Received: 12 October 2019 | Revised: 18 February 2020 | Accepted: 24 March 2020

DOI: 10.1111/petr.13714

WILEY

CASE REPORT

Pediatric liver transplantation from a living donor in mitochondrial disease: Good outcomes in DGUOK deficiency?

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Abstract

DGUOK deficiency is an autosomal recessive mitochondrial disorder characterized by hepatic and neurological manifestations. In patients with liver failure, the decision to perform LT can be difficult due to the likelihood of progressive neurological disease. We present a case of a 9-month-old boy who had DGUOK deficiency (E227K/R118H genotype) intact neurological status and liver failure. His MRI indicated extensive white matter changes, which created hesitation to perform LT. After a multidisciplinary evaluation, he underwent LT from a living donor at 11 months of age. Six years post-transplant, he has had no significant complications and no progression of neurological symptoms. Our case supports that even in the presence of neurological MRI findings, but in the absence of significant neurological symptoms, LT represents a viable option in DGUOK-deficient patients who have the E227K/R118H mutation combination along with liver failure.

KEYWORDS

DGUOK, liver failure, living donor, pediatric liver transplantation

1 | INTRODUCTION

DGUOK deficiency is an autosomal recessive mitochondrial DNA depletion disorder, caused by mutations in the *DGUOK* gene, located on chromosome 2. The defect leads to impaired purine metabolism and subsequent reductions in mitochondrial DNA. Similar to other mitochondrial DNA depletion syndromes, DGUOK most commonly presents with hepatic and neurological symptoms ranging from hepatomegaly and jaundice to hypotonia and nystagmus. Liver biopsy may further reveal cholestasis, cirrhosis, and iron deposition. Due to these disparate symptoms, treatment may be difficult and involves a multidisciplinary team.[1]

For patients with liver failure, LT is controversial. An older series suggested neurological symptoms are a contraindication to LT, while more recent reports argue that LT can improve prognosis for selected patients despite some neurological abnormalities.[1,2] We present a case of a now 6-year-old boy with the E227K/R118H mutation combination who underwent LT for liver failure caused by DGUOK deficiency.

2 | CASE

A 9-month-old African American boy born to non-consanguineous parents was referred to the emergency room by his pediatrician for hepatomegaly, poor weight gain, and jaundice. His mother reported that she had noted some jaundice approximately 2 months prior and that he had difficulty gaining weight and suffered from gastroesophageal reflux. Laboratories on presentation were significant for ALT of 101, AST of 136, total bilirubin of 2.6, INR of 2.10, AFP of 28 940, and ammonia of 83. Testing for acute hepatitis, urine organic acids, alpha one anti-trypsin, inborn errors of bile acid

Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DGUOK, deoxyguanosine kinase; EBV, Epstein-Barr virus; INR, International normalized ratio; LT, liver transplantation.

metabolism, and tyrosinemia was negative. An urgent liver biopsy was performed which revealed advanced cirrhosis and granular bright red cytoplasm in numerous hepatocytes. Electron microscopy revealed variably numerically increased and morphologically abnormal mitochondria that are typical for primary mitochondriopathy. MRI/MRS revealed diffusion restriction throughout the brain, without evidence of cerebral atrophy, infarction, or edema. These changes were thought to be suggestive of a mitochondrial or channelopathy disorder, and LT was placed on hold. Specifically, the MRI showed T2 hyperintensity in the periventricular and deep white matter. There was also T2 hyperintensity in the deep gray matter within the internal capsules and brainstem (Figure 1). The patient's hepatic function declined, and he had worsening jaundice, coagulopathy, and ascites. However, he was neurologically intact, playful, and interactive. Whole mitochondrial gene sequencing did not reveal disease-related mutations. However, the mtDNA depletion panel showed heterozygosity for two mutations in *DGUOK* (E227K/R118H). A repeat MRI, 2 weeks after the first, did not show progression of disease. The case was discussed extensively with genetics, neurology, and the parents, and he was relisted for transplant and underwent living-related liver transplant from his father at 11 months of age. At 6 years post-transplant, his course was complicated by one episode of acute rejection, which occurred 2 months post-transplant, as well as elevated EBV levels for which his immunosuppression was reduced. He is in the first grade and is neurologically and developmentally normal.

