Predictors of the Late Renal Outcome after Posterior Urethral Valves Ablation in a Developing Country: Long Term Study

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Abstract

Introduction: Posterior urethral valves are the commonest form of obstructive uropathy in pediatrics and a common cause of chronic kidney disease (CKD) during childhood with estimated renal failure rate of 25-40%.

This study aims at evaluating long term changes in kidney and bladder functions of children with posterior urethral valves after ablation, and at assessing predictors of late renal outcome, considering challenges in Egypt as a developing country.

Materials and Methods: A retrospective study of 30 surgically managed PUVs patients who attended at Alexandria University Children's Hospital for follow up. Patients underwent surgery between 2005 and 2016. Mean postoperative follow up period was 6.7±3.8 years (range 3.1 to 14.6 years). Data collected included age at presentation, clinical presentation, serum creatinine (initial, nadir, and last follow up), eGFR at last follow up, renal ultrasound (initial, and last follow up), voiding cystourethrogram (initial, and last follow up), and urodynamic studies at last follow up.

Results: Thirty patients underwent PUVs ablation at a median age of 9 months. Ten (33.3%) patients were diagnosed antenatally. At the last follow up visit, 14 (46.7%) patients had moderate-severe CKD. Twenty-five (83.3%) patients had abnormalities in their urodynamic studies. Univariate analysis showed the need for re-ablation, use of anti-cholinergics, high initial serum creatinine, high nadir creatinine, presence of VUR, history of febrile UTIs and presence of proteinuria were significantly associated

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with low eGFR. Multivariate analysis showed that high nadir creatinine and presence of VUR were independent factors associated with lower e-GFR at last follow-up. Antenatal diagnosis was significantly associated with better e-GFR.

Conculsion: Nadir creatinine and vesicoureteral reflux have high prognostic value for late renal functions, and antenatal diagnosis is associated with better renal functions in patients with posterior urethral valves.Increasing family awareness, antenatal care facilities,and referal to tertiary care centers are priorities for promoting the antenatal diagnosis and management in developing countries.Facilities and training for prenatal intervention should be encouraged.

Keywords

- Posterior urethral valves
- Urodynamic studies
- Bladder funtion
- Nadir creatinine

Introduction

Posterior urethral valves (PUVs) are considered one of the most common causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in children.[1]

Urinary outflow obstruction during early development caused by PUVs has serious long-term consequences on the structure and function of the developing kidney and bladder.[2] Valves ablation is the treatment of choice aiming at preservation of kidney and bladder functions. [3]

We aimed to assess the long-term outcome of treating PUVs in children, on bladder and kidney functions, and identifying predictive factors of long-term renal functions, focusing on potential limitations in developing countries.

Materials and Methods

A retrospective study of 30 surgically managed PUVs patients who attended Alexandria University Children's Hospital for follow up visits between January 2018 and December 2019 was carried out. Patients underwent surgery between 2005-2016; with a mean postoperative follow up period of 6.7±3.8 years (range 3.1 to 14.6 years). Data retrieved from patients records included age at presentation, clinical presentation, serum creatinine (initial, nadir), preoperative renal ultrasound and preoperative voiding cystourethrogram. During the last follow up visit, serum creatinine, eGFR, renal ultrasound, voiding cystourethrogram and urodynamic studies of patients were investigated. The formula for eGFR was as follows: eGFR (mL/min/1.73m^2) = 0.413×height in centimeter/serum creatinine in mg/dL. [4]

Urodynamics (UDS) were performed using Solar Silver Urodynamics-Medical Measurement System (MMS), in the form of free uroflowmetry with post-void residual urine (PVR) estimation and pressure flow study. Bladder contractility index

(BCI) and bladder outlet obstruction index (BOOI) were also calculated. [5]

The study was approved by the Ethical Committee of the Faculty of Medicine. Informed parental consent was obtained for every enrolled patient.

Statistical analysis was carried out using IBM SPSS version 20.0.

Results

Patients were followed-up after ablation for a mean of 6.7±3.8 years (range 3.1 to 14.6 years). Ten (33.3%) patients were diagnosed antenatally, none of them had prenatal intervention. Twenty (66.7%) patients were diagnosed postnatally, with a median age at presentation of 3.5 months (range:0 to 33 months). Median age at valves ablation (either primary ablation or after temporary vesicostomy) was 9 months (range:7 days to 42 months). Obstructive symptoms and urosepsis were the most common clinical presentations before ablation. **Table 1** shows the presenting manifestations of our patients.

