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CASE REPORT | PEDIATRICS

Liver Transplantation as a Treatment for Severe Refractory Vitamin E Deficiency Related to Progressive Familial Intrahepatic Cholestasis Type 2 in a Pediatric Patient

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ABSTRACT

Refractory vitamin E deficiency is thought to have irreversible effects on neurologic function. We report an adolescent boy with severe refractory vitamin E deficiency due to progressive familial intrahepatic cholestasis (PFIC) type 2. His consequent neurologic dysfunction included severe ataxia, dysmetria, dysarthria, and cranial nerve VI palsy. He underwent liver transplantation at age 13 due to his neurologic dysfunction; and afterward, he had marked improvement in neurologic function. We demonstrate that in a patient with PFIC 2 and severe refractory vitamin E deficiency, liver transplant can improve vitamin E absorption, prevent further neurological sequelae, and reverse prior neurologic dysfunction.

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) type 2 is a chronic cholestatic condition caused by deficiency of the bile salt export pump (BSEP). Deficiency of BSEP and subsequent cholestasis can cause severe fat-soluble vitamin deficiencies, including vitamin E deficiency.[1] Vitamin E deficiency can be associated with severe neurologic effects that are generally thought to be irreversible if levels are not repleted.[2]

CASE REPORT

A 13-year-old boy presented with a presumed diagnosis of PFIC type 1. He was observed to have cholestatic liver disease at age 1 with normal gamma glutamyl transpeptidase and had worsening pruritus that was unresponsive to ursodiol and rifampin until age 3.5, when the PFIC type 1 diagnosis was made based on clinical history. He underwent Roux-en-Y partial biliary diversion at age 3.5, which resolved his pruritus. The patient maintained appropriate growth and development until age 12, at which point he had acute onset of regression of speech, loss of fine and gross motor milestones, cerebellar ataxia, severe dysarthria, word scanning, slow speech, new refractive amblyopia, and concern for vision loss. Magnetic resonance imaging of his brain and 24-hour video electroencephalogram were normal. His neurologic findings were all attributed to severe vitamin E deficiency, as levels were undetectable at the outside hospital. He was started on high oral doses of vitamins A, D, E, and K. He had progressive worsening of neurologic function despite gastrojejunostomy tube feeds with hydrolysate formula and a trial of parenteral nutrition for optimal provision of micronutrients. He was tried on multiple oral forms of vitamin E (standard, water-soluble, and pegylated) with total intake up to 8,435 international units (IU) vitamin E daily; the recommended daily allowance for a 13-year-old boy is 16 IU daily. Five months later, he continued to have undetectable vitamin E levels despite ensuring compliance.

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At the time of his presentation to our institution, trials of transdermal and parenteral vitamin E were attempted without detectable levels. Vitamin D on 50,000 IU biweekly was 5.3; vitamin A was normal on 10,000 IU daily, and international normalized ratio ranged from 1.0–1.3 on 10 mg vitamin K orally daily. He had no other medical history and no history of consanguinity. His weight was 33 kg (<3 percentile), and his height was 148.1 cm (<3 percentile). He was anicteric, had bilateral clubbing, and had no hepatosplenomegaly. A gastrojejunostomy and biliary drain were present. He was noted to have absent deep tendon reflexes in his lower extremities, ataxic gait, intention tremor, dyssynergia, dysmetria, dysarthria, slowing of rapid alternating movements. He also had decreased sensation to vibration bilaterally in toes, and decreased muscle bulk in the lower extremities. He had intact speech comprehension, but had significant dysarthria and scanning speech. The remainder of his exam was unremarkable. After 1 year of high-dose supplementation, tocopherol levels were un-detectable. Genetic testing showed that the patient was a compound heterozygote for two missense mutations (c.3457C>T and c.499G>A) in the *ABCB11* gene, confirming the diagnosis of PFIC 2. Given significant neurologic morbidity, the patient was listed for liver transplant with model for end-stage liver disease (MELD) score of 6, with a pending appeal for higher MELD. He received an anonymous orthotopic left lateral segment living donor liver transplant 18 days after listing. For post-transplant immunosuppression, he received tacrolimus, mycophenolate mofetil, and a short course of corticosteroids. His post-transplant course was uncomplicated. With extensive physical therapy and occupational therapy, he was ambulating with a walker by the time he was discharged from the hospital. Preoperative and postoperative day (POD) 8 vitamin E alpha levels were undetectable. Vitamin E supplementation was started POD 15; vitamin E level on POD 22 was 0.6 mg/dL and on POD 39 was 7.8 mg/L.

The patient is now 16 years old, ambulates independently, can run briefly, can speak in full sentences, and has markedly improved coordination. He continues to improve his motor and language skills and has greatly improved his quality of life, but he still has residual ocular problems and cranial nerve VI palsy.

DISCUSSION

Cholestasis is a decrease in bile flow that can be due to biliary obstruction, such as an anatomic abnormality, or be secondary to impaired hepatocellular biliary secretion, such as that which occurs in congenital hepatic transport defects like PFIC types 1–3. The primary functions of bile include excretion of cholesterol and absorption of hydrophobic micronutrients by solubilizing these products in the intestinal lumen. Regardless of the etiology of the cholestasis, bile accumulates in the liver, which causes damage and results in lower concentrations of intestinal luminal bile. This subsequently leads to a reduction in absorption of fat-soluble vitamins A, D, E and K, as these require immersion in bile for absorption.[3]

Vitamin E deficiency can cause neuromuscular manifestations as well as hemolysis. Neuromuscular manifestations of vitamin E deficiency are primarily of neuropathic and myopathic origin. Most cases of severe vitamin E deficiency leading to neurologic symptoms are thought to be irreversible if detectable serum levels are unable to be achieved. Case reports of vitamin E deficiency due to steatorrhea causing reversible neurologic symptoms after supplementation and achievement of detectable serum levels have been reported.[4,5] We found no reports of refractory vitamin E deficiency caused by PFIC 2 or other cholestatic causes leading to severe neurologic dysfunction being markedly improved by liver transplantation. Fat-soluble vitamin deficiency, especially vitamin E deficiency, can be difficult to manage in patients with PFIC 2 and other forms of cholestasis. We have demonstrated that in a patient with PFIC 2 and severe refractory vitamin E deficiency, liver transplant can improve vitamin E absorption, prevent further neurological sequelae, and can reverse prior neurologic dysfunction.

DISCLOSURES

Author contributions: E. Collyer wrote the manuscript. V. Hupertz, B. Eghtesad, and K. Radhakrishnan provided scholarly oversight and edited the manuscript. K. Radhakrishnan is the article guarantor.

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