

# Early Liver Transplantation for Neonatal-Onset Methylmalonic Acidemia

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## abstract

With conventional dietary treatment, the clinical course of methylmalonic acidemia due to cobalamin-unresponsive methylmalonyl-CoA mutase (MCM) deficiency is characterized by the persistent risk of recurrent life-threatening decompensation episodes with metabolic acidosis, hyperammonemia, and coma. Liver transplant has been proposed as an alternative treatment and anecdotally attempted in the last 2 decades with inconsistent results. Most criticisms of this approach have been directed at the continuing risk of neurologic and renal damage after transplant. Here, we report the perioperative and postoperative clinical and biochemical outcomes of 2 patients with severe MCM deficiency who underwent early liver transplant. In both cases, liver transplant allowed prevention of decompensation episodes, normalization of dietary protein intake, and a marked improvement of quality of life. No serious complications have been observed at 12 years' and 2 years' follow-up, respectively, except for mild kidney function impairment in the older patient. On the basis of our experience, we strongly suggest that liver transplant should be offered as a therapeutic option for children with cobalamin-unresponsive MCM deficiency at an early stage of the disease.

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Drs Spada, Calvo, and Porta conceptualized and designed the study and drafted the initial manuscript; Drs Brunati, Peruzzi, dell'Olio, and Romagnoli acquired and interpreted the data and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Methylmalonyl-CoA mutase (MCM; EC 5.4.99.2) deficiency is the most common cause of methylmalonic acidemia (MMA; Online Mendelian Inheritance in Man 251000). After an initial symptom-free period ranging from hours to days after birth, affected neonates present with acute neurologic deterioration. Typically the progression of symptoms moves from feeding refusal, vomiting, progressive weight loss, generalized hypotonia, and abnormal posturing and movements, through lethargy, seizures, and coma, leading to severe brain damage or death within a few days, if not promptly treated. Neonatal catabolism precipitates the first acute metabolic decompensation, characterized by metabolic acidosis, hyperammonemia, and progressive encephalopathy. Similar life-threatening episodes,

generally triggered by intercurrent illness or fasting and necessitating specific emergency treatment, are also common later in life despite optimal medical treatment.<sup>1</sup>

Conventional long-term management of MCM deficiency relies on a substrate reduction approach, based on stringent restriction of protein dietary intake and antibiotic administration, aimed to reduce the precursors of propionyl-CoA (ie, valine, methionine, isoleucine, threonine, and odd-chain fatty acid metabolism by gut flora), and on carnitine supplementation. In cobalamin-responsive MCM deficiency, this therapy can be supplemented with an enzyme enhancement approach, ensured by vitamin B<sub>12</sub> administration.<sup>1</sup> These management strategies have improved survival but

have not modified the neurodevelopmental outcome. Progressive neurocognitive deterioration is almost invariably present. Relapsing episodes of acute metabolic decompensation are associated with a high risk of basal ganglia stroke, responsible for severe motor disabilities. Long-term complications with selective organ impairment are common, and cardiomyopathy and pancreatitis represent severe life-threatening events.<sup>2,3</sup>

As previously suggested,<sup>4</sup> bulk enzyme supplementation by liver transplant could be more effective in treating severe MCM deficiency. After the first attempt in 1997,<sup>5</sup> liver and kidney transplants have been anecdotally performed in MMA, with questionable results.<sup>6–10</sup> Because of the lack of consensus and guidelines on transplantation in MMA, reports on additional experience may help challenge earlier conclusions and instigate debate on newer clinical options.

Here we report our experience on this issue, describing the perioperative and postoperative clinical and biochemical outcome of 2 patients with severe MCM deficiency treated by early liver transplant.

## CASE REPORTS

### Patient 1

A newborn boy was diagnosed with severe cobalamin-unresponsive MCM deficiency at our metabolic center 15 years ago. Clinical onset was at 2 days of life, with progressive life-

threatening neurologic deterioration, polyuria, and excessive weight loss. Clinical, biochemical, and molecular features are summarized in Table 1.

