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Neurodevelopmental Outcome in Infants with Lower Urinary Tract Obstruction Based on Different Degrees of Severity

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Abstract
Objective: To determine postnatal neurodevelopmental (ND) outcomes for children with congenital lower urinary tract obstruction (LUTO) based on disease severity. ***Methods:*** Twenty male infants with LUTO were classified prenatally as Stage 1 (normal amniotic fluid and renal function; $n = 5$), Stage 2 (signs of obstruction with preserved renal function; $n = 13$), and Stage 3 (signs of severe renal damage; $n = 2$). ND status was assessed using the Developmental Profile-3 test in 5 developmental domains (physical, adaptive behavior, social-emotional, cognitive, and communication). Each domain was considered to be delayed if standard scores were 2 or more SD below the mean. ND outcomes were compared between cases with an expected normal renal function (LUTO Stage 1) and those with impaired renal function (LUTO Stages 2 and 3). Results from cases with Stage 2 were also compared to those from Stage 3. ORs were calculated to predict risk for adverse ND outcome for each domain considering prenatal and postnatal factors. ***Results:*** Gestational age (GA) at the diagnosis of LUTO was similar between both groups (Stage 1: 24.85 ± 7.87 vs. Stages 2 and 3: 21.4 ± 4.31 weeks; $p = 0.24$). Twelve of 15 cases with Stage 2 or 3 underwent vesicoamniotic shunt placement compared to none of Stage 1 fetuses ($p < 0.01$). No differences in GA at delivery were detected between the groups (37.9 ± 1.6 vs. 35.1 ± 3.6 weeks; $p = 0.1$). One of the infants in the Stage 2 and 3 groups received a kidney transplant during follow-up. One case (20%) from Stage 1 group required dialysis during the first 6 months of life, and 1 case from Stage 2 to 3 group required it during the first 6 months ($p = 1.0$), whereas 3 additional cases needed dialysis from 6 to 24 months ($p = 0.6$). Mean age at Developmental Profile 3 (DP-3) testing was 20.3 ± 12.3 months (Stage 1: 11.2 ± 8.6 vs. Stages 2 and 3: 23.4 ± 13.4 months; $p = 0.07$). Fifteen of the 20 patients (75%) had

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no ND delays. Of the 5 patients with ND delays, 4 received dialysis. No differences in ND outcomes between infants with LUTO Stage 1 and those with Stages 2 and 3 were detected except for a trend toward better physical development in Stage 1 (102.6 ± 11.6 vs. 80.7 ± 34.9; $p = 0.05$). Infants diagnosed with LUTO Stage 3 showed significantly lower adaptive scores than those diagnosed with Stage 2 (Stage 2: 101.9 ± 22.3 vs. Stage 3: 41.5 ± 30.4; $p = 0.04$) and a nonsignificant trend for lower results in physical (85.8 ± 33.0 vs. 47.5 ± 38.9; $p = 0.1$) and socio-emotional (94.7 ±17.9 vs. 73.5 ± 13.4; $p = 0.1$) domains. Infants who received dialysis showed 15-fold increased risk (95% CI 0.89–251) for delayed socio-emotional development ($p = 0.06$). Diagnosis of fetal renal failure increased the risk for delays in the adaptive domain 30-fold (95% CI 1.29–93.1; $p = 0.03$). Infants with abnormal renal function had 19 times (95% CI 1.95–292) increased risk for delays in the physical domain ($p = 0.03$). ***Conclusions:*** While most patients with LUTO do not exhibiting ND delays, our results support the importance of ND monitoring, especially in severe forms of LUTO, as increased severity of this condition may be associated with poorer ND outcomes.

Introduction

Lower urinary tract obstruction (LUTO) occurs in 2.2 of every 10,000 births and is most commonly caused by posterior urethral valves [1]. It has high morbidity and mortality, with mortality rates reported between 33 and 75% in the perinatal period when untreated [2]. Typical ultrasound features of LUTO include marked distension of the bladder associated with hydroureteronephrosis [3]. While mild forms of the disease may lead to minimal clinical sequelae, the more severe forms commonly lead to oligohydramnios, a distended urinary tract, and renal dysplasia [3]. The loss of urinary flow into the amniotic space also leads to lung hypoplasia, and this may be a fatal complication [4]. Renal function is often significantly impaired, with some reports showing >50% of LUTO patients having end-stage renal disease (ESRD) requiring dialysis soon after birth [5, 6], and 25–30% will require dialysis or renal transplant by the age of 5 years [7]. ESRD is a known risk factor for poor neurodevelopmental (ND) outcomes, with earlier onset during infancy associated with greater risk of impairment [8–12].