Table 1: Presenting manifestations of the 30 patients

Presenting manifestations	No.	(%)
Antenatal hydronephrosis	10	(33.3)
Obstructive symptoms	17	(56.7)
Urosepsis	16	(53.3)
Febrile UTIs	5	(16.7)
Renal failure	3	(10)
Day-time incontinence	2	(6.7)

Before ablation, mean serum creatinine was 1.43±1.07 mg/dL. All patients had hydronephrosis (Bilateral in 93%, grade 3 and 4 in 90% of the renal units). Vesicoureteral reflux (VUR) was found in 24 (80%) patients (unilateral in 14 and bilateral in 10). Most (70.6%) of the refluxing renal units were of grades IV and V.

After ablation, 25 (83.3%) patients received bladder pharmacotherapy (anticholinergics, alpha-blockers or both), while clean intermittent catheterization was required in 6 (20%) patients. Nineteen (63.3%) patients needed further surgeries, as illustrated in **Table 2**. Twenty-four (80%) patients had febrile urinary tract infections (UTIs) during follow-up.

Mean nadir creatinine was 0.61±0.45 mg/dL (range: 0.2-1.9 mg/dL). At last follow-up, mean

Table 2: Initial and subsequent surgical interventions in the patients

Surgical interventions	**No.**	**(%)**
Primary ablation	22	(73.3)
Vesicostomy then ablation	8	(26.7)
Subsequent surgeries after ablation	19	(63.3)
Re-ablation	11	(36.7)
Mitrofanoff	4	(13.3)
Uretrostomies	4	(13.3)
Dilatation of urethral stricture	2	(6.7)
Vesicostomy after ablation	1	(3.3)
Right nephrectomy	1	(3.3)
Bladder neck incision	1	(3.3)

serum creatinine was 1.37±1.5 mg/dL, it was within normal range in 13 (43.3%) patients. Serum creatinine was not significantly different from this value at presentation.

At last follow up, mean eGFR was 64.4±39.5 mL/min/1.73m^2. In 16 (53.3%) patients, eGFR was>60 mL/min/1.73m2, while 14 (46.7%) patients had moderate to severe CKD (eGFR<60 mL/min/1.73m^2 for≥3 months). One (3.3%) patient was on maintenance hemodialysis (ESRD). Twenty-two (73.4%) patients had proteinuria (nephrotic range in 26.7% of the patients).

At last follow-up, hydronephrosis was still present in 90% of patients, but there was a significant reduction in cases with bilateral hydronephrosis (p=0.005) and significant improvement in grade of hydronephrosis (p<0.001). There was signifcant reduction in the frequency (p = 0.025) and grade of VUR (p=0.007).

At last follow up, urodynamic abnormalities were detected in 25(83.3%) patients **Table 3**.

BOOI showed obstruction in 2(6.7%) patients, due to bladder neck hypertrophy as diagnosed through cystoscopy after exclusion of residual valves. Fifty-seven percent of the patients who were above 5 years of age at last follow up had day-time incontinance. Incontinence was due to detrusor overactivities in 6 (33.3%) patients, overflow in 6 (33.3%) patients, bladder hypocompliance in 3 (16.7%) patients, and both detrusor overactivities and bladder hypocompliance in 3 (16.7%) of the incontinent patients.

On univariate analysis for the predictors of long term predictors of renal functions, the need for re-ablation, use of anti-cholinergics, high initial serum creatinine, high nadir creatinine, presence of VUR, history of febrile UTIs and presence of proteinuria were significantly associated with low eGFR. Multivariate analysis showed that high nadir creatinine and presence of VUR were

Table 3: Urodynamic findings among the patients at last follow-up (N=30)

UDS parameters	Value
Uroflowmetry	
Maximum flow rate (mL/s) range (mean±SD)	5–22 (12.72±4.51)
Low no. (%)	8 (26.7)
Post-void residual (mL) range (mean±SD)	0-150 (31±43.26)
Significant no. (%)	11 (36.7)
Pressure-Flow study	
Bladder capacitySD range (mean)	-2.78 – 1.4 (0)
Small capacity no. (%)	3 (10)
Compliance(mL/cmH_2O) range (mean±SD)	3.5–56 (28.16±16.44)
Hypocompliance no. (%)	8 (26.7)
Reduced sensation no. (%)	5 (16.7)
Detrusor overactivities no. (%)	19 (63.3)
Maximum flow rate (mL/s) range (mean±SD)	4–23 (13.58±5.13)
Low no. (%)	8 (26.7)
Post-void residual(mL) range (mean±SD)	0–250 (42.83±64.70)
Significant no. (%)	11 (36.7)
Pdet@Qmax* (cmH_2O)range (mean±SD)	8–82 (44.53±19.48)
Bladder contractility index range (mean±SD)	35–182 (111.52±40.49)
Strong contractility > 130 no. (%)	5 (16.7)
Weak contractility <65 no. (%)	8 (26.6)
Bladder outlet obstruction index range (mean±SD)	2-47 (18.58±11.91)
Obstructed (>40) no. (%)	2 (6.7)
Equivocal (20–40) no. (%)	11 (36.7)

* Pdet@Qmax: Detrusor pressure at maximum flow rate

independent factors associated with lower e-GFR at last follow-up. Meanwhile, age at presentation, age at ablation, mode of surgical intervention and bladder dysfunction had no statistical significant impact on long-term renal outcome. Antenatal diagnosis was significantly associated with better e-GFR.

