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Original Article

The Impact Of Consanguinity On Severity Of Posterior Urethral Valve.

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ABSTRACT:

Background: Posterior urethral valve (PUV) is one of the frequent causes of obstructive uropathies at birth. When inadequately managed, it leads to vesicoureteric reflux disease, recurrence of UTIs, voiding disorder, and chronic renal insufficiency. These valves have been observed among siblings, twin children, and the subsequent generation. However, their occurrence rate and association with consanguineous have never been investigated.

Objective: To assess the frequency and impact of kinship on the severity of the posterior urethral valve at our center.

Study Design: A Retrospective Study

Place and duration of study: from Jan 2012 to April 2020 department of Urology MTI,LRH Peshawar

Material and method: in our study Patients were diagnosed via voiding symptoms, ultrasound, and confirmation by VCUG and cystoscopy. In all patients, the history of consanguineous marriage and any history of PUV in the family was acquired. All cases were evaluated for renal function with BUN and creatinine, including eGFR, as per Schwartz's formula. A nuclear scan was performed in all patients to rule out renal scaring and split renal function.

Results: The mean age of children who underwent valve fulguration was 4.34 + 2.7 years. Family history of first-degree cousin marriage was found in 56 (33.0%) patients. Statistical analysis of clinical parameters of the posterior urethral valve, including the degree of hydronephrosis, vesicoureteric reflux, and chronic kidney disease, showed that the product of cousin marriage had more severe disease.

Conclusion: One-third of PUV patients had a history of consanguineous marriages in this study. These cases develop early renal insufficiency as well as a more severe disease.

Keywords: Posterior urethral valve, Consanguinity, Severity, Renal insufficiency

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INTRODUCTION:

Cousin marriages are common in many societies, with an estimated worldwide cousin marriage rate of 10-18.5%.[1] In Pakistan, consanguineous marriages account for 38-59% in various studies. Furthermore, these marriages are more common among first-degree cousins (80%) and in rural families. [2] There is plenty of evidence regarding the association of consanguinity with congenital anomalies. The incidence of congenital malformation in cousin marriage is found to be as high as 38-59% 5, 6. The proportion of PUV Among the congenital malformations related to the kidney and urinary tract (CAKUT), the rate is between 2.1% and 36.4% [3]. In a study by Nabeel SB et al., 40.4% of fetuses with CAKUT were reported as products of consanguineous marriages. The incidence of the posterior urethral valve was reported as 1 in 8000 live births [4]. It's a life-threatening congenital anomaly affecting the urinary tract. If not timely managed with adequate procedure, it causes voiding dysfunction, vesicoureteral reflux, repeated urinary tract infections (UTIs)And various levels of insufficiency of the renal tract in one-half of these cases. In developed countries, with the availability of antenatal fetal ultrasonography, a significant number of cases are being diagnosed hydroureteronephrosis, and a persistently distended fetal bladder[6]. However, in our part of the world where antenatal care is not well established, most of the children with PUV present late after birth with obstructive lower urinary symptoms, UTIs, or failure to thrive. Endoscopic ablation of PUVs by using a cold knife or laser therapy is currently the gold standard treatment [7].Historically, posterior urethral valves have been observed in the siblings, in the twins, and subsequent generations, but their association with kinship has not been investigated. This study aimed to assess the impact of kinship on the posterior urethral valve in terms of disease severity[8].

MATERIAL AND METHODS:

This retrospective study was undertaken at Department of Urology Leading Reading Hospital Peshawar after getting Approval from the **Ethical Committee (MTI-LRH-IRB 2230-2019)**. Medical records of 168 PUV patients who had undergone posterior urethral valve fulguration were assessed from Jan 2012 to April 2020. The patients were evaluated initially, with voiding symptoms, ultrasound of kidney, ureter, and bladder (KUB), and voiding cystourethrogram (VCUG), during final confirmation of PUV was done under anesthesia with cystoscopy. A consultant oncologist performed ultrasonography, and their observation on the degree of hydronephrosis was graded as mild, moderate, and severe degree. The history of cousin marriages(first-degree) and history of PUV in the family was noted from each patient record. Laboratory evaluation included CBC, a urine dipstick and microscopy, urine culture, renal functions assessment with BUN and creatinine, and eGFR using the Schwartz formula. A nuclear scan was performed to rule out renal scaring and split renal function. The Kidney Disease & Outcome Quality Initiative (KDOQI) Group definition of Chronic Kidney Disease (CKD) was opted to classify renal damage. For analysis, the cohort was stratified into two groups according to the presence of consanguinity. Products of first-degree cousin marriages were assigned group A, while group B patients were products of cousins' marriages. Clinical parameters of disease severity, including the degree of hydronephrosis, grade of VUR, and grade of chronic kidney disease, were compared between the two groups. Data were entered and analyzed in t h e SPSS software version 17.0. The researched statistics were presented as tables of frequencies. The continuous variables were compared using the student's t-test, and the categorical variables using Chi-Square or Fischer's exact test. A p-value of < 0.05 was considered significant.

