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Research Article

The Familial Occurrence of Posterior Urethral Valve: A Possible Clue Towards Genetic Etiology

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Abstract

Purpose: Congenital Anomalies of Kidney and Urinary Tract (CAKUT) are a collective term used to denote anomalies affecting kidney and urinary system. Posterior urethral valve is one such anomaly affecting only boys (common cause of ESRD). Though CAKUT occur sporadically, 10% of these are known to develop in families, raising the possibility of genetic etiology. This study was to look for PUV occurring in siblings and review its genetic aspects.

Methodology: A retrospective review was conducted on 215 boys with PUV, treated over 10 years to look for possible siblings from same family affected with PUV. The clinical characters, family pedigree, imaging and surgical data of siblings with PUV were analyzed.

Results: 215 boys were treated for PUV and 187 were available for follow up. There were eleven boys from five families affected with PUV. The initially managed boys presented with bladder outlet obstruction and subsequent siblings were picked up antenatally or postnatally when they were clinically suspected to have bladder outlet obstruction. Two of the families had history of consanguineous marriage. Ten patients underwent endoscopic treatment and 1 child needed vesicostomy.

Conclusion: The exact etiology in causation of PUV is unknown. The predicted familial occurrence of CAKUT in ten percent of patients and our observation of five percent of PUV occurring in siblings warrants a relook into the genetic aspects of PUV.

Keywords: *Posterior Urethral Valves (PUV); Posterior Urethral Valves; Screening; Posterior Urethral Valves in Siblings; Familial Posterior Urethral Valves; CAKUT*

Introduction

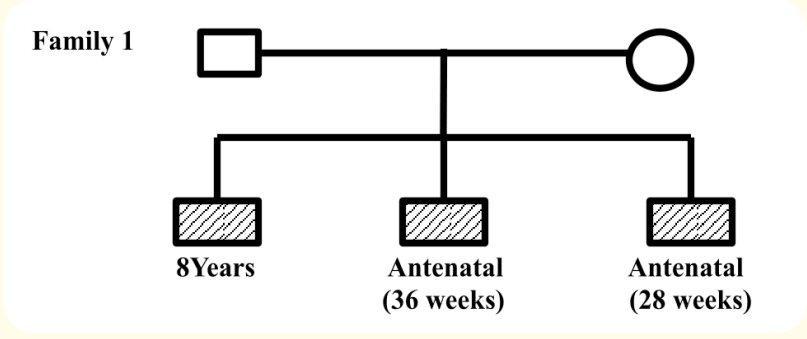
Congenital anomalies of kidney and urinary tract (CAKUT) represent 20% to 30% of all antenatally diagnosed fetal congenital anomalies in developed countries. These include developmental defects of both upper and lower urinary tract and 10% of these anomalies are known to occur in families [1]. Among CAKUT, renal hypodysplasia and Posterior urethral valves (PUV) are the most common indications for renal transplantation in children. Unlike other CAKUT, PUV are considered to occur sporadically with occasional case reports in siblings. The key event in development of renal tract is the interaction of ureteric bud and metanephric blastema, which is governed by various genes and environmental factors. The pathology in human CAKUT is a mixture of direct reduction in nephron number (primary effect), which may be irreversible and later bladder dysfunction (secondary effect), which can continue postnatally. Antenatal interventions in urinary tract obstructions have not improved prognosis, but early detection and intervention may reduce secondary effects of ongoing obstruction [2]. We came across 13 siblings from 6 families affected with PUV (6% of 215 children with PUV) over 10 years. Our series of familial PUV along with the reported familial PUV elsewhere, reiterates the possibility of genetic etiology in familial PUV.