After the diagnosis of LUTO is made, the challenge becomes identifying which fetuses would benefit from intervention. Overall, it is accepted that those with normal karyotype, lack of other congenital anomalies, and presenting with oligohydramnios or anhydramnios and favorable urinary biochemistry would be considered good candidates [13]. Fetal intervention is predominantly aimed at restoration of amniotic fluid volume for prevention of pulmonary hypoplasia and urinary decompression for attenuation of ongoing renal damage [14–18]. Treatment options for this subset of fetuses include vesicoamniotic shunting (VAS) which is most commonly used, valve ablation via cystoscopy, and vesicostomy [3]. VAS is the most common antenatal treatment for LUTO. After this intervention, 91% of cases with severe forms of LUTO survived at 1 year of age [19] and survival increased when compared to expectant management (OR 2.53, 95% CI 1.08–5.93) [17, 19].

Long-term follow-up in this population has been limited [6, 19–22]. In a cohort study of 18 male children (mean age 5.8 years) treated prenatally with VAS, 78% of parents reported that their children had "normal development"; however, details regarding functioning within individual developmental domains, such as physical, adaptive, or cognitive functioning, were not reported, and a standardized measure of development was not used [19]. The assessment of ND outcomes in infants with LUTO considering different degrees of severity, has also not been reported to date. This information may be helpful for prenatal counseling of these patients. Thus, the primary aim of this study is to determine ND outcomes for children with congenital LUTO based on disease severity. As a secondary aim, we tried to identify prenatal and postnatal predictors that may be associated with an adverse ND outcome for this condition.

Material and Methods

This study was approved by the Institutional Review Board (H-35770), and written consent was obtained from each participating mother. Patients with a prenatal diagnosis of LUTO who received perinatal management at our institution were considered eligible to participate in this study. Inclusion criteria were consenting pregnant women who had a singleton male fetus with an ultrasound diagnosis of LUTO established by the visualization of an enlarged bladder, bilateral hydroureters and hydronephrosis with or without cystic parenchymal renal disease [23, 24], no additional fetal structural anomalies, and normal chromosome testing.

Diagnosis of LUTO Severity

All patients referred to our institute with a prenatal diagnosis of LUTO were evaluated using the standardized multidisciplinary approach previously published by our group [25]. In summary, the patients underwent comprehensive obstetric ultrasound, fetal echocardiography, genetic consultation, and consultation with maternal fetal medicine, pediatric nephrology, and urology spe-

Table 1. Prenatal LUTO classification

	Stage I (mild LUTO)	Stage II (severe LUTO, with prenatal findings suggestive of preserved fetal renal function)	Stage III (severe LUTO, with prenatal findings suggestive of fetal abnormal renal function)
Amount of amniotic fluid (>18 weeks)	Normal	Oligohydramnios or anhydramnios	Oligohydramnios or anhydramnios
Echogenicity of fetal kidneys	Normal	Hyperechogenic	Hyperechogenic
Renal cortical cysts on ultrasound	Absent	Absent	Can be present
Sonographic appearance of renal dysplasia	Absent	Absent	Can be present
Fetal urinary biochemistry (>18 weeks)	Favorable	Favorable within 3 consecutive evaluations	Not favorable after 3 consecutive evaluations

LUTO classification as defined by Ruano et al. [25]. LUTO, lower urinary tract obstruction.

cialists. Only patients with a confirmed diagnosis of LUTO (megacystis, bilateral hydroureter, and hydronephrosis) with oligohydramnios/anhydramnios were offered vesicocentesis to assess the fetal urinary biochemistry and bladder refill. Also, genetic testing with amniocentesis or cordocentesis was offered to these patients. If the results of the initial fetal bladder tap were unfavorable, a second vesicocentesis was offered to allow for evaluation of a fresh urine sample. This procedure was repeated for a third time in select cases.

