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Orthotopic Liver Transplantation for Ornithine Transcarbamylase Deficiency With Hyperammonemic Encephalopathy

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• Ornithine transcarbamylase (OTC) deficiency is an X chromosome-linked disorder causing hyperammonemic encephalopathy with a very poor prognosis. We describe here two patients with OTC deficiency, one a late-onset female patient (case 1) and the other a neonatal-onset male patient (case 2), who were successfully treated with orthotopic liver transplantation (OLTx). The OTC activity in the excised liver was 10% and 0% of control, respectively. Hyperammonemic encephalopathy was controlled with medical therapy in case 1 until the age of 5 years, but the complicated course in case 2 in which hyperammonemia required peritoneal dialysis and hemodialysis in the neonatal period necessitated OLTx with a reduced-size liver at the age of 80 days. Both patients had restoration of serum ammonia level to normal in 2 and 3 days after liver replacement, and both patients have normal neurological and developmental status after 2 and 0.5 years of postoperative follow-up. These cases illustrate not only the metabolic cure of this disorder, but also the need to preserve neurological integrity by aggressive medical management of the hyperammonemia preoperatively and early surgical intervention when indicated, even if this is required very early in life.

INDEX WORDS: Orthotopic liver transplantation; ornithine transcarbamylase deficiency; urea cycle enzyme deficiency; hyperammonemic encephalopathy; reduced-size liver transplantation.

ORNITHINE transcarbamylase (OTC) deficiency is an X chromosome-linked disorder that causes hyperammonemia and elevated blood glutamine levels.[1-4] The acute development of these metabolic abnormalities causes brain edema, which often progresses to coma and death.[1-6] Patients with urea cycle enzyme abnormalities including OTC deficiency have undergone liver transplantation as a substitutive treatment for medical therapy.[3,5,7,8] This article describes two cases of OTC deficiency with hyperammonemic encephalopathy that were successfully treated with orthotopic liver transplantation.

CASE REPORTS

Case 1

A girl with an uncomplicated gestation and delivery presented with vomiting and feeding intolerance at about 3 weeks of age. Her ammonia level was elevated to 337 μmol/L, which could be controlled by protein restriction. At the age of 1 year, serum amino acid analysis showed an elevated glutamine level. Despite treatment with benzoate, citrulline, and carnitine, she experienced periodic episodes of hyperammonemic encephalopathy ranging from lethargy to coma and was referred to our institution at the age of 5 years in July 1991. Her only presenting symptom was a mildly ataxic gait. Her ammonia level was 151 μmol/L, serum glutamine level was 108 μmol/dL (control, 32 to 87 μmol/dL). She had a body weight of 26 kg, blood urea nitrogen less than 2mg/dL, and mildly elevated liver enzymes.

On July 17, 1991, she underwent orthotopic liver transplantation from a 6-year-old donor of identical blood type and body weight, using a piggy-back method[9] and Roux-en-Y choledochojejunostomy. FK 506 (Tacrolimus; Fiujisawa Pharmaceutical Co, Osaka, Japan) and steroids were used as immunosuppressive agents, and the postoperative course was uneventful. From the resected native liver, OTC enzyme analysis showed a residual activity of about 10% (235 μmol/h/g weight of liver; control, 2417 μmol/h/g weight of liver). Carbamyl phosphate synthetase I, arginosuccinate synthetase, arginosuccinase, and arginase enzyme activities were within normal ranges. Plasma ammonia levels returned to a normal range on the second postoperative day. She has had no neurological deficits, and after a 2-year follow-up, she is doing well without protein restriction and has normal development.

Case 2

A boy with a full-term uncomplicated delivery manifested symptoms of lethargy and decreased breast feeding frequency at around 24 hours of age. By 36 hours, he began vomiting with concomitant respiratory alkalosis and an elevated ammonia level of 334 μmol/L. The serum glutamate level was elevated (28 μmol/dL; control, 0 to 10 μmol/dL) and citrulline was nondetectable. Urinary orotic acid was markedly elevated (173 μmol/min creatinine; control, 0 to 3 μmol/min creatinine). From the liver biopsy performed at the age of 27 days, OTC enzyme activity was completely nondetectable. The other urea cycle enzyme activities were normal. He was placed on a low-protein diet, benzoate, and phenylacetate. Despite this therapy, episodic hyperammonemia developed, associated with severe lethargy, and peritoneal dialysis and hemodialysis were required. On October 2, 1993, he was transferred to our institution with an ammonia level of 130 μmol/L. His liver enzyme levels were slightly elevated. He was profoundly lethargic but with no focal neurological deficits. All other systems were within normal range.

