Renal outcomes of children born with posterior urethral valves at a tertiary center: A 15-year retrospective review

Alexandra Bain[1], Callum Lavoie[1], Sara Rodriguez-Lopez[2], Darcie Kiddoo[3]
[1]Division of Urology, University of Alberta Hospital, Edmonton, AB, Canada; [2]Division of Pediatric Nephrology, Stollery Children's Hospital, Edmonton, AB, Canada; [3]Division of Pediatric Urology, Stollery Children's Hospital, Edmonton, AB, Canada

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Corresponding author: Dr. Alexandra Bain, Division of Urology, University of Alberta Hospital, Edmonton, AB, Canada; abain@ualberta.ca

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ABSTRACT

Introduction: Posterior urethral valves (PUVs) is a congenital condition in which an obstruction in the urethra prevents drainage of urine from the bladder in males, with up to 60% of children diagnosed developing chronic kidney disease (CKD). The primary aim of this study was to identify novel factors that may predict development of CKD and end-stage real disease (ESRD) in children with PUVs to potentially address modifiable factors and delay progression. The secondary aim was to compare rates of catheterization and incontinence between our patients and other case series to provide information to parents about long-term bladder outcomes.
Methods: A single-center, retrospective cohort study was performed of all children referred to our multidisciplinary clinic for PUV diagnosis between 2005 and 2019. Univariable associations of

KEY MESSAGES

- PUV is a congenital condition in which an obstruction in the urethra prevents drainage of urine from the bladder in males
- Up to 60% of children with PUV develop CKD and 30% will develop daytime incontinence.
- Our clinic uses a unique multidisciplinary format where all PUV patients are seen by pediatric nephrology, pediatric urology, and a nurse practitioner. This allows for close followup, early intervention, and more effective teaching around long-term bladder care for families
- This review demonstrates that a multidisciplinary approach to the care of PUV patients allows for better family education around the complications and morbidity of PUV, in addition to early intervention of bladder dysfunction to help preserve renal function.

different variables with the composite outcome CKD or ESRD were evaluated.
Results: Thirty of 46 patients (65%) developed CKD, with the majority (40%) being stage 2 CKD (n=12). Seven of 30 patients (23%) developed ESRD requiring renal replacement therapy. Fourteen of 26 (30%) required clean intermittent catheterization (CIC) initiation with a median CIC initiation age of 4.3 years. Creatinine nadir post-valve ablation, oligohydramnios, and initiation of CIC are significant predictors in developing CKD.
Conclusions: This review reiterates that children born with PUVs have a high morbidity rate, with a high proportion developing CKD. Using a multidisciplinary approach to PUV patient care allows for better family education, early intervention of bladder dysfunction, and possibly better long-term preservation of renal function.

INTRODUCTION

Posterior urethral valves (PUVs) is a congenital condition in which an obstruction in the urethra prevents drainage of urine from the bladder in males. The estimated incidence of PUVs is 1/4000 – 1/5000 births, with approximately 35% being diagnosed antenatally and 55% being diagnosed postnatally.[1] This condition implies a high morbidity as up to 60% of children diagnosed with PUVs will develop chronic kidney disease (CKD) and up to 25% of them will develop end stage renal disease (ESRD) requiring dialysis or kidney transplantation.[2] This occurs because early obstruction in utero causes renal damage secondary to obstructive uropathy and renal dysplasia to varying degrees.[3]

Known factors associated with an increased risk of developing CKD include early diagnosis before birth and early evidence of poor kidney and bladder function.[1-2] Early diagnosis often means more severe renal dysplasia and bladder dysfunction, which can further damage the kidneys. The obstruction caused by PUVs leads to bladder hypertrophy and higher voiding and storage pressures, which causes changes in bladder wall morphology and ultimately results in poor emptying with elevated post void residuals. These elevated pressures lead to structural changes seen both in the ureters and kidneys.[3]

