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Progressive neurologic disability in methylmalonic acidemia despite transplantation of the liver

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Abstract Methylmalonic acidemia unresponsive to cobalamin is often fatal in infancy. Patients have been considered candidates for hepatic transplantation and experience has been that the procedure eliminates the life-threatening episodes of ketoacidosis that characterize this disease. Conclusion: experience with a 24-year-old patient treated with hepatic transplantation indicates that this procedure does not prevent progressive renal failure and neurologic dysfunction.

Keywords Methylmalonic acidemia · Neurologic degeneration · Renal failure · Transplantation of liver

Introduction

Methylmalonic acidemia is an inborn error of branched-chain amino acid metabolism in which the activity of methylmalonyl Co mutase (E.C.5.4.99.2) is deficient [13]. Patients with the mut° disease do not respond to cobalamin, and most have repeated episodes of life-threatening ketoacidosis. A majority of these patients die in infancy or childhood, and the survivors have often had major retardation of mental development [12,17]. It has been thought that neurologic abnormalities observed in these patients have been the result not of the abnormal biochemical milieu, but rather of the acute episodic metabolic decompensations and their attendant acidosis, hyperammonemia, dehydration, shock and apnea [13]. On the other hand, acute metabolic stroke has been observed in patients with methylmalonic acidemia [8, 10, 19], related organic acidemias [6, 7], as well as other inborn errors of metabolism [14].

The poor prognosis of this disease has led to interest in treatment by hepatic transplantation [4, 11, 21]. Renal failure is another late complication of methylmalonic acidemia [1, 3, 22]. This consideration has led some workers to undertake combined transplantation of liver and kidney [20].

It is the purpose of this report to describe a young adult with methylmalonic acidemia who developed an unusual progressive neurologic syndrome and progressive renal failure despite hepatic transplantation at 22 years of age.

Case report

The patient, a 24-year-old Mexican-American female, first developed symptoms in the 1st week of life following an uneventful pregnancy and delivery at term. At that time she developed recurrent vomiting and failure-to-thrive, was hypotonic and lethargic and had hepatomegaly. Laboratory evaluation revealed metabolic acidosis and leukopenia, and methylmalonic acid was found in the urine. Complementation analysis of fibroblasts performed at Yale University by J. Mahoney, established the diagnosis of mut° methylmalonic acidemia. A brother had died at 2 months of age.

The patient was treated by dietary restriction of threonine, methionine, valine and isoleucine. Supplementation with cyanocobalamin and hydroxocobalamin were without effect on concentrations of methylmalonate. Carnitine supplement was given starting at 14 years of age. She did not receive intermittent therapy with metronidazole to control intestinal bacteria. She had over the years many admissions to hospital for the treatment of acute metabolic decompensation with metabolic acidosis, usually precipitated by intercurrent infection. By 20 years of age she had had 76 admissions.

At 13 years of age, psychometric evaluation gave her a Wechsler IQ of 76 and a Vineland social maturity scale of 83. At 17 years of age her weight was at the 50th percentile, height was at the 15th percentile and neurological examination was negative. At age 17 years she could ride a bicycle and rollerblade, but tired easily. At

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this time, signs of renal impairment appeared with intermittent elevation of BUN to 11–14 mmol/l (32–39 mg/dl) and creatinine of 124–177 μmol/l (1.4–2.0 mg/dl).

At age 17.5 years she developed sacrococcygeal pain, disturbed gait and weakness in the lower extremities. Neurological examination was unrevealing, and lack of leg strength was thought to be a reflex response to pain. Two months later she began using a wheelchair at school. Walking was difficult and painful, and she continued to tire easily. The uric acid level was 756 μmol/l (12.7 mg/dl), and treatment was begun with 100 mg of allopurinol daily. Over the next year basal renal function tests obtained while she was healthy and well hydrated revealed BUN, creatinine and uric acid levels ranging from 8 to 21 mmol/l (23–59 mg/dl), 124 to 168 μmol/l (1.4 and 1.9 mg/dl), and 440 to 738 μmol/l (7.4–12.4 mg/dl), respectively. She had lost 6 kg in 7 months. Bicarbonate supplementation was required to maintain stable acid-base balance. MRI scans of the kidney and of the back were negative. Roentgenograms did show osteoporosis. By 21 years of age her BUN was 19 mmol/l (52 mg/dl) and creatinine 150 μmol/l (1.7 mg/dl).

At 22 years of age she underwent orthotopic liver transplantation. Dialysis was carried out prior to surgery, and she did well. The creatinine ranged from 177 to 203 μmol/l. Immunosuppressive medications included tacrolimus, prednisone and mycophenolate-mofetil. Three months later her BUN was 40 mmol/l (109 mg/dl) and creatinine 990 μmol/l (11.2 mg/dl). She stopped making urine, and a program of hemodialysis was begun. Concentrations of methylmalonate in the blood ranged from 427 to 4490 μmol/l prior to transplantation with a preponderance of levels over 1000 μmol/l. Following transplantation and on dialysis they ranged from 300 to 681 μmol/l. Dietary restriction of protein containing precursors of propionate could be relaxed following transplantation, but the advent of renal failure led to protein restriction by the nephrologists.

