PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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Pediatrics 2003;111;1262

Isolated Hepatocyte Transplantation in an Infant With a Severe Urea Cycle Disorder

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ABSTRACT. *Objective.* **Transplantation of isolated hepatocytes in animal models has been shown to correct inborn errors of metabolism. Based on these studies and our experience with hepatocyte transplantation in a child with Crigler-Najjar syndrome, isolated hepatocyte transplantation was performed to attempt metabolic reconstitution in a male infant with severe ornithine transcarbamylase (OTC) deficiency.**

Methods. **An infant with an antenatal diagnosis of OTC deficiency was managed intensively to prevent hyperammonemia. Isolated hepatocytes were obtained by collagenase perfusion of donated livers not used for transplantation. Hepatocytes were infused in batches over the first 4 weeks of life via an umbilical venous catheter positioned in the portal vein. Immunosuppression consisted of tacrolimus and corticosteroids.**

Results. **Over 4 billion viable hepatocytes were transplanted during the first 3.5 weeks of life. A period of metabolic stability was achieved between days 20 and 31 during which normal protein intake was tolerated while phenylbutyrate was weaned. During this time, plasma ammonia and glutamine remained within normal limits. Hyperammonemia reappeared abruptly on day 31 of life. Protein tolerance diminished to baseline; metabolic stability was subsequently reattained only following successful liver transplantation at 6 months of age.**

Conclusions. **Isolated hepatocyte transplantation appeared to result in temporary relief of hyperammonemia and protein intolerance attributable to OTC deficiency. The metabolic stability achieved was lost after 11 days presumably because of rejection of the transplanted cells because of insufficient immunosuppression. Future attempts at isolated hepatocyte transplantation for inborn errors of metabolism in humans should include adequate immunosuppression and a liver biopsy as a means of proving hepatocyte engraftment and function. *Pediatrics* 2003;111:1262–1267; *hepatocyte transplantation, infant, ornthine transcarbamylase deficiency, urea cycle disorder.***

ABBREVIATIONS. OTC, ornithine transcarbamylase; DV, ductus venosus; OLT, orthotopic liver transplantation; IV, intravenous.

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Received for publication May 13, 2002; accepted Sep 19, 2002.

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Isolated hepatocyte transplantation has been shown to be effective in restoring biochemical function in animal models of liver-based metabolic disease. The first demonstration of this technique was in reconstituting bilirubin glucuronidase activity in deficient Gunn rats over 20 years ago.[1] Since then a number of animal models have confirmed the efficacy of this approach.[2–5] We have previously published our experience with isolated hepatocyte transplantation in the treatment of a child with Crigler-Najjar syndrome type 1.[6] Biochemical and clinical evidence of transplanted hepatocyte engraftment and function remained present for >2 years following the procedure. Muraca et al[7] have also published their experience of isolated hepatocyte transplantation in a 47-year-old woman with glycogen storage disease type 1a. In principle, this technique is applicable to any metabolic disease in which the deficient enzyme is primarily expressed in the hepatocyte, where a small increase in enzyme activity can be expected to have a significant clinical effect on the outcome of the disease, and where the defect has not already caused structural liver damage such as cirrhosis.

Urea cycle disorders appear to fulfill these criteria. Although other tissues (eg, gut and kidney) express some urea cycle enzymes, only the hepatocyte has the full metabolic capability to detoxify ammonia to urea.[8] Severe, and commonly fatal, neonatal presentations of certain urea cycle disorders (eg, ornithine transcarbamylase [OTC] deficiency) may differ from later onset and more manageable phenotypes by only a relatively small increase in the deficient enzyme activity.

