ARTICLE

Renal outcomes of neonates with early presentation of posterior urethral valves: a 10-year single center experience

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Abstract

Objective Evaluate renal outcomes and early predictive factors in infants with congenital posterior urethral valves who required catheter or surgical urinary tract decompression within the first 7 days of life.

Study design A 10-year retrospective study at a single hospital. Primary outcomes were estimated glomerular filtration rate (eGFR) and development of end stage renal disease (ESRD).

Results Of 35 infants, 50% developed eGFR <90 mL/min/1.73 m^2 and 15% progressed to ESRD. Nadir creatinine, need for invasive ventilation in the newborn period, and need for surgical diversion after catheter diversion were associated with worse outcomes. 50% of infants requiring invasive ventilation as neonates developed eGFR <60 mL/min/1.73 m^2 in childhood.

Conclusions Half of infants with early presentation and intervention developed significant renal insufficiency in childhood, similar to children with later presentation or who had fetal intervention. Invasive ventilation in the newborn period and need for surgical urinary diversion are associated with worse outcomes.

Introduction

Congenital posterior urethral valves (PUV) is the most common cause of lower urinary tract obstruction (LUTO) in males, accounting for more than half of pregnancies complicated by LUTO, and results in a spectrum of urologic and renal sequelae [1, 2]. Overall, infants with PUV have poor renal outcomes. The current literature indicates that 20–65% of patients with PUV will develop chronic kidney disease (CKD) and 8–21% will progress to end stage renal disease

(ESRD) during childhood. Furthermore, there have been minimal improvements in outcomes over time [3–11].

Due to the poor prognosis, significant effort has been put forth to develop interventions for this population, particularly focusing on fetal interventions to relieve the obstruction and allow normal renal and pulmonary development. Fetal intervention, primarily by vesico–amniotic shunting or fetal cystoscopic ablation, has been attempted for nearly 40 years. The cumulative literature suggests that while in utero intervention may reduce perinatal mortality, fetal mortality remains high at 40–60%. Furthermore, these interventions have not improved postnatal outcomes and are associated with surgical complications [12–16].

Although the anatomic anomaly in PUV is relatively uniform, the evaluation of potential interventions has been limited by significant heterogeneity in available cohorts. Reported outcomes combine patients with perinatal and childhood diagnoses, varying severity of obstruction, and both fetal and postnatal interventions. In addition, patients with poor outcomes, such as early death or need for subsequent interventions, are often excluded from data analysis. Such heterogeneity likely also contributes to difficulties in identifying factors predictive of renal outcomes. Small studies have inconsistently shown association of antenatal diagnosis, prematurity, oligohydramnios, renal parenchymal

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changes, nadir creatinine, vesicoureteral reflux, bladder dysfunction, and younger age at diagnosis with worse renal outcomes; however in multivariate analyses only nadir creatinine has been predictive [4–11, 17–23].

Given the challenges associated with the heterogeneity of this patient population, the aim of this study was to isolate a specific cohort of infants with severe LUTO caused by PUV who presented and had intervention in the first week of life, to evaluate renal outcomes and early predictive factors.

Materials and methods

Subjects and data management

This study was approved by the Institutional Review Board at Boston Children's Hospital. Requirement for consent was waived by the Board. Study data were collected and managed using REDCap electronic data capture tools hosted at the study institution [24]. Eligible subjects for this study were male infants born during a retrospective 10-year study period from January 1, 2005 to December 31,2014 who received treatment at a single tertiary children's hospital for severe LUTO from PUV in the first week of life. Patients treated at the institution for PUV were identified through a data warehouse query using ICD-10 code Q64.2 (Congenital PUV) or CPT procedure code 52400 (Cystourethroscopy with incision, fulguration, or resection of congenital PUV, or congenital obstructive hypertrophic mucosal folds). Patients identified using this query were then reviewed for study inclusion by review of electronic medical records. Patients were included in data collection and analysis if they were: (1) confirmed to have PUV in medical records and (2) had catheter or surgical intervention for urinary tract decompression during the first week of life ($n = 35$). The aim was to isolate a homogeneous population of infants with severe LUTO, therefore presentation by 7 days of life was selected as it is likely that infants with severe LUTO would develop clinical signs within this time period, and infants with less severe LUTO would likely remain undetected. Patients that were excluded included those who presented after the first week of life or who underwent antenatal urinary tract intervention. Although some excluded patients presented during infancy, many presented during childhood. Children who transferred care after infancy or came to the study institution for second opinion were also excluded.

Outcome measures and methods of analysis

The primary outcome measure was the estimated glomerular filtration rate (eGFR) at last follow-up, and was only used after age 2 years. eGFR was calculated using the bedside Schwartz equation [25]. ESRD was defined as eGFR <15 mL/min/1.73 m^2 or requirement for renal replacement therapy.

