

## Risk Factors Associated with Chronic Kidney Disease in Infants With Posterior Urethral Valve: A Single Center Study of 110 Patients Managed By Valve Ablation And Bladder Neck Incision

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**Purpose:** Concurrent valve ablation and bladder neck incision is suggested as an effective and safe treatment approach in posterior urethral valve children with prominent bladder neck. We evaluated chronic kidney disease risk factors in these children.

**Materials and methods:** We retrospectively reviewed medical records of children with posterior urethral valve and included those younger than 18 years old who underwent valve ablation and bladder neck incision at our institution. We recorded patient demographics, presenting symptoms, laboratory and radiographic data. Our primary outcome was chronic kidney disease defined as stage 3 chronic kidney disease or higher. Renal outcome risk factors such as preoperative vesicoureteral reflux and serum creatinine, age at diagnosis, adjuvant urinary diversion were analyzed.

**Results:** A total of 110 patients met our inclusion criteria. The median age at diagnosis was 10.4 months (range 14 days to 12 years). Prenatal diagnosis in 72.7% was the most common presentation. Mean follow-up duration was 3 years and 12 (10.9%) patients progressed to chronic kidney disease. Preoperative serum creatinine greater than 1 mg/dL was the only factor associated with progression to chronic kidney disease.

**Conclusion:** In our group of children with posterior urethral valve ablation and bladder neck incision, initial creatinine value of greater than 1 mg/dL is more probably associated with renal impairment while; vesicoureteral reflux, age at diagnosis, presenting symptoms, and adjuvant urinary diversion were not significant prognostic factors. Further randomized controlled evaluations are required to analyze the effects of concurrent valve ablation and bladder neck incision on renal outcome.

**Keywords:** creatinine; kidney failure, chronic; renal insufficiency, chronic; urethra; urethral obstruction

### INTRODUCTION

PUV (Posterior Urethral Valve) is the most significant congenital cause of lower urinary tract obstruction in male children leading to progressive renal damage and end-stage renal disease in a proportion of them.<sup>(1-3)</sup>

Although valve ablation is the treatment of choice for relieving obstruction in PUV patients, the risk of chronic kidney disease (CKD) remains notable even after ablating the valves.<sup>(4)</sup>

We have performed endoscopic valve ablation and Bladder neck incision (BNI) from 1996 for PUV patients with prominent bladder neck. BNI is considered beneficial in boys with bladder neck obstruction and the combination with valve ablation in PUV patients with prominent bladder neck is suggested as being safe and effective.<sup>(5-7)</sup>

Regarding the promising results of concurrent valve ablation and BNI, it has become our premier surgical option in PUV management;<sup>(8,9)</sup> but the prognostic significance of factors determining renal outcome in PUV patients undergoing the combination surgery is unclear

and few studies are addressing the aforementioned issue.

Therefore, we tried to identify CKD risk factors in PUV patients who underwent valve ablation with BNI at our center.

### MATERIALS AND METHODS

#### Study population

Children who underwent surgical ablation of PUV with BNI at our pediatric center of excellence, Tehran, Iran from 2007 to 2017 were evaluated retrospectively.

#### Inclusion and exclusion criteria

In this study, we included children younger than 18 years old who underwent posterior urethral valve ablation with BNI at our institution over a period of 10 years.

Exclusion criteria were incomplete data, previous surgical intervention, and less than two years of follow-up.

#### Procedures

We performed urethral catheter drainage followed by endoscopic valve ablation with BNI in all children as

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Received March 2020 & Accepted September 2020

**Table 1.** Comparison of patients' characteristics at diagnosis and last follow up.

Variables	CKD(N = 12)	Non-CKD(N = 98)	p-Value <sup>a</sup>
Age at diagnosis ≤ 1year, N( % )	7 (58.3%)	76 (77.5%)	NS
Age at diagnosis, month; mean ± SD(range)	24.3 ± 32.6 (1-96)	13.5 ± 25 (0.5-144)	NS
UTI, N( % )	2 (16.7%)	8 (8.2%)	NS
VUR, N( % )	10 (83.3%)	74 (75.5%)	NS
Cr at diagnosis > 1mg/dL, N( % )	9 (75%)	16 (16.3%)	<0.05
Cr at diagnosis, mg/dL; mean ± SD(range)	1.88 ± 0.92 (0.5-2.8)	0.99 ± 1.85 (0.3-14)	NS
Cr at last followup, mg/dL; mean ± SD(range)	1.75 ± 0.65 (0.6-3)	0.52 ± 0.11 (0.3-1.1)	<0.05
Valve ablation with BNI, N( % )	9 (75%)	83 (84.7%)	NS
Upper tract diversion, N( % )	3 (25%)	15 (15.3%)	NS
Bilateral VUR, N( % )	8 (80%)	52 (70.3%)	NS
VURD syndrome <sup>b</sup> , N( % )	0 (0%)	19 (19.4%)	NS

**Abbreviations:** BNI: Bladder Neck Incision; CKD: Chronic Kidney Disease; Cr: Creatinine; NS: Non Significant; UTI: Urinary Tract Infection; VUR: Vesicoureteral Reflux; VURD: Vesicoureteral Reflux Dysplasia

<sup>a</sup>; p-value < 0.05 is significant.

