Published in final edited form as:

Mol Genet Metab. 2010 ; 100(Suppl 1): S84–S87. doi:10.1016/j.ymgme.2010.02.012.

Early orthotopic liver transplantation in urea cycle defects: Follow up of a developmental outcome study

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Abstract

Patients with neonatal urea cycle defects (UCDs) typically have high mortality and poor neurological outcome unless they receive liver transplantation. Neurologic outcome may be better with liver transplantation before age 1 year. We report on a follow up on an initial prospective study performed to assess developmental outcome after early liver transplant using the Griffiths scales. Developmental testing up to 7 years after transplantation showed average developmental quotients (DQs) of 69 for four children who underwent transplantation before one year of age (latest DQs were 47, 63, 95 and 96), and 80 for a patient who underwent transplantation at three years of age (latest DQ was 88). We conclude that a combination of early liver transplantation, aggressive metabolic management and early childhood intervention improve the neurologic outcome of children with UCDs.

Keywords

Urea cycle; liver transplantation; ornithine transcarbamylase; carbamoyl phosphate synthase; Griffiths scale

1. Introduction

The urea cycle occurring in the liver is essential for nitrogen excretion and defects in that pathway lead to a propensity for hyperammonemia and consequent neurological damage. Urea cycle defects (UCDs) have an incidence between 1/8200 [1] to 1/53700 [2] and the course of patients with these conditions varies greatly, even with optimal treatment [3]. Neonates with UCDs typically present within hours/days after birth with lethargy, poor feeding, vomiting and

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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tachypnea and progress rapidly to coma. Rapid and aggressive treatment is required for survival, but they typically have a poor prognosis in terms of survival and neurological outcome. Treatment options include a low protein diet with replacement of certain amino acid, drugs providing alternative pathways for nitrogen excretion and occasionally dialysis and liver transplantation [3–5]. Among 88 patients studied, only 15% survived 10 years [6]. In a more recent study of 260 patients, more than 50% survived 5 years [7]. Survivors often have severe neurologic disease such as mental retardation, cerebral palsy, cortical blindness or epilepsy [8]. Liver transplantation can be very beneficial in UCDs as it can prevent subsequent metabolic decompensations, but the preexisting neurological status, dependent on the severity of hyperammonemic episodes, is a major factor in the final outcome [9].

Liver transplantation in the 1980s and 1990s was generally avoided in children younger than one year of age, to avoid potentially greater risks of death and morbidity. Advances in surgical techniques and management of immunosuppression now allow transplantation at an earlier age, with mortality rates not different from those for older children [10]. We hypothesized that aggressive metabolic management with early transplantation and early childhood intervention might result in improved neurologic outcomes, because of fewer episodes of hyperammonemia. We performed a prospective developmental outcome study using the Griffiths Scales 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 had previously reported the first three evaluations for 4 patients, and have now completed the study on 5 patients with follow up to 8 years of age for which the Griffiths Scale is validated [11].

2. Materials and Methods

2.1 Study design

The clinical study was approved by the Texas Children's Institutional Review Board. Patients were recruited before transplantation, and consent was obtained from the caregivers. Inclusion criteria included patients with UCDs who underwent orthotopic liver transplantation at Texas Children's Hospital after January 2000. We performed a prospective developmental outcome study using the Griffiths Scales. The children were evaluated by an accredited tester using the Griffiths Mental Developmental Scales [12] which were revised in 1984 [13] and restandardized in 1996 [14]. The second and third authors (PJP and GM) are developmental behavioral pediatricians and performed the evaluations. The mean Griffiths score and each of the 5 subscales have a mean of 100, a standard deviation of 10.8, and can be used in children up to 8 years of age. The patients received early childhood intervention (such as occupational or speech therapy) when indicated.

2.2 Clinical management

Patients were treated before transplantation with aggressive control of hyperammonemia, including protein restriction, citrulline or arginine supplementation, an ammonia scavenger drug (enteral sodium phenylbutyrate) and intravenous sodium phenylacetate and sodium benzoate at times of decompensations. All patients had gastrostomy tubes placed shortly after diagnosis, to facilitate dietary and pharmacological management. Patients who presented in the newborn period all underwent hemodialysis. Insulin administration with glucose was used for resistant hyperammonemia. Liver transplantations were from deceased donor segments [15]. The post-transplantation immunosuppression regimen comprised tacrolimus and steroids.

3. Results

Five children with UCDs were recruited and transplanted between 2000 and 2003; 2 male patients with X-linked ornithine transcarbamylase deficiency and 2 male patients with carbamoyl phosphate synthase 1 (CPS1) deficiency, all of whom had neonatal presentations and underwent liver transplantation before 1 year of age, and 1 female patient with partial X-linked ornithine transcarbamylase (OTC) deficiency that was intractable to medical therapy, who underwent transplantation at 37 months of age. See Figure 1A for a summary and details about the hyperammonemia episodes. All children had metabolic cures of hyperammonemia and have unrestricted diets. We have previously reported the immediate post-transplantation period [11] and the rationale for transplantation of patient C [16]. There was 1 death 40 months after liver transplantation caused by hepatic artery thrombosis in the immediate post-transplantation period leading to biliary strictures which eventually caused end-stage liver disease. The patient also had necrosis of the left lobe of the liver, *pseudomonas* peritonitis, cardiomyopathy, failure to thrive and hypotonia. The 7-year survival rate is thus 80%. One patient was lost to follow-up (patient B).