Her neurologic abnormality continued to progress. First, she had begun to walk with a limp; then it became difficult to pick up her legs or swing them into a car. She lost voluntary control of her legs for ambulation and later of her arms. At the time of report she was learning to write and draw using tools held in her mouth. She had developed acute spasmodic contractions of the legs, causing them to kick out uncontrollably; she had accidentally broken a window in this way. In order to inhibit these movements, she employed velcro and bungee cord to keep her legs restricted to the wheelchair. She was alert, articulate, and a talented singer who performed publicly with a voice that showed no sign of weakness. Family history was negative for neurologic or renal disease. A sister was well. There was no consanguinity.

On examination her weight was 53.6 kg (25th percentile), her height 160.5 cm (40th percentile) and her head circumference 52 cm (2nd percentile). Her blood pressure was 106/70 and the pulse 96 beats per minute. She was alert, articulate and talkative. There was a shunt in the left arm and a gastrostomy tube in the abdomen. She had a small keloid on the left ear at the site of an original piercing. She sat strapped at the waist and chest because of inability to control her trunk. On removal of the belts she experienced a total body spasm in which the head and neck went backwards and generalized muscle spasms involved the legs, abdomen, chest and face. On muscle testing her cranial nerves were intact and her shoulder shrug strong. Her arms were flaccid. There was limited mobility at the left shoulder. She could not voluntarily move either leg, although muscle mass was not reduced. Reflexes were unobtainable in the arms. Knee jerk testing elicited a very weak quadriceps contraction on the right, while on the left a light tap induced one of her spasms and the leg kicked violently forward. There were no fasciculations. Sensory examination was normal. Careful examinations by a number of neurologists revealed no evidence of neuropathy. Physical examination was otherwise noncontributory.

Laboratory evaluation revealed a methylmalonate concentration of 384 μmol/l in the blood; methylcitrate was 30 μmol/l. Amino acid analysis of the plasma revealed a glycine concentration of 1029 μmol/l, alanine 545 μmol/l, threonine 130 μmol/l, methionine 32 μmol/l, valine 100 μmol/l, isoleucine 42 μmol/l, and leucine 37 μmol/l. Her albumin was 3.0 g/l, BUN 9 mmol/l, potassium 4.6 mEq/l (25 mg/dl), phosphorus 1.3 mmol/l (4.0 mg/dl), calcium 2.3 mmol/l (9.2 mg/dl), glucose 5.2 mmol/l (95 mg/dl) and creatinine 830 μmol/l (9.4 mg/dl). She had not been taking carnitine since the transplantation, and her plasma free-carnitine was 1.1 μmol/l, total 2.7 μmol/l. Ultrasonography revealed small echogenic kidneys with thin cortices consistent with end stage renal disease. CT and MRI of the brain were normal; there were no lesions in the basal ganglia or white matter. The EEG was normal. Other recognizable causes of involuntary movements were excluded including the dystonia DYT1 genotype which was normal. Copper and ceruloplasmin levels were normal. Organic acid analysis revealed normal levels of glutaric acid, and plasma concentrations of phenylalanine were normal. Treatment was initiated with carnitine (1.2 g bid) and liberalization of protein intake was begun. Efforts have been undertaken to obtain a kidney.

Discussion

Methylmalonyl CoA mutase is expressed in all tissues of the body. Therefore, it is not surprising that concentrations of methylmalonate in body fluids do not become normal following transplantation of a liver, although they do become appreciably lower. Concerns about the possibility of central nervous system complications of this disease have been raised because concentrations of methylmalonate in the cerebrospinal fluid have been observed not to decrease after transplantation [9]. Experience with this patient provides the first real evidence of neurologic disease as a late effect in the transplanted patient.

The syndrome of neurologic disability displayed by this patient appeared to be unique among patients with methylmalonic acidemia, but few have lived this long. In contrast to the neurologic picture of younger patients with the mut° disease, cognitive function was good, and there was no evidence of stroke. Weakness began distally in the legs and progressed to complete loss of function and to involvement of the upper extremities. Involuntary movements of the legs involved muscle spasms throughout the legs with strong quadriceps contraction straightening the leg. More general spasms of body musculature resembled myochymia. Dystonia and weakness profound enough to lead to a wheelchair-bound state has been observed in methylmalonic acidemia [19]. This has been associated with neuroradiologic evidence of abnormality in the basal ganglia which has frequently been encountered in disorders of propionate metabolism [6, 7, 8, 11]. It has been thought that these manifestations have been the result of acute metabolic stroke [6, 7, 8], but it is clear there can be continuing metabolic damage to the basal ganglia [19].

Immunosuppression with tacrolimus employed for transplantation of the liver has also been associated with neurologic complications, but these were usually manifested as tremor and headache, neither of which she has had, and they are usually reversible on reducing the dose of the drug [2, 9]. Nephrotoxicity has also been observed with high doses, including increased plasma creatinine levels, decreased creatinine clearance, and decreased urine output [5, 16].

A variety of renal complications have been observed in patients with methylmalonic acidemia [3, 15, 18], including renal tubular acidosis observed in infancy [23], and these have been thought to be direct consequences of the systemic methylmalonic acid accumulation. It is clear from experience with this patient that following transplantation of the liver, and the subsequent improvement that takes place in systemic methylmalonate concentrations, renal dysfunction does not reverse, but rather it relentlessly progresses to renal failure. Similarly, the onset of neurologic dysfunction predated transplantation. However, there was major progression following transplantation. Both the progressive renal and neurologic manifestations observed were clearly not related to catastrophic metabolic decompensation, suggesting both arise as intrinsic processes resulting from the primary metabolic disorder.

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