<sup>b</sup>: Unilateral massive VUR into a dysplastic kidney.

the initial treatment management, while high urinary diversion (cutaneous ureterostomy or pyelostomy) was done if renal function or hydronephrosis did not improve after 48 hours of lower drainage or urosepsis secondary to pyonephrosis occurred.

Urethral valves were fulgurated using bugbee electrodes with an appropriate cystoscope. Incision of bladder neck was done at 6 o'clock position by cutting current, just proximal to verumontanum and not deep into the adventitia.

Cutaneous vesicostomy is not our advocated procedure for urinary drainage in PUV patients.

### Evaluations

After institutional review board approval, medical records including demographics, age at diagnosis, prenatal findings (oligohydramnios, urinary system abnormalities), the evidence of vesicoureteral reflux (VUR), urinary ascites, laboratory data before and after relief of obstruction like serum Creatinine(Cr), Glomerular Filtration Rate (GFR), urinalysis, urine culture and type of surgical intervention were gathered. In all included patients, PUV diagnosis was made using voiding cystourethrogram (VCUG) and confirmed via cystoscopy, and VUR was graded from I to V according to the standard classification on VCUG.

Serum Cr at diagnosis and last follow-up were recorded. Regarding the diversity of age at diagnosis of involved patients and different range of normal values for each age group, we categorized serum Cr at diagnosis as ≤ one mg/dL or more.

Our primary outcome was CKD.

Patients were classified into two groups; with or without CKD at the last follow-up. CKD was defined as stage 3 CKD (GFR less than 60 ml/minute/1.73 m<sup>2</sup> by Schwartz formula for children less than 18 years old and by the Modification of Diet in Renal Disease study equation in adults)(10) or higher according to Kidney Disease Outcome Quality Initiative guidelines.

The data for the calculation of GFR at diagnosis was not accessible for many of our patients.

Patients not willing to continue follow-up visits after two years were not excluded from the study but their last data sufficient for GFR calculation were included.

### Statistical analysis

Statistical analysis was carried out by SPSS statistics for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA) version 13. Numerical variables were reported

as mean, standard deviation, and range. The chi-square and Fisher exact tests were used to analyze the association between categorical variables and Student's T-test was used for comparison of means between groups. A p-value of less than .05 is considered statistically significant.

### RESULTS

A total of 110 patients fulfilled our inclusion criteria. The mean age at diagnosis was 14.7 ± 26.13 months (range from 14 days to 12 years) which 75.5% (83 patients) were within one-year-old and 24.5% (27 patients) were older.

The range of follow-up period was 2-8 years (mean 3 years).

The clinical presentation was prenatal diagnosis in 80 (72.7%), febrile urinary tract infection in 10 (9.1%), voiding disturbances or urinary incontinence in 24(20.9%), and one patient was diagnosed during evaluation for renal failure.

CKD was detected in 12 (10.9%) of patients at the last follow-up. 6 patients (5.45%) aggravated into end-stage renal disease of which 4 (3.63%) died due to uremic complications.

Univariate analysis of the risk factors for CKD in the two groups is listed in **Table 1**.

92 patients (83.6%) were treated only with endoscopic valve ablation and BNI while high urinary diversion as ureterostomy or pyelostomy was required additionally in 13 (11.8%) and 5 (4.5%) patients, respectively. Although not statistically significant but upper tract urinary diversion was more necessary in CKD group, 3 of 12 patients (16.7 %) compared to 15 of 98 patients (83.3 %) in non-CKD group ( $p = .25$ ).

We considered the age at diagnosis as the date of surgical relief of PUV; since we performed valve ablation with BNI not so far after diagnosis.

CKD developed in 7 (8.4%) of patients diagnosed within one-year-old age and in 5 (18.5%) of those diagnosed later; which is statistically insignificant ( $p = .15$ ).

The mean serum Cr at diagnosis was 1.09 ± 1.8 (.3-14) mg/dL and at last follow-up was .65 ± .44 (.3-3) mg/dL. Elevated initial serum Cr greater than one mg/dL was seen in 22.7% of cases and it was more significant in the CKD group ( $p = .001$ ).

84 (76.3%) of patients had VUR at diagnosis which was bilateral in 60 patients (54.5%), right sided in 10 (9.1%), and left sided in 14 patients (12.7%).

The presence of VUR ( $p = .77$ ) or its laterality ( $p = .48$ ) was not associated with an increased risk of CKD in our study. VUR improved after valve ablation and BNI spontaneously in most of our patients and anti-reflux surgery was rarely required.

## DISCUSSION

Despite improvements in the medical and surgical treatment of PUV, it remains one of the main causes of CKD in children.<sup>(3)</sup> The incidence of CKD was 10.9% in our study.

Although numerous studies have been conducted addressing prognostic factors affecting PUV management outcome, there is still controversy regarding which factors determine the renal out-come.