RESULTS:

A total of 168 patients were treated for posterior urethral valve. The mean age was 4.34 ± 2.7 years. Straining at voiding was the commonest symptom in 114 (67.8%), urinary tract infections in 112 (66.7%), poor stream in 123 (73.2%), and urinary dribbling in 102 (60.7%), while urinary retention was present in 35 (20.8%). The family history of the cousin's marriage (first-degree) was present in 56 (33.3%) patients (group A), while the remaining 112 (66.6%) had no cousin marriage (group B). Furthermore, PUV was found in 6 (3.5%) male siblings of the child having a family history of cousin marriage. As antenatal services in our part of the world are poor, only 48 (28%) patients were diagnosed with antenatal-based ultrasonographic findings of hydronephrosis and distended bladder. Out of the 48 boys, 17 (35%) had a Parental history of cousin marriage. Hydronephrosis at presentation was seen in 135 (80%) patients, with 47 (35%) patients having severe hydronephrosis. Out of these 47 patients with severe grade hydronephrosis, 33 (70%) patients had a family history of cousin marriage. When comparing severe hydronephrosis between the two groups, it was observed that an extreme degree of hydronephrosis was more prevalent in group A (p-value <0.002). (Table 1) Vesicoureteric reflux (VUR) on VCUG was seen in 80 (48%) patients. High-grade VUR was observed in 39 (49%) patients, and out of these, 21 (54%) were the product of cousin marriages. Bilateral reflux was observed in 35 (21%) patients, and out of these bilaterally refluxing patients, 23 (64%) had a history of consanguinity. On comparative analysis, high-grade VUR and bilateral VUR were significantly more in group A patients (p-<0.002). (Table 2) Chronic kidney disease was found in 49 (29%) patients at presentation. Of these, 21 (38%) had a history of consanguineous marriage. Severe renal insufficiency, having an eGFR of below 60, was found in 17 (10%) patients, out of which 11 patients had a history of consanguinity. When comparing the impact of kinship on renal insufficiency between the two groups, overall, the effect was statistically insignificant (p-value 0.068). However, when severe renal insufficiency (eGFR<60) was compared between the two groups, it was noted that children of cousin marriages had significantly more severe renal insufficiency (p-value 0.005). (Table 3).

Table I: Hydronephrosis

Patients n=168 (336 renal units)	Hydronephrosis present 135 (80%)		Hydroneph roses absent 33 (20%)	Severe hydronephr osis 47 (35%)	Mild to moderate hydronephrosis 88 (65%)
Group A	56 (33%)	47 (84%)	10 (30%)	33 (70%)	**13 (15%)**
Group B	112 **(67%)**	88 **(79%)**	23 (20%)	14 (30%)	**75 (85%)**

Table II: Vesicoureteric reflux (VUR)

	Patients n=168 (336 renal units)	VUR present 80 (48%)	VUR absent 88 (52%)	High- grade VUR 39 (49%)	Low- grade VUR 41 (51%)
Group A	56 (33%)	42 (75%)	14 (25%)	21 (37%)	**21 (37%)**
Group B	**112 (67%)**	**38 (34%)**	**74 (66%)**	**18 (16%)**	**20 (18%)**

Table: - III. Association of family history of cousin marriages with severity of posterior urethral valves

Severity parameters		Yes	No	P-value
Severe hydronephrosis	**Group A**	**33 (59%)**	**23(41%)**	**<0.002**
	Group B	**14 (12%)**	**98 (87%)**	
High-grade VUR (Grade 3-5)	**Group A**	**21 (37%)**	**35 (62%)**	**<0.002**
	Group B	**18 (16%)**	**94 (84%)**	
Bilateral VUR	**Group A**	**21 (37%)**	**35 962%)**	**<0.002**
	Group B	**14 (12%)**	**98 (87%)**	
Chronic kidney disease	**Group A**	**21 (37%)**	**35 (62%)**	**<0.068**
	Group B	**49 (29%)**	**119(71%)**	
Severe CKD (eGFR<60)	**Group A**	**11(20%)**	**45(80%)**	**0.005**
	Group B	**6 (5%)**	**106 (95%)**	

