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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Abstract

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 symp-

toms, 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. 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 one 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 one 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.

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.[1-3]

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.[4]

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.[5-7]

Regarding the promising results of concurrent valve ablation and BNI, it has become our premier surgical option in PUV management;[8,9] but the prognostic significance of factors determining renal outcome in PUV patients undergoing the combination surgery is unclear and there are few studies 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 was 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 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 and 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^2 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 King Disease Outcome Quality Initiative guidelines.

The data for 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 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.

Result

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 %) comparing to 15 of 98 patients (83.3 %) in non-CKD group ($p = .25$).

We considered 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 $.65 \pm .44$ (.3-3) mg/dL.

Elevated initial serum Cr greater than one mg/dL was seen in22.7% of cases and it was more significant in 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%).

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 medical and surgical treatment of PUV, it remains one of the main causes of CKD in children.[3] 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 outcome.

Application of BNI simultaneously with valve ablation has been proposed as an effective treatment modality that may reduce bladder dysfunction and consequently renal damage.[8,9]

We conducted a retrospective and non-randomized study to help clarify the significance of various factors on long-term renal outcome in our group of patients on whom we have performed endoscopic 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.[11] In the severe distended ureter, relief of bladder obstruction may not be able to drain the upper urinary system sufficiently due to failed peristalsis and coaptation, therefore cutaneous pyeloureterostomy seems more efficient.[11]

Proponents of high urinary diversion believe that temporary pyeloureterostomy doesn't interfere with bladder function in long term as well as improving the renal function by adequate drainage of pyelocaliceal system.[12-14]

High urinary diversion was done in 16.3% of our patients in case of pyonephrosis or when hydronephrosis or renal failure did not improve after 48 hour of bladder drainage.

There is conflicting data regarding urinary diversion in PUV patients.[13,14] Some authors believe that renal function is independent from the kind of treatment modality chosen for patients as they emphasize on the role of congenital renal dysplasia which makes these patients prone to progressive renal failure.[15-17]

In our study, CKD occurred in 9 (9.8%) patients treated simply with valve ablation and BNI which was not significantly 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 factors like severity of disease at initial presentation other than the kind of therapy started for the patient.[17,18] However, to help clarify the role of urinary diversion in renal protection of patients with PUV, larger randomized-controlled studies comparing different treatment modalities are necessary.

Age at diagnosis has been suggested to influence renal outcome in PUV patients.[19,20] 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.[21]

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.[17,22]

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.[17,22]

Serum Cr level at diagnosis has been mentioned as the most significant prognostic indicator in PUV patients.[23-25] In our study, CKD occurred in 3.5% of patients when serum Cr at diagnosis

was ≤ one mg/dL and amount increased to 36% when initial serum Cr was above one 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.[23,25-27]

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 decompression, bladder function status and etc.

In our study, 84 patients (76.3%) had VUR on their initial VCUG of which 27 patients (32.1%) showed complete resolution after surgical relief of obstruction.

Our data is similar to other studies showing a prevalence of 50-70% for PUV patients with VUR at the time of diagnosis[28] and a resolution of up to 50% for VUR after surgical correction.[29]

We did not find any correlation between 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 statistically significant (p = .48).

Though our study confirms the results of most prior ones,[26,30] but some authors believe that bilateral VUR implies poorer renal outcome[4,25] and unilateral severe VUR protecting contralateral kidney by its pop-off mechanism is a good prognostic factor.[17]

In our study, CKD did not develop in cases with vesicoureteral reflux dysplasia syndrome (unilateral massive 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).

Conclusion

Our findings are consistent with the emerging significance of initial serum Cr and GFR values in the final renal 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

References

1. Hebenstreit D, Csaicsich D, Hebenstreit K, Muller-Sacherer T Berlakovich G, Springer A. Long-term outcome of pediatric renal transplantation in boys with posterior urethral valves. J Pediatr Surg. 2018; 53:2256-60.
2. Uthup S, Binitha R, Geetha S, Hema R, Kailas L. A follow-up study of children with posterior urethral valve. Indian J Nephrol. 2010; 20: 72-5.
3. Vasconcelos MA, ACS ES, Gomes IR, Carvalho RA, Pinheiro SV, Colosimo EA, et al. A clinical predictive model of chronic kidney disease in children with posterior urethral valves. Pediatr Nephrol. 2019; 34:283-94.
4. Engel DL, Pope JC, IV, Adams MC, Brock JW, III, et al. Risk factors associated with chronic kidney disease in patients with posterior urethral valves without prenatal hydronephrosis. J Urol. 2011; 185:2502-6.

5. Trockman BA, Gerspach J, Dmochowski R, Haab F, Zimmern PE, Leach GE. Primary bladder neck obstruction: urodynamic findings and treatment results in 36 men. J Urol. 1996; 156: 1418-20.

6. Androulakakis PA, Karamanolakis DK, Tsahouridis G, Stefanidis AA, Palaeodimos I. Myogenic bladder decompensation in boys with a history of posterior urethral valves is caused by secondary bladder neck obstruction? BJU Int. 2005; 96:140-3.

7. Misseri R, Combs AJ, Horowitz M, Donohoe JM, Glassberg KI. Myogenic failure in posterior urethral valve disease: real or imagined? J Urol. 2002; 168(4Pt2): 1844-8.