OTC deficiency is an X-linked defect of urea synthesis. Three basic phenotypes are recognized: severely affected infant boys who develop profound hyperammonemia soon after birth, the older male child presenting with recurrent hyperammonemia, and the affected female heterozygote with recurrent hyperammonemia. The neonatal form is usually fatal, but survival with aggressive therapy with and without liver transplantation has been documented, although the developmental outcome of these patients is frequently less than optimal.[9–12]

There has been success with auxiliary liver transplantation in OTC deficiency, suggesting that <100% of normal liver OTC activity would be adequate to significantly improve the patient's outcome or even effect a cure.[11,13] Precisely how much activity is required is not clear; however, isolated hepatocyte

transplantation may be expected to improve a patient's nitrogen tolerance. We now describe our experience with a prenatally diagnosed male infant with severe OTC deficiency, treated with hepatocyte transplantation.

CASE HISTORY

A 21-year-old primigravid woman who was an asymptomatic heterozygote for OTC deficiency (mutation A209V: GCG to GTG) was referred to our program. She was pregnant with an affected male fetus diagnosed by amniocentesis. Several male infants had died in the extended family, one of whom was positively diagnosed as OTC deficiency (mother's half-cousin), and the mutation was traced through the family. At 37 weeks gestation, labor was induced because of pregnancy induced hypertension. The infant was delivered in good condition (Apgar scores of 7^{1} and 8^{5}) with a birth weight of 3.4 kg. Umbilical venous (cord blood) ammonia level at birth was 94 μmol/L.

A peripheral venous cannula, an umbilical venous catheter, and a radial arterial line had been placed within an hour of birth. Intravenous (IV) glucose, sodium phenylacetate, sodium benzoate, and arginine hydrochloride were started as prescribed by Brusilow.[8] Under angiographic control, a 7-French internal jugular hemodialysis catheter was placed and the umbilical venous catheter was directed into the portal vein. High flow across the ductus venosus (DV) at this time prevented immediate hepatocyte infusion. On return to the pediatric intensive care unit, arterial ammonia had risen to 146 μmol/L, and hemodialysis was started. The patient continued on dialysis for 3 days, and interrupted only for trips to radiology for hepatocyte infusion. Immunosuppression was commenced using tacrolimus and methylprednisolone.

The first infusion of isolated hepatocytes into the portal vein took place at 10 hours of age. Isolated hepatocytes were infused into the portal vein on several occasions over the following 3.5 weeks (see Fig 1). Initially, the infant showed significant protein intolerance appropriate for the known metabolic defect. Following transplantation of 4 billion hepatocytes, a period of increased protein tolerance was seen between days 20 and 30 of life. However, this metabolic stability was not sustained and could not be reproduced with repeat attempts at hepatocyte transplantation. The subsequent attempts took place between days of life 37 and 51, when a further 3.3 billion hepatocytes (~70% freshly isolated) were infused through the umbilical venous catheter, and between days 113 and 116, when 1.7 billion viable, freshly isolated, hepatocyte were infused via a percutaneously placed transhepatic portal vein catheter. Throughout the whole period of hepatocyte transplantation, approximately the first 3 months of life, the infant was monitored very closely. He maintained normal growth and development during this period and had no abnormal neurologic signs or symptoms.

The decision to proceed with orthotopic liver transplantation (OLT) was made when it became clear that the final attempt at hepatocyte transplantation had not produced a significant metabolic effect. OLT was conducted successfully at the age of 6 months. The postoperative period was complicated by respiratory difficulties and cytomegalovirus hepatitis in the allograft. He made a full recovery from these complications and is now well >2 years post-OLT and appears developmentally appropriate. His progress continues to be followed closely.

METHODS

Management of Hyperammonemia

The primary goal was to maintain optimal neurodevelopmental outcome for the infant; therefore, an aggressive strategy to preempt hyperammonemia in the hours after birth and to treat episodes of hyperammonemia as soon as they occurred was planned. This strategy had 3 main components: close biochemical monitoring, limiting nitrogen load by restricting protein input and preventing catabolism, and supporting nitrogen elimination with utilization of alternative metabolic pathways of nitrogen excretion and hemodialysis.

Biochemical Monitoring

Ammonia levels were checked on umbilical venous blood at birth, and arterial ammonia levels were measured as soon as arterial access was established. Arterial ammonia levels were then checked at least every 4 hours for the first few days. Throughout the periods of hepatocyte transplantation, ammonia levels were measured a minimum of twice a day. Blood glucose levels were also estimated frequently to ensure hypoglycemia never occurred. Plasma amino acid levels were measured daily.

