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Long-term Follow Up of Posterior Urethral Valve Patients and Predictors of Outcome, Cairo University Specialized Pediatric Hospital

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ABSTRACT

Background: Posterior urethral valves (PUVs) are reported to occur in 1/5000-8000 live births. It represents the most frequent cause of bladder outlet obstruction in children and is associated with significant morbidities and even mortality**.**

Objective: The aim of the current study is to record the long-term follow up of posterior urethral valve (PUV) patients and the effect of different predictors on outcome**.**

Patients and methods: A total of 30 boys with PUV initially presented between January 2010 and December 2018 and strictly fulfilled our follow up protocol. We collected their data retrospectively; the last follow-up data were recorded and analyzed.

Results: Median age at presentation was 6.3 months and mean age at last follow-up 5.67 ± 2.78 years, duration of follow up was 1.8-10 years. Lower urinary tract dysfunction (LUTD) was present in 19 boys (63%). 10 patients (33%) developed chronic renal failure at the last follow-up. Vesicoureteric reflux was a risk factor for occurrence of LUTD (p=0.007). Diurnal incontinence was a predictor for both upper and lower urinary tract dysfunction (p=0.011), (p=0.004) respectively. Mean value of Nadir serum creatinine was increased in patients with renal impairment (p<0.001), makes it a good predictor of future renal function with a cut-off value of 0.75 mg/dl. With a cut-off value of 2.28, the posterior/anterior urethra ratio was a good predictor for the success of PUV ablation (p<0.001). SWRD score $\geq$ 4 statistically correlated with upper tract deterioration (p<0.005) but not to LUTD.

Conclusions: Daytime dribbling and significant post voiding urine volumes were predictors of poor outcome. Nadir serum creatinine with a cut-off value of 0.75 mg/dl was a good predictor of future renal function. With a cut-off value of 2.28, the posterior/anterior urethra ratio was a good predictor for the success of PUV ablation.

Keywords: Posterior urethral valve, Vesicoureteric reflux, Valve fulguration, Vesicostomy, Follow-up, Cairo University.

INTRODUCTION

Posterior urethral valves (PUVs) are reported to occur in 1/5000-8000 live births [(1)]. It can be associated with other congenital anomalies [(2)].It represents the most frequent cause of bladder outlet obstruction in children and is associated with significant morbidities, urine tract infection(UTI), chronic renal failure (CRF), and even mortality [(3)].

Mortality rates decreased from 36% to less than 10% in the past few decades [(4, 5)]. PUV is a common cause of CRF and end-stage renal failure (ESRD) in children and account for approximately 35% of children who require renal transplantation [(6)]. Approximately 22% of patients with PUV progress to ESRD during a median follow-up of 31 years [(7)].

Being an important cause of ESRD in children, we decided to study the effect of different factors and their impact on the course of the disease and outcome during long term follow up for PUV children.

PATIENTS AND METHODS

A retrospective study included a review of 30 patients during their regular follow-up. All of them initially presented between January 2010 and December 2018.

- **Inclusion criteria**: Patients diagnosed with posterior urethral valve and underwent initial surgical intervention in the form of either valve ablation or vesicostomy and fulfilled our follow up protocol.
- **Exclusion criteria**: Patients who refused to join and those who have not completed our follow up protocol after surgical management. Follow up protocol:
  1. Urine analysis, urine culture and serum creatinine after 1week, 1month and every 3 months during the first year then every 6 months.
  2. Abdominopelvic U/S after 1week, 1month and every 3 months during the first year then annually.
  3. Voiding cystourethrogram (VCUG) once after 3months then annually.
  4. Radio-isotope renal scan after 6 months to record the baseline renal functions then annually.
  5. Check cystoscopy was done if needed during the follow up period depending on the presence of obstructive symptoms or persistent dilatation of the posterior urethra in the VCUG imaging.