Materials and Methods

This study was conducted in a tertiary care private hospital. The medical records of posterior urethral valves managed over 10 years in our institute were reviewed for possible siblings from same family being affected. Two hundred and fifteen patients were managed for PUV over 10 years (2005 - 2015) and 187 patients were available for follow up. Of the 187 patients, 81 (43.3%) patients had evidence of antenatal hydronephrosis (antenatal Group) and 106 (55%) patients presented postnatally (postnatal group), without prenatal renal tract dilatation. Micturating cystourethrogram (MCU) and cystoscopy confirmed PUV and patients underwent endoscopic valve ablation or diversion. Postoperatively all patients received prophylactic antibiotics (depending on VUR, a minimum of 3 months) and oxybutynin (0.2 mg/kg/day) till they were toilet trained or till they could understand double voiding/timed voiding. Follow up included urinalysis at 1 month and 3 months post-surgery and then 6 monthly for 4 - 5 years after which the frequency is reduced. Initial postoperative ultrasound was done at 3 months post-surgery and then every 3 - 6 months initially and then (depending on status of upper tracts and clinical progression) annually or once in 2 years.

Results

Retrospective chart review showed six families, with more than one sibling (a total of 13 patients) managed for PUV in the study period. Thus 6% of 215 patients managed for PUV occurred in families. Excluding one family with twin siblings (lost to follow up), 11 siblings from 5 families were studied. Four of the families had 2 siblings each affected with PUV and one family had all 3 male siblings affected. All the initially managed siblings presented with features of bladder outlet obstruction. The subsequent siblings presented after parents noticed voiding dysfunction or when the child developed UTI. Few of these patients were being followed for antenatal hydronephrosis and confirmed to have PUV during postnatal evaluation. The family pedigree of affected siblings is shown in figure 1. Two families had history of consanguineous marriage.