Limiting Nitrogen Load

Initially, protein restriction was absolute with IV glucose infused at a rate of 8 to 10 mg/kg/min. Adequate glucose input can be expected to prevent catabolism for a few days, but then low plasma levels of branched-chain amino acids and, in the case of urea cycle disorders, arginine deficiency will stimulate endogenous protein breakdown. Therefore, arginine supplementation was commenced early. After 48 hours of IV glucose, enteral feeding was introduced with a combination of Pro-Phree, a protein free formula, and Cyclinex-1, an essential amino acid only formula (both Ross Products Division, Buffalo, NY) initially aiming at 0.5 g protein/kg/d.

Alternative Nitrogen Excretion Pathways

IV sodium phenylacetate/sodium benzoate (Ucyclyd Pharma, Inc, Glen Burnie, MD) 250 mg/kg (of each drug) loading over 90 minutes followed by 250 mg/kg/d by continuous infusion. Arginine hydrochloride was also loaded IV at a dose of 200 mg/kg and then given at a continuous rate of 200 mg/kg/d. IV infusion of phenylacetate and benzoate was continued for 6 days, until the glutamine level in the blood had fallen into the normal range. Oral phenylbutyrate (500 mg/kg/d) was introduced at this time. L-carnitine was supplemented at a dose of 10 mg/kg/d.

Hemodialysis

A hemodialysis catheter (7-French) was placed shortly after birth, and hemodialysis was commenced at first sign of increasing ammonia levels and was to continue until ammonia levels were consistently within the normal range.

Isolated Hepatocyte Transplantation

Approval was obtained from the University of Nebraska Medical Center Institutional Review Board and from the Food and Drug Administration (under Investigational New Drug BB-6880) to use hepatocyte transplantation to treat patients with life-threatening liver-based metabolic deficiencies, the hepatocyte-transplantation protocol was explained to the mother, and she gave written informed consent for her infant's participation.

Human hepatocytes are isolated by collagenase perfusion of donated livers not taken for transplantation. The methods employed for isolation and processing of hepatocytes as well as viability testing has been previously described by our group.[6] All hepatocyte infusion numbers are given as number of viable hepatocytes by trypan blue exclusion. By this method median viability was 75% (range: 51%–94%). Freshly isolated hepatocyte were preferred but ~80% of cells infused during the first month were cryopreserved because fresh hepatocytes were not available in sufficient quantities. Under angiographic control, the previously placed umbilical venous catheter was directed into the portal vein. High blood flow was noted across the DV. To prevent systemic distribution of infused cells, a catheter balloon was inflated in the DV. The catheter lumen opened proximal to the balloon in the left portal vein and contrast demonstrated all blood flow diverted through the liver (Fig 2). An attempt was made to permanently occlude the DV with an embolization coil. However, when the blood flow was obstructed, the DV dilated and the device migrated to the main pulmonary artery. There was no desaturation or evidence of cardiovascular instability and the coil was retrieved angiographically without incident. The DV closed spontaneously at 17 to 18 days. After closure of the DV, a greater number of hepatocytes could be infused at one time.

Infusions were conducted once or twice daily when transplantable cells were available. Monitoring of intravascular pressure was done at 10- to 15-minute intervals. Qualitative flow characteristics were evaluated whenever pressures rose >5 mm Hg. Infusions were paused when intraportal pressure rose >8 to 10 mm Hg, if flow slowed and would have been paused had macroscopic emboli appeared or shunting into collateral vessels occurred. Saline was then infused until the pressure and flow were rechecked. This