Fetal renal function was evaluated using a combination of fetal renal ultrasound parameters and urinary biochemical markers [26]. Patients were staged according to our published Prenatal Classification of LUTO Severity [25] (Table 1) considering the amount of amniotic fluid, urinary biochemistry, and presence of renal cysts or signs of renal dysplasia. VAS placement was offered to patients with evidence of significant obstruction and favorable fetal renal function parameters (Stage 2 LUTO, $n = 13$). Further details on VAS placement are included in the online supplementary Materials (for all online suppl. material, see www.karger.com/doi/10.1159/000504977. Following shunt placement, weekly ultrasounds were performed, and repeat placement was offered if the shunt was obstructed or dislodged. The number of shunts that are placed during the entire pregnancy and gestational age (GA) at placement were recorded. Those patients with Stage 1 LUTO, defined as normal amniotic fluid level and normal fetal renal functioning ($n = 5$), were treated expectantly with weekly ultrasound follow-up. Patients with Stage 3 ($n = 2$) were not considered as candidates for VAS placement and were followed on a weekly basis as well [26–29]. Fetal renal failure was diagnosed by the presence of ultrasonographic signs suggestive of renal dysplasia: hyperechogenic kidneys with renal cortical cysts and absence of cortico-medullary differentiation, in addition to the presence of nondilated or mildly dilated thick wall fetal urinary bladder with progressively decreasing amount of amniotic fluid if detected at any time during the course of the pregnancy. One of the parameters that was recorded at each follow-up ultrasound scan was the amniotic fluid index, where indices <5 cm was considered as severe oligohydramnios. Postnatal renal function was defined for the purpose of this study as abnormal if at 6 months of age creatine was ≥0.5 mg/dL [26].

Delivery timing and route were based on standard obstetric principles. After delivery, all surviving infants were evaluated and followed by pediatric specialists, including pediatric urologists, nephrologists, and neonatologists. A voiding cystourethrogram and postnatal cystoscopy were performed to evaluate the bladder and the urethra in all cases. Postnatal renal function, the requirement of dialysis, and the need for renal transplant were also recorded.

ND Assessment

The mothers of surviving infants with prenatally diagnosed LUTO were interviewed by a Developmental Behavioral Pediatrician using a standardized child development assessment instrument, the DP-3 [30, 31]. The DP-3 includes 180 items, each describing a particular ND skill. The respondent indicates whether or not the child has mastered the skill in question. Standard scores are obtained for overall general development as well as for the following 5 ND scales: Physical (assessment of large and small muscle coordination, strength, stamina, flexibility, and sequential motor skills), adaptive behavior (ability to cope independently with the environment- to eat, dress, work, take care of self, and others), social-emotional (interpersonal skills, social/emotional understanding, functioning in social situations, manner in which child relates to peers, and adults), cognitive (intellectual abilities and skills prerequisite to academic achievement), and communication (expressive and receptive communication skills, including written, spoken, and gestural language) [30, 31]. Additionally, the combination of the scores obtained from these 5 developmental domains was used to calculate a general development standard score (GDS), which represents the overall development in each child. For those patients whose standard score in an individual ND domain was <50, a developmental quotient was calculated (by dividing the infant's developmental age equivalent determined by the DP-3 by their chronological age and multiplying by 100), and these developmental quotients were used in place of standard scores for these patients. This was done for 3 of the 20 patients and included 3

Table 2. Maternal characteristics

	LUTO Stage 1 (n = 5)	LUTO Stages 2 and 3 (n = 15)	p value
Maternal age, years	26.83±7.93	26.94±4.69	0.96
Race	5 (100)		0.32
White		10 (66.7)	
Afro-American		4 (26.7)	
Asian		1 (6.7)	
Hispanic ethnicity	2 (40)	13 (86.7)	0.07
Maternal BMI at enrolment, kg/m^2	27.51±4.3	29.83±8.24	0.45
Primiparous	3 (60)	3 (20)	0.13

Results are expressed as mean ± SD and number of cases (percentages) when appropriate. p represents the comparison between both groups. Quantitative data were compared using t test for independent groups and quantitative data were compared using chi-square or Fisher's tests.

LUTO, lower urinary tract obstruction; BMI, body mass index.

