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Liver or Combined Liver-Kidney Transplantation for Patients with Isolated Methylmalonic Acidemia: Who and When?

The hereditary disorders of vitamin B_{12} (cobalamin) and methylmalonic acid metabolism comprise a major group of organic acid disorders that are collectively common inborn errors of metabolism.[1] Affected patients are medically fragile and suffer multisystemic complications, such as lethal metabolic instability, metabolic stroke, pancreatitis, end-stage renal failure, growth impairment, osteopenia, optic nerve atrophy, and neurocognitive delay.[2] The frequency of these complications and their precipitants, long-term sequelae, and optimal treatment regimens remain ill-defined. In many patients, severe symptoms persist despite conventional medical and nutritional therapy, which stands in contrast to the recent practices adopted in the US and other countries to screen all newborns for a large number of metabolic diseases including MMA.[3]

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Isolated methylmalonic acidemia (MMA) has 3 major distinct genetic etiologies related to the activity of the 5′deoxyadeno-sylcobalamin-dependent enzyme methylmalonyl-CoA mutase

LKT	Liver-kidney transplantation
MMA	Methylmalonic acidemia
MUT	Methylmalonyl-CoA mutase

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(MUT) and the enzymes that synthesize the vitamin B_{12} cofactor.[2] Mutations in the genes encoding the MUT apoenzyme, mitochondrial adenosylco(I)balamin transferase (MMAB), and in the *MMAA* gene product, a G protein chaperone, define the *mut*, *cblB*, and *cblA* complementation groups, respectively. The most common and severe form of isolated MMA is caused by a defect in the MUT apoenzyme itself.[4] The resulting disorder, designated *mut* MMA, is further divided into biochemical phenotypes according to enzyme activity. Cells from patients with absent MUT activity are designated mut^0, and cells with detectable but abnormal activity are designated mut^-. Children with the *cblA* or, rarely, *cblB* form of MMA have a greater chance of responding clinically to supplemental vitamin B_{12} and usually are not as severely affected as children with the mut^0 subtype.[5]

The prognosis for long-term survival in vitamin B_{12}-nonresponsive forms of MMA is unquestionably poor.[4-9] This poor prognosis has been verified repeatedly since the first studies on outcome were published in the early 1980s and persists more than 3 decades later; the mortality of *mut* MMA was ~60% or higher in the 1980s[5,6] and improved only slightly, to ~40%, by the first decade in the 2000s.[4-9] The unacceptably high mortality and significant morbidity experienced by patients with mut^0 and *cblB* MMA has led centers to pursue elective liver transplantation and combined liver-kidney transplantation (LKT) as a treatment for the metabolic instability that can eventually lead to demise.[10-14]

The first patients with MMA treated by liver transplantation and LKT were reported in the late 1990s, and it was anticipated that metabolic correction might be complete after transplantation, similar to what is noted in other inborn errors of metabolism for which LKT is curative, such as primary oxalosis type I.[10,15] The degree of biochemical correction seen after liver transplantation or LKT in patients with MMA, although ameliorated compared with the pretransplanted state, was markedly incomplete, however. All reported patients with mut^0 MMA who underwent liver transplantation or LKT, including the patients described by Niemi et al in this issue of *The Journal*,[16] continue to exhibit persistent and significant biochemical abnormalities. The massive metabolic perturbations experienced by the patients after transplantation highlights the fact that for patients with MMA and related organic acidemias, circulating metabolites are only partly predictive of transplantation efficacy. Transplant recipients experience clinical improvements in the face of persistent metabolic abnormalities owing to the provision of MUT activity in the liver, which restores activity to the hepatic propionate oxidation pathway and corrects the mitochondrial dysfunction that characterizes the cellular phenotype of MMA in both animal models and tissues from patients.[17-20]

Since the 1990s, numerous patients with MMA have undergone either liver transplantation or LKT.[4,11-14,21-28] Some of these patients have been reported briefly within larger series, and others have been reported as individual cases or in small series, and many remain unpublished. The experience to date, with the exception of a group of patients treated early in life by transplantation of a living-related donor liver in Asian transplant centers,[13,14,22] has largely described results in older children, adolescents, and young adults. Many of the reported patients have not been precisely characterized with respect to cellular enzymology and/or molecular genetics, making informative decisions regarding patient care from the review of the available literature particularly challenging. Whether the best practice is to offer transplantation primarily to older patients when they reach the later phases phase of renal failure (chronic kidney disease stage III-IV), with either isolated kidney transplantation or combined LKT, or to offer elective liver transplantation to infants and young children is unknown. A longer waiting period before transplantation prolongs the exposure to disease-related complications and may increase long-term morbidity; moreover, the most severely affected patients may perish before they present for renal transplantation.

It is recognized that liver transplantation in patients with MMA largely protects against metabolic instability and the need for frequent hospitalizations, which in itself leads to an improved quality of life for patients and their families. On the other hand, it is not curative, because high levels of methylmalonic acid persist in the blood and cerebrospinal fluid posttransplantation,[24,28] and patients remain at risk for long-term extrahepatic complications of MMA, such as renal insufficiency, basal ganglia injury, and optic nerve disease.[25,26,28-30] Dietary management and regular metabolic monitoring should be continued for life in all patients with MMA, regardless of whether or not they have received a transplantation.

Isolated kidney transplantation has been advocated as an alternative to the more complicated liver transplantation and LKT procedures,[31-35] even before the terminal stages of chronic renal failure, as a form of "cell therapy."[36] One of the first patients with MMA treated by isolated renal transplantation was initially claimed to have the mut^0 subtype and only much later, after kidney transplantation and a successful pregnancy, was precisely characterized and found to harbor a milder, vitamin B_{12}-responsive *cblA* form of MMA.[34,37,38] Thus, the observations from this patient and all claims surrounding the efficacy of isolated kidney transplantation as a means to treat patients with mut^0 emanating from this patient are invalid, and serve as a reminder that enzymatic subtyping as well as molecular genetics are needed to inform the decision making surrounding transplantation in patients with MMA.[37,38] Moreover, 1 kidney transplant recipient with MMA developed hepatoblastoma, neurologic deterioration, and multiorgan failure, and other patients exhibited metabolic decompensation and neurologic complications posttransplantation.[36] Long-term