Long-term clinical, biochemical and radiological outcomes were reviewed. We recorded the last follow up

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data of those patients and evaluated their upper and lower tract function. Patients were evaluated by history taking including the presence of lower urinary tract symptoms (LUTS), occurrence of recurrent FUTIs, the need for anticholinergics and the use of clean intermittent catheterization (CIC)

Lower urinary tract dysfunction was defined to be in patients with one of the following: Diurnal incontinence, nocturnal enuresis, urgency, urge incontinence, hesitancy, intermittent voiding, and weak stream. All of these symptoms were only relevant above the age of five except intermittency which is physiological up to the age of three if not accompanied by straining, however, if straining is observed it denotes an abnormality even if present early in infancy. Total incontinence and weak stream were considered relevant symptoms from early infancy [(8)].

Upper urinary tract dysfunction **was defined as the presence of *chronic kidney disease* (CKD) or *end-stage renal disease* (ESRD)** which were defined based on estimated glomerulo-filtration rate (GFR) and according to the staging of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative[(9)].

Acute renal failure **(ARF):** According to Shull equation for calculation of the predicted pediatric creatinine clearance [(10)]. Difference between the estimated clearance at diagnosis and the assumed baseline clearance was calculated and ARF was defined according to pediatric-modified RIFLE criteria [(11)].

Operative details were recorded including the method of initial surgical intervention (valve fulguration or vesicostomy), check cystoscopies and other surgical procedures done.

Investigations: at time of diagnosis and during follow up were recorded including laboratory and radiological. The last follow-up data were recorded to compare it with the pre-operative data.

Serum creatinine reference range for patients < one year was defined according to nomograms published by **Boer *et al*.**[(12)]. While reference range for patients > one year was defined according to nomograms published by Savory[(13)].

Hydronephrosis was graded based on the society of fetal urology grading system[(14)].

Ascending and voiding cystourethrography **(ACU)** was done for all patients to see the improvement in bladder shape, capacity and grade of reflux, ACU was used to calculate both the posterior/anterior urethra ratio and the SWRD score.

Urodynamic studies were carried out for 12 toilet trained patients who complained of LUTS.

Posterior/anterior urethra ratio (PAR)*:*

PAR was calculated by dividing maximum posterior urethral diameter by anterior urethral diameter using images taken during voiding cystourethrogram. Distances were measured by an on-screen distance measurement tool. PAR was then correlated with success of posterior urethral valve management which was defined as biochemical and radiological improvement, regression of hydroureteronephrosis and decrease in post voiding residual urine. PAR was correlated to the estimated GFR measured by nuclear imaging to assess its effect on the upper tract function [(15)].

SWRD score:

Based on shape of the bladder, trabeculations of the bladder wall, presence of reflux, and presence of bladder diverticulum, SWRD score was calculated using the voiding cystourethrogram (VCUG). The SWRD scoring gives a minimum score of 0 for radiographically normal bladders to a maximum score of 7 for the most radiographically abnormal bladders [(16)]. SWRD score was correlated with the presence of lower tract dysfunction and to the prognosis of upper tract function using nuclear imaging to assess if there is any significant relation.

Ethical consideration

An approval of the study was obtained from Cairo University urology department ethical committee. Parents of each patient signed an informed written consent for acceptance of participation in the study.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the ShapiroWalk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) was done to calculate difference between two or more groups of qualitative variables. When the anticipated frequency is less than 5, Fisher's exact test was utilized in its place. Quantitative data were expressed as mean and standard deviation (SD). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) or Mann-Whitney U test (non- parametric data). The ideal cut-off ratio for the investigated diagnostic indicators was established using Receiver Operating Characteristics (ROC) curve. P value ≤ 0.05 was considered significant.

RESULTS

86.7% (26) of our patients initially presented between the age of one month and one year, while 10% (3) presented between the age of one year and five years and only one patient presented older than 5 years. The mean follow-up period was 62.64 (SD 28.67) months. The age of the patients at the last follow-up ranged from 2 to 13 years with a mean age of 5.67 (SD 2.78) years. Of those patients, 50%were

between the age of two years and five years while 46.6% were between 5 and 10 years and only one patient was older than 10 years. At initial presentation, acute renal failure was present in 26 (86.7%) boys. **Table 1** shows the frequency of different symptoms at presentation.

Table 1. Presenting symptoms of the studied patients.