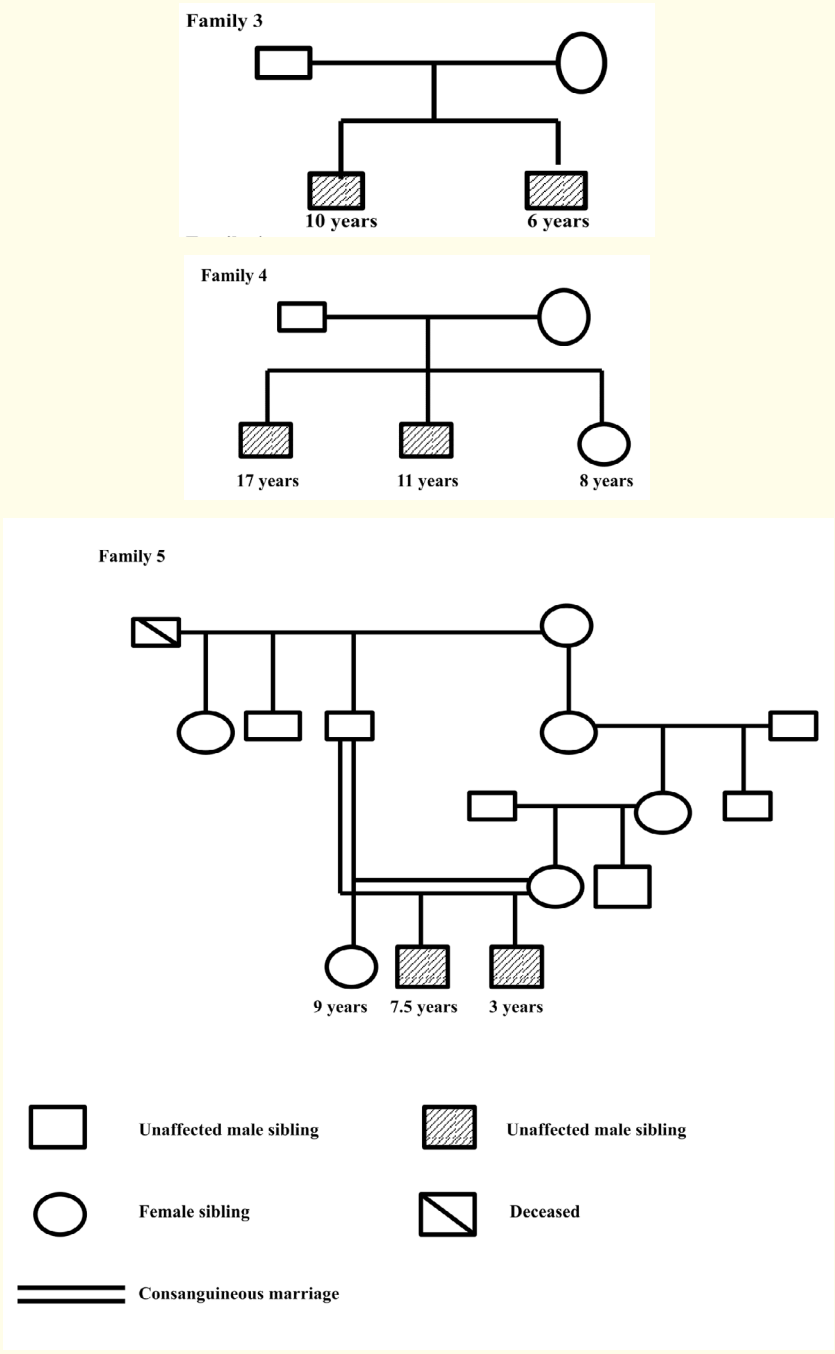


Figure 1: *Family Pedigree of siblings affected with PUV.*

The clinical characteristics of affected siblings are represented in table 1. The age (range) at diagnosis was 28 weeks (antenatal) to 9 years. Three siblings had antenatal hydronephrosis and others presented postnatally with features of bladder outlet obstruction. The mean (± standard deviation) initial creatinine was 0.42 mg/dl (0.65 ± 0.62) with a range of 0.28 - 2.5 mg/dl and nadir creatinine was 0.26 mg/dl (0.3 ± 0.08) with a range of 0.2 - 0.5 mg/dl. Cystourethroscopy and valve ablation was done in 10 patients and one child underwent

vesicostomy due to bleeding during valve ablation. At 8 months, this child with vesicostomy underwent closure with valve ablation. All the treated patients were on close follow up over duration of 1.5 years to 10 years (mean 8.8 years) with regular urinalysis, renal tract ultrasound and long term prophylactic antibiotics in those with vesicoureteral reflux. The nadir creatinine of one child who presented with renal failure (initial creatinine 2.5 mg/dl) is normalized and at last follow up all children have normal creatinine. Two patients had voiding dysfunction during follow up and repeat MCU and cystoscopy showed residual valve in 1 patient, which was re-ablated. The other patient has frequent daytime nighttime wetting and is under close follow up.

	Family 1			Family 2		Family 3		Family 4		Family 5	
Sibling	1	2	3	1	2	1	2	1	2		
Age at Diagnosis	36 weeks#	8 years	28 weeks#	9 years	3 years	2 years	32 weeks#	6 months	3 years	8 months	11 months
Peak Creatinine (mg/dl)	2.5	0.6	0.5	0.3	0.28	0.5	0.5	0.4	0.5	0.45	0.6
Nadir Creatinine (mg/dl)	0.5	0.3	0.2	0.35	0.2	0.36	0.3	0.3	0.35	0.28	0.24
Vesicoureteral reflux (VUR)	Right (Gr.4)	No	No	No	No	Right Gr.3	Bilateral Gr 2	No	Left Gr 2	No	Left Gr.4
Age at last follow up	7 years	15 years	1 year	15 years	9 years	10 years	6 years	17 years*	11 years	7.5	3 years
Voiding dysfunction	*yes	no	no	no	**yes	no	no	no	no	no	No

Table 1: *Characteristics of 11 affected siblings with PUV from 5 families.*

#Antenatal renal tract dilatation

**Has both day time and night time wetting*

***Transient voiding dysfunction-Had residual valve, which was ablated*

Discussion

Posterior urethral valves are a rare congenital anomaly causing bladder outflow obstruction in boys. The incidence of PUV is 1 in 4000 to 25000 live births and is generally considered a sporadic disease. Increased incidence of PUV has been diagnosed prenatally [3], non-twin siblings [4-6] and also in successive generations [7]. These cases of familial occurrence of PUV suggest possibility of genetic defect.