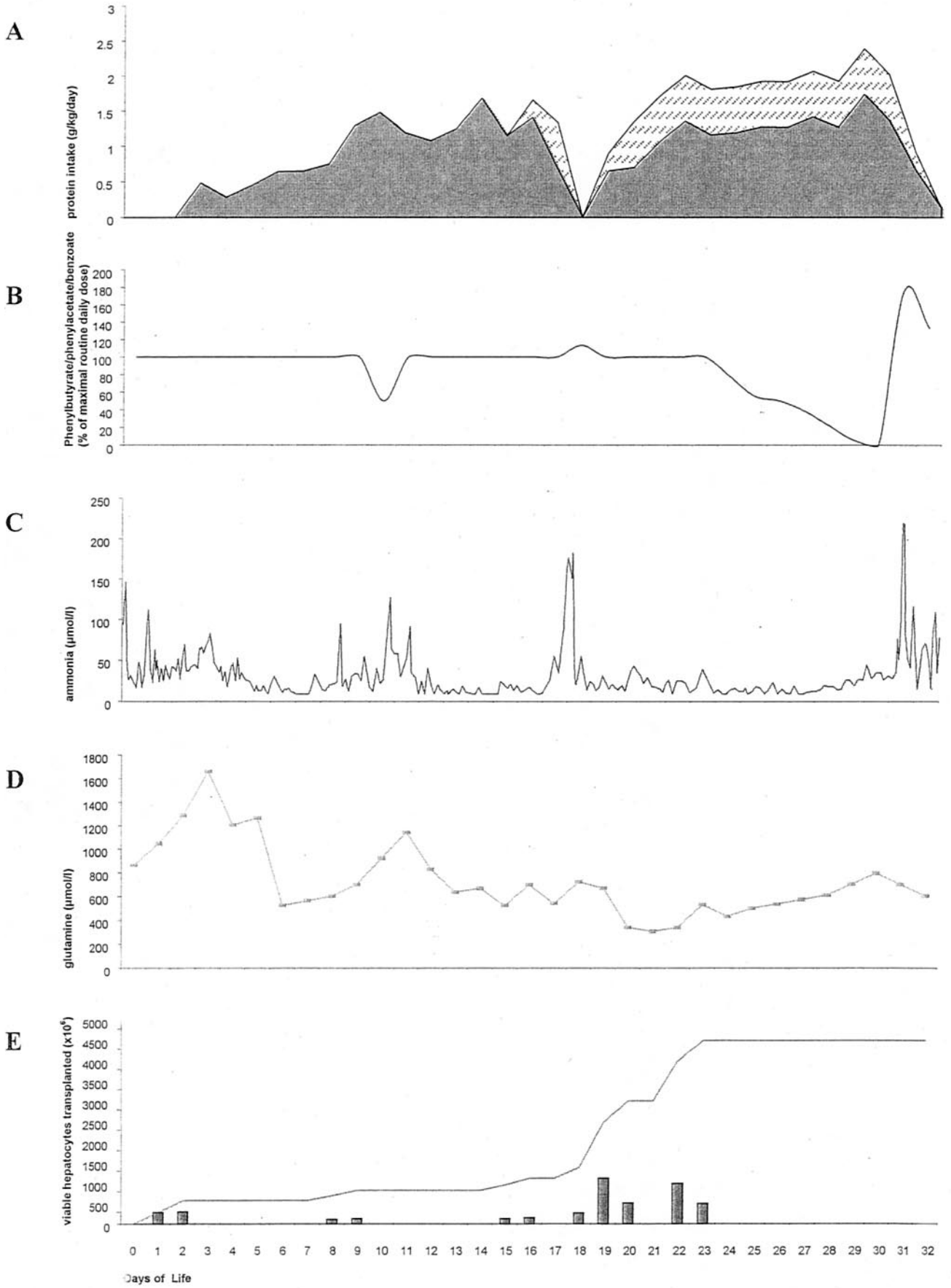

Fig 1. A newborn male infant with severe OTC deficiency underwent hepatocyte transplantation beginning on the first day of life. A metabolic response was seen between days 24 and 32 when the infant demonstrated full protein tolerance. Protein intake, drug therapy, ammonia and glutamine levels, and hepatocyte infusions over the first 32 days of the patient's life are shown. A, Protein intake: measured