Bladder dysfunction including daytime incontinence is a significant sequela of PUVs, with incontinence rates ranging from 4-35%.[4] Long term, children may develop valve bladder syndrome with poor emptying and high bladder pressures. Small case studies in Europe have shown that early intervention with a bladder regimen and early toilet training, in addition to teaching families about clean intermittent catheterization (CIC) can help preserve renal function and improve bladder function over time.[4]

There is little literature regarding long-term renal and urinary continence outcomes for children with PUVs in Canada. In Edmonton, we use a multidisciplinary approach with nurse practitioners, pediatric urologists and nephrologists to manage patients and intervene when necessary. Two methods of early intervention to preserve renal function include the early institution of clean intermittent catheterization, and overnight catheter drainage when necessary.

These are typically indicated when patients present with urinary tract infections or incontinence with urodynamics showing concerning features of high bladder pressures and/or incomplete emptying.

The purpose of this study is to identify novel factors that may predict development of CKD and ESRD in children with PUVs to potentially address modifiable factors, delay progression and council families. Additionally, we aim to compare rates of catheterization and incontinence between our patients and other case series to provide further information to parents about long term bladder outcomes.

METHODS

Design, setting, and patients

We performed a single centre retrospective cohort study of children less than 18 years old with PUVs. All patients with PUV referred to our multidisciplinary clinic at the Stollery Children's Hospital between 2005-2019 were eligible for inclusion in the study. Exclusion criteria included patients with insufficient data due to patient death or city re-location with no access to previous medical records. Patients were identified through our electronic medical record and diagnostic codes from patients seen in our combined pediatric Nephrology/Urology clinics. Ethical approval was obtained from the Health Research Ethics Board of Alberta (HREB 00094537).

Data collection

Data from children with PUVs were collected retrospectively from electronic and paper charts. Patient characteristics collected included date of birth, gestational age at time of birth, age at time of analysis, birthweight, obstetrical ultrasound dates and amniotic fluid levels, presence of hydronephrosis, age at the time of valve ablation, serum creatinine prior to valve ablation, creatinine nadir following valve ablation, and annual height, weight and creatinine at follow up appointments. Additional data collected included voiding cystourethrogram (VCUG) and urodynamics results, incontinence rates, need for additional surgery (vesicostomy or Mitrofanoff), and age at time of dialysis or transplant.

Definitions

An estimated glomerular filtration rate (eGFR) below 90 ml/min/1.73 m^2 was considered abnormal according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[5] CKD stages were defined as CKD stage 1: eGFR >90 ml/min/1.73 m^2, stage 2 eGFR 60-90 ml/min/1.73 m^2; stage 3a: 45-60 ml/min/1.73 m^2; stage 3b: 30-45 ml/min/1.73 m^2; stage 4: 15-30 ml/min/1.73 m^2; stage 5 (ESRD): <15 ml/min/1.73 m^2. The Schwartz formula was used to calculate eGFR for all patients at each follow up visit.

Statistical analysis

Continuous variables were described as mean [standard deviation (SD)], as median value [interquartile range (IQR)], or frequency (N) with proportion (%), depending on variable distribution.

Factors associated with CKD or ESRD

Univariable associations of various variables with the composite outcome CKD or ESRD (patients on dialysis or with a kidney transplant) were evaluated using Student's t-tests, Mann–Whitney U-tests, $\chi 2$, or Fisher's exact tests, as appropriate. A p value of less than 0.05 was considered to be statistically significant. Stata (14.2)® statistical software (College Station, TX, USA) was used for statistical analysis. We were unable to perform a multivariate analysis due to our small patient sample size.