Despite conventional medical treatment, the patient had 10 acute metabolic decompensation episodes progressing to coma during the first 2 years of life (1 episode during the first year, 9 during the second), necessitating life-saving emergency treatment. Because of his unfavorable clinical course, the patient was placed in the national pediatric liver transplant waiting list at 30 months of age. Mild generalized hypotonia, upper limb choreiform movements, and slight psychomotor retardation were observed despite normal brain MRI. Whole liver transplant was performed at 3 years, with no intraoperative and postoperative complications on tacrolimus and mycophenolate mofetil therapy. Posttransplant follow-up is ongoing, with 12 years of clinical, biochemical, and imaging evaluations. Life-threatening decompensation episodes were eradicated. Protein dietary intake was gradually increased from 0.8 g/kg per day to 1.5 g/kg per day without adverse effects. Carnitine supplementation was maintained (75 mg/kg per day). Perioperative and longitudinal biochemical evaluations showed sustained (~80%) and stable reduction of plasma methylmalonate (Figure 1). At time of writing, creatinine level is 1.05 mg/dL (normal range 0.47–0.73) and renal function is stable (Figure 1), with normal proximal and distal tubular function.

Improvement of hypotonia was observed as of 2 years after transplant, but minor upper limb choreiform movements persist. Normal intellectual development was documented by the Wechsler Intelligence Scale for Children, Fourth Edition test, performed at 11 and 14 years of age with comparable results (IQ 104; percentile rank 60.2; 95% confidence interval [CI], 98–110), with normal skills in verbal comprehension, perceptual reasoning, processing speed, and superior skills in working memory. Currently, the patient is 15 years old, and his quality of life by Morioka's standards<sup>11</sup> continues to be excellent.

### Patient 2

Twelve years after the diagnosis of patient 1, a second newborn with similar clinical presentation, onset at 2 days of life with acute encephalopathy and polypnea, received a diagnosis of severe MCM deficiency (Table 1). No additional decompensation episodes were recorded in the first months while the patient was on standard treatment. Given the encouraging long-term results achieved by the first patient, patient 2 was placed in the national pediatric liver transplant waiting list at 6 months of age.

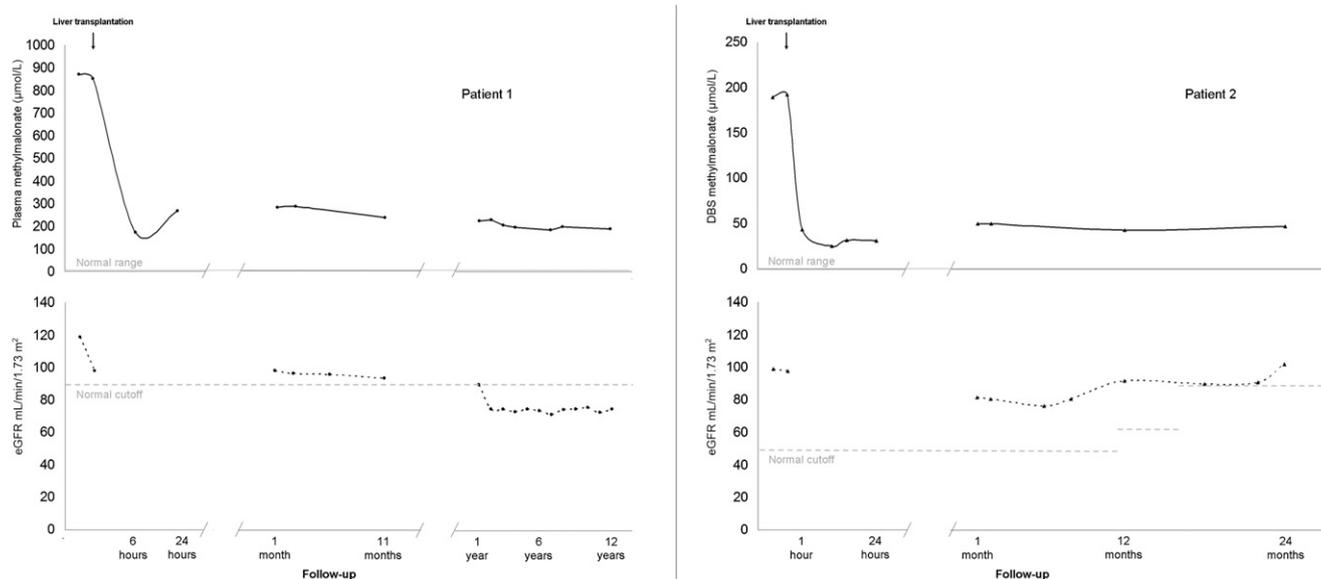
Split-liver transplant was performed at 9 months with no surgical complications. Intraoperatively, basal methylmalonate concentrations were concomitantly assessed in portal and peripheral blood and revealed similar levels (131.5  $\mu\text{mol/L}$  and 124.4  $\mu\text{mol/L}$ , respectively), consistent with complete hepatic MCM deficiency.