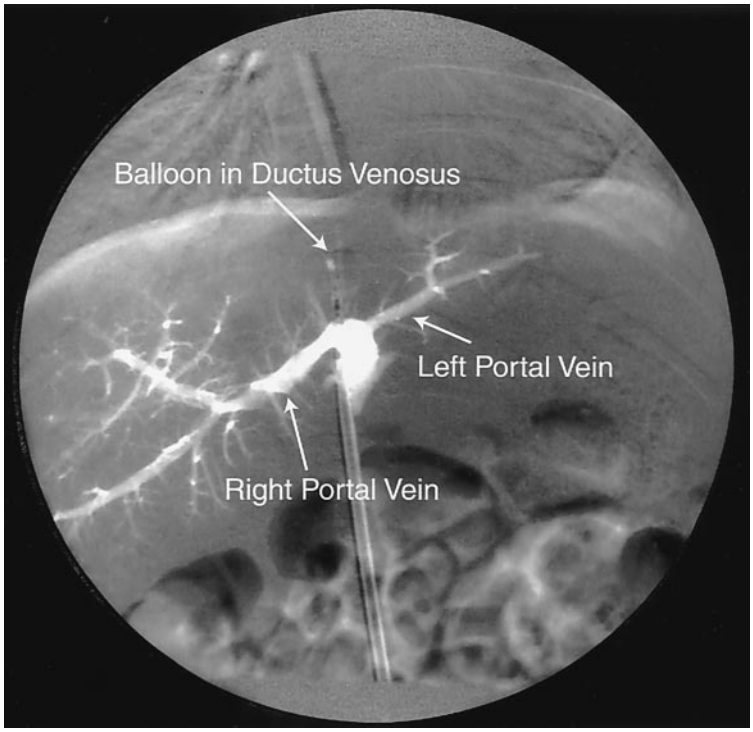

Fig 2. Transplanted hepatocytes were infused via a catheter placed in the umbilical vein. Before day 18 of life the DV remained patent and needed to be occluded to prevent systemic distribution of infused hepatocytes. The figure shows an angiogram with contrast injected through the umbilical venous catheter demonstrating left and right portal veins with a catheter balloon occluding the patent DV.

was done at 5- to 10-minute intervals until improvement allowed resumption of hepatocyte infusion. If no improvement was seen in 30 minutes, the infusion was halted. Between infusions the umbilical catheter was pulled back into the umbilical vein in an attempt to maintain the tract but to limit the risk of portal vein thrombosis. A new sterile catheter was placed each time the portal vein was accessed. Heparin was not infused either with hepatocyte infusions nor in between infusions. In total, the umbilical vein was catheterized for 51 days. A segmental left intrahepatic portal vein occlusion was identified on angiography during the first 2 weeks of hepatocyte infusions, but it was not associated with any clinical or biochemical change in liver function.

Two months after the UVC had been removed, the final attempt at hepatocyte transplantation was performed via a percutaneously placed transhepatic portal vein catheter.

Immunosuppression

Immunosuppression was commenced using tacrolimus aiming at blood levels of 5 to 10 nmol/L. An IV bolus of methylprednisolone (10 mg/kg) was given with the first infusion of hepatocytes. Steroids were then gradually weaned over 2 weeks from 1 mg/kg/d to 0.25 mg/kg/d of prednisone and continued at this dose long-term.

RESULTS

It had been estimated before the procedure that ~1 billion viable hepatocytes would need to be transplanted and this total was achieved at the 4th hepatocyte infusion. Twenty-four hours later, in an attempt to test for any increase in protein tolerance, protein input was increased by the addition of expressed breast milk and the phenylbutyrate dose was halved. This rapidly resulted in an increase in ammonia and glutamine levels that resolved on increasing the phenylbutyrate to its previous dose.

Over the next 7 days only one further hepatocyte infusion took place. On day 17 there was another spike in the ammonia levels. Protein intake was stopped, and IV phenylacetate and benzoate restarted. Subsequent to this, the DV closed spontaneously, and it was then possible to infuse considerably larger numbers of hepatocytes.

