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ORIGINAL ARTICLE

Presentation of an Acquired Urea Cycle Disorder Post Liver Transplantation

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The liver's role as the largest organ of metabolism and the unique and often critical function of liver-specific enzyme pathways imply a greater risk to the recipient of acquiring a donor metabolic disease with liver transplants versus other solid organ transplants. With clinical consequences rarely reported, the frequency of solid organ transplant transfer of metabolic disease is not known. Ornithine transcarbamylase deficiency (OTCD), although rare, is the most common of the urea cycle disorders (UCDs). Because of phenotypic heterogeneity, OTCD may go undiagnosed into adulthood. With over 5000 liver transplant procedures annually in the United States, the likelihood of unknowingly transmitting OTCD through liver transplantation is very low. We describe the clinical course of a liver transplant recipient presenting with acute hyperammonemia and encephalopathy after receiving a liver graft form a donor with unrecognized OTCD. ***Liver Transpl 13:1714-1716, 2007.*** © **2007 AASLD.**

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CASE REPORT

A 59-year-old Caucasian female underwent uncomplicated, whole organ liver transplantation for end-stage liver disease secondary to cryptogenic cirrhosis. The procedure was performed by a piggyback technique with choledochocholedochostomy with a graft from a young adult male who did not meet extended donor criteria. She was stable, nonencephalopathic, and nonhospitalized at the time of transplant. She had a past medical history of diabetes, hypothyroidism, sleep apnea, and gastric bypass surgery but no previous neurological disease or serum ammonia assays.

The patient was transferred in stable condition to the medical ward and was tolerating diet, was ambulating, and had clear mentation by postoperative day (POD) 1. Initial immune suppression included corticosteroids and mycophenolate mofetil. Tacrolimus (0.02 mg/kg twice daily) was initiated on POD 1. Prophylactic antimicrobials included ceftizoxime and oral ganciclovir. POD 1 duplex ultrasonography confirmed normal allograft arterial and venous flow, and biliary tube cholangiography showed a normally functioning choledochocholedochostomy.

She suddenly became unresponsive on POD 2. On initial assessment, no acute metabolic, hematologic, or cardiopulmonary abnormalities were noted, and labs confirmed improving graft function and no significant coagulopathy. The patient was transferred to the intensive care unit. Brain computerized tomography revealed diffuse cerebral edema. Bacteriologic and virologic studies of blood, urine, and cerebrospinal fluid were negative. However, her ammonia level was 608 μmol/L (normal range, 12-47), with a confirmation test result of 744 μmol/L. The marked hyperammonemia in the setting of improving graft function raised concerns for a UCD acquired by the patient from the donor through liver transplantation. The donor's medical history was reviewed. He was 27 years old, with a history of cerebral palsy and seizure disorder, and had died following complications of seizures but had no known metabolic disease.

While testing for a UCD was underway, the hyperammonemia was treated with lactulose, supplementation with sodium benzoate, L-arginine, and ornithine hydrochloride. Hemodialysis was also performed in an effort to reduce hyperammonemia. Ammonia levels decreased to 111 and 47 μmol/L on POD 3 and POD 4, respectively. Systemic and central nervous system infections

Abbreviations: OTCD, ornithine transcarbamylase deficiency; POD, postoperative day; UCD, urea cycle disorder.

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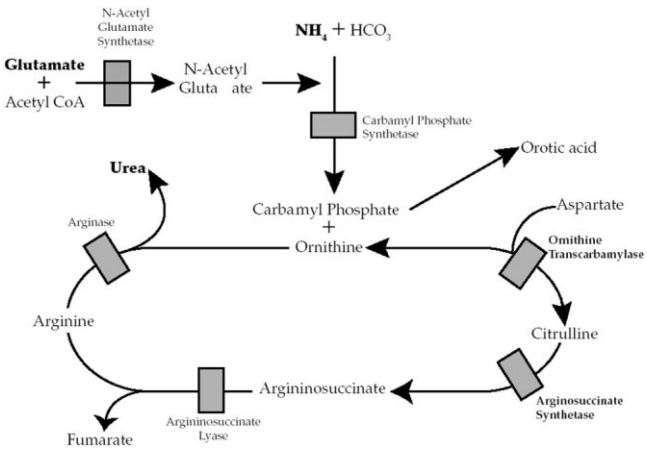