Table 3. Perinatal characteristics

	LUTO Stage 1 (n = 5)	LUTO Stages 2 and 3 (n = 15)	p value
GA at delivery, weeks	37.9±1.62	35.12±3.63	0.12
Delivery <32 weeks of GA	0	3/15 (20)	0.54
Delivery <37 weeks of GA	1/5 (20)	8/15 (53.3)	0.32
Newborn weight, g	3,353.40±581.58	2,767.86±796.59	0.15
Newborn weight percentile[1]	43.43±32	44.35±31.13	0.95
Newborn height, cm	50.34±1.95	46.41±4.62	0.09
Newborn height percentile[1]	54.87±30.3	22.18±33.48	0.08
Head circumference, cm	34.46±1.28	32.53±3.38	0.24
Head circumference percentile[1]	41.84±19.5	53.49±38.56	0.43

[1] WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height, and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.

p: Results are expressed as mean ± SD or ratios and percentages. Comparisons between both groups were carried out by t test for independent samples for quantitative data. Chi-square or Fisher test was performed to compare qualitative data.

LUTO, lower urinary tract obstruction; GA, gestational age.

physical and 2 adaptive developmental quotients. Standard scores were interpreted as delayed if they were 2 or more SD below the mean (standard score ≤70) or not delayed (standard score >70). The proportion of cases in each LUTO stage with a delayed neurodevelopment domain or GDS was calculated.

Statistical Analyses

Student t test for independent samples and Pearson's χ^2 or Fisher's exact tests were used to compare quantitative and qualitative data, respectively. Comparisons of ND outcomes were performed by comparing cases with the diagnosis of LUTO with expected normal renal function before birth (Stage 1) versus those with expected abnormal renal function (Stages 2 and 3). Results from DP-3 test between infants from Stage 2 to 3 were also compared. ORs of having an abnormal ND outcome (delayed GDS [≤70], or developmental delay in each developmental domain [standard score ≤70]), were calculated using GA at delivery <37 weeks, fetal intervention (VAS placement), fetal renal failure, postnatal renal function, severe oligohydramnios, LUTO Stage 2, LUTO Stage 3, need for dialysis and renal transplant as independent variables on a binary logistic regression. Results were considered significant at a p value <0.05. All statistical calculations were done using SPSS statistical software version 17.0 (SPSS for windows, SPSS Inc., Chicago, IL, USA).

Table 4. Renal function

	LUTO Stage 1 (n = 5), n (%)	LUTO Stages 2 and 3 (n = 15), n (%)	p value
GA at the diagnosis of LUTO, weeks	24.85±7.87	21.4±4.31	0.24
Severe oligohydramnios detected during the pregnancy[1]	0	10 (66.7)	0.06
Fetal renal failure[2]	1 (20)	2 (13.3)	1.0
Proportion of cases in which a VAS was placed	0	12 (80)	<0.01
Cases who received 1 shunt	–	7/12 (58.33)	–
Cases who received 2 shunts	–	3/12 (25)	–
Cases who received >2 shunts	–	2/12 (16.67)	–
GA at first shunt placement, weeks	–	22.62±5.58	–
Postnatal diagnosis			0.06
Posterior urethral valves	3 (60)	12 (80)	
Urethral atresia	0	2 (13.3)	
PBS	0	1 (6.7)	
Reflux	2 (40)	0	
Postnatal surgery	3 (60)	10 (66.7)	1.0
Postnatal renal function			0.72
Normal	3 (75)	9 (60)	
Abnormal	1 (25)	6 (40)	
Kidney transplant during follow-up	0	1 (6.7)	1.0
Need for dialysis at ≤6 months	1 (20)	1 (6.7)	1.0
Age at initiation of dialysis, days	15	4	0.44
Need for dialysis until 2 years of life	1 (20)	4 (26.7)	1.0

[1] Oligohydramnios defined as AFI <5 cm.

[2] Fetal renal failure was diagnosed by the presence of ultrasonographic signs suggestive of renal dysplasia: hyperechogenic kidneys with renal cortical cysts and absence of cortico-medullary differentiation, in addition to the presence of nondilated or mildly dilated thick wall fetal urinary bladder with progressively decreasing amount of amniotic fluid.

Results are expressed as mean ± SD or ratios and percentages. Comparisons between both groups were carried out by t test for independent samples for quantitative data. Chi square or Fisher test was performed to compare qualitative data.

LUTO, lower urinary tract obstruction; GA, gestational age; VAS, vesicoamniotic shunt; PBS, prune Belly syndrome.