Developmental testing with the Griffiths Scales was performed on an average of 5 occasions, 12 months apart, up to 7 years after transplantation. Full-scale indices for the 4 children who underwent early transplantation (now averaging 9 years of age) showed average developmental quotients of 69 across all ages (range 51–86), whereas the average developmental quotient for the female who underwent transplantation at 35 months was 80, the last being 88 (this patient was diagnosed with mild speech apraxia). The average DQ at last measurement for the three surviving patients with early OLT was 85. See Figure 1B for year-by-year progression of the average developmental quotient, and Figure 1C for the average patient's score across all years in each sub-scale.

4. Discussion

Among 5 patients who underwent liver transplantation for UCDs, 2 had developmental quotients below 70 at their last evaluations (patients B and E). Patient B had an initial hyperammonemia episode which peaked at 2377 $\mu\text{M/L}$, a factor which is known to strongly influence subsequent intellectual development [17]. This patient's disabilities were most marked in the area of speech and language. Patient E had multiple medical complications from the liver transplantation that led to his death. The more severe post-operative course likely affected his development. The other 3 patients actually had progressive increases in their developmental quotients across the years, to which early childhood intervention and therapies might have contributed.

The 5-year survival rate for transplantation from a deceased donor in all metabolic diseases confounded is 80% (N=947), and 84% for all liver diseases transplanted <1 year of age (N=686) [18]. Liver transplantation can be performed even at an earlier age, with a reported 5-year patient survival rate as high as 86% in children <5 kg [19], and a 1-year survival rate of 88% in infants <90 days [20]. Liver transplantation in UCDs has been performed in at least 59 patients, with an overall survival of 93% (mean follow-up of 3 years), leading to a life free of hyperammonemia episodes, special diets or alternative pathway medication, despite the citrulline levels often remaining low in CPS1 and OTC deficiencies and high in citrullinemia type 1 [21]. Further neurological deterioration is prevented by liver transplantation [22], and magnetic resonance spectroscopy abnormalities are corrected [23]. Progressive neurological improvement was observed in 3 of our cases and in other reports [24]. Remaining neurological impairments were noted in 5 of 51 patients transplanted for various UCDs (4/21 when considering only OTC and CPS1 deficiencies) [25], and these impairments can usually be attributed to pre-transplantation neurological insults or transplantation complications [22,26–

28]. In contrast, in a recent study of cognition among 92 children with UCDs (not transplanted) by Krivitzy et al. [29], the full-scale IQ in 13 patients with neonatal onset UCDs averaged 65.5 (half had intellectual disabilities with intelligence quotients <70).

The 14 females with partial OTC reported to have been transplanted have all fared very well neurologically after liver transplantation [25,28,30–33]. In the study by Krivitzy et al., 13% of 26 females with OTC had intellectual disabilities (this includes patient ascertained by family history combined with genetic testing), compared to a 33% rate of intellectual disability among males [29]. From studies focusing on partial OTC deficiency, we know that 82% of carriers can remain asymptomatic [34], and that among symptomatic women, 4/13 have IQs lower than 70 [35] and 10/23 have IQs lower than 80 [36].

We conclude that a combination of early liver transplantation, aggressive metabolic management and early childhood intervention leads to improvements in the neurologic outcome of children with UCDs including OTC and CPS1 deficiencies. The case for citrullinemia and argininosuccinic aciduria is more complicated given that hyperammonemic crises can be more effectively prevented and managed in these conditions. Moreover, because of the importance of these enzymes in directly regulating arginine bioavailability and nitric oxide production and their widespread expression with potential requirement in organs outside of the liver, the risk/benefit consideration for medical therapy vs. orthotopic liver transplantation is less clear [37]. At least in the case of OTC and CPS1 deficiency, we recommend early liver transplantation in the first year of life especially if the peak and duration of hyperammonemia has been effectively limited by initial rescue therapy.

Acknowledgments

This work was funded in part by NIH/ORD U54 RR019453 and the Baylor College of Medicine General Clinical Research Center (RR00188), Mental Retardation and Developmental Disabilities Research Center (HD024064). We acknowledge the contributions of an excellent clinical research team including Ms. Mary Mullins, Susan Carter, and Alyssa Tran.

Abbreviations

PND	prenatal diagnosis
NB	newborn
UCDs	urea cycle defects
OLT	orthotopic liver transplantation
CPS1	carbamoyl phosphate synthase
OTC	ornithine transcarbamylase

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Figure 1.

A) Patient characteristics. *Hyperammonemia duration is considered as the time above 300 μ M/L [17]. PND: prenatal diagnosis; NB: diagnosis in newborn period. B) Average developmental quotient according to age for each patient. C) Average score across the years for each sub-scale, per patient. Practical reasoning is assessed starting at 4 years of age. Error bars represent standard error of the mean.