Figure 1. The urea cycle.

were ruled out. An external ventricular drain was placed to reduce intracranial pressures. Urine collection analysis for urea cycle metabolites on POD 3 revealed a markedly elevated excretion of orotic acid, 984 mmol/mol creatinine (controls, 1.0-3.2), a finding diagnostic of OTCD. Liver retransplantation was considered; however, despite correction of the hyperammonemia and aggressive supportive care, the patients' neurologic condition deteriorated, meeting brain death criteria by POD 4, and life support was withdrawn.

Postmortem examination of the brain confirmed cerebral edema, with diffuse autolysis, hyperacute laminar cortical and hippocampal neuronal necrosis consistent with acute encephalopathy, and global anoxic injury. The liver was grossly icteric, with intact vascular and biliary anastomosis. Histologically, the liver had moderate cholestasis, mild microsteatosis and preservation injury, and mild acute cellular rejection.

DISCUSSION

The suspicion of a UCD in this case was based on the identification of severe hyperammonemia in the setting of otherwise improving graft function, which quickly ruled out other causes of hyperammonemia such as primary nonfunction or vascular graft injuries. The diagnosis of OTCD was confirmed by the high urinary orotic acid levels.

Nitrogen metabolism and excretion are dependent on the urea cycle (Fig. 1). Excess nitrogen from protein breakdown is converted to ammonia, which is metabolized predominantly by hepatocytes via the urea cycle into nontoxic and more readily excreted urea. The central nervous system lacks an effective urea cycle and depends on glutamine formation for ammonia removal. In the setting of acute hyperammonemia, glutamine accumulates in astrocytes, leading to osmotic swelling and cerebral edema. Ammonia may also directly impair cerebral energy metabolism and neuroastrocyte trafficking of amino acids and monoamines. Deficiencies of enzymes associated with the urea cycle constitute the UCDs. The most common of these is OTCD, a mitochondrial matrix enzyme and the only UCD with X-linked inheritance. An Italian prospective screening study detected OTCD in only 1 of 69,904 children.[1] However, with over 244 mutations and 13 polymorphisms for the OTC gene identified by 2002[2] and with novel mutations being newly discovered, the mutation carrier rate is probably underestimated by current epidemiologic data.

Total or severe OTCD typically affects male infants who present with fatal hyperammonemia. Partial deficiency more commonly affects females, exhibits a wider spectrum of phenotypes, and can present later in life with episodic hyperammonemic crisis under conditions of stress.[3] Variable phenotypic expression and clinical presentations, even for the identical gene mutations in single-family analysis, have been demonstrated.[4] Symptoms of late-onset OTCD can range from mild irritability or nausea during episodes of stress and hyperammonemia to associated neuropsychiatric changes, seizures, coma, or death. Individuals may manifest protein toxicity, can have developmental and cognitive deficits, and often instinctively follow a low-protein or vegetarian diet. Late-onset OTCD may evade diagnosis well into adulthood, with a potential for organ donation from unrecognized carriers. An affected liver graft's limited capacity for nitrogen metabolism may be overwhelmed by the stresses of liver transplantation, with potential hyperammonemia-related neurological sequelae in the recipient.

