Pediatr Nephrol (2001) 16:848–851

BRIEF REPORT

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Kidney transplantation in a girl with methylmalonic acidemia and end stage renal failure

Received: 7 February 2001 / Revised: 27 June 2001 / Accepted: 28 June 2001

Abstract Methylmalonic acidemia (MMA) is an inborn error of organic acid metabolism that occurs in infancy with hypotonia, vomiting, dehydration, lethargy and failure to thrive and is biochemically characterized by metabolic ketoacidosis, hyperammonemia and sometimes hyperglycinemia. It results from deficiency of methylmalonyl-CoA mutase activity due to a defect in the mutase apoenzyme or to deficient function of one of the enzymes required for metabolism of its cofactor vitamin B_{12}. Tubulointerstitial nephritis with progressive impairment of renal function is one of the most frequent long-term complications. We describe a case of a 17-year-old girl with methylmalonic acidemia unresponsive to vitamin B_{12} therapy. The clinical symptoms appeared at 4 months of life. She progressed into end stage renal disease and in January 1996 she started on hemodialytic treatment. In November 1996 we performed a kidney transplant. At present, urinary excretion of methylmalonic acid is normal and the renal function of the transplanted kidney is normal without any rejection episodes. We think that a kidney transplant could be a good therapeutic choice for the metabolic alterations in MMA with end stage renal disease. Indeed it would seem that the small methylmalonyl-CoA mutase activity present in the transplanted kidney could be sufficient to ensure normal metabolism of organic acids. Otherwise, the therapeutic goal can be achieved with a protein-restricted diet.

Keywords Methylmalonic acidemia · Kidney transplant

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Introduction

Methylmalonic acidemia (MMA) is an autosomal recessive disorder of organic acid metabolism, usually detected during the 1st year of life. MMA is due to a defect of methylmalonyl-CoA mutase-apoenzyme activity or defective adenosylcobalamin (coenzyme) synthesis [1, 2]. Defect of the coenzyme may be treated with high pharmacological doses of hydroxocobalamin (B_{12}) with a consequent reduction in the production of methylmalonate and a less severe clinical course [3]. Infants with B_{12}-unresponsive forms are treated with a low-protein diet, carnitine and metronidazole therapy [3–5]. With appropriate treatment an increasing number of children are surviving longer [6]. As a result, long-term complications are becoming apparent. Some degree of neurological impairment and mental retardation was found mostly in children with early onset of MMA; instead children with late onset have a normal neurological development [2]. Moreover, cardiomyopathy [7] and chronic progressive loss of renal function are frequent and serious complications of long-term survivors with MMA [8–11]. The main problem after end stage renal disease is to combine the metabolic correction of the primary disease with that of the renal insufficiency. Indeed, in these patients, to obtain the correction of the MMA and of the end stage renal disease, as in those with primary hyperoxaluria type 1 [12], combined liver kidney transplantation is considered a possible therapeutic option. We report the successful treatment, obtained with a kidney transplant, of a girl with MMA in end stage renal failure and 48 months of follow-up.

Case history

We refer to a girl suffering from MMA who underwent a kidney transplant at the age of 17 years. The pregnancy was uneventful and delivery was at term. The girl was in good general condition until 3 months of age, at which point she presented growth

Table 1 Urinary excretion of methylmalonic acid (mmol/24 h), urinary methylmalonic acid/creatinine ratio (mmol/mmol creatinine), urinary methylmalonic acid/BUN ratio (mmol/mmol BUN) before (PreTx) and after (PostTx) renal transplantation and renal functional parameters after kidney transplant (*UMM acid* urinary methylmalonic acid)

	PreTx	PostTx								
Months		2	6	12	18	24	30	36	42	48
UMM acid	8.16	0	0	3.2	3.5	5.1	7.2	9.4	4.1	4.6
UMM acid/creatinine ratio	14.84	0	0	0.25	0.39	0.47	0.85	1.36	0.48	0.5
UMM acid/BUN ratio	0.028	0	0	0.0014	0.0022	0.0017	0.0031	0.0093	0.0030	0.0045
Serum creatinine (mg/dl)		1	0.9	0.8	1	0.9	0.7	1.1	1	1
BUN (mg/dl)	57	10	11	10	8	9	9	11	13	14
$GFR_{(creatinine)}$ (ml/min/1.73 m^2)		50	65	75	85	80	75	58	59	67
$GFR_{(99TcDTPA)}$ (ml/min/1.73 m^2)				65		64		63		62
Proteinuria (mg/24 h)		90	85	111	76	90	108	85	50	37
RTP (%)		92.84	92.5	92.42	91.25	90.99	82.28	69.35	88.76	97
FENa (%)		0.55	1.05	1.10	0.61	1.61	1.32	1.07	1.12	0.27