Symptoms	Number	Percent
Straining	11	36.7
Dribbling	7	23.3
Urinary retention	12	40.0
Dysuria	4	13.3
Abdominal distention	10	33.3
Fever	10	33.3
Vomiting	4	13.3
Hematuria	1	3.3

Renal US findings recorded that 100% of the patients had hydronephrosis with grades I, II, and III in 4 (13.3%), 13 (43.3%) and 13 (43.3%) boys respectively.

Two boys (6.7%) had unilateral hydronephrosis and 28 (93.3%) had bilateral hydronephrosis. Ascites with perinephric collection was present in 2/30 (6.7%) and perinephric hematoma was present in 1/30 (3.3%) on the left side. At the last follow-up, the hydronephrosis showed total resolution in 9/30(30%) boys, while 21/30 (70%) boys still had hydronephrosis.

VCUG at presentation revealed that 20/30 (66.7%) boys had reflux, 7/20 (35.0%) had low grade and 13/20 (65.0%) had high-grade reflux. Eleven (55.0%) patients had unilateral VUR and 9 (45.0%) had bilateral VUR.

Follow up VCUG showed 21/30(70%) boys with no reflux while 9/30 (30%) boys still had reflux.

At presentation, 25 (83.3%) boys had UTI. Three cases had microscopic hematuria and 1 case showed gross hematuria.

At the last follow-up, 11 (36.7%) boys had UTI, none were complicated with febrile UTI and none had hematuria.

Out of the 12 patients who were evaluated by urodynamic studies, 2/12 (16.7%) patients showed an increased bladder capacity during the filling cystometry associated with myogenic failure during the voiding phase, their ages were four and eight years. During the filling phase, 7/12 (58.3%) patients aged 3-6 years, showed decreased bladder capacity for age and bladder hypo-compliance while detrusor over-activity was observed in only 2/12 (16.7%) patients.

Our initial surgical intervention was endoscopic valve ablation in 16/30 (53.3%) patients using the cold knife and 14/30 (46.7%) underwent temporary vesicostomy. Patients with temporary vesicostomy had delayed valve fulguration either before or at the time of vesicostomy closure. 14/30 (46.7%) patients underwent check cystoscopies during follow up period. The findings were: residual valve in 3 (21.4%) patients and ring urethral stricture in one patient managed by laser (7.1%). One patient underwent urgent nephrectomy and vesicostomy on presentation due to refractory gross hematuria with intrarenal hemorrhage.

At the last recorded follow-up data, Upper and lower urinary tract functions were evaluated and presented in **Table 2**.

Table 2. Lower tract symptoms and upper and lower tract function of the studied patients at the last follow-up.

Recent lower tract symptoms	Number	Percent
Flow (good)	15	50
Intermittency	5	16.7
Dysuria	3	10.0
Daytime dribbling	10	33.3
Nocturnal enuresis	19	63.3
Stress incontinence	1	3.3
Urge incontinence	1	3.3
Total incontinence	1	3.3
Clean intermittent catheterization	6	30
Lower and upper urinary tract function	**Number**	**Percent**
Lower tract function		
Lower tract Dysfunction according to symptoms	19	63.3
No LUTD symptoms	11	36.7
Significant post voiding residual urine (n= 30)	**9**	**30**
Upper tract function by DTPA (n= 26)		
CKD	9	34.6
ESRD	1	3.8
Good	16	61.5

Lower urinary tract dysfunction was not statistically related to the method of treatment used whether primary fulguration (p=0.643) or vesicostomy (p=0.919). Upper urinary tract function was not statistically related to either primary fulguration (p=0.315) or vesicostomy (p=1.000).

There was a statistically significant relation between lower urinary tract dysfunction and presence of vesicoureteric reflux (p=0.007). Presence of daytime and nocturnal incontinence were the most significant predictors of lower urinary tract dysfunction.

There was a statistically significant relation between good upper urinary tract function and the absence of daytime dribbling (p=0.011) or the absence of post voiding residual urine in ultrasonography (p=0.031) However, it demonstrated no significant statistical relation with the presence of vesicoureteric reflux (p=0.347).

