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Neurologic Outcome of Urea Cycle Disorder Liver Transplant Recipients May Be Predicted by Pre-Transplant Neurological Imaging

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Abstract

Liver transplantation treats the hepatic affection of urea cycle defects (UCDs), however irreversible neurologic damage pre-transplant is difficult to assess providing transplant teams with ethical dilemmas for liver transplantation. The purpose of our study was to determine whether pre-transplant neuroimaging can predict developmental outcomes post-liver transplant in children with UCDs.

Methods—Patients undergoing liver transplantation for UCD's at Cincinnati Children's between 2002 & 2012 were identified. Neurologic assessments prior to and after transplantation were categorized into mild, moderate, or severe disability. Neuroimaging data were categorized into mild, moderate, or severe by a single pediatric neuro-radiologist.

Results—15 patients were identified of whom 8 had neuroimaging prior to transplantation. Of the 8 patients that had neuroimaging, 4 were categorized as severe, 1 moderate, and 3 had no to mild delay. All 4 patients whose imaging was severe were found to have moderate to severe neurologic delay. Of the 3 patients with no to mild changes on neuroimaging 2 out of 3 were found to have no to mild delay on developmental assessments after transplantation.

Conclusion—Neuroimaging may be a helpful tool in determining developmental prognosis and outcomes post-liver transplantation for UCDs. Further studies maybe needed to validate our preliminary findings.

Keywords

Liver Transplantation; Pediatric; Inborn Error of Metabolism

Introduction

Urea Cycle Disorders (UCDs) result from defects in the metabolism of waste products during the breakdown of protein and other nitrogenous compounds. Any significant interruption or deficiency in an enzyme of the urea cycle, particularly of the first four steps (Carbamoyl Phosphate Synthetase I, Ornithine transcarbamylase, Arginosuccinate synthase,

and Argininosuccinate Lyase), can lead to an accumulation of ammonia that results in profound morbidity in the patient if not treated quickly (1), (2). Clinical presentations from such accumulations include lethargy, seizures, hypoventilation, and coma. Studies have shown that while orthotopic liver transplantation leads to near complete correction of metabolic deficiencies and accumulation of nitrogen byproducts, the neurologic consequences from such events may continue (3), (4). Predicting the neurologic outcome and prognosis for improvement over time in patients with UCDs can be very difficult prior to transplantation (5), (6). Factors such as frequency and duration of hyperammonemic events, peak levels of hyperammonemia, and age of transplantation are all known to correlate with poor neurologic outcomes (7). Neurologic prognosis continues to be an important factor in the difficult decisions both for the family and healthcare providers in assessing the child's transplant candidacy (8). Further characterizing which patients will have a good neurologic prognosis would be helpful for providing adequate early guidance to families and providing realistic expectations for long-term outcomes. Early studies have indicated that UCD transplant recipients with normal cognitive evaluation prior to transplantation continue to have near-normal cognitive development post-transplant (9). Most patients with UCDs receive imaging at some point in the course of their diagnosis and early hospital course, particularly after episodes of altered mental status, lethargy or seizure activity. In this study we attempt to determine whether pre-transplant neuroimaging can reliably predict post-transplant neurologic outcome based upon the severity of changes seen on brain imaging.

Patients and methods

This single center retrospective study was evaluated and approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center. Between 2002 and 2012 a total of 15 patients were identified at our institution to have undergone liver transplantation with a primary diagnosis of UCD's including Citrullinemia, OTC deficiency, and CPS deficiency. Indications for referral to Cincinnati Children's Hospital Liver Transplant Center include abnormal Ohio and West Virginia newborn screening, particularly those with inborn errors of metabolism and from local Hepatologists. Cases were reviewed such that neurologic assessments after transplantation were categorized into three separate categories (mild, moderate, and severe) of developmental disability. Developmental assessments consisted of progress notes and neurologic exams during clinic visits after transplantation (n = 11) or from formal Early Learning Accomplishment Profile (ELAP) as performed by a developmental specialist (n = 4). The ELAP provides a validated, systematic method for observing the skill development of children functioning in the birth to 36 month age-range. ELAP assessments were determined as mild, moderate and severe based on age equivalence of global developmental delay. For those without formal assessments, the developmental delay was assessed via progress note HPI and physical exams which were taken from clinic visits with neurology, developmental specialists, or hepatologists. Neurologic exams in these progress notes were reviewed with respect to expected milestones. Moderate neurologic delay consisted of patients who had reached 50-75% of expected milestones, whereas severe developmental delay patients would meet less than 50%. Brain MRIs conducted before transplantation were reviewed independently and blinded to developmental outcomes by a

single pediatric neuroradiologist. Imaging was categorized based on basal ganglia and cortex changes and distinguishing criteria taken from previous studies that have attempted to correlate neuroimaging with developmental outcome after hypoxic coma (18). Briefly, changes in cortex and basal ganglia were each graded 0–3 and summed such that 1–2 (mild), 3–4 (moderate), and 5–6 (severe). Only MRI imaging was analyzed. Patient neurologic assessments after transplantation were compared with the severity of pre-transplantation neuroimaging category.