On October 8, 1993, at the age of 80 days (body weight 6 kg), he underwent orthotopic liver transplantation using a reduced-size left lateral lobe liver graft from a 5-year-old 26 kg donor of identical blood type. The operation was performed using a piggy-back

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method[9] and Roux-en-Y choledochojejunostomy. Immunosuppression was with FK 506 and steroids. Except for intraabdominal bleeding necessitating reexploration on day 1 and seizures on day 2 (ammonia 69 μmol/L), his recovery was steady. By the third postoperative day, the ammonia level as well as his serum amino acids and urinary orotic acid levels returned to normal. A mild acute cellular rejection was treated with increased steroids, and a pleural effusion resolved with total parenteral nutrition. On 6-month follow-up, he has been well with no neurological or developmental impairment.

DISCUSSION

OTC deficiency is clinically classified into two groups, neonatal-onset male patients and late-onset female patients. We had one of each. Because the structural gene encoding for the OTC enzyme protein is located on the short arm of the X-chromosome, Xp 21.1,[2] the homozygous male patient typically is completely enzyme deficient and subsequently has encephalopathy caused by hyperammonemia, which presents as irritability, poor feeding, vomiting, and lethargy, usually within the first week of life.[1-3,5,6] These neonatal-onset patients have poor prognoses.[1-3,5,6]

In contrast, the heterozygous female patient has a partial enzyme deficiency because of random inactivation of the X-chromosome caused by lyonization.[1-3,5] These patients have variable clinical symptoms that manifest later in life, occurring after 1 month of age, or possibly not at all.[1-3,5] Our female patient (case 1) had partial enzyme deficiency with late-onset symptoms, whereas our male patient (case 2) completely lacked the OTC activity and consequently had acute onset of symptoms shortly after birth and required peritoneal dialysis and hemodialysis, despite which hyperammonemia was refractory to treatment.

A serum ammonia level greater than 200 μmol/L causes diffuse brain edema.[2] With the rapid elevation of ammonia, irreversible brain edema and herniation develop, which invariably result in death without prompt intervention.[1-6] The initial medical therapy consists of protein restriction, benzoate, phenylacetate, arginine, citrulline, pyridoxine, and folic acid administration, and peritoneal dialysis or hemodialysis.[1,2,4,5] These therapies are burdensome and can have side effects of developmental impairment secondary to malnutrition.[4,5] Moreover, despite medical intervention, most of the patients have recurrent hyperammonemia, which is easily precipitated by catabolic stress, such as starvation, dehydration, surgical operation, and infection.[1,2,4,5] Both of our patients (especially case 2) were prone to hyperammonemic encephalopathy even when treated optimally, and required liver transplantation as a last resort.

Liver transplantation has been attempted on patients with urea cycle enzyme abnormalities, including OTC deficiency, because the liver is responsible for producing urea cycle enzymes. In the reported cases[3,5,7,8] and our two cases, serum ammonia levels decreased promptly after transplantation and then serum amino acid profile and urinary orotic acid returned to normal range. Our patients emerged unscathed neurologically, in contrast to several reported patients who were left impaired despite complete metabolic correction.[3,8]

According to Msall et al,[10] the most important prognostic factor, because it is correlated to brain damage and impairment of intellectual function, is the duration of neonatal hyperammonemic coma. Consequently, early diagnosis and aggressive management are the keys to nervous system protection. Recently, the prenatal diagnosis of OTC deficiency using chorionic villus sampling has become available[2,11] and may facilitate more effective early treatment, particularly of homozygous male patients with this disorder in their family histories. It is important in all cases to avoid catabolic stress such as dehydration, malnutrition, or infection. Liver transplantation may be indicated in the neonatal period, and although this may be technically difficult, the risks of proceeding in expert hands are less than those of irreversible brain damage.

In conclusion, for patients with OTC deficiency who have hyperammonemic encephalopathy, orthotopic liver transplantation is an appropriate treatment. In addition to early attempt of transplantation, aggressive management of pretransplantation hyperammonemia, especially in the neonatal period, and avoidance of catabolic stresses are important for preventing neurological damage.

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