alive

missing enzymes—point out that it entails sacrificing the otherwise normally functioning native liver.

Neither liver transplant nor renal transplant bring back to normal urinary excretion of methylmalonic acid. However, the case we report and the review of the literature as summarized in Table 2 suggest that there is a possibility that renal transplant, in addition to treat renal failure, may improve urinary excretion of methylmalonic acid and contribute to stabilize clinical conditions, whereas liver transplant does not seem to improve significantly the clinical picture, and its effectiveness on the disease is hampered by the incidence of severe complications.

Urinary excretion of methylmalonic acid after transplantation is reported only occasionally. However, it is of interest to observe that in two patients treated with liver transplant only [30, 37], urinary concentration of methylmalonic acid remained as high as 3.65 mmol/mmol of creatinine in one and 2.00 mmol/mmol of creatinine in the other. On the contrary, in three cases of combined liver and kidney transplant [38, 39], methylmalonic acid concentration in the urine decreased to 0.6, 0.9, and 0.66 mmol/mmol of creatinine, and finally in our case, it went down to 0.906 mmol/mmol of creatinine. These findings suggest that the beneficial effect of kidney transplantation may be more significant than that of liver transplantation.

At present, the benefit of renal transplant is only speculative, as there are no data on the mutase enzyme activity (namely, the enzyme activity needed for normal metabolism of MMA and the amount sufficient to prevent organ damage) and on the actual role of the kidney in the overall balance of mutase enzyme activity. The 26-year and 7-month-old patient described in this report is now 120 months after renal transplant, by far the longest follow-up in the literature. Her renal function is normal, and her urinary excretion of MMA, although still above normal limits, is stable at levels significantly lower than before transplant. During the 120 months' follow-up, there have been no clinical symptoms of her primary disease, no further crises of metabolic acidosis, and no histological signs of relapse at renal biopsies at 4 and 10 years. Histology is compatible with chronic allograft nephropathy and with the renal function of our transplant but is indistinguishable from chronic interstitial nephropathy secondary to MMA. The latter, however, is believed to be related to high concentrations of methylmalonic acid and its metabolites [16]. The echocardiographic finding of cardiomyopathy initially was explained with the combined effects of hypertension and MMA progression. However, it persists after the blood pressure has long returned to normal and the urine concentration of methylmalonic acid has been consistently reduced.

We feel confident in saying that in this case, renal transplant has proved effective and sufficient in treating the disease, even if urinary excretion of methylmalonic acid did not return fully to normal and cardiomyopathy did not regress but remained stable. Literature reports of other similar cases, although with shorter follow-ups are equally suggestive. However, further investigations are needed to prove whether kidney transplant can always be a safer and more satisfactory alternative to liver transplantation in MMA.

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