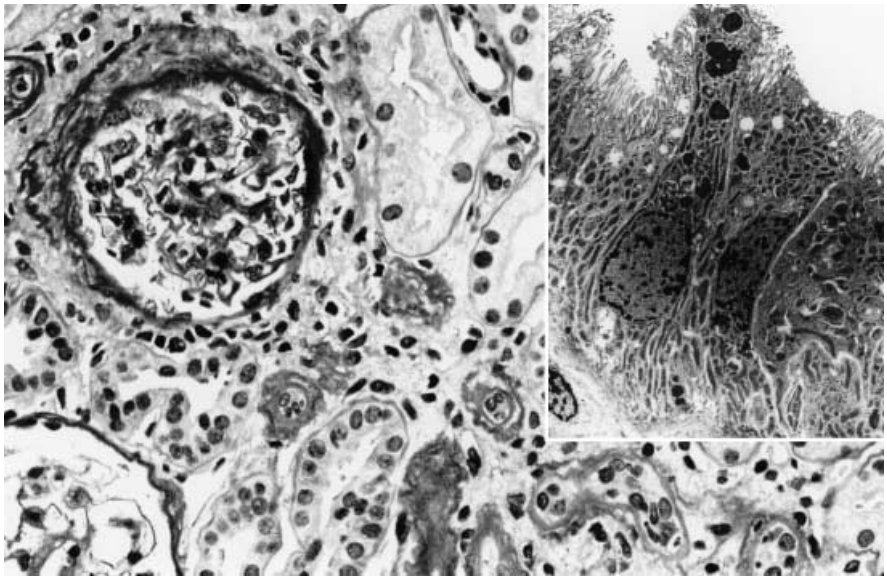

Fig. 1 Renal biopsy showed focal chronic parenchymal damage with interstitial and periglomerular fibrosis, focal tubular atrophy, and infiltrating mononuclear cells; epithelial cells of histologically normal tubuli do not reveal relevant substructural alterations. *Inset* An EM picture from the proximal tubular epithelium. PAS, ×210 (*inset* UrPb, ×1640)

retardation. At the age of 4 months she had frequent episodes of vomiting that progressively became constant at the end of each meal.

The diagnosis of vitamin B_{12}-unresponsive MMA was made at the age of 9 months following coma due to hyperammonemia. Consequently, she started a low-protein diet (≅0.6 g/kg/day) and treatment with carnitine and sodium bicarbonate. At age 16.5 years she began treatment with hemodialysis due to progressive kidney damage.

Her general conditions before transplantation were satisfactory. Her physical examination revealed normal neurological development and schooling appropriate for her age; she was slightly below the 3rd percentile for both height and weight. Furthermore, she presented concentric-hypertrophic cardiomyopathy with a good ejection fraction. Her blood pressure was well controlled by treatment with amlodipine (2.5 mg q.d.). At the age of 17.5 years she received a kidney transplant. There were no complications during her postoperative course, except for an allergic reaction to the antilymphocyte serum, which was therefore interrupted. At present she receives a standard immunosuppressive therapy with prednisone (5 mg/day), micophenolate (500 mg b.i.d.) and cyclosporine A (3.33 mg/kg/day) without any problems. On the 4th day post-transplantation her renal serum parameters were completely normalized (serum creatinine = 0.6 mg/dl). In order to avoid acute metabolic decompensation, we tried to reduce production of methylmalonic acid by placing our patient on an amino-acid-free diet for the first 7 days post-transplantation. She was then placed on a high-calorie, low-protein diet (0.5 g protein/kg/24 h), which was gradually increased to 1.0 g protein/kg/24 h during the 1st month post-transplantation.