Application of BNI simultaneously with valve ablation has been proposed as an effective treat-ment modality that may reduce bladder dysfunction and consequently renal damage.<sup>(8,9)</sup>

We conducted a retrospective and non-randomized study to help clarify the significance of vari-ous factors on long-term renal outcome in our group of patients on whom we have performed en-doscopic valve ablation with BNI.

Vesicostomy is not our choice for urinary diversion in PUV patients as we believe that effective bladder drainage is obtained by proper valve ablation and catheterization.<sup>(11)</sup> In the severe dis-tended ureter, relief of bladder obstruction may not be able to drain the upper urinary system suf-ficiently due to failed peristalsis and coaptation, therefore cutaneous pyeloureterostomy seems more efficient.<sup>(11)</sup>

Proponents of high urinary diversion believe that temporary pyeloureterostomy doesn't interfere with blad-der function in long term as well as improving the renal function by adequate drainage of the pyelocaliceal sys-tem.<sup>(12-14)</sup>

High urinary diversion was done in 16.3% of our pa-tients in case of pyonephrosis or when hy-dronephrosis or renal failure did not improve after 48 hours of blad-der drainage.

There is conflicting data regarding urinary diversion in PUV patients.<sup>(13,14)</sup> Some authors believe that renal function is independent from the kind of treatment mo-dality chosen for patients as they emphasize on the role of congenital renal dysplasia which makes these pa-tients prone to pro-gressive renal failure.<sup>(15-17)</sup>

In our study, CKD occurred in 9 (9.8%) patients treated simply with valve ablation and BNI which was not sig-nificantly different from 3 patients (16.7%) with upper urinary diversion.

Our findings are similar to previous studies suggesting that long-term renal function is affected by other fac-tors like severity of disease at initial presentation oth-er than the kind of therapy start-ed for the patient.<sup>(17,18)</sup>

However, to help clarify the role of urinary diversion in renal protection of patients with PUV, larger rand-omized-controlled studies comparing different treat-ment modali-ties are necessary.

Age at diagnosis has been suggested to influence re-nal outcome in PUV patients<sup>(19,20)</sup> 72.7% of our patients were diagnosed prenatally. Some authors claim that prenatal diagnosis may improve the renal prognosis due to earlier relief of obstruction and slowing the renal damage process.<sup>(21)</sup>

On contrary, others have concluded that diagnosis at

an older age may be an indicator of a milder and more benign form of disease which caused later presentation.<sup>(17,22)</sup>

75% of our patients were diagnosed within one year of age. Our analysis of age at diagnosis and final renal outcome did not show any difference between patients diagnosed before and after one year of age. Our study is similar to earlier ones.<sup>(17,22)</sup>

Serum Cr level at diagnosis has been mentioned as the most significant prognostic indicator in PUV patients.<sup>(23-25)</sup> In our study, CKD occurred in 3.5% of patients when serum Cr at diagnosis was  $\leq 1$  mg/dL and the frequency increased to 36% when initial serum Cr was above 1 mg/dL which the difference was statistically significant ( $p = .001$ ).

Our results, similar to previous studies, indicate that higher initial serum Cr levels determine a poorer renal outcome.<sup>(23,25-27)</sup>

The retrospective method of our study limited us in gathering data necessary for other important clinical factors in renal prognosis such as serum Cr level at one-year age, nadir Cr after a time of bladder decompres-sion, bladder function status and etc.

In our study, 84 patients (76.3%) had VUR on their ini-tial VCUG of which 27 patients (32.1%) showed com-plete resolution after surgical relief of obstruction.

Our data is similar to other studies showing a preva-lence of 50-70% for PUV patients with VUR at the time of diagnosis<sup>(28)</sup> and a resolution of up to 50% for VUR after surgical correction.<sup>(29)</sup>

We did not find any correlation between the presence of VUR (either bilateral or unilateral) and final renal outcome ( $p = .77$ ). Otherwise, CKD developed in 8.3% of patients with unilateral VUR compared to 13.3% of patients with bilateral VUR, which the difference was not statisti-cally significant ( $p = .48$ ).

Though our study confirms the results of most prior ones,<sup>(26,30)</sup> but some authors believe that bi-lateral VUR implies a poorer renal outcome<sup>(4,25)</sup> and unilateral severe VUR protecting contrala-teral kidney by its pop-off mechanism is a good prognostic factor.<sup>(17)</sup>

In our study, CKD did not develop in cases with vesi-coureteral reflux dysplasia syndrome (uni-lateral mas-sive VUR into a dysplastic kidney) and in 13.2% of patients with other patterns of VUR at diagnosis; but the difference was not statistically significant ( $p = .12$ ).

## CONCLUSIONS

Our findings are consistent with the emerging signifi-cance of initial serum Cr and GFR values in the final re-nal outcome of PUV patients undergoing valve ablation with BNI. Further prospective studies are necessary to clarify the prognostic significance of different renal risk factors.

## CONFLICT OF INTEREST

None declared by the auctors.

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