Results

Prenatal Renal Study

Twenty-four patients were enrolled in this study, but ND assessment could only be performed on 20 patients, as 4 patients were lost to follow-up postnatally. Five cases were classified as Stage 1, 13 cases were classified as Stage 2, and 2 cases as were classified as Stage 3. Twelve patients underwent VAS placement, and 8 did not. All of the patients that had undergone a fetal intervention were classified as LUTO Stage 2. Patients that did not undergo fetal intervention were classified as LUTO Stage 1 in 5 cases, Stage 2 in 1 case, and Stage 3 in 2 cases. Fetal intervention cases required 1 shunt placement in 8 cases, 2 shunt placements and 5 interventions in 1 case, and 3 interventions were needed in 2 cases. Mean GA at first intervention was 22.6 ± 5.6 weeks, and in cases where multiple shunt placements were necessary, the latest shunt placement was performed at 31.1 weeks. No differences in maternal body mass index or other maternal characteristics were detected between groups (Table 2).

Perinatal characteristics between groups were similar (Table 3). No significant differences in GA at delivery, rate of preterm delivery, or delivery at <32 weeks were detected. More than half of the cases from Stage 2 to 3 were delivered at <37 weeks (53.3%) and 20% were delivered at <32 weeks. The latter were cases diagnosed as Stage 2, which is related to the 18.8% rate of PPROM that

Table 5. ND assessment results

	All LUTO patients (n = 20)	LUTO Stage 1 (n = 5)	LUTO Stages 2 and 3 (n = 15)	p value*
Age at test, months	20.35±12.34	11.2±8.58	23.4±13.43	0.07
General development	98.94±17.3	99.2±7.72	98.83±20.34	0.97
Delayed general development	2/17 (11.8)	0	2/12 (16.7)	1.0
Physical development	83.15±38.75	102.6±11.63	80.73±34.95	0.05
Delayed physical development	4/20 (20)	0	4/15 (26.7)	0.53
Adaptative development	94.7±29.82	101.2±3.56	93.87±30.75	0.38
Delayed adaptative development	3/20 (15)	0	3/15 (20)	0.53
Social-emotional development	93.1±16.56	96.6±8.73	91.93±18.56	0.59
Delayed social-emotional development	3/20 (15)	0	3/15 (20)	0.53
Cognitive development	93.65±15.25	97.4±14.71	92.4±15.72	0.54
Delayed cognitive development	1/20 (5)	0	1/15 (6.7)	1.0
Communication	99.3±13.28	98.4±8.79	99.6±14.72	0.86
Delayed communication development	1/20 (5)	0	1/15 (6.7)	1.0
Number of cases with ≥1 delayed domains	5 (25)	0	5 (33.3)	0.26

Delayed development was determined if standard score was <2 SD, so if ≤70. * $p < 0.05$.

Results are expressed as mean ± SD or ratios and percentages. Comparisons between both groups were carried out by t test for independent samples for quantitative data. Chi-square or Fisher test were performed to compare qualitative data.

ND, neurodevelopmental; LUTO, lower urinary tract obstruction.

occurred at <32 weeks for all patients. Also, newborn characteristics (Table 3), including birth weight, neonatal length, and head circumference, were comparable between both groups.

The diagnosis of oligohydramnios was made at a later GA in the cases diagnosed with Stage 1 than in those with Stage 2 and 3 (Table 4). At the time of developmental assessment, none of the Stage 1 and 13% of the Stage 2 and 3 infants required a renal transplant. Dialysis was necessary in one of the Stage 1 infants (20%) and 4 of the Stage 2 and 3 infants (26.7%) during the first 2 years of life.

ND Assessment

The mean patient age at the time of ND assessment was 20.35 ± 12.3 months, with a mean GA at delivery of 36 ± 2.5 weeks. On the DP-3, 15 of the 20 patients (75%) with LUTO did not evidence a delay in any ND domain. Of these 15 patients, 80% (n = 12) had a GDS in the average range (standard score >84), and 20% had a GDS in the above average range (standard score >115). Considering the entire cohort of LUTO infants, the proportion of cases that showed delays in different developmental scales ranged from 5% in the communication and cognitive domains to 20% in the physical development domain (Table 5).