In the pre-transplantation period, when the patient was on a hypoproteic diet (0.5 g protein/kg/day) and in hemodialysis, the urinary level of methylmalonic acid was about 8.16 mmol/24 h (≅14.844 mmol/mmol creatinine). After the transplant there was a rapid decrease and at the 2nd month post-transplantation the urinary level of methylmalonic acid was unmeasurable. Due to these unexpected and encouraging results, the girl's protein intake was liberalized. The urinary excretion of methylmalonic acid, which remained unmeasurable for about 1 year, gradually increased to 9.4 mmol/24 h (≅1.36 mmol/ mmol creatinine) by the 36th month post-transplantation. Thus, we again suggested restricting her protein intake (0.7 g protein/kg/day). After about 12 months of the diet, the urinary excretion of methylmalonic acid gradually decreased to 0.5 mmol/mmol creatinine (48 post-

tx month) (Table 1). The transplanted kidney has always presented good glomerular and tubular function, and no acute rejection episode. The glomerular filtration rate was determined every 3 months with the creatinine clearance method, over a 24-h collection, and every year with the ^{99m}Tc-DTPA method (Table 1).

Four years after the transplant the girl is in good general condition and she showed a good compliance with the immunosuppressive and nutritional therapy. The concentric-hypertrophic cardiomyopathy is echographically stable and her blood pressure is at the 75th percentile for her age without any changes in her antihypertensive treatment. We recently performed a biopsy of the transplanted kidney. Renal biopsy showed moderate chronic tubulointerstitial damage. Ultrastructural studies did not reveal significant alterations of tubular epithelial cells (Fig. 1).

Discussion

Conservative therapy of MMA has not given optimal results in pediatric patients with vitamin B_{12}-unresponsive MMA. Various therapeutic strategies have been experimented with, all of which aim at a permanent correction of the metabolic defect. A liver transplant early in life has also been performed in two children [2] with MMA and without end stage renal disease, but it did not seem to resolve the metabolic complications of the disease. Indeed, one child died following metabolic complications post-transplantation and the other survived but with high methylmalonic acid excretion. Naturally these patients suffered from the most severe form of the disease, the one characterized by early onset.

In MMA, end stage renal failure is the most important long-term complication [10]. When the children undergo hemodialysis we have better control of methylmalonic acid serum concentrations, but it is not the best choice for their quality of life.

To correct the loss of renal function in patients with MMA, some authors performed combined kidney-liver transplantation so as to combine the correction of both the metabolic defect and the renal dysfunction [13]. Instead, other authors opted for renal transplantation alone [14].

The children who underwent combined kidney-liver transplantation [13] are described as being in good general condition and the patient's urinary methylmalonic acid excretion is 0.66 mmol/mmol creatinine.

Along with our patient, one other patient with kidney transplantation alone [14] for MMA has been described in the literature, but he was an adult patient. Calcar et al. [14] refer to a patient in good general condition after about 3 years of follow-up regardless of an episode of acute rejection. They report a considerable decrease in methylmalonate urinary excretion after transplantation. Indeed, the transplanted kidney not only clears plasma methylmalonate, but also provides a source of methylmalonyl coenzyme A mutase able to guarantee sufficient metabolic activity in relation to methylmalonic acid levels. Various studies seem to confirm that the transplanted kidney could provide about 18% of the mutase enzyme activity normally provided by the liver [15].

Our patient similarly presented low urinary excretion of methylmalonic acid post-transplantation. This was attributed to the transplanted kidney's excretion of methylmalonic acid, the new source of active enzyme, and the initially low-protein diet. Furthermore, a biopsy performed 4 years after transplantation on a kidney that had never presented an episode of acute rejection revealed no lesions that could be specifically correlated to recurrence of the primary disease.

Therefore, considering also the small number of cases, at present we believe that there is not sufficient evidence to sustain a preference for any of the proposed treatment strategies.

However, the therapeutic effects of kidney transplantation alone are very suggestive, i.e., low urinary excretion of methylmalonic acid and no recurrence of the primary renal disease in the transplanted kidney. Certainly a longer follow-up is needed, along with a better understanding of the different metabolic conditions of the disease, which could in turn help clarify the results obtained so far.

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