**TABLE 1** Clinical, Biochemical, and Molecular Characteristics of 2 Children With Diagnoses of Cobalamin-Unresponsive MCM Deficiency

Patient	Neonatal Presentation Features (2 d of life)						MCM Activity <sup>b</sup>	MCM B <sub>12</sub> Responsiveness Testing <sup>a</sup>				Genotype
	Wt Loss	pH	pCO <sub>2</sub> (mm Hg)	HCO <sub>3</sub> <sup>-</sup> (mmol/L)	NH <sub>3</sub> ( $\mu\text{mol/L}$ )	MMA ( $\mu\text{mol/L}$ )		In Vivo (Urine)				
								In Vitro	24 h	3 d	7 d	
1	15%	7.1	18	7	545	18 523	<1%	—	11 708	10 892	13 814	G158V/R467X
2	17%	7.0	15	5	489	20 142	<1%	0.58; 0.58	6453	4538	5680	R228Q/Q734X

<sup>a</sup> In vitro test: propionate incorporation in fibroblasts in medium with and without high vitamin B<sub>12</sub> concentration. In vivo test: daily parenteral OH-cobalamin (1 mg) was administered for 1 wk and urine methylmalonate concentration (mmol/mol creatinine) assessed at 24 h, 3 d, and 7 d.

<sup>b</sup> In pmol/minute per mg protein.



**FIGURE 1** Early perioperative and long-term methylmalonate concentrations (continuous lines) assessed in plasma (normal range 0.05–0.30  $\mu\text{mol/L}$ ) and in dried blood spot (DBS, normal range 0.07–0.46  $\mu\text{mol/L}$ ) and eGFR (dotted lines) in 2 patients with severe MCM deficiency treated by liver transplant.

Significant clearance of peripheral methylmalonate was observed immediately after the left split-liver graft reperfusion (43.5  $\mu\text{mol/L}$  after 60 minutes), consistent with a prompt effectiveness of the transplanted organ in metabolizing methylmalonil-CoA to succinyl-CoA (Figure 1).

Clinical and biochemical follow-up were uneventful while the patient was on a tacrolimus and mycophenolate mofetil immunosuppressive regimen. Longitudinal renal function assessments showed a stable estimated glomerular filtration rate (eGFR), with a transient slight decrease in the first 6 months after liver transplant, followed by progressive improvement up to pretransplant values. Carnitine supplementation has been maintained (100 mg/kg per day). Normal tolerance to catabolism due to fasting or intercurrent infections has been obtained by liver transplant and a significant increase in protein dietary intake (from 0.8 g/kg per day to 1.8 g/kg per day). After 2 years' follow-up, the patient shows adequate neurologic development as

assessed by the Bayley-III scale (cognitive functions: composite score 90; percentile rank 25; 95% CI, 83–99; receptive and expressive communication: composite score 86; percentile rank 18; 95% CI, 80–94; gross and fine motor skills: composite score 88; percentile rank 21; 95% CI, 81–97).