None of the patients with Stage 1 LUTO exhibited ND delays. Of the patients with Stage 2 LUTO, 23% (3 of 13) had a delay in one or more ND domain. Both patients with Stage 3 LUTO (significant renal impairment without fetal intervention) were found to be developmentally delayed. When ND outcomes were compared between infants diagnosed as Stage 2 vs. 3, lower scores were detected in the latter, with significantly lower scores in adaptive domain (Stage 2 101.92 ± 22.32 vs. Stage 3 41.5 ± 30.41; $p < 0.01$) and a trend toward lower scores in social-emotional (Stage 2 94.77 ± 17.93 vs. Stage 3 73.5 ± 13.43; $p = 0.13$) and physical domains (Stage 2 85.85 ± 32.96 vs. Stage 3: 47.5 ± 38.89; $p = 0.15$). There was a higher proportion of cases with abnormal general development (0 vs. 66.7%. $p = 0.02$), physical development (6.7 vs. 60%; $p = 0.03$), adaptive development (0 vs. 60%; $p < 0.01$), and socio-emotional development (0 vs. 60%; $p < 0.01$) in those who received dialysis (n = 5) compared to those that did not (n = 15). Online supplementary Table 1 Overall, there was a trend toward lower scores in all domains from the group of infants undergoing dialysis when compared to those that did not receive it. Online supplementary Table 1, reaching statistical significance in physical, adaptive, and social-emotional domains.

Of the 5 patients (25%) who evidenced ND delays, 3 exhibited delays in >1 ND domain, and all of them had received dialysis. Delays in physical development were the most common delays (4 out of 5 patients).

The odds of delayed physical development were 19.5 times higher (95% CI 1.29–292.1; $p = 0.03$) with the diagnosis of postnatal abnormal renal function, 3 times higher with severe oligohydramnios (95% CI 0.24–36.32; $p = 0.38$), and 7 times higher in patients who eventually required dialysis (95% CI 0.6–81.68; $p = 0.12$). Patients on dialysis had 14 times the odds of delayed general development (95% CI 0.45–434.1; $p = 0.13$) and 15 times the odds of having delayed social emotional development (95% CI 0.89–251.05; $p = 0.06$).

With regard to survival rates at 2 years of age, at the time of this assessment, 10 patients were <2 years of age. At the time of submission, 8 of these patients had survived past 2 years of age and 2 were lost to follow-up.

Discussion

Although LUTO is one of the most severe congenital diseases that can be diagnosed during fetal life, and severe LUTO is usually associated with high perinatal mortality and morbidity resulting from pulmonary hypoplasia and ESRD [7], we found that a majority of patients with LUTO did not exhibit ND delays. We found that the presence of developmental delays increased with the severity of LUTO and that neurodevelopment was most impaired for those patients requiring dialysis. We also found that for those LUTO patients with more impaired renal functioning, physical and adaptive development were more negatively impacted than cognitive or communication development.

Some investigators have advocated for utilizing fetal urinalysis for fetal triage and the allocation of risk of postnatal renal damage prospectively [15, 32]. Other authors have advocated that overall diagnostic accuracy of such testing is low and may be unreliable when deciding on treatment [33]. Although we found that renal functioning at birth was abnormal for LUTO patients compared to the general population, we found no differences in renal functioning at birth between Stage 1 and 2 LUTO patients.

The assessment of severity of renal disease in fetal life using ultrasound and urinary indices has shown a correlation with renal function postnatally. The classification of fetal renal function using the Texas Children's severity staging is a useful tool to evaluate patients who are considered candidates for fetal intervention and to counsel families to establish their expectations for postnatal outcomes. Nevertheless, there is a significant gap in knowledge of the expectations that families may have regarding the ND outcomes that may be expected in this population. Previous studies have been limited to informal assessments without the use of standardized developmental measures. Additionally, patterns of developmental delay across individual domains of development have not previously been reported in this population [19].

We observed that the majority of infants with LUTO had normal ND outcomes. This is consistent with previously published reports that have shown that children with mild to moderate renal disease have IQ, academic achievement, and attention/executive functioning that fall within age appropriate expectations [34]. The prevalence of parent-reported ND disorders is 15% for all children and 9% for children between 2 and 3 years of age, while based on direct developmental assessment, 13% of children at 9 and 24 months have been reported to have delays in their development [35, 36]. Although the overall rate of developmental delay in our cohort of LUTO cases was higher (25%), when broken down by individual developmental domain, only 10% (2 of 20) patients showed delays in cognitive and/or language domains.