Congenital anomalies of kidney and urinary tract (CAKUT) and PUV: PUV is part of a conglomerate of anomalies known by the acronym-CAKUT [8]. CAKUT accounts for 40 - 50% of pediatric and 7% of adult end-stage renal disease worldwide [9]. Ninety percent of these occur sporadically and 10 % of these are known to occur in families (Familial CAKUT), except for posterior urethral valves, which occur sporadically. Among CAKUT, renal hypodysplasia and PUV are associated with highest need for dialysis and subsequent renal transplantation in children. There are also reports of occurrence of CAKUT in certain geographical areas and few reports of increased incidence of PUV in consanguineous marriages [9-11].

PUV Genetics: The genetic aspects of occurrence of PUV are not clear. There are many genes involved in development of normal urinary tract and abnormality in these genes may be involved in causation of renal tract anomalies. The renal anomalies are supposed to carry a common genetic cause [12]. Though the occurrence in families is low, a minor mutation of genes involved in normal embryogenesis is possible. While there are more than 20 genes identified in causation of Familial CAKUT [1], definite genetic defect in PUV is lacking. Evidence for genetic abnormality in PUV comes from few studies. A genetic association has been reported between renal damage in PUV and polymorphisms of two renin-angiotensin system genes, ACE (angiotensin converting enzyme) and AGTR2 (angiotensin II receptor type 2 [13]. Two conditions, prune belly syndrome (PBS) and urofacial syndrome mimic PUV at birth, where both show features of bladder outlet obstruction, with enlarged bladder and dilated upper tracts, though there is no evidence of valves. In both these conditions gene

mutations have been identified [14]. Weber., *et al*. [1] reported a homozygous loss of function mutation in CHRM3 (Cholinergic Receptor, Muscarinic 3) in five brothers from a single consanguineous family with four male descendants affected by PUV and one boy with Prune belly syndrome (PBS) and a healthy girl, suggestive of autosomal recessive inheritance. Two more gene mutations HNF1B (Hepatocyte nuclear factor-1-beta), encoding a transcription factor, and ACTA2 (Alpha actin 2), encoding a cytoskeletal protein, have been reported in PBS. Similarly in the urofacial syndrome, where mutations of LRIG2 (Leucine-Rich Repeats and Immunoglobulin-Like Domains 2) and HPSE2 (Heparanase-2), encoding proteins localized in nerves invading the fetal bladder, has been defined [14].

Submicroscopic chromosomal imbalances (Copy number variations-CNV) have been reported in a few studies of CAKUT. Caruana G., *et al*. [15] using single-nucleotide polymorphism (SNP) microarrays, screened 178 children presenting with the CAKUT and identified CNV in 10.1% (18/178) of the patients; in 6.2 % of the total cohort, novel duplications or deletions of unknown significance were identified, and the remaining 3.9 % harbored CNV of known pathogenicity. CNVs were inherited in 90 % (9/10) of the families tested and overall multicystic dysplastic kidney (30%) and posterior urethral valves (24%) had a higher incidence of CNV. Thus they suggested screening for CNV's in families with CAKUT.

Common theories of origin of CAKUT/PUV

Coexistence of upper and lower tract anomalies in CAKUT suggests that same genes expressed in upper urinary tract and lower urinary tract and mutations would disturb normal development of kidney and lower urinary tract. In experimental studies there is lack of coordination between severity of obstruction and dysplasia [7], suggesting that the renal parenchymal changes are due to abnormal interaction of ureteric bud to metanephric blastema and obstruction is an epiphenomenon. Thus abnormal budding [16] can lead to both renal as well as urinary tract pathology.

Though the exact embryo pathogenesis of PUV is unclear, the most accepted hypothesis is of wolfian or mullerian duct origin, first alluded to by Lowsley [17] and Stephens FD., *et al*. [17,18] proposed that type 1 valves are due to abnormal integration of mesonephric duct into urethra and defect of urogenital diaphragm in type 3 PUV . Mackie and Stephen's postulated that primary event in CAKUT occurs early in budding process. These changes during budding process impacts renal development and also can cause renal hypoplasia/dysplasia. Taken together initial maldevelopment due to impaired budding followed by obstruction causing further renal damage is possible.

