

Developmental Outcomes With Early Orthotopic Liver Transplantation for Infants With Neonatal-Onset Urea Cycle Defects and a Female Patient With Late-Onset Ornithine Transcarbamylase Deficiency

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ABSTRACT. Urea cycle defects (UCDs) typically present with hyperammonemia, the duration and peak levels of which are directly related to the neurologic outcome. Liver transplantation can cure the underlying defect for some conditions, but the preexisting neurologic status is a major factor in the final outcome. Multicenter data indicate that most of the children who receive transplants remain significantly neurologically impaired. We wanted to determine whether aggressive metabolic management of ammonia levels after early referral/transfer to a metabolism center and early liver transplantation would result in better neurologic outcomes. We report on 5 children with UCDs, ie, 2 male patients with X-linked ornithine transcarbamylase deficiency and 2 male patients with carbamoyl phosphate synthase deficiency, all of whom had neonatal presentations and underwent orthotopic liver transplantation before 1 year of age, and 1 female patient with partial X-linked ornithine transcarbamylase deficiency that was intractable to medical therapy, who underwent transplantation at 35 months of age. Developmental testing with the Griffiths scale was performed on 3 occasions each, 12 months apart, up to 45 months after transplantation. Full-scale indices for 3 children who underwent early transplantation showed average developmental quotients of 67. All 5 children had metabolic cures. There were no deaths (30-month survival rate: 100%). One child is currently listed for repeat transplantation because of bile duct stenosis and cirrhosis. We conclude that early liver transplantation and aggressive metabolic management improve early neurologic outcomes for children with UCDs, but longer follow-up monitoring is needed. *Pediatrics* 2004;114:e523–e526. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0198; *urea cycle defect, liver transplantation, ornithine transcarbamylase deficiency, development, outcome.*

ABBREVIATIONS. UCD, urea cycle defect; CPS, carbamoyl phosphate synthase; OTC, ornithine transcarbamylase; EBV, Epstein-Barr virus; OLT, orthotopic liver transplantation.

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Accepted for publication May 13, 2004.

doi:10.1542/peds.2004-0198

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Inherited disorders of the urea cycle are characterized by high ammonia levels and altered amino acid metabolism. There are 6 well-characterized urea cycle defects (UCDs), ie, *N*-acetylglutamate synthase, carbamoyl phosphate synthase (CPS), X-linked ornithine transcarbamylase (OTC), arginosuccinate synthase, arginosuccinate lyase, and arginase deficiencies. Arginase deficiency is not typical of the other UCDs, because it presents not with hyperammonemia but with spastic diplegia. Presentation of the other UCDs can be quite variable, from catastrophic neonatal illness and acute episodic encephalopathy in childhood or adulthood to chronic neurologic disorders.¹

Neonates with UCDs typically have a normal birth weight and an uneventful initial peripartum period. They present within hours to days after birth with a catastrophic illness, starting with poor feeding, lethargy, vomiting, and tachypnea and then progressing rapidly to coma attributable to hyperammonemia. Rapid treatment is required for survival, with neurologic and overall outcomes being related to the level and duration of hyperammonemia.^{2,3} Prompt reduction of ammonia levels through hemodialysis and pharmacologic therapy that directs nitrogen waste to alternate pathways has reduced mortality rates at 1 year of age from 86% to 8%. However, one-half of the survivors still die before entering school, and 80% to 100% of the remainder have severe developmental disabilities.^{4,5} There are no data to suggest that treatments, overall outcomes, and neurologic outcomes differ between CPS and OTC deficiency.

Long-term management of cases of UCDs requires strict dietary protein restriction, administration of sodium phenylbutyrate to stimulate alternate pathways of nitrogen disposal, and prompt recognition and treatment of intercurrent illnesses to prevent catabolism and hyperammonemia. Frequent episodes of recurrent hyperammonemia have negative effects on neurologic outcomes but are a common problem because of the difficulties with long-term dietary and pharmacologic management.²

Orthotopic liver transplantation (OLT) is an alternative to medical therapy for severe UCDs. OLT results show nearly complete metabolic correction and cessation, but not reversal, of neurologic deficits.⁶ Originally, transplantation was avoided among children <12 months of age, because it was thought

that there were greater risks of death and morbidity. Advances in surgical techniques and management of immunosuppression now allow transplantation at an earlier age, with mortality rates equal to those for older children.⁷ We hypothesized that aggressive metabolic management and earlier transplantation might result in improved neurologic outcomes, because of fewer episodes of hyperammonemia.