## DISCUSSION

Acute metabolic decompensation episodes, severe comorbidity, and disappointing prognosis *quoad vitam* hamper the clinical course of MMA managed by conventional substrate reduction therapy. Cumulative observations in patients with early-onset cobalamin-unresponsive MCM deficiency revealed an 80% mortality rate by 7 years of age, with >50% of survivors suffering from chronic encephalopathy.<sup>2,3</sup> Although improvements in conventional medical management have allowed a reduction of mortality in patients born after 1990, growth retardation, poor nutritional status, renal impairment, and neurologic damage remain invariable complications of the disease.<sup>12</sup>

In this scenario, liver transplant is a potential alternative for the management of severe MCM deficiency, providing the greatest mutase enzyme activity among transplantable solid organs (5 times greater than that of kidney transplants).<sup>13</sup> However, criticisms have been raised about the observation that a liver transplant is a palliative treatment rather than a cure for MMA, because MCM deficiency persists in other tissues after the procedure.<sup>14</sup>

To the best of our knowledge, 25 patients with severe MCM deficiency treated by isolated liver transplant have been reported so far.<sup>15–19</sup> Significant persistent curtailment (~80%) without normalization of the preoperative methylmalonic acid concentration has been generally reported, with reduction or disappearance of metabolic decompensation episodes in most patients.<sup>12,15,19</sup>

Some improvements were also obtained by isolated kidney transplants, although they are limited to patients with MMA and advanced chronic kidney disease.<sup>20,21</sup>

Disappointing outcomes have been recorded as well. In fact, potential persistent intrathecal methylmalonate synthesis is considered a permanent risk factor for metabolic stroke,<sup>9,22</sup> and renal failure and neurologic disabilities have been reported in 16% to 22% of transplant recipients, besides a significant perioperative risk.<sup>15</sup> However, current perception of the role of liver transplant in MCM deficiency should be considered in the light of the widely heterogeneous age at surgery and clinical condition of the few patients who underwent transplant.

One of the delicate issues in transplants for metabolic conditions is timing. Postponing a transplant to a later stage could lead to additional neurologic insults and probably inferior neurodevelopmental outcomes.<sup>23</sup> Recent data suggest that children with organic acidemia and hyperammonemia undergoing transplant at the youngest ages have the highest risk of graft loss, which is often related to technical difficulties during surgery.<sup>24</sup> However, the reported increased morbidity in younger children should be considered carefully, given the limited experience of some centers with liver transplants in very small children, potentially contributing to suboptimal results.<sup>25</sup> Additionally, children with these rare conditions are looked after by tertiary specialists in metabolic units, often with no direct links to the transplant centers, so that the patients are proposed for liver transplant when the margins for recuperation are limited.<sup>22</sup>

Relying on an experienced liver transplant center,<sup>26</sup> we treated by early liver transplant 2 patients with severe MCM deficiency. This “partial enzyme replacement” approach was chosen after careful assessment of an acceptable risk for the patients, balancing the natural course under conventional treatment, the

transplant risks, and the expected clinical benefits from the procedure. In our strategy, liver transplant was planned early, before any relevant neurologic or renal morbidity had developed, thus optimizing the effectiveness of transplant on the predictable course of the disease. No preoperative dialysis was performed,<sup>27</sup> and a metabolic specialist monitored all phases of the transplants. The posttransplant follow-up protocol included trimestral multidisciplinary medical assessments and yearly brain imaging. In both our patients, liver transplant allowed prevention of decompensation episodes; preservation of renal function, thus avoiding the need for combined liver–kidney transplants (recommended when eGFR < 20 mL/minute per 1.73 m<sup>2</sup>); normalization of dietary protein intake; and a marked improvement in quality of life. After 12 years of clinical and laboratory follow-up, the first patient reveals normal intellectual outcome, stabilization of peripheral methylmalonic acid concentration, and only mild renal function impairment. At 2 years’ follow-up, the clinical course in the second patient is uncomplicated.

### CONCLUSIONS

Based on our experience, we strongly suggest considering early liver transplant (ideally within the first year of life) as the most suitable therapeutic option in cobalamin-unresponsive MCM deficiency. Nonetheless, contingent local factors should be carefully weighted in the risk evaluation at assessment, and close long-term clinical and metabolic follow-up should be maintained even after liver transplant.

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### ABBREVIATIONS

CI: confidence interval  
eGFR: estimated glomerular filtration rate  
MCM: methylmalonyl-CoA mutase  
MMA: methylmalonic acidemia

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