Clinical Outcomes of Neonatal Onset Proximal versus Distal Urea Cycle Disorders Do Not Differ

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Objective To compare the clinical course and outcome of patients diagnosed with one of 4 neonatal-onset urea cycle disorders (UCDs): deficiency of carbamyl phosphate synthase 1 (CPSD), ornithine transcarbamylase (OTCD), argininosuccinate synthase (ASD), or argininosuccinate lyase (ALD).

Study design Clinical, biochemical, and neuropsychological data from 103 subjects with neonatal-onset UCDs were derived from the Longitudinal Study of Urea Cycle Disorders, an observational protocol of the Urea Cycle Disorders Consortium, one of the Rare Disease Clinical Research Networks.

Results Some 88% of the subjects presented clinically by age 7 days. Peak ammonia level was 963 μM in patients with proximal UCDs (CPSD or OTCD), compared with 589 μM in ASD and 573 μM in ALD. Roughly 25% of subjects with CPSD or OTCD, 18% of those with ASD, and 67% of those with ALD had a "honeymoon period," defined as the time interval from discharge from initial admission to subsequent admission for hyperammonemia, greater than 1 year. The proportion of patients with a poor outcome (IQ/Developmental Quotient <70) was greatest in ALD (68%), followed by ASD (54%) and CPSD/OTCD (47%). This trend was not significant, but was observed in both patients aged <4 years and those aged ≥4 years. Poor cognitive outcome was not correlated with peak ammonia level or duration of initial admission.

Conclusion Neurocognitive outcomes do not differ between patients with proximal UCDs and those with distal UCDs. Factors other than hyperammonemia may contribute to poor neurocognitive outcome in the distal UCDs. *(J Pediatr 2013;162:324-29)*.

The urea cycle consists of 5 biochemical steps required for the conversion of ammonia to urea.[1] A deficiency of any of these enzymes reduces or halts flux through the urea cycle, typically resulting in acute hyperammonemia. Complete deficiencies of the proximal urea cycle enzymes carbamyl phosphate synthetase 1 (EC 6.3.4.16) and ornithine transcarbamylase (OTC; EC 2.1.3.3) are considered to cause more severe hyperammonemia compared with deficiencies in distal urea cycle enzymes, such as argininosuccinate synthase and argininosuccinate lyase.[2] In the latter disorders, the excretion of amino acids citrulline or argininosuccinate provides an alternative pathway for waste nitrogen excretion.[2] Intuitively, lower levels of blood ammonia should result in reduced neurotoxicity. However, there is some evidence that patients with argininosuccinate synthase deficiency (ASD) or argininosuccinate lyase deficiency (ALD) are equally or more severely impaired than those with carbamyl phosphate synthetase 1 deficiency (CPSD) or OTC deficiency (OTCD),[3,4] suggesting additional mechanisms of brain injury.[5,6]

We wished to determine whether infants with proximal urea cycle disorders (UCDs) who present with neonatal disease experience different outcomes than did those with distal UCDs.

Herein we summarize the clinical course and outcomes of patients with neonatal onset of CPSD, OTCD, ASD, and ALD who survived beyond the neonatal period. We report that: (1) the majority of these patients present in the first week of life; (2) most of them have an event-free "honeymoon" period of variable duration after the initial neonatal insult; and (3) neurocognitive outcomes do not differ between patients with proximal UCDs and those with distal UCDs.

ALD	Argininosuccinate lyase deficiency
ASD	Argininosuccinate synthetase deficiency
CPSD	Carbamyl phosphate synthetase 1 deficiency
DQ	Developmental quotient
FSIQ	Full-scale intelligence quotient
OTC	Ornithine transcarbamylase
OTCD	Ornithine transcarbamylase deficiency
UCD	Urea cycle disorder
UCDC	Urea Cycle Disorders Consortium

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Methods

We used data collected as part of the Longitudinal Study of Urea Cycle Disorders (ClinicalTrials.gov ID: NCT00237315), a "natural history" observational protocol of the Rare Diseases Clinical Research Network's Urea Cycle Disorders Consortium (UCDC), comprising 14 research sites at academic centers in the United States, Canada, and Europe.[7,8] This report is based on a subset of participants enrolled in the previously described Institutional Review Board–approved Study,[7,8] which includes consented volunteers of all ages with a confirmed diagnosis of a UCD. Only those diagnosed with CPSD, OTCD, ASD, or ALD contributed data to this study. As in the parent Longitudinal Study, data are derived from abstracts of medical records. At each encounter, the participant and/or guardian(s) were interviewed, and a clinical evaluation and standard battery of laboratory investigations were performed. All study data were entered into the UCDC database maintained by the Data Management and Coordinating Center of the Rare Disease Clinical Research Network.