Genes and signaling molecules involved in the regulation of budding, branching and kidney induction (e.g. Ret, Gdnf, Pax2, Bmp4 and etc.,) strongly supports the important theory of Mackie and Stephen's [1]. As an extension of budding theory, the same budding process -abnormal disintegration of wolfian duct may also be responsible for development of PUV (Figure 2), which has been proposed earlier [19].

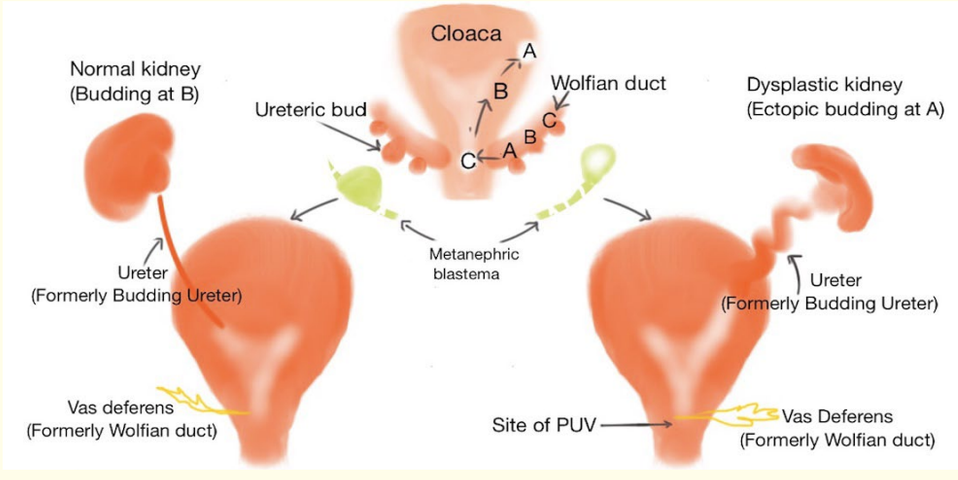


Figure 2: *Primary anomaly in CAKUT is abnormal budding. The interaction between ureteric bud and metanephric blastema is critical for the ontogeny of both ureter and metanephros, and abnormal interactions can result in various forms of congenital anomalies of the kidney and urinary tract (CAKUT) (reflux, hypodysplasia, obstruction, etc.). When the ureteric bud arises at normal site (B) it induces the metanephros to form normal kidney and when it arises at ectopic site (A) a dysplastic kidney develops. This can also explain the renal dysplasia associated with PUV where the abnormality of mesonephric duct causes PUV with inherent renal dysplasia and obstruction which ensues can further add to renal damage (Figure modified from Pope JC., et al) [7].*

Screening for PUV in siblings: Familial occurrence of PUV is rare, but considering the long term consequences of PUV, more research in genetic aspects of PUV is needed. Due to oligogenic nature of genes, genetic counseling is not practical except in those CAKUT with known gene mutation. Routine clinical (and imaging) screening for PUV in the siblings will shed light on the true incidence of asymptomatic PUV and also enables early diagnosis. The screening we recommend is serial antenatal ultrasound starting in second trimester and if there is any evidence of urinary tract dilatation or megacystitis, they are followed postnatally with serial renal ultrasound and urinalysis. If there is doubt of PUV (clinically) or when there is increasing renal tract dilatation on subsequent scans, they are subjected to micturating cystourethrogram (MCU) early. In siblings without antenatal renal abnormalities, a clinical assessment and renal ultrasound may be recommended in all male siblings and parents are advised to keep a watch on any change in voiding pattern. By screening, delayed diagnosis is avoided and the good prognostic disease can be managed appropriately.

Limitations to Our Study

Small sample size. We haven't done genetic studies in our cohort of familial PUV.

Conclusion

The exact etiology of posterior urethral valve is unknown. Familial occurrence of posterior urethral valve, may point towards a genetic etiology. The high propensity for these patients to develop end stage renal disease is a cause for concern. Though no known genetic mutations have been identified in causation of PUV, their occasional occurrence in siblings may be an indication for routine screening. By routine screening of male siblings, PUV can be detected early and early initiation of treatment may confer a better prognosis.

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