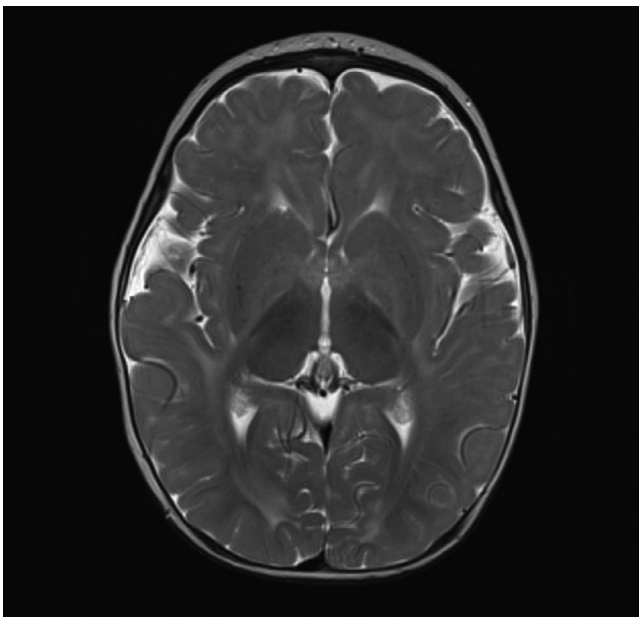

FIGURE 1 Brain MRI showing extensive white matter changes

3 | DISCUSSION

DGUOK is a multisystemic mitochondrial DNA depletion syndrome that may manifest as liver failure. Historically, LT was discouraged due to poor outcomes particularly in patients with neurological abnormalities such as nystagmus and hypotonia.[2] More recently, Grabhorn et al suggested that mild or stable neurological symptoms should not preclude LT in DGUOK deficiency patients. In their series of two patients with mild-to-moderate neurological symptoms, including hypotonia and developmental retardation, both patients successfully underwent LT reporting good neurodevelopment 5 and 8 years after follow-up.[1] Additionally, Waich et al reported a case of an infant with hepatocellular carcinoma who underwent living donor LT from her mother at 8 months of age, before the DGUOK diagnosis was made. At 36 months of age, the patient had normal psychomotor development.[3] These reports demonstrate that the symptoms alone are not sufficient to determine the outcome of LT as cases with neurological involvement had varied outcomes between no neurological deterioration, reversed neurological deterioration, severe neurological deterioration, and even death. Our patient's MRI showed T2 hyperintensities which have been implicated in stroke-like syndromes in mitochondrial disorders. This caused some concern as to the potential progression of neurological disease after LT.

These cases, including ours, support LT in the absence of significant neurological abnormalities, for patients with DGUOK deficiency in liver failure. Additionally, the last case as well as ours received living-related LT demonstrating that parents who may be carriers can also serve as donors.[3] Although the parents are the most readily available donors, and often the most willing to donate to their child, more distant relatives should be considered for alternatives and if possible unrelated donors.[1]

Ours is the first report of the E227K/R118H mutation combination causing disease. We review phenotypes and outcomes of various mutations causing DGUOK (Table 1). The E227K mutation has been previously reported as exhibiting a milder phenotype in a patient who was also compound heterozygous for R142K. It was proposed that this mutation does not hinder the protein function as severely as truncated mutations.[4] Our subject presented at 9 months

TABLE 1 Genotypic information on the E227K and R118H mutations

Genotype	Phenotype	Outcome	Study
R142K/E227K	Isolated liver failure with cirrhosis, steatosis and glycogen storage	Responded well to LT	Salviati at al [4]
E227K/Exon 4 deletion (DGUOK)	Progressive liver dysfunction, nystagmus, and developmental problems at 4 mo of age (older brother with same mutations died at 4 mo of age due to progressive liver failure)	At 4 mo of age, patient failed to reach additional developmental milestones	Lee et al [5]

of age, which is older than in previous series possibly portending a milder disease. In contrast, the E227K/exon four deletion in *DGUOK* combination was reported in an infant who developed nystagmus and progressive neurological deterioration. The case's older sibling with the same mutations developed nystagmus and severe liver failure, passing away at 4 months of age.[5]

In summary, we demonstrate that LT is not contraindicated in patients with mitochondrial liver disease. However, we strongly recommend a multidisciplinary team including genetics, neurologists, and ethicists, be assembled when deciding on LT as the genotype, and other systemic symptoms may determine long-term outcomes. Moreover, the family must be fully informed regarding the potential for progression of neurological symptoms even after LT and be allowed to participate in all aspects of decision-making. This was especially important in our case, which showed that potential carrier parents can also serve as donors.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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How to cite this article: Hassan S, Mahmoud A, Mohammed TO, Mohammad S. Pediatric liver transplantation from a living donor in mitochondrial disease: Good outcomes in DGUOK deficiency?. *Pediatr Transplant*. 2020;00:e13714. https://doi.org/10.1111/petr.13714