Discussion

Prenatal diagnosis allows early intervention before irreversible renal and bladder pathological changes occur. In this study 33.3% of the patients were diagnosed antenatally, which is consistent with prenatal detection rate ranging between

31% - 42.3% in developed countries.[6, 7] However, antenatal diagnosis was less frequent (3.9%-25%) in other series in developing countries. [8-10] Yet, none of the prenatally diagnosed cases had a chance of prenatal intervention due to limited medical infrastructures and limited surgical experience.

Median age for postnatal diagnosis was 3.5 months, denoting late diagnosis in many cases. In the literature, median age of postnatal diagnosis varied from two months[7, 9] up to 22 months.[11] These variations may be due to differences in parents' awareness and availability of health facilities, and referral system of such cases to tertiary referral centers.

Primary valves ablation was done in 73.3% of our patients. valves ablation was also the most common initial surgery in many reports.[7, 10] In our cohort, median age at valves ablation, whether initially or after vesicostomy was 9 months; similar to that reported by Rianthavorn and Parkpibul. [12] In contrast, median age of ablation reported by Coquillette et al was 13 days, as their study was on neonates. [16]

Nineteen (63.3%) cases in our study needed further surgical management. Re-ablation was done for 11 patients (36.7%). Bilgutay et al[7]stated that 42% of their patients required more than one operation. In other studies, only 10%-15.4% of the patients required re-ablation. [7, 8, 13] The higher percentage in the current series may be due to loss of follow-up of many patients with asymptomatic courses after ablation, or may be due to limited availability of suitable sized neonatal endoscopes leading to inefficient primary ablation.

Mean serum creatinine at presentation was similar to mean values reported in other studies. [7, 10, 14] Mean nadir creatinine was in accordance with values reported by other authors.[7, 13] Nadir creatinine was <1mg/dL in 90% of our patients and was comparable to the study by Coquillette et al[15] who reported similar values in 85% of their patients. Proteinuria was found in 73.4% of our cases. It was reported to be between44.5-55% by other authors.[16, 17]

VUR was found in 80% of patients. In the literature, VUR among PUVs patients varied from 37.7% -81%.[8, 9, 11] The higher incidence of VUR among our patients may be due to late presentation of our patients and higher incidence of bladder dysfunction among them. VUR had a high grade in 70.6% of the refluxing units; nearly the same percentage was reported in other studies. [18, 19]

Incontinence was found in 57% of patients, aged more than 5 years at last follow-up. Incontinence was reported in 7-35% of the cases in other studies. [20, 21] Incontinence in our patients was due to detrusor overactivities, overflow and bladder hypocompliance. In the literature, other possible causes include reduced bladder sensation, nephrogenic diabetes insipidus or sphincteric injury during valves ablation. [22]

Bladder function abnormalities were detected in 83.3% of our patients. Parkhouse et al[23] reported bladder dysfunction in about 75% of their cases. Bladder hypocompliance was found in 26.7% of our patients, similar to the finding of Puri et al. [24] However, other studies reported higher percentages of hypocompliance (46-57%).[13, 25] This could be due to the frequent use of anticholinergics among our patients. Detrusor overactivity was recorded in 63.3% of our patients, similar to the percentage reported by Sarhan et al.[13] In contrast, Ansari et al[25] found detrusor overactivity in 20% of the patients.

Hypocontractile bladder was found in 26.6% of our patients and was reported in only 12% by Ansari et al, [25] but in 56% of cases in a study by Androulakakis et al. [26] Significant PVR was detected in 36.7% of our patients, and in 26-56% in other studies. [26, 27] The disparity in the reported frequencies of urodymanic abnormalities in PUV patients may be due to selection bias as some studies did UDS only for PUV patients who had urinary complaints, or due to differences in the defintions of UDS for abnormalities such as hypocompliance. [28]

At last follow-up, 14 patients (46.7%) had moderate to severe CKD and one patient (3.3%) was on maintenance hemodialysis (ESRD). In a systematic review, CKD was reported in 0–32% of PUV patients and ESRD in 0-20% of them. [21] The discrepancy in the results may be attributed to differences in definition of CKD, time of valves ablation and quality of medical care.