Patients with poor kidney functions had a mean nadir serum creatinine substantially higher than patients with good renal functions (p<0.001). Receiver operating curve (ROC) analysis found that nadir serum creatinine was a predictor of renal dysfunction (p<0.001) with a cut-off value of 0.75 mg/dl and area under curve (AUC= 0.913) with 95% CI = 0.785-1.040 yielding a 70% sensitivity and 93.7% specificity (**Figure 1**).

16/30 (53.3%) patients were found to have successful PUV ablation (improved creatinine, decrease in degree of hydronephrosis and postvoiding urine volume) while 14/30 (46.7%) were found to have unsuccessful ablation. Success of PUV ablation was correlated with the postoperative PAR.

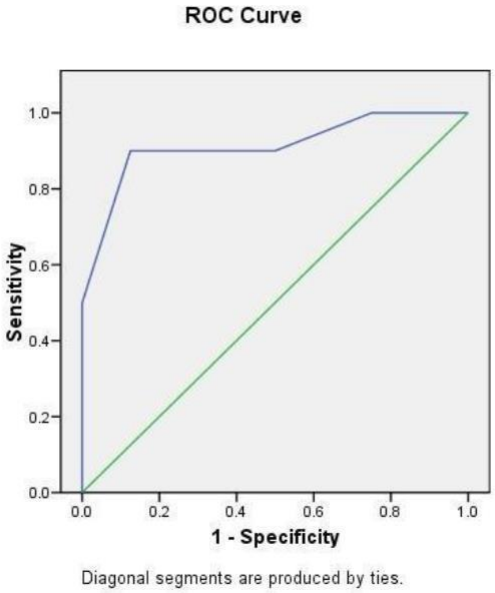

Figure 1. Receiver operating curve (ROC) for Nadir serum creatinine to predict the presence of renal dysfunction in children with PUV.

According to the ROC analysis, we found that the posterior/anterior urethra ratio (PAR) was a predictor for the success of PUV ablation (p<0.001) with a cut-off value of 2.28 and area under curve (AUC=0.929) with 95% CI =0.826-1.031 yielding 100% sensitivity and 85.7% specificity (**Figure 2**).

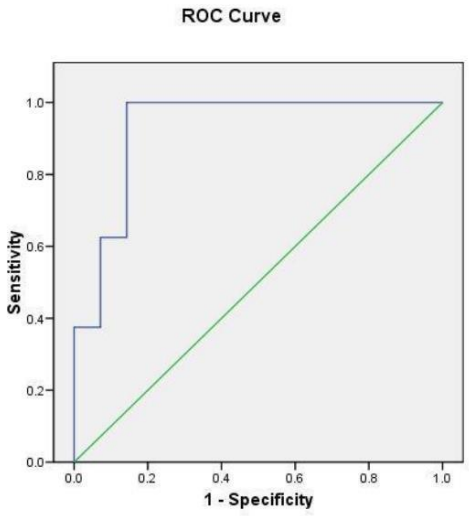

Figure 2. Receiver operating curve (ROC) for posterior/anterior urethra ratio (PAR) to predict the success of PUV ablation.

Using this cut-off, the PAR of 12 (40%) patients was above 2.28 and all of them had unsuccessful valve ablation. 18 (60%) patients had PAR below 2.28 of whom 16 patients had successful valve ablation during the follow-up. There was a statistically significant relationship between the prognosis of upper tract function according to the estimated (GFR) and the PAR (P<0.0001), mean PAR for patients with poor upper tract function was 2.78 (SD 0.46) and 1.9 (SD 0.24) for patients with good upper tract function.

SWRD score was calculated for all patients and there was no statistically significant relation between SWRD score and the presence of lower tract dysfunction, (p=0.299), however, all patients with SWRD score $\geq$ 4 had clinically significant lower tract dysfunction at their last follow-up.

There was a statistically significant relationship between SWRD score and the prognosis of upper tract function (p<0.005), all patients with SWRD score 4 or above developed poor upper tract function according to the estimated GFR at their last follow-up.

DISCUSSION

The majority of patients in this study were diagnosed during the neonatal period and infancy, with the predominance of this age group at presentation as reported by **Bajpai *et al*.**[17].

The most common presenting symptoms in our study were urine retention and straining. These results were in concordance with the reports from **Mirshemirani *et al***

who stated that 51% of their patients presented with weak flow [18].