Covariates included birth gestational age, race, prenatal, and postnatal ultrasound (US) findings, presence of vesicoureteral reflux, nadir creatinine in first year of life, duration of follow-up, other renal or urologic surgical interventions, and any respiratory support required during the newborn or follow-up period. Prenatal US findings included hydroureter, oligohydramnios, renal parenchymal changes, and bladder changes. Postnatal US findings included hydroureter and renal parenchymal changes. Postnatal US findings were assessed at two time points, at first postnatal US and at 1 year of age. Nadir creatinine was categorized as <1 mg/dL or ≥1 mg/dL based on findings in the existing literature, and excluded values after dialysis initiation.

Analysis

Descriptive statistics were calculated. Differences in eGFR at last follow-up between groups by race, birth gestational age, respiratory supports in the newborn period, ultrasound findings, nadir creatinine, vesicoureteral reflux, and other surgical interventions were assessed with either the Kruskal–Wallis test or Mann–Whitney U test. Post hoc pairwise comparisons following the Kruskal–Wallis test were performed with Dunn's test with the Bonferroni correction. A Kaplan–Meier curve was used to analyze time to development of eGFR <60 mL/min/1.73 m^2 (Fig. 1). Stata version 13.1 (StataCorp LLC, College Station, TX) and SPSS version 24 (IBM Corp, Armonk, NY) were used in the analysis. Statistical significance was set at 5%.

Results

Of 112 children treated for PUV at the study institution between 2005 and 2014 who did not have antenatal intervention, 35 infants presented and had catheter or surgical urinary tract decompression within the first week of life. The remaining 77 presented after 1 week of age. The demographics and characteristics of participants are shown in Table 1. There were 32 (91%) singleton births and 3 (9%) twin births. One infant died at 20 days of life. This infant was included in patient characteristics, however due to the absence of follow-up, analyses that required follow-up data were completed using data from the surviving 34 infants.

Mean laboratory follow-up was 54 months, although clinical follow-up was frequently longer. During this time period, 17 (50%) infants developed eGFR <90 mL/min/1.73 m^2, including nine (26%) with eGFR <60 mL/min/

Fig. 1 Overall renal survival defined as last eGFR of 60 mL/min/1.73 m^2 or greater without a renal transplant
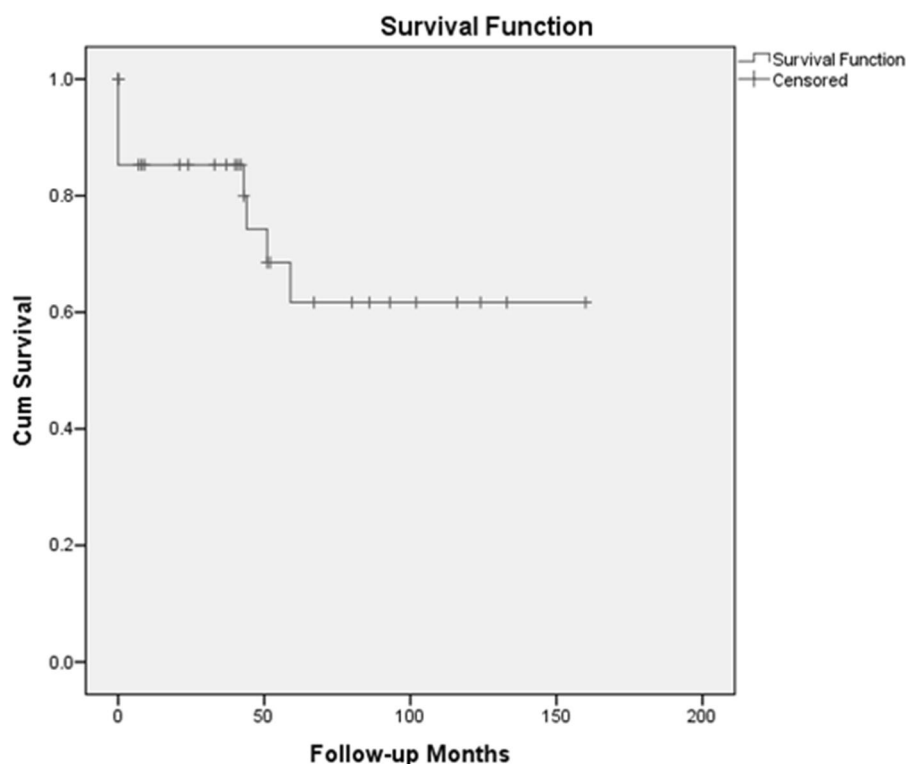
1.73 m^2 and five (15%) progressed to ESRD (Table 1). All five infants who progressed to ESRD received renal transplants during the study period. Two children included also had other significant medical conditions. One child developed acute lymphoblastic leukemia in infancy, and one child was diagnosed with neurofibromatosis type 1.