Results

Of the 15 patients identified to have received liver transplants for UCDs between 2002 and 2012 a total of 8 patients had neuroimaging before transplantation. The five patients without any neuroimaging were not different from those that received imaging with respect to age, gender, or diagnosis (Table 1). Those patients without neuroimaging typically had fewer issues with hyperammonemia, seizures, or altered mental status. Of the eight patients that had neuroimaging, four patients were graded as having severe changes seen on neuroimaging, three as mild, and one as moderate. There were three deaths in the cohort. All four patients whose imaging was categorized as severe prior to transplantation were found to have continued severe neurologic delay according to the ELAP assessments or progress notes. Three out of the four patients with severe imaging received an ELAP assessment from 11 months to 24 months of age. ELAP assessments include evaluations of gross motor, fine motor, cognitive, self-help, and socio-emotional domains. Patients whose developmental age were assessed as < 50th percentile of chronological age were listed as severe neurologic delay. Of the three patients with mild to no changes on neuroimaging (graded as 0–1) before transplantation, two of the three were found to have intact to mild delay on developmental assessments after transplantation. There was one death in the mild and severe neuroimaging categories and one death where no neuroimaging was performed. The mild neuroimaging patient had mild neurocognitive delay prior to death according to progress notes, whereas the patient with severe neuroimaging had severe developmental delay prior to demise.

Discussion

Although liver transplantation has become a treatment option for patients with UCDs and other inborn errors of metabolism, recipients often continue to have poor neurologic outcomes. This study indicates that those children with severe changes seen on brain imaging all continued to have moderate to significant developmental delay despite a successful liver transplant (Table 4). The data was of less prognostic value for those patients with neuroimaging that showed mild to moderate changes. Despite this however Brain MR/ neuroimaging prior to transplantation may be a helpful prognostic tool for allocation discussions as well as informing and educating parents about outcomes. While previous studies have looked at whether neuroimaging correlates with neurodevelopmental outcomes in hypoxemia (10), (11), this is a first look into application of such imaging criteria to hyperammonemic events and relating to Urea Cycle Defects. A distinct limitation of our study was its retrospective nature and it was limited also by lack of complete developmental testing and the subjectivity of progress notes. We do believe however that our study supports the addition of standardized neuroimaging to the pre-transplant evaluation of all UCD

patients given the strong correlation between severe changes on MRI and developmental outcome. Most if not all of the patients considered for candidacy receive MR/MRA of the abdomen during evaluation for transplant and as such we suggest that MRI Brain be routinely added as well. Having objective evidence to show to families prior to transplant along with data that correlates developmental outcome will no doubt be helpful in setting expectations along with preparing resources for developmental needs in these patients. Finally, we also suggest based on these findings that formal neurologic assessments be added to routine follow ups in all UCD patients as this is likely under-represented in care for these patients given our findings. A larger prospective multi-center study with structured follow up will be necessary to confirm these early findings and hopefully provide evidence based criteria for neuroimaging to help guide critical listing and prognostic decisions for this rare population.

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Abbreviations

SOT	Solid Organ Transplantation
UCD	Urea Cycle Defects
CPS	Carbamoyl Phosphate Synthetase I
OTC	Ornithine transcarbamylase