Gross hematuria was a rare clinical entity proclaimed by Diamond as a case report in a neonate at day 1; he was later treated by valve ablation [19]. Gross hematuria was also present in one patient in our study presented at 1 month of age; however, it was managed by urgent nephrectomy and vesicostomy.

Vesicoureteric reflux has been observed in the literature in about 25%-50%of patients with posterior urethral valves [20]. In our study vesicoureteric reflux at presentation revealed close rates to those reported in the literature. About 66.7% of our studied patients had vesicoureteric reflux of whom 35.0% had low-grade reflux (I-II-III) and 65%had high-grade reflux (IV-V).

About 53.3% of our patients underwent valve ablation only and46.7% underwent vesicostomy. **Mirshemirani *et al*** reported a secondary vesicostomy rate of 42.85%due to failure of response to urinary catheterization drainage, associated severe VUR, urinary leakage, or unsuccessful valve ablation [18].

Check cystoscopy for our patients revealed residual valves in 21% which is close to the results by **Mirshemirani *et al*** who reported residual valves in 15.3% of their cases [18].

The reported incidence of urethral stricture following endoscopic valve ablation in the literature was between 3.6–25% [3], however, it was found in only 1(7.1%) patient in our series.

LUTs have been reported to occur in 13–38% of valve patients [21]. Daytime wetting is the most common problem [5]. In our study, the presence of daytime dribbling was significantly related to the presence of lower tract dysfunction, also the presence of vesicoureteric reflux at presentation was a significant risk factor for prediction of lower tract dysfunction at the follow-up. Absence of both daytime dribbling and significant residual urine in ultrasonography contributed in the good prognosis of the upper urinary tract with a significant statistical relation. Yet the presence of vesicoureteric reflux was not involved in the prognosis of the upper tract function. **DeeFor *et al*** stated that it is unclear whether high grade vesicoureteral reflux at diagnosis could be a poor prognostic sign or not[22].

In our study, the initial method of surgical intervention did not differ in the outcome of both upper and lower tract functions. Similarly, **Narasimhan *et al*** concluded that both valve fulguration and vesicostomy were equally effective for neonatal valve and achieve similar renal function [23].

ROC analysis in our study signified that PAR was a predictor for success of PUV ablation with a cut-off value of 2.28 which was consistent with the finding of **Babu *et al*** who suggested that an upper limit of PAR >2.2 was proposed to predict failure, however, 42% of his patients above this cut off did not show any biochemical or radiological deterioration [15]. On the contrary, all our patients with PAR above 2.28 showed both biochemical and radiological deterioration during their follow-up. We consider PAR as a good predictive tool for the prognosis of PUV patients especially after correlation with renal nuclear imaging which proved that persistent dilatation of the posterior urethra may affect the prognosis of upper tract function.

Niyogi *et al* used the SWRD score as a prognostic indicator for the need of CIC or intervention as augmentation cystoplasty, Mitrofanoff procedure and nephrectomy for non-functioning kidneys during follow-up [16]. We found that post PUV ablation, SWRD score can be a useful tool to predict the future outcome of the upper tract function but unfortunately, we could not prove its ability to detect the lower tract function which may be attributed to the small number of patients who did urodynamic evaluation.

CONCLUSION

Posterior urethral valve is a disease that can range from severe obstruction to minimal form that may be manifested later in life. Bladder dysfunction and renal deterioration are common sequels. VUR is a common finding and its persistence during the follow up period is significantly associated with the presence of lower urinary tract dysfunction.

Nocturnal enuresis is the most common symptom in patients complaining of lower tract dysfunction. Diurnal incontinence and significant post voiding urine volume denote lower tract dysfunction and is a significant predictor of poor renal outcome. The method of primary surgical intervention did not show any significant relation to the long term outcomes of both the upper and lower tract. Nadir serum creatinine is a good predictor of future renal function with a cut-off value of 0.75 mg/dl. A cut- off value of 2.28, the posterior/anterior urethra ratio is a good predictor for the success of PUV ablation. Lifelong nephrological and urological follow-up after valve ablation till adolescence and adulthood is mandatory for PUV patients.

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