By day 23, the patient had received 11 hepatocyte infusions with a total of 4.4 billion viable hepatocytes harvested from 7 separate donors. From this point on, it was possible to rapidly increase the protein intake to 1.5 g/kg from formula and an estimated 0.5 g/kg from breastfeeding. The estimates of breastfeeding intake were based on the amount of urine output in excess of his measured intake. Over a period of 7 days, he was weaned completely from phenylbutyrate.

On day 31, he became hyperammonemic with a peak ammonia level of 219 μmol/L. Protein intake was again discontinued, and he was loaded with IV phenylacetate and benzoate and then continued on a continuous infusion of these drugs. Within 36 hours, oral feeding and medications were reintroduced; however, at no point thereafter could the protein intake be increased above 1 g/kg/d nor could the phenylbutyrate dose be reduced. Trough blood ta-

protein intake from formula feeds are represented by the gray area and additional estimated protein intake from breastfeeding is represented by the hatched area. B, Drug therapy: doses are represented as a percentage of the routine daily dosage for an infant with severe OTC deficiency; ie, phenylbutyrate 500 mg/kg/d enterally, or phenylacetate 250 mg/kg/d and benzoate 250 mg/kg/d IV. C, Plasma ammonia level: arterial samples were obtained for the first 6 days, venous levels were obtained subsequently. D, Plasma glutamine levels. E, Hepatocyte infusions: bars represent the day of infusions and the number of viable hepatocytes infused on each occasion. The line represents the cumulative total number of hepatocytes infused.

crolimus levels, over the first 32 days of life, showed a median value of 10 ng/ml (range: 7–19).

Over the next 2.5 months, 2 further attempts at hepatocyte transplantation were undertaken. On neither occasion was any response seen, despite the fact that there was no sensitization to donor HLAs as evidenced by negative panel reactive antibodies. Attempts to wean phenylbutyrate or increase protein intake led to rapid elevation of plasma glutamine and hyperammonemia.

DISCUSSION

The aim in the care of this child was to preserve neurodevelopment while achieving a definitive cure for the inborn error of metabolism. This was to be achieved by aggressive medical management from birth, isolated hepatocyte transplantation with the hope of avoiding whole organ liver transplantation. OLT was to be considered if the metabolic defect was not improved by hepatocyte transplantation.

Over a period of 3.5 months, this male infant with severe OTC deficiency received 15 separate hepatocyte infusions with a total of almost 10.5 billion hepatocytes from 10 different donors. The patient remained well with no proven septic complications, and plasma ammonia, for the most part, remained below 50 μmol/L. On each occasion, hyperammonemia responded promptly to protein withdrawal, IV glucose, phenylacetate, and benzoate. Throughout, the patient exhibited no abnormal neurology, no reduction in conscious level, no vomiting, and no seizures. Although our goal was to avoid the need for whole organ transplantation, bridging this infant to OLT unscathed is, in itself, a successful outcome. He is now a healthy 3-year-old child on a normal diet with age-appropriate neurodevelopment.

The clinical aims, having been achieved, leave us to question whether the hepatocyte transplantation contributed to the excellent outcome for this child. Overall, it probably did not, but there is strong evidence to suggest OTC activity was restored only to be lost subsequently. The period of metabolic stability between the third and fourth weeks of life was unlike any other time before OLT. This occurred after the transplantation of almost 5 billion viable hepatocytes. Full enteral protein intake was tolerated with reducing doses of phenylbutyrate. Plasma ammonia and glutamine levels remained within the normal ranges despite these changes.

It was assumed the acute hyperammonemia that appeared on day 31 was attributable to infection, but no pathogen was identified on culture, and the infant did not appear clinically septic. In retrospect, the transplanted hepatocytes were presumably lost to simple acute rejection. The major risk period for acute rejection is between 5 and 10 days posttransplant, which was the period since the previous hepatocyte infusion.