References

1. Todo S, Starzl TE, Tzakis A, et al. Orthotopic liver transplantation for urea cycle enzyme deficiency. *Hepatology*. 1992; 15:419–422. [PubMed: 1544622]
2. Ozanne B, Nelson J, Cousineau J, et al. Threshold for toxicity from hyperammonemia in critically ill children. *Journal of hepatology*. 2012; 56:123–128. [PubMed: 21703182]
3. McBride KL, Miller G, Carter S, Karpen S, Goss J, Lee B. 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. *Pediatrics*. 2004; 114:e523–e526. [PubMed: 15466081]
4. Bachmann C. Outcome and survival of 88 patients with urea cycle disorders: a retrospective evaluation. *Eur J Pediatr*. 2003; 162:410–416. [PubMed: 12684900]
5. Campeau PM, Pivalizza PJ, Miller G, et al. Early orthotopic liver transplantation in urea cycle defects: follow up of a developmental outcome study. *Molecular genetics and metabolism*. 2010; 100(Suppl 1):S84–S87. [PubMed: 20223690]
6. Whittington PF, Alonso EM, Boyle JT, et al. Liver transplantation for the treatment of urea cycle disorders. *Journal of inherited metabolic disease*. 1998; 21(Suppl 1):112–118. [PubMed: 9686349]
7. Uchino T, Endo F, Matsuda I. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. *Journal of inherited metabolic disease*. 1998; 21(Suppl 1):151–159. [PubMed: 9686352]
8. Msall M, Monahan PS, Chapanis N, Batshaw ML. Cognitive development in children with inborn errors of urea synthesis. *Acta paediatrica Japonica; Overseas edition*. 1988; 30:435–441.
9. Kim IK, Niemi AK, Krueger C, et al. Liver transplantation for urea cycle disorders in pediatric patients: a single-center experience. *Pediatric transplantation*. 2013; 17:158–167. [PubMed: 23347504]

10. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *The New England journal of medicine*. 2006; 355:685–694. [PubMed: 16914704]
11. Christophe C, Fonteyne C, Ziereisen F, et al. Value of MR imaging of the brain in children with hypoxic coma. *Am J Neuroradiol*. 2002; 23:716–723. [PubMed: 11950675]

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Table 1

Recipient characteristics

Case	Age at diagnosis	Age at transplant	TxDate	Tx Diagnosis	Sex	Imaging
A	DOL1	4.2	2/1/03	Citrullinemia	F	Y
77B	DOL3	0.8	9/27/03	OTC Deficiency	M	N
C	DOL3	6	1/24/04	Urea Cycle Defects	F	Y
D	DOL3	0.9	5/11/04	OTC Deficiency	M	Y
E	DOL3	1	5/13/05	OTC Deficiency	M	Y
F	Prenatal	0.8	10/10/05	Citrullinemia	M	Y
G	Prenatal	0.2	12/24/07	Citrullinemia	M	N
H	DOL4	0.4	2/14/08	OTC Deficiency	M	Y
I	DOL2	2.2	6/2/08	OTC Deficiency	M	N
J	DOL 2	0.2	1/25/09	OTC Deficiency	M	Y
K	Prenatal	0.2	8/18/10	Citrullinemia	M	N
L	DOL 2	0.5	4/13/11	Citrullinemia	M	Y
M	DOL 1	0.4	5/10/11	Urea Cycle Defects	F	Y
N	DOL 10	1.7	5/27/11	Citrullinemia	M	N
O	DOL6	0.2	Jul-11	CPS deficiency	F	Y

Table 2

Neuroimaging categorization

Case	BG	hemispheric	score	Imaging assessment	Neurologic delay	Neurologic Assessment Type
A	0	2	2	Mild	Normal- demise	Progress note- 5 y.o
B	N/A					
C	2	0	2	Mild	Severe	Progress Note- 12 y.o
D	N/A					
E	3	2	5	Severe	Severe- demise	Progress Note- 1 y.o
F	N/A					
G	N/A					
H	0	0	0	Normal	Mild	Progress Note- 4 y.o
I	N/A					
J	3	3	6	Severe	Severe	ELAP 24 months*
K	N/A				Demise	
L	3	2	5	Severe	Severe	ELAP 16 months
M	3	1	4	Moderate	Mild	ELAP 11 months
N	N/A					
O	3	3	6	Severe	Severe	ELAP 11 months

* ELAP assessment of developmental age by Patient. J: 12 months at 24 months of age, Patient L: 6–7 months at 16 months of age, Patient M: 9 months at 11 months of age, Patient O: 5–6 months of age at 11 months

Table 3

Indications for neuroimaging

Case	
A	Seizure
B	N/A
C	Metabolic Disorder
D	Abnormal Behaviors/staring
E	Seizure
F	Seizure
G	N/A
H	Seizure
I	N/A
J	Hyperammonemia/Seizure
K	N/A
L	Hyperammonemia
M	Hyperammonemia/Seizure
N	N/A
O	Hyperammonemia/Seizure

Table 4

Correlation

Category	PPV	NPV	Chi2 P value	OR	95% CI
Mild	66.6	80	0.186	8	0.309–206.5
Moderate	0	100	NA	NA	NA
Severe	100	75	0.02	21	0.638–690.6