METHODS

We retrospectively reviewed our experience with aggressive metabolic control of ammonia levels, strict dietary management, and use of early (<12 months of age) OLT. All patients with neonatal-onset UCDs who underwent early OLT after January 2000 were identified. An additional patient was enrolled prospectively. One female patient with late-onset OTC deficiency was also enrolled. As previously reported,⁸ that patient was selected for transplantation because of poor metabolic control. The decision to perform transplantation in that case was made after a multifaceted attempt to characterize maximally the patient's biological phenotype, as part of a multifaceted risk/benefit assessment.⁸ A chart survey was performed to record details of initial presentation, subsequent hyperammonemic episodes, transplantation, and current medical status. After obtaining informed consent through an institutional review board-approved protocol, we prospectively performed developmental testing. The children were evaluated by an accredited tester using the Griffiths Mental Developmental Scales,⁹ which were restandardized in 1996.¹⁰ The mean Griffiths score and each of the 5 subscales have a mean of 100 and a SD of 10.8. Development was compared with historical control findings reported in the literature.

RESULTS

All patients have now been monitored for ≥ 30 months after transplantation. Patient characteristics are noted in Table 1. All patients had gastrostomy tubes placed shortly after diagnosis, to facilitate dietary management. Patients who presented in the newborn period all underwent hemodialysis. A rare blood type prevented 1 patient (patient 2) from undergoing transplantation until 11 months of age. No deaths occurred among the liver transplant recipients, for a 30-month survival rate of 100%. One patient (patient 3) had hepatic artery thrombosis, biliary stricture with subsequent biliary cirrhosis, necrosis of the left lobe of the liver, *Pseudomonas* peritonitis, and cardiomyopathy. He has experienced subsequent failure to thrive and is currently listed for repeat liver transplantation. One patient (patient 5) experienced immediate posttransplant arterial thrombosis in the graft vessel, which required operative removal, followed by complete recovery. One patient (patient 1) experienced mild acute rejection

(increased liver transaminase levels, confirmed with biopsy), which responded to augmentation of immunosuppressive medication. None of the surviving patients has required readmission or additional therapy because of rejection. One of the 5 patients (patient 5) experienced biopsy-proven, mild, localized, posttransplant lymphoproliferative disorder. This was treated with tonsillectomy/adenoidectomy and autologous Epstein-Barr virus (EBV)-specific cytotoxic T lymphocyte infusion, as part of an experimental phase I trial (Epstein-Barr Virus Infections Lymphoproliferative Disorders). All patients have unrestricted diets and, with the exception of some with slightly low citrulline levels, have normal plasma amino acid profiles. Results of the testing with Griffiths Mental Developmental Scales are presented in Table 2. Neurologic examinations revealed hypotonia for 1 patient (patient 3, with failure to thrive) and mild speech apraxia for the partially OTC-deficient female patient (patient 5).

DISCUSSION

OLT has become a useful therapy for severe UCDs, particularly CPS deficiency and hemizygous male OTC deficiency.¹¹⁻¹⁴ Many reports note the success of this therapy in providing metabolic control and preventing additional episodes of hyperammonemia, preserving neurologic function.¹² When transplantation is performed later, however, neurologic compromise already exists and is not corrected.

Our results with early OLT indicate that transplantation is possible and neurologic outcomes are improved, compared with later transplantation. Historical control findings obtained from the literature (findings for patients with UCDs who received liver transplants at >1 year of age) demonstrated generally poor outcomes. Maestri et al⁵ noted that 2 of 3 of their transplanted patients were "profoundly delayed," whereas the other (who underwent early transplantation) was normal at 8 months of age. A survey of major North American transplant centers by Whittington et al⁶ identified 16 patients, 2 of whom were female patients with partial OTC deficiency. With exclusion of the partially OTC-deficient female patients, 2 of 14 patients had severe neurologic impairment (no social interaction, ambulation, or communication), 3 of 14 had moderate impairment (limited social interaction, bipedal ambulation, and communication with gestures), 8 of 14 had mod-

TABLE 1. Patient Characteristics

| Subject, Gender | Diagnosis (Age) | Initial Hyperammonemia, Duration, h (Peak, $\mu\text{g}/\text{dL}$) | Subsequent Hyperammonemia, No. of Episodes (Highest Peak, $\mu\text{g}/\text{dL}$) | Age at Transplantation, mo | Status |
|-----------------|-----------------|--|---|----------------------------|---|
| 1, male | CPS (NB) | 34.5 (979) | 2 (353) | 5 | Well |
| 2, male | OTC (prenatal) | 14 (1212) | 9 (353) | 11 | Well |
| 3, male | CPS (NB) | 27 (1431) | 3 (482) | 3.5 | FTT, bile duct stenosis, cirrhosis, listed for retransplant |
| 4, male | OTC (prenatal) | 20.5 (1302) | 2 (786) | 8 | Well |
| Average | | 24 (1231) | 0.58 episodes/mo | 6.9 | |
| 5, female | OTC (30 mo) | (299) | 5 (253) | 35 | Well |

Hyperammonemia duration is time at $>300 \mu\text{g}/\text{dL}$. FTT indicates failure to thrive; NB, newborn.