8. Kajbafzadeh AM, Payabvash S, Karimian G. The effects of bladder neck incision on urodynamic abnormalities of children with posterior urethral valves. J Urol. 2007; 178: 2142-9.

9. Keihani S, Kajbafzadeh AM, Kameli SM, Abbasioun R. Long-term impacts of concurrent posterior urethral valve ablation and bladder neck incision on urinary continence and ejaculation. J Urol. 2017; 99: 278-80.

10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130: 461-70.

11. Nasir AA, Ameh EA, Abdur-Rahman LO, Adeniran JO, Abraham MK. Posterior urethral valve. World J Pediatr. 2011; 7: 205-16.

12. Farhat W, McLorie G, Capolicchio G, Khoury A, Bagli D, Merguerian PA. Outcomes of primary valve ablation versus urinary tract diversion in patients with posterior urethral valves. Urology. 2000; 56: 653-7.

13. Jaureguizar E, Lopez Pereira P,Martinez Urrutia MJ,Espinosa L, LobatoR. Does neonatal pyeloureterostomy worsen bladder function in children with posterior urethral valves? J Urol. 2000; 164(3 Pt 2): 1031-3.

14. Tayib AM, Alsayyad AJ. Management of obstructive uropathy with cutaneous ureterostomy in posterior urethral valve. Saudi J Kidney Dis Transpl. 2012; 23: 355-7.

15. Heikkila J, Holmberg C, Kyllonen L, Rintala R, Taskinen S. Long-term risk of end stage renal disease in patients with posterior urethral valves. J Urol. 2011;186: 2392-6.

16. Ghanem MA, Nijman RJ. Long-term followup of bilateral high (sober) urinary diversion in patients with posterior urethral valves and its effect on bladder function. J Urol. 2005; 173: 1721-4.

17. Akdogan B, Dogan HS, Keskin S, Burgu B, Tekgul S. Significance of age-specific creatinine levels at presentation in posterior urethral valve patients. J Pediatr Urol. 2006; 2: 446-52.

18. Chua ME, Ming JM, Carter S, ElHout Y, Koyle MA, Noone D, et al. Impact of adjuvant urinary diversion versus valve ablation alone on progression from chronic to end stage renal disease in posterior urethral valves: A single institution 15-year time-to-event analysis.J Urol. 2018;199:824-30.

19. Sarhan O, Zaccaria I, Maacher MA, Muller F, Vuillard E, Delezoide AL, et al. Long-term outcome of prenatally detected posterior urethral valves: single center study of 65 cases managed by primary valve ablation. J Urol. 2008; 179(1): 307-12.

20. Ziylan O, Oktar T, Ander H, Korgali E, Rodoplu H, Kocak T. The impact of late presentation of posterior urethral valves on bladder and renal function. J Urol. 2006; 175(5): 1894-7.

21. Hutton KA, Thomas DF, Irving HC, Arthur RJ, Smith SEW. Prenatal detection of posterior urethral valves: Is gestational age at detection a predictor of outcome? J Urol. 1994; 152: 698-701.

22. Kibar Y, Ashley RA, Roth CC, Frimberger D, Kropp BP. Timing of posterior urethral valve diagnosis and its impact on clinical outcome. J Pediatr Urol. 2011; 7:538-42.

23. Sarhan O, El-Dahshan K, Sarhan M. Prognostic value of serum creatinine levels in children with posterior urethral valves treated by primary valve ablation. J Pediatr Urol. 2010; 6: 11-4.

24. Ansari MS, Gulia A, Srivastava A, Kapoor R. Risk factors for progression to end- stage renal disease in children with posterior urethral valves. J Pediatr Urol. 2010; 6: 261-4.

25. Otukesh H, Sharifiaghdas F, Hoseini R, Fereshtehnejad SM, Rabiee N, Kiaiee MF, et al. Long-term upper and lower urinary tract functions in children with posterior urethral valves. J Pediatr Urol. 2010; 6: 143-7.

26. Nickavar A, Otoukesh H, Sotoudeh K. Validation of initial serum creatinine as a predictive factor for development of end stage renal disease in posterior urethral valves. Ind J Pediatr. 2008; 75:695-7.

27. Nimako B, Lazarus J, Dewan P, Nourse P, Gajjar P. Are early prognostic indicators reliable in posterior urethral valves management? African J Urol.2018; 24:243-7.

28. Lopez Pereira P, Martinez Urrutina MJ, Espinosa L, Lobato R, Navarro M, Jaureguizar E. Bladder dysfunction as a prognostic factor in patients with posterior urethral valves. BJU Int. 2002; 90:308-11.

29. Puri P, Kumar R. Endoscopic correction of vesicoureteric reflux secondary to posterior urethral valves. J Urol. 1996; 156; 680-682.

30. Sarhan OM, El-Ghoneimi AA, Helmy TE, Dawaba MS, Ghali AM, Ibrahiem el-HI. Posterior urethral valves: Multivariate analysis of factors affecting the final renal outcome. J Urol. 2011; 185: 2491-5.

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

Variables	**CKD(N = 12)**	**Non-CKD(N = 98)**	***P*- Value[a]**
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[b], 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

[a]: *P*-value <0.05 is significant.

[b]: Unilateral massive VUR into a dysplastic kidney.