On univariate analysis, the need for re-ablation, use of anti-cholinergics, high intial creatinine, high nadir creatinine, presence of VUR, history of febrile UTIs and presence of proteinuria were significantly associated with low eGFR. Multivariate analysis showed that high nadir creatinine and presence of VUR were independent factors associated with lower e-GFR at last follow-up **Table 4**. In accord with our results, Mcleod et al,[29]found that the presence of VUR, high nadir creatinine and use of anticholinergics were associated with need for renal replacement therapy on univariate analysis, while on multivariate analysis, nadir creatinine was the only independent factor. Nadir creatinine was the only independent predictor of final renal function in other studies as well. [7, 13, 30]

In our study, the presence of proteinuria was significantly associated with lower e-GFR at last follow-up in univariate analysis. Proteinuria was reported as statistically significant risk factor for CKD. [31]

Parkhouse et al[32] reported significant relation between incontinence and CKD or progression to ESRD. In our study and in that of Ghanem et al, [33] no correlation was found between incontinence and e-GFR. In harmony with our results, Ghanem et al[33] and Lopez-Pereira et al[34] reported that VUR is a common cause of impaired renal function. On the contrary, Ezal et al[31] found that neither VUR nor UTI had significant impact on renal function.

Ghanem et al[33] found that hypocompliance and detrusor overactivity unfavorably correlated with renal function, but this relation was not proved in our study. According to Ansari et al,[30] BCI and hypocompliance were significantly associated with poor renal function, whereas BOOI was not. In our study, neither BCI nor BOOI had significant effect on the e-GFR.

Antenatal diagnosis was significantly associated with better e-GFR at last follow-up on both univariate and multivariate analyses. Sarhan et al[35] also reported better long-term outcome in patients who were detected prenatally. In contrast, antenatal diagnosis did not decrease the rate of renal function

Table 4: Univariate and multivariate analyses for the parameters affecting the e-GFR (n = 27*)

Parameters affecting	Univariate		†Multivariate	
e-GFR	r	p	B (95%C.I)	p
Age at diagnosis (months)	-0.193	0.334		
Antenatal diagnosis	0.490‡	0.009 ‡	21.570(1.081 – 42.658)	0.040‡
Primary ablation	0.192	0.338		
Vesicostomy then ablation	-0.192	0.338		
Age at ablation (months)	-0.228	0.253		
Need for re-ablation	-0.411‡	0.033‡	-27.888(-57.497 - -1.721)	0.063
Anticholinergics	-0.421‡	0.029‡	9.366 (-19.161 - 37.893)	0.499
Alpha-blockers	-0.014	0.943		
Creatinine at presentation	-0.563‡	0.002‡	-7.510(-18.424 - 3.404)	0.165
Nadir creatinine*	-0.641‡	<0.001‡	-40.641(-66.644 - -14.437)	0.004‡
Presence of VUR at presentation	-0.437‡	0.023‡	-19.407(-37.450 - -1.763)	0.033‡
Febrile UTIs	-0.496‡	0.009‡	-12.097 (-40.309 - 16.116)	0.380
Incontinence at last follow-up	-0.125	0.535		
Bladder capacity	-0.173	0.388		
Bladder compliance	-0.278	0.160		
Post-void residual urine	-0.145	0.471		
Detrusor overactivities	-0.302	0.126		
BCI	0.074	0.712		
BOOI	-0.188	0.347		
Proteinuria	-0.541‡	0.004‡	0.648 (-4.018 – 5.314)	0.774

r: Correlation coefficient
B: Unstandardized coefficients
C.I: Confidence interval
UTIs: Urinary tract infections
VUR: Vesicoureteral reflux
BCI: Bladder contractility index
BOOI: Bladder outlet obstruction index
* Nadir creatinine was not available in three patients.
†: All variables with p<0.05 were included in the multivariate analysis
‡: Statistically significant at $p \leq 0.05$

decline in the study of Vasconcelos et al. [17]

This paper reflected challenges in PUVs management in Egypt as a developing country, in the form of limited prenatal diagnosis and prenatal management. Increasing family awareness, antenatal care facilities, and referral to tertiary care centers are priorities for promoting the antenatal diagnosis and management in developing countries. Facilities and training for prenatal intervention should be encouraged.

Conculsion

Nadir creatinine and vesicoureteral reflux have high prognostic value for late renal function. Antenatal diagnosis is associated with better renal function in patients with posterior urethral valves.

Ethical Consideration

This study is approved by the Ethics Committee of the Faculty of Medicine – Alexandria University with EC serial Protocol Number 18-00506**.**

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Conflict of interest

None of the authors have any conflicts of interest to declare

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