DISCUSSION:

The most frequent cause of congenital obstructive uropathy is PUV. When adequate and timely not intervened, it leads to vesicoureteric reflux, recurrence of UTI, and chronic renal insufficiency in as many as 65% of these cases[9]. Depending upon the severity of obstruction and availability of antenatal scans, approximately 60- 70% of cases are being diagnosed prenatally 12. In our series, most patients presented late, and their mean age was 4.34 ± 2.7 years due to a lack of regular antenatal scanning and the non-availability of pediatric urologyservices[10]. The majority of patients in other series presented during the first year of life 2, 14-16. Valve fulguration during early postnatal life has shown better preservation of renal function and possibly bladder dynamics[11]. Postnatally, children present either with obstructive symptoms like straining to void, poor stream, urinary dribbling, and retention or with features of infections including fever and sepsis[12]. In our study, the most common mode of presentation was a poor stream(73%), followed by straining at voiding (68%), urinary tract infection (67%), urinary dribbling (61%), and urinary retention (21%). Talabi AO et al. observed obstructive symptoms in 100% of patients and fever in 19%[13]. Other series have also reported obstructive as the commonest clinical presentation with poor stream in 43-91%, dribbling in 15- 51%, urinary retention in 25%, and urinary tract infections in 22- 60% of children 12,17,18. In our study, hydronephrosis at presentation was seen in 80% of patients, while 35% had severe hydronephrosis. Similar frequency (77-98%) has been reported in many series [14]. In most series, the Prevalence of vesicoureteric reflux in patients with posterior urethral valves has been said to be 35-72%, which is comparable to our results of 48% [15]. However, in some studies, the frequency of VUR was reported in 22-30% only Mirshemirani A et al., 16 and Rishikesh Velhal et al. reported bilateral VUR in up to 30%, with 64% having high grade (III-V), which is comparable to our study, 21% and 49%, respectively. Talabi AO et al· [16]. Chronic kidney disease was found in 29% of patients at presentation in our study, while in literature, it was observed in 36-90%14,16,18,23. Soliman et al. observed the posterior urethral valve as the cause of CKD in 60% of cases[17]. The overall prognosis of a rear urethral valve case depends on multiple prognostic indicators such as age at diagnosis, vesicoureteric reflux, and creatinine level. High-grade reflux is the most common condition involved with the occurrence of severe dysplasia and renal scarring, especially if the child develops febrile urinary tract infections. There is no clear relationship between VUR and renal failure. Few investigators have witnessed an association between VUR and poor renal outcomes, whereas many other studies have observed no such association[18,19]. In the study by Nasir AA et al., children with reflux have six times greater chances of developing impaired renal function at follow-up. Guru N et al.also reported a poor outcome in children having higher nadir creatinine ($p<0.001$), bilateral VUR ($p<0.05$), and UTIs ($p<0.05$) [20]. DeFoor W et al. reported that among 13% of patients who progressed to end-stage renal disease, 93% had VUR, 87% bladder dysfunction, and 80% increased nadir creatinine at presentation[21]. Similar findings were published by Aylin N et al., who found high-grade reflux was found to be significantly associated with CKD and ESRD. Pathologically, the posterior urethral valve is a congenital process occurring sporadically, with cases reported in brothers and future generations, but its occurrence and relationship with consanguineous marriage have not been assessed[22]. In our study, we observed that consanguinity was found in 1/3 of patients, which is quite high, probably because cousin marriages are more prevalent in our country. When comparing clinical parameters of disease severity between the two groups, it was observed that compared to group B, a severe degree of hydronephrosis (p-value <0.002), high-grade VUR, and bilateral VUR (p-<0.002) was more common in group A. Similarly, when comparing the impact of kinship on renal insufficiency between two groups, overall, the effect was statistically insignificant (p-value 0.068) [23]. However, when severe renal insufficiency (eGFR<60) was compared between the two groups, it was noted that children of cousin marriages had more severe renal insufficiency (p-value 0.005) (Table 3)

CONCLUSION:

This study highlights that a significant proportion of PUV patients have a history of consanguinity. These cases have very severe disease as well as early renal insufficiency. Further trials are needed to assess the true genetic association of diseases

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