RESULTS

Characteristics of the cohort

Fifty-six patients were referred for management of PUVs between 2005 - 2019, data from 46 patients was available for analysis (Table 1). Reasons for insufficient data include patient death (n=1) and city re-location with no access to previous medical data (n = 9). Median follow up time was 8(9) years. Fourty-four cases had pre-natal ultrasounds with 32 (72%) being diagnosed with suspected PUVs prenatally and 18 (40%) of these patients developed oligohydramnios or anhydramnios during the pregnancy. Median age at time of PUV ablation was 11(29) days old. Fourty-four (96%) patients had hydronephrosis on their first post-natal ultrasound and 24 (54%) of them had either improvement or complete resolution of hydronephrosis post-valve ablation. Thirty patients (65%) developed CKD with 7 of them (23%) developing ESRD requiring renal replacement therapy. This represents 15% of the total cohort. Four patients required dialysis before undergoing a kidney transplant and 3 patients received a kidney transplant pre-emptively. Median (IQR) age at the time of initiation of dialysis and at the time of transplantation was 3 (11) weeks and 3.6 (6.6) years respectively. Out of the remaining 23 patients, 40% (n=12) had stage 2 CKD, 27% (n=8) had stage 3 CKD and 10% (n=3) had stage 4 CKD.

Out of all patients reviewed, 44% (n=20) had daytime incontinence, 30% (n=14) required CIC initiation and 13% (n=6) required overnight catheter drainage. Median (IQR) age of initiating CIC was 4.3 (4.2) years of age. Six out of 7 patients with ESRD required CIC, with 4 of them (67%) beginning after transplant and 2 (33%) beginning prior to transplant. Four patients underwent a Mitrofanoff for ease of catheterization and 5 patients underwent a vesicostomy due to concerning findings seen on urodynamics and worsening renal function with known catheter compliance issues. Concerning findings on urodynamics included elevating detrusor pressures, decreased compliance, hypercontractility, and urinary retention.

Predictors of CKD

When looking at the outcome of developing CKD (including ESRD) there were various factors associated on univariate analysis (Table 2). A low level of amniotic fluid on prenatal ultrasounds was significantly associated with the development of CKD (p=0.006), and patients were 13 times more likely to develop CKD compared to those with normal amniotic fluid levels (OR 13.9, 95% CI 1.58-123.9, p=0.018). All 3 fetuses with absent amniotic fluid (anhydramnios) developed CKD. The maximum serum creatinine prior to valve ablation and the serum creatinine nadir in the first year or life were significantly higher in the CKD group (p= 0.002 and p=0.0001, respectively) (Fig 1 and 2). Additionally, initiation of CIC was significantly associated with developing CKD (p=0.009) (Table 2).

DISCUSSION

Our study shows that a high proportion of patients with PUV developed CKD (65%) and among them up to 23% progressed to ESRD, which represents 15% of the whole cohort. These results reiterate the high morbidity of this condition. This is in keeping with a study conducted in Eastern Canada by Warren et al, who reported 11% of PUV patients progressing to ESRD.[6] These negative outcomes in this population raise the need for finding factors associated with poor prognosis and preventive strategies to delay progression of renal dysfunction. We have not been able to identify novel predicting factors for renal dysfunction in our study, but we have confirmed that early evidence of decreased renal function (as evidenced by low amniotic fluid and persistently elevated serum creatinine early in life) as well as bladder dysfunction are significant predictors of CKD.

Our analysis showed that the creatinine nadir following PUV ablation is a significant predictor in developing CKD, in keeping with current literature.[1,7-8] If there is not a significant drop in the creatinine nadir following valve ablation, this likely indicates that there has already been significant renal damage from obstruction in utero that will not recover despite valve ablation and relief of the obstruction. Additionally, oligohydramnios prenatally may indicate low fetal urine output which is evidence of early renal dysplasia and a poor prognostic sign for renal function in the future.[7]