15 (43%) children required invasive mechanical ventilation in the neonatal period. Ten (29%) of these children needed high-frequency ventilation. Eleven (32%) required surgical urinary diversion by nephrostomy tube, ureterostomy, or vesicostomy after attempt of catheter drainage rather than, or in addition to ablation of valves.

Among those who survived the newborn period, there were no significant differences in eGFR at last follow-up by race, gestational age, prenatal, or postnatal US findings, or presence of VUR (Table 2). All children with nadir creatinine ≥1 mg/dL developed ESRD. In addition, all children with nadir creatinine ≥1 mg/dL were diagnosed with ESRD within the first month of life. There was a significant number of preterm patients included in this study, with 50% of included patients born before 37 weeks gestation, however there was no difference in overall renal survival between very preterm (<32 weeks gestation), moderate or late preterm (32–36 weeks gestation), or term infants (37 or greater weeks gestation) ($p = 0.62$). Figure 1 summarizes overall renal survival of all included patients, defined as last eGFR of 60 mL/min/1.73 m^2 or greater without a renal transplant.

Infants who required invasive ventilation in the newborn period had lower eGFR at the end of the follow-up period (56 mL/min/1.73 m^2) compared with infants who did not require invasive ventilation (95 mL/min/1.73 m^2) ($p = 0.05$). In addition, 80% of infants who developed ESRD required invasive ventilation in the newborn period. Infants who required surgical urinary diversion other than valve ablation had lower eGFR (57 mL/min/1.73 m^2) at last follow-up than those with sufficient diversion by catheter drainage (87 mL/min/1.73 m^2).

Discussion

In this cohort, 50% of infants with PUV who presented and required catheter or surgical urinary tract decompression in the first week of life developed significant renal insufficiency or ESRD during the study period. These results are concordant with other published cohorts of all children with PUV. We found that elevated nadir creatinine, invasive mechanical ventilation, and requirement for surgical urinary diversion other than routine ablation of valves were predictive factors of eGFR < 60 and ESRD. Given the progressive nature of renal disease associated with PUV, we would anticipate that eGFR would continue to decline over time in this cohort of patients, and further study to trend renal function through childhood and into adulthood is needed, including comparison with children who present at

Table 1 Patient characteristics

	Total ($n = 35$)
Race	
Caucasian	18 (51%)
Black	10 (29%)
Other	7 (20%)
Gestational age (weeks)	
28–31 + 6	3 (9%)
32–36 + 6	14 (40%)
≥37	18 (51%)
Respiratory support in newborn period	17 (49%)
Noninvasive ventilation only	2 (6%)
Invasive ventilation	15 (43%)
HFOV/HFJV	10 (29%)
Respiratory support after newborn discharge	0 (0%)
Age at newborn discharge (days; median, IQR)	24 (11, 30)
Ultrasound findings—prenatal	
Hydroureter	31/34 (91%)
Oligohydramnios	15/34 (44%)
Parenchymal changes	16/34 (47%)
Bladder changes	22/34 (65%)
Ultrasound findings—postnatal	
Hydroureter	28/33 (85%)
Parenchyma echogenic	27/30 (90%)
Parenchyma thin	20/28 (71%)
Ultrasound findings—1 year of age	
Hydroureter	22/30 (73%)
Parenchyma echogenic	22/30 (73%)
Parenchyma thin	19/30 (63%)
Nadir creatinine in 1st year of life (mg/dL)	
<1	29 (85%)
≥1	5 (15%)
VUR	
None	7 (20%)
Unilateral	10 (29%)
Bilateral	17 (49%)
Unknown	1 (3%)
Age at PUV ablation (days; median, range)	13 (0–456)
Other surgical interventions	
Nephrostomy tube, ureterostomy, or vesicostomy	11 (32%)
Ureteral reimplantation or nephrectomy	7 (35%)
Lab Follow-up duration (months; median, IQR)	43 (24, 80)
eGFR at last follow-up (mL/min/1.73 m^2)	
≥90	17 (50%)
60–89	8 (24%)
30–59	3 (9%)
15–29	1 (3%)
<15	5 (15%)