There is no practical strategy to screen organ donors for unrecognized late-onset OTCD. Donor exclusion for a history of seizures or neuropsychiatric disease seems unreasonable on the basis of the apparent rarity of this scenario and current organ shortage. Suspicion of undiagnosed late-onset OTCD in potential organ donors may be facilitated by a history of encephalopathy, seizures, or neurologic disorders, but more subtle symptoms of episodic nausea, lethargy, irritability, or dietary protein avoidance may be the only features in more atypical cases. Marked hyperammonemia in a potential donor with a suggestive history would raise sufficient concern to prevent donation. However, ammonia levels can normalize soon after a crisis, and mild to moderate hyperammonemia or even the absence of hyperammonemia with a suggestive history should also preclude donation until further evaluation is completed. Orotic aciduria can be rapidly detected by novel liquid chromatography/mass spectrometry methods[5] and is used to differentiate OTCD from carbamyl phosphate synthase I deficiency. Marked orotic aciduria, as in this case, is virtually diagnostic of OTCD, but deficiencies of arginase, argininosuccinate synthetase, or argininosuccinate lyase or only partial OTCD can result in mild increases (Fig. 1). Mild orotic aciduria may also be present in patients with severe trauma.[6] The time constraints of deceased donor organ donation may limit genetic testing or enzymatic assays on liver tissue in suspected but unconfirmed cases of late OTCD, although provocative testing with protein loading or allopurinal challenge may be considered. On the other hand, the setting of live donation would allow for com-

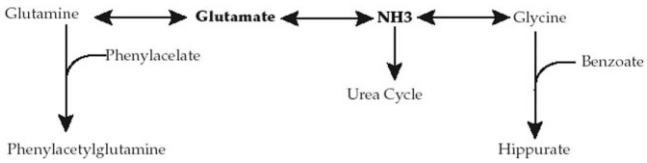

Figure 2. The alternate pathway of nitrogen removal.

prehensive testing in a prospective donor. In a recent series, outcomes of living donor liver transplantation for UCDs using heterozygous carriers was acceptable, but those using male donors hemizygous for OTCD were not because of the risk of sudden-onset fatal hyperammonemia.[7]

Immediate evaluation of acute neurological changes post transplant should focus on likely etiologies, such as acute central nervous system events, seizure, adverse drug effect, and more common metabolic abnormalities. Nevertheless, determination of ammonia levels in this case significantly expedited correct diagnosis. Screening for UCDs includes testing for elevated serum levels of precursor amino acids, glutamine and alanine, decreased serum levels of citrulline, and increased urinary orotic acid and uridine. Mutation analysis for UCDs is not readily available but when available would precede liver biopsy for measurement of enzyme activity.[8]

Treatment of OTCD with hyperammonemia is directed at minimizing precipitating stressors, decreasing ammonia levels, managing encephalopathy, and considering liver retransplantation. Reported precipitants have included increased dietary protein intake, childbirth, infection, gastrointestinal bleed, and medications (allopurinol), but exacerbations can occur spontaneously. The precipitants of hyperammonemic crisis in this case were postulated to be surgical stress and possible exacerbation of underlying OTCD by allograft reperfusion injury. Dietary protein restriction and high caloric intake minimize protein catabolism and are universally indicated. Rapid reduction of ammonia levels is most effectively achieved by hemodialysis in cases with significant neurologic compromise.[9] Adjunctive medical treatment therapy includes stimulation of the alternative pathway for ammonia and glutamine metabolism (Fig. 2) through supplementation with sodium benzoate and sodium phenylacetate and priming of the urea cycle by supplementation of its substrates arginine or citrulline.[10] Extreme hyperammonemia during exacerbation can be transient, and it is difficult to attribute the rapid correction of ammonia levels in this case to medical intervention alone. Supportive care would include standard-of-care measures for reducing and monitoring increased intracranial pressures. Unfortunately, even with prompt diagnosis, treatment may not be effective once cerebral edema has developed, as was the case here.

This scenario is rare on the basis of a review of the transplant literature, with only 2 reports of transmission of UCDs through liver transplantation.[11,12] Multiorgan transplantation using a donor with late-onset OTCD resulted in fatal hyperammonemia in the liver graft recipient and successful outcomes in the kidney, heart, and lung recipients.[11] The molecular adsorbent recirculation system was successful in lowering dialysis-unresponsive hyperammonemia with recipient survival following transmission of glutamine synthetase deficiency.[12] To our knowledge, this is the first reported case of OTCD transmission through solid organ transplantation from North America.

This case highlights the potential for transferring clinically important enzymatic and metabolic derangements through liver transplantation. There is currently no practical role or method to screen for OTCD in deceased organ donors; however, testing ammonia levels in recipients with acute neurologic decompensation can bring immediate attention to the possibility of transferred OTCD.

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