Participants underwent neuropsychological and developmental evaluation at the time of enrollment and then at specific ages throughout the study period (6 months, 18 months, 4 years, 8 years, 15 years, and 18 years). The tests captured neuropsychological and developmental function and were designed to be pertinent to the subject's age and developmental level for global intellectual/developmental functioning: age 0-3 years, Cognitive Scale from the Bayley Scales of Infant and Toddler Development, Third Edition; age 3-5 years, Full-Scale IQ (FSIQ) from the Wechsler Preschool and Primary Scales of Intelligence–Third Edition; age 6-18 years, FSIQ from the Wechsler Abbreviated Scale of Intelligence. If an individual was unable to complete the appropriate test for his or her age group, a developmental quotient (DQ) score was obtained by dividing age equivalence score on the Bayley Scales by chronological age.

We obtained from the Data Management and Coordinating Center data for all enrolled participants with CPSD, OTCD, ASD, and ALD who were hospitalized during the first 30 days of life with either a peak recorded plasma ammonia level of ≥200 μmol/L (normal, <35 μmol/L) or genetic analysis demonstrating mutations associated with neonatal-onset disease. Patients presenting after the first 30 days of life were excluded, because such a later presentation was suggestive of the presence of residual urea cycle function. Finally, patients for whom data from the initial hospitalization were not available were excluded as well. We also report on the current number of deceased patients known to have had neonatal-type disease who were not enrolled in the longitudinal study but were captured by our review of medical records.

We used the χ^2 test (for ordinal categories) and ANOVA/ANCOVA to compare maximal ammonia levels during the first hospitalization among 3 diagnostic cohorts (CPSD/OTCD vs ASD vs ALD), to evaluate whether patients with proximal UCD (CPSD or OTCD) presented with higher ammonia levels than those with distal UCD (ASD or ALD). For evaluating differences in duration of the interval between first and second hospitalization for hyperammonemia, we used a competing-outcomes proportional hazards model to analyze whether this parameter differed by diagnostic cohort to account for groupwise differences in the presence of liver transplantation as well as other covariables. For comparing neurocognitive development (DQ/IQ categories), we used logistic and ordinal logistic regression to compare the odds of greater DQ or IQ by diagnostic cohort. These analyses also controlled for other differences between cohorts.

Given the various psychometric tests used by the UCDC Longitudinal Study to assess neurocognitive function, we felt that it was inappropriate to compare subject scores as a single continuous variable. Thus, we first created categories of cognitive/developmental functioning for the entire cohort (poor outcome vs non-poor outcome; **Table I**). We then applied a broader categorical score to individuals aged ≥4 years (**Figure 1**). Children aged <4 years were not included in this second analysis, given the difficulties in applying the concept of IQ in this age group. Not only are IQ scores at this younger age less stable and not highly predictive of later IQ, but the lowest attainable score on the Bayley Scales is 55, and this floor reduces the comparison accuracy of individuals at the lower end of the spectrum. The categories for this second analysis were the same as in a model described previously.[9]

Results

Of the 500 subjects enrolled in the UCDC Longitudinal Study, 103 subjects with neonatal-onset UCD met our inclusion criteria, including 8 with CPSD, 30 with OTCD, 37 with ASD, and 28 with ALD. We combined CPSD and OTCD into a single "proximal UCD" entity of 38 subjects because these disorders are indistinguishable in terms of clinical presentation and amino acid abnormalities. Selected sociodemographic and clinical characteristics of the study sample,

Table I. Intellectual/developmental outcome by diagnosis

	CPSD/OTCD (n = 38)	ASD (n = 37)	ALD (n = 28)	All subjects (n = 103)
Neuropsychological testing, n	30	28	25	83
Poor cognitive outcomes, %*	47	54	68	55
Age <4 years, n	14	8	8	30
Mean age, years	1.6	1.6	1.8	1.6
Mean Bayley Cognitive Score	76.4	79.6	70.6	75.8
Poor cognitive outcomes, %	43	25	50	40
Age ≥4 years, n	16	20	17	53
Mean age, years	10.0	14.5	11.9	12.1
Poor cognitive outcomes, %	50	70	76	66

*Poor outcomes include functioning in the range of delayed cognitive development (Bayley Cognitive Score <70) or in the range consistent with an intellectual disability (ie, Bayley Cognitive Scale or FSIQ score from the Wechsler Abbreviated Scale of Intelligence/Wechsler Preschool and Primary Scale of Intelligence III <70).