Our findings are consistent with previous studies that have shown the need for dialysis during infancy has a negative impact on neurodevelopment [37]. In a study of 21 patients who required dialysis prior to 24 months of age, 71% had evidence of ND impairment based on neuropsychological testing and evaluation with multiple specialists, including a neurologist, physiotherapist, and occupational therapist [37]. In addition, children with ESRD diagnosed during infancy have been shown to have lower cognitive functioning, lower academic achievement, and deficits in executive functioning when compared to sibling controls [8]. Further, adults with a history of ESRD during childhood have been shown to have lower educational achievement, an increased rate of unemployment, and a lower likelihood to live independently [38]. Chronic kidney disease has been correlated with impaired attention regulation and inhibitory control in pediatric patients from 6 to 21 years of age, which directly impacts learning as well as functioning at home and in the community [39].

In our cohort, patients with more impaired renal function had increased risk for physical and adaptive impairments. Given these results, therapeutic interventions

(such as physical and occupational therapy) for this population should be considered at an early age to address these deficits to maximize long-term outcomes. The benefits of early intervention programs, as mandated by Part C of the Individuals with Disabilities Education Act, are well established, as 71% of all early intervention participants at <3 years of age show greater than expected growth in knowledge and skills, and 52% of these participants exit early intervention programs with development within age appropriate limits [40].

It has been hypothesized that the uremia and anemia associated with chronic kidney disease may alter metabolism in the brain and impact both neuronal myelination and synaptic development [41]. If such altered neuronal metabolism occurs during infancy and early development, it could be further hypothesized that the effect on ND outcomes would be more significant.

A strength of this study is that it is the first study to report ND outcomes using a standardized developmental assessment measure in children with LUTO. In previous studies based on informal parent report of "normal" or "abnormal" development (without the use of a standardized developmental measure), additional information regarding differences within specific domains of development have not been able to be reported. Furthermore, our study provides evidence regarding the pre- and postnatal variables that are most predictive of ND impairments in specific ND domains using a standardized developmental assessment measure.

Limitations of our study include its small sample size. However, our sample size is similar in size to studies reporting outcomes in children with ESRD [8, 9]. ND assessment in our study was completed with a standardized measure based on parent interview; however, direct clinical confirmation was not performed. Despite this limitation, it has been previously shown that parental reporting of both language and motor abilities in children with and without ND disabilities is comparable to and not significantly different from direct assessment [42, 43]. Although our study accounted for many pre- and postnatal variables, we did not account for additional factors, including comorbid medical conditions, sociodemographic differences, and psychosocial risk factors that can influence neurodevelopment in the first few years of life [44]. Additionally, although maternal and perinatal characteristics did not vary among groups, the average age for ND assessment for infants with Stage 1 LUTO was lower than that for infants with Stages 2 and 3 LUTO (11 vs. 23 months); however, this was not a significant difference ($p = 0.07$). Finally, more severe developmental delays will present during infancy, while milder ND delays may present when children are older. Thus, our patients undergoing assessment at a younger age should have close ND monitoring over time.

Conclusions

A majority of infants in our study with LUTO are not exhibiting ND delays. Rates of delayed development do not significantly differ between those who underwent fetal intervention and those who did not. Increased rates of delay in physical and adaptive development are seen with increased severity of LUTO and are higher than reported in the general population. Based on our results, infants receiving dialysis can be identified as one of the groups of LUTO infants with a high risk for ND delays. These findings support the need for ongoing longitudinal ND follow-up of all LUTO patients, regardless of severity or history of fetal intervention, to monitor ND outcomes.

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Statement of Ethics

This study was approved by the Baylor College of Medicine Institutional Review Board with all mothers providing written informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Sonia Monteiro conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Magdalena Sanz Cortes conceptualized the study, conducted statistical analyses and interpretation, collected data contributed to drafting the initial manuscript, and reviewed and revised the manuscript. Dr. Rodrigo Ruano con-

ceptualized and designed the study, participated in data gathering, data analysis and interpretation of the results, and reviewed and revised the manuscript. Dr. Robert Voigt assisted in the conceptualization and design of the study. He reviewed and revised the manuscript. Dr. Peter S. Yun was involved in data gathering, analysis and interpretation of the results of the analysis. He reviewed and revised the manuscript. Dr. Ahmed A. Nassr participated in data gathering, was involved in analysis and interpretation of results, and reviewed and revised the manuscript. Drs. Chester J. Koh, David R. Roth, Michael Braun, Joseph Angelo, Isabel Moscardo, Jimmy Espinoza, Alireza A. Shamshirsaz, and Michael Belfort contributed to the clinical care of these patients, interpretation of the results, and review of the manuscript.

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