It is currently estimated that 55% of patients with PUVs will have underlying bladder dysfunction.[3,9] In our practice, PUV patients who continue to have incontinence or recurrent UTIs beyond toilet-trained age will undergo urodynamics to assess if there are any concerning findings including decreased compliance, hypercontractility, or urinary retention. Additionally, video urodynamics can identify any vesicoureteral reflux or residual valves causing bladder dysfunction. If there are concerning findings on urodynamics, we initiate CIC in these patients to protect their upper urinary tracts. Our analysis showed that initiation of CIC was a significant predictor in developing CKD and 30% of our patients are performing CIC. However, it is unknown whether the initiation of CIC delayed the deterioration of renal function in our patients and for how long. Moreover, the majority of our patients currently have not yet progressed past mild CKD, which may be in relation to early management of bladder dysfunction, in addition to our multidisciplinary approach at each follow up visit. At every initial consult and follow-up

visit, all patients with PUV see pediatric nephrology, pediatric urology and our pediatric urology nurse practitioner. We have found that this improves communication between specialties in addition to allowing for better education on long-term bladder care and management of complications derived from CKD for patients and their families.

Our rates of CIC and incontinence are consistent with other case series, and our mean age of CIC initiation at 4.3 years is close to age initiation where a benefit in bladder pressures has been observed[10]. Recent case series have examined outcomes of CIC initiation in children with PUVs and concluded that initiation of CIC before the age of 4 had a better likelihood of avoiding the need for urinary diversion or bladder reconstruction for elevated pressures.[10] Previous studies have demonstrated that there is a correlation between advanced CKD and daytime incontinence in children with PUVs which reflects how bladder dysfunction may cause upstream elevated pressures and further renal damage even post valve ablation.[7] The initiation of CIC and overnight catheter drainage can be challenging in PUV patients due to their sensate urethras.[10] In our multidisciplinary clinic, we utilize both our Pediatric Urology Nurse Practitioner and Child Life specialists to help mitigate this process both with the patients and their guardians. We provide multiple opportunities for hands on lessons where CIC is taught in a step-wise, progressive fashion. These sessions begin with introduction to CIC catheters and visual aids demonstrating how to perform CIC. Our nurse practitioner and child life specialists teach guardians how to keep the patient calm during CIC, and once the patient is older they encourage the patient to get involved and learn how to perform CIC themselves.

Limitations

There are limitations to this study, including the small sample size that limits our ability to evaluate potential predictors of CKD on multivariable analysis. Given the methodology used to collect the data, external validity may be limited by selection bias, as those who are followed in our combined nephrology urology clinic may have a more severe presentation. Lastly, practice in regards to bladder intervention may have changed with time, in light of increasing evidence of potential protective factors with early catherization. The early data captured in this review may not accurately reflect current practice. Additionally, pregnancy termination has not been accounted for in the denominator and therefore absolute incidence for all children with PUV cannot be determined.

CONCLUSIONS

In conclusion, our review demonstrates that children born with PUVs have a high morbidity rate with a high proportion developing CKD, and it is again demonstrated that evidence of decreased renal function and bladder dysfunction at an early age are significant predictors of developing CKD. In our experience, the combination of having a multidisciplinary follow up clinic including pediatric urologists, nephrologists and nurse practitioners ensures close patient follow-up in addition to early and effective management of bladder dysfunction and medical complications of CKD.