The acute rejection and the loss of transplanted OTC activity resulted, we believe, from inadequate immunosuppression. A low level of immunosuppression was desirable, and there was reason to believe it would be adequate. Hepatocytes are thought to express major histocompatibility complex class I antigens weakly and major histocompatibility complex class II hardly at all.[14] When acute rejection is observed in liver allografts, only rarely do the hepatocytes appear to be involved. Usually it is the biliary and endothelial cells that are under immunologic attack. It has also been suggested that intraportal injection of allogeneic cells may induce immunologic tolerance.[15] Finally, no suggestion of acute rejection had been seen in the child treated with hepatocyte transplantation for Crigler-Najjar. For these reasons, it was thought that the dose of tacrolimus could be limited and thereby limit side effects, while still maintaining adequate immunosuppression. This may not have been an accurate assumption, which is endorsed by the finding of high immunogenicity of infused murine hepatocytes by Bumgardner et al.[16] Possibly more important was insufficient steroid therapy. Unlike organ transplantation, where a large bolus of steroids is given at the time of transplantation when all the foreign antigens are presented to the patient's immune system, in this patient allogeneic hepatocytes were infused in batches over an extended period of time. A protective steroid bolus was only administered with the very first hepatocyte infusion. Therefore, it is probable that acute rejection was the result of inadequate steroid therapy at the time of each infusion. Another factor possibly contributing was the number of different donors employed. Multiple donors were necessary because we have found that the hepatocyte isolation techniques retrieve only a fraction of the hepatocytes in a donated liver, and that the lack of reliable cryopresevation techniques has hampered our ability to use a single donor.

Subsequent infusions of hepatocytes did not reproduce the response seen between days 20 and 31. Perhaps the patient became sensitized and formed neutralizing antibodies to the later batches of hepatocytes. Because the panel reactive antibodies screen was negative, it is possible that antibodies were formed to OTC itself. Another possibility is that too few hepatocytes were given with the last 2 attempts. We did not see an effect until the viable cell count exceeded 4 billion, which is at least 4 times greater than our original estimate, based on our experience with the Crigler-Najjar child. It appears that to scale down the number of hepatocytes on the basis of body weight severely underestimates the number of cells required.

CONCLUSIONS

Given the good final outcome and the evidence of transient metabolic improvement, we are encouraged to attempt this procedure again should the opportunity arise. The technique is applicable not only to the severely affected infant with a urea cycle disorder but also to symptomatic OTC-deficient female heterozygotes in whom a small increase in OTC activity may prevent the recurrent hyperammonemic crises and preserve their neurodevelopmental well-being. However, we suggest maintaining immunosuppression in the range appropriate for OLT, with steroid boluses to be repeated with each infusion of

hepatocytes; not underestimating the number of viable hepatocytes to be infused; limiting the number of separate donors; and, in newborns, delaying the first infusion of hepatocytes until after spontaneous closure of DV. Finally, we would plan to be more ready to biopsy the liver to demonstrate enzyme activity when indirect evidence points to transplanted OTC activity.

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THERAPEUTIC TOUCH

"Therapeutic Touch (TT). The fanciful ideas behind TT is that conditions ranging from tension headaches to stress are alleviated by smoothing the blockage of the 'human energy field' that supposedly surrounds us. Without touching the patient the therapist strokes the field. One problem: no such field exists. TT is literally nothing but hand-waving. It's nonsense. And yet we have federal tax money studying TT, through the National Center for Complementary and Alternative Medicine. The agency is a monument to Congress-inspired, government-funded pseudoscience. The TT-subsidizing agency has its roots in the Office of Alternative Medicine, created in 1992. . . The office started out with a budget of a few million dollars. After 5 years in existence, it had no new treatments that I saw to show for the money it handed out. Despite its anemic track record, it was argued, with classic political reasoning, that the office should be expanded in role and elevated in status. So in 1998 it was reincarnated as the aforementioned National Center. Its latest budget: $113 million."

Forbes. October 28, 2002

Noted by JFL, MD

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