TABLE 2. Griffiths Developmental Scale Results

| Subject | Visit | Age, mo | Scale Results* | | | | | | Practical Reason |
|---------|-------|---------|----------------|-------------|-----------------|----------|------------|-------------|------------------|
| | | | Overall | Gross Motor | Personal-Social | Language | Fine Motor | Performance | |
| 1 | 1 | 24 | 51 | 69 | 50 | 52 | 50 | 50 | 82 |
| | 2 | 34 | 70 | 94 | 58 | 71 | 71 | 58 | |
| | 3 | 49 | 83 | 98 | 73 | 94 | 61 | 90 | |
| 2 | 1 | 28 | 86 | 100 | 96 | 73 | 77 | 82 | 76 |
| | 2 | 41 | 80 | 117 | 78 | 63 | 68 | 73 | |
| | 3 | 50 | 76 | 100 | 60 | 68 | 84 | 76 | |
| 3 | 1 | 11 | 56 | 48 | 70 | 65 | 67 | 72 | 82 |
| | 2 | 20 | 51 | 45 | 63 | 59 | 78 | 82 | |
| | 3 | 33 | 47 | 34 | 47 | 42 | 52 | 61 | |
| Average | | | 66.7 | 78.3 | 66.1 | 65.1 | 67.6 | 71.6 | 80.0 |
| 5 | 1 | 48 | 71 | 69 | 82 | 51 | 82 | 94 | 55 |
| | 2 | 58 | 68 | 69 | 83 | 48 | 69 | 83 | |
| | 3 | 71 | 82 | 90 | 76 | 82 | 87 | 87 | |

* Developmental scale results are standardized ratios (mean: 100; SD: 10.8).

erate/mild impairment (definite social interaction, fair ambulation, possibly with spasticity, and some use of language), and 1 of 14 had mild impairment (full ambulation, perhaps some fine or gross motor impairment, use of language, and mild developmental delay). Our cohort demonstrated only mild/moderate developmental delays and, other than hypotonia, no evidence of abnormalities in neurologic examinations (corresponding to the mild impairment group described above). Speech appeared most delayed of all developmental areas; however, all transplant-treated patients had at least some language. Gross motor delays from the UCD may not be as severe as shown here, because 1 patient was also limited by poor growth and failure to thrive. All patients were ambulatory, able either to cruise furniture or to walk. Practical reasoning was in the low-normal range for the 2 children for whom this could be measured.

Decisions regarding the timing of transplantation and whether to perform transplantation at all for female patients with OTC deficiency are complicated. Our female subject was previously reported to have undergone a detailed risk-benefit assessment that took into account in vivo measures of urea cycle capacity, historical success of medical management, and socioeconomic factors that affected adherence to medical follow-up treatment and access to a tertiary care metabolism center. Early transplantation is generally recommended if metabolic control is poor, with good neurologic outcomes if there are minimal deficits before transplantation.^{12,14} Follow-up monitoring demonstrates good long-term developmental progress in our case.⁸

The mortality and complication rates appear similar to those for patients who undergo transplantation at a later age.¹⁵ EBV-positive posttransplant lymphoproliferative disorder is a common problem related to immunosuppression.¹⁶ This is more likely among younger children who have not experienced seroconversion to EBV. The 1 child in this report has not experienced significant problems related to localized posttransplant lymphoproliferative disorder.

Treatment before transplantation continues to be challenging, despite pharmacologic therapy. We im-

plemented aggressive management of feeding with gastrostomy tube placement, careful titration of protein intake with monitoring of essential amino acid levels at steady-state intakes, and rapid treatment of illnesses with prompt hospitalization, intravenous fluid management, intravenous Ammonul (Ucyclyd Pharma, Inc, Scottsdale, AZ) administration, and insulin administration with glucose for resistant hyperammonemia. Novel approaches have included the recent experimental use of hepatocellular transfer, which has provided complete but only short-term metabolic improvement.¹⁷

Aggressive metabolic control and early OLT for infants with neonatal-onset UCDs appear to yield improved neurologic outcomes with similar mortality and morbidity rates, compared with those for patients who receive transplants later. Although not a panacea, this approach may be the preferred treatment, especially when presymptomatic diagnoses are made with expanding comprehensive newborn screening via tandem mass spectrometry. Long-term follow-up monitoring for this group and other groups is indicated, although it appears likely that outcomes will still be stratified on the basis of time of diagnosis, duration of hyperammonemia, and frequency of hyperammonemic episodes before transplantation.

ACKNOWLEDGMENTS

This work was supported by the Baylor College of Medicine General Clinical Research Center (National Institutes of Health grant RR00188) and the Mental Retardation and Developmental Disabilities Research Center (National Institutes of Health grant HD024064).

We acknowledge the contributions of the Biochemical Genetics physician, nursing, and dietary staff at the Texas Children's Hospital and the Urea Cycle Disorders Rare Disease Clinical Research Centers (National Institutes of Health grant RR019453).

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