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Figures and Tables

Table 1. Descriptive analysis of patient characteristics			
Length of followup (years), median (IQR)	8 (9)	Recurrent UTIs, n (%) Yes No	N=46 22 (48) 24 (52)
Gestational age at birth (weeks), median (IQR)	37 (4)	CKD, n (%) Yes No	N=46 30 (65) 16 (35)
Birth weight (grams), median (IQR)	3150 (590)	CKD stage, n (%) Stage 2 Stage 3a Stage 3b Stage 4 Stage 5 (ESRD)	N=30 12 (40) 4 (13.5) 4 (13.5) 3 (10) 7 (23)
Amniotic fluid level, n (%) Normal Low normal Low Absent	N=44 26 (59) 2 (4.5) 13 (29.5) 3 (7)	Medications, n (%) Acidosis Hypertension	N=32 (70) 14 (30) 18 (39)
Oligohydramnios, n (%) Yes No	N=44 17 (39) 27 (61)	Proteinuria (urine protein/creatinine >30 mg/mmol) Yes No	N=46 28 (61) 18 (39)
Pre-natal vesicoamniotic shunt, n (%) Yes No	N=46 2 (4) 44 (96)	Catheterizable channel, n (%) Mitrofanoff Vesicostomy	N=9 (20) 4 (9) 5 (11)
PUV diagnosis, n (%) Prenatal Postnatal	N=46 32 (70) 14 (30)	Cr peak prior to ablation (mmol/L), median (IQR)	156 (115)
Age at PUV ablation (days), median (IQR)	11 (29)	Cr nadir in first year of life (mmol/L), median (IQR)	33 (38)
VUR as per VCG, n (%) Grade 1 Grade 4 Grade 5	N=40 11(27.5) 11 (27.5) 18 (45)	Cr nadir <88 umol/L in first year of life, n (%) Yes No Unknown	N=46 31 (68) 8 (17) 7 (15)
Age at start of CIC (years), median (IQR)	4.3 (4.2)	Recurrent valve ablation, n (%) Yes No	N=46 5 (11) 41 (89)
CIC, n (%) Yes No	N=46 14 (30) 32 (70)	Urodynamics, n (%) Normal Atonic bladder	N=27 12 (45) 2 (7)

		Hypercontractile Poor compliance	9 (33) 4 (15)
Overnight catheterization, n (%) Yes No	N=46 6 (13) 40 (87)	Hydronephrosis post-PUV ablation, n (%) Resolved Improved Same Worse	N=44 8 (18) 16 (37) 15 (34) 5 (11)
Daytime incontinence, n (%) Yes No Too young to diagnose*	N=46 20 (44) 19 (41) 7 (15)	Hydronephrosis at first post-natal ultrasound, n (%) Yes No	N=46 44 (96) 2 (4)

*Age cutoff use to diagnose daytime incontinence correlates to International Children's Continence Society recommended age cutoff of 5 years of age to characterize urinary continence disorders. CKD: chronic kidney disease; CIC: clean intermittent catheterization; ESRD: end-stage renal disease; IQR: interquartile range; PUV: posterior urethral valves SCr: serum creatinine; UTI: urinary tract infection; VCUG: voiding cystourethrogram; VUR: vesicoureteral reflux.

Table 2. Univariate analysis of factors associated with development of CKD

	No CKD, n=16	**CKD, n=30**	**p**
Gestational age (weeks), median (IQR)	37.5(2)	37(4)	0.95
Weight at birth (grams), median (IQR)	3320 (680)	3147 (710)	0.35
Prenatal PUV diagnosis, n (%) Prenatal Postnatal	 10 (62) 6 (38)	 22 (73) 8 (27)	0.33
Amniotic fluid, n (%) Normal Low normal Low Absent	 14 (88) 1 (6) 1 (6) 0 (0)	 12 (43) 1 (3) 12 (43) 3 (11)	**0.006**
Age (days) at valve ablation, median (IQR)	8 (23)	12 (41)	0.18
Urodynamics, n (%) Normal Hypercontractile Poorly compliant Atonic	 4 (66) 1 (17) 1 (17) 0 (0)	 8 (40) 8 (40) 3 (15) 1 (5)	0.69

Recurrent UTIs, n (%)	7 (44)	15 (50)	0.46
Recurrent PUV ablation, n (%)	2 (13)	3 (1)	0.58
Daytime incontinence, n (%)	4 (33)	16 (59)	0.12
CIC, n (%)	1 (6)	13 (43)	**0.009**
Overnight drainage, n (%)	1 (6)	6 (20)	0.06
Maximum SCr prior to ablation, median (IQR)	101 (89)	189 (155)	**0.002**
Cr nadir in first year of life, median (IQR)	29 (11)	48 (68)	**0.0001**

CKD: chronic kidney disease; CIC: clean intermittent catheterization; IQR: interquartile range; PUV: posterior urethral valves SCr: serum creatinine; UTI: urinary tract infection.