Table 2 Factors associated with kidney function

	Total ($n = 34$)	Mean eGFR (mL/min/1.73 m^2)	p-value
Race			
Caucasian	18	76.19	0.97
Black	10	78.83	
Other	6	80.63	
Gestational age (weeks)			
28–31 + 6	3	106.84	0.56
32–36 + 6	14	70.96	
≥37	17	78.21	
Invasive ventilation in newborn period			
No	20	95.50	0.05
Yes	14	56.53	
Ultrasound findings—prenatal			
Hydroureter	31	74.32 (113.18)	0.09
Oligohydramnios	15	64.53 (88.18)	0.14
Parenchymal changes	16	72.89 (82.07)	0.84
Bladder changes	22	80.05 (73.53)	0.56
Ultrasound findings—postnatal			
Hydroureter	28/33	83.00 (63.91)	0.50
Parenchyma echogenic	27/30	79.38 (87.06)	0.97
Parenchyma thin	20/28	78.86 (86.54)	0.88
Ultrasound findings—1 year of age			
Hydroureter	22/30	84.41 (90.01)	0.62
Parenchyma echogenic	22/30	82.85 (94.30)	0.81
Parenchyma thin	19/30	76.02 (102.98)	0.12
Nadir creatinine in 1st year of life (mg/dL)			
<1	29	91.15	<0.001
≥1	5	0	
VUR			
None	7	85.81	0.70
Unilateral	10	83.34	
Bilateral	17	71.14	
Nephrostomy tube, ureterostomy, or vesicostomy	11	57.12 (87.61)	0.04

a later age. Children who present at a later age may be at a lower risk for CKD and ESRD, as their pathology is likely associated with only partial obstruction, and may progress at a different rate. The follow-up duration in this study was similar to published cohorts and further emphasizes the need for extended follow-up in all subpopulations of children with PUV.

The renal outcomes of our cohort were similar to those reported for patients who have received fetal intervention for PUV. Efforts to date to improve outcomes by fetal intervention have been relatively unsuccessful and are associated with high fetal and perinatal morbidity and

mortality [12–16]. Furthermore, the ability to antenatally recognize and prognosticate the LUTO patients who are at the greatest risk for CKD and ESRD is limited. If technological and scientific developments allow for optimization of fetal interventions, the ability to identify those at greatest risk for CKD will be important to select the correct patients who can benefit from these interventions.

Our cohort contributes to understanding how elements of early care during fetal monitoring and neonatal intensive care could inform outcomes. Our cohort contained a significant number of premature infants and infants who required mechanical ventilation in the neonatal period. The need for invasive ventilation was associated with lower eGFR. This observation is similar to prior studies that also suggest that need for respiratory support may portend worse renal outcomes. Prior studies of patients with PUV have found an association of oligohydramnios with need for respiratory support after birth [26] and an association of early ventilator support with the development of CKD [11]. Although pulmonary hypoplasia of varying severity is associated with other congenital anomalies of the kidney and urinary tract, this has not been typical of PUV. In fact, no children in this cohort had signs of respiratory insufficiency during the follow-up period. These findings suggest that while respiratory failure in the neonatal period may be associated with the development of significant CKD in childhood, it does not appear to lead to long-term pulmonary morbidity in children with PUV. As in other studies, we hypothesize that the need for pulmonary support in the neonatal period is likely related to a combination of factors including oligohydramnios and prematurity. Although there was no association of oligohydramnios with eGFR in our cohort, oligohydramnios was significantly associated with need for invasive ventilation (data not shown). There is also existing literature suggesting an association of prematurity with CKD [27]. Further studies are needed to clarify the causes of neonatal respiratory compromise in children with PUV.

Nadir creatinine ≥1 mg/dL in the first year was found to be significantly associated with low eGFR in this study, supporting previously reported findings. Notably, all infants with elevated nadir creatinine in this study were diagnosed with ESRD and initiated on dialysis within the first month of life; therefore this variable may have limited use as an early predictive factor for the later development of CKD and ESRD. If more sensitive markers of renal function are identified and validated, they may allow an opportunity to more accurately identify changes in renal function sooner than serum creatinine, especially in the neonate.

Important limitations of this study include the retrospective design, single institution experience, small sample size and short duration of follow-up, although similar to existing literature. Prenatal US reports were not universally available and reported prenatal findings relied on documentation in admission and consult notes and likely are underreported. The postnatal US findings were fairly uniformly documented in this institution but results still may be subjective in certain cases.

Conclusions

Half of infants with PUV who presented and had catheter or surgical urinary tract decompression in the first week of life have poor renal outcomes during childhood, however they appear to have similar outcomes compared to published cohorts that include children with later presentation and children after fetal intervention. Infants who required invasive ventilation in the newborn period or required surgical urinary diversion beyond valve ablation after catheter drainage had worse renal outcomes.

Compliance with ethical standards

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