Congenital anomalies of kidney and urinary tract in siblings: An uncommon condition

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ABSTRACT

Congenital anomalies of kidney and urinary tract (CAKUT) are important causes of chronic kidney disease (CKD) in childhood. Most do not have a definite identifiable genetic defect and occur in isolation. Rarely, familial occurrence of CAKUT has been reported. The burden of CKD to a family in a developing country is enormous, and if more than one child is afflicted with the condition, the situation is almost catastrophic. We present here two families with siblings having upper and lower urinary tract obstruction.

Key words: Bilateral pelviureteric junction obstruction, congenital anomalies of kidney and urinary tract, obstructive uropathy

Introduction

Congenital anomalies of kidney and urinary tract (CAKUT) occur in about 0.5% of all pregnancies and contribute to almost 50% of abdominal masses detected in infancy.[1] These include pelviureteric junction obstruction (PUJO), multicystic dysplastic kidneys, single kidneys, vesicoureteric reflux, duplex systems, and obstructive uropathies. Anomalies such as PUJO and multicystic dysplastic kidneys are mostly unilateral. End-stage renal disease due to CAKUT is a common childhood presentation. Although genetic defects have been identified for some structural anomalies occurring with syndromes, most CAKUT occur in isolation. It is rather unusual to see CAKUT in siblings. We present here two families having two siblings each afflicted with CAKUT, one with bilateral PUJO and the other with posterior urethral valves (PUV).

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Case Reports

Case 1: Bilateral pelviureteric junction obstruction in two brothers

A 5-year-old boy presented to the outpatient department with recurrent abdominal pain and fever off and on for the last 6 months. General physical and systemic examination of the child was normal. Urine examination revealed pyuria and urine culture grew *Escherichia coli*. Blood urea and serum creatinine levels were 35 mg/dL and 0.6 mg/dL, respectively. The urinary tract infection was treated with appropriate antibiotics and further evaluation was carried out. Ultrasonography of the abdomen revealed right-sided hydronephrosis with suspicion of PUJO; the left kidney appeared normal. The micturating cystourethrogram (MCUG) did not reveal any abnormality. A radionuclide scan showed bilateral obstructive hydronephrosis with moderate impairment of the left kidney. The child underwent a pyeloplasty of the left kidney followed by pyeloplasty of the right kidney 3 months later. A Diethylene triamine penatacetic acid (DTPA) scan after 8 months of surgery showed mild hydronephrosis of both kidneys with preserved parenchymal function and slow but non-obstructed drainage pattern (differential function: Right kidney 49%, left kidney 51%). Subsequently, the child has been under regular follow-up of our pediatric nephrology clinic. At present, the child is 13 years old and has CKD stage 3 (estimated glomerular function rates (eGFR) 50 mL/min/1.73 m^2 by Schwartz formula).

The younger sibling of this patient presented with

bilateral antenatal hydronephrosis detected in the second trimester of pregnancy. The child was born at term of a non-consanguineous marriage. Postnatal investigations confirmed bilateral PUJO. The first postnatal ultrasound showed bilateral hydronephrosis with right kidney measuring 5.2 × 3 cm in size and left kidney 6.6 × 3.8 cm in size without ureteric dilatation. The MCUG was normal. The DTPA scan at 45 days of age revealed right kidney with well-preserved function with obstructive hydronephrosis and grossly enlarged left kidney with moderately impaired function and obstructive hydronephrosis (differential function: right kidney 64% left kidney 36%). The child underwent pyeloplasty of the left kidney at 2 months of age and pyeloplasty of the right kidney at 8 months. A DTPA scan 1 year after surgery showed both kidneys with normal function and partial mechanical obstruction; differential function of right kidney was 45% and left kidney 55%. Subsequent scans have also shown similar findings. This child is now 8 years old and is on regular follow-up at our clinic (CKD stage 1). The family has another male child aged 17 years who has no renal abnormality. The ultrasounds of both parents revealed no abnormality.

Case 2: Posterior urethral valves in two brothers

A 10-year-old boy presented with anemia. He gave a history of straining during micturition for the last few years. He was hypertensive (BP 130/90 mmHg). General physical and systemic examination was normal. Investigations revealed hemoglobin of 7.5 gm/dL with normocytic, normochromic anemia. His blood urea and serum creatinine levels were 78 mg/dL and 2.3 mg/dL, respectively, and venous blood gas revealed acidosis. An ultrasound of the abdomen revealed right kidney of 14.7 × 8.8 cm and left kidney of 13.4 × 6.8 cm in size, with gross hydroureteronephrosis and significant post-void residue of urine in the bladder. An MCUG showed irregular bladder outline with multiple sacculations and small diverticuli and dilated posterior urethra. The DTPA scan showed bilateral enlarged hydronephrotic kidneys with near-normal function. The child underwent valve fulgration. At present, this child is 16 years of age and has CKD stage 3 (eGFR 32 mL/min/1.73 m^2). He is hypertensive. He is on conservative management (supplements and antihypertensive) for his renal failure.

A younger brother of this patient was evaluated for short stature and generalized weakness at 6 years of age. An ultrasound showed right kidney of 3 × 1.6 and left kidney of 8 × 4.5 cm, with dilated upper ureters. An MCUG showed irregular large bladder with narrowed posterior urethra. The DTPA was suggestive of nonfunctioning right kidney and mild to moderate impairment of left kidney with non-obstructive hydronephrosis. The child underwent cystoscopic fulgration of the valves. Since then, the child is on regular follow-up and is 11 years old now. He has CKD stage 4 (eGFR 26 mL/min/1.73 m^2) and is on conservative management. The ultrasound scan of the abdomen of other siblings (one brother and sister) and both parents, who have a non-consanguineous marriage are normal.

Discussion

Based on end-stage renal disease data from different registries, CAKUT contributes to CKD in 45-60% of the pediatric patients.[2] Non-syndromic CAKUT is more frequent. CAKUT includes a wide spectrum of anomalies such as renal hypoplasia, dysplasia, horse shoe kidney, ectopic kidney, PUJO, vesicoureteric reflux, megaureters, obstructive uropathy, and neurogenic bladder. The overall incidence of CAKUT in all pregnancies is around 0.5%, with a higher predisposition in male fetuses.[1] Familial occurrence of the condition is rather uncommon.

Various theories have been proposed for the occurrence of a wide anatomical spectrum of renal anomalies. These include a stress on the developing kidney due to partial obstruction of the outflow tract and ectopic budding of the ureters from the Wolffian ducts. Recently, it has been proposed that a primary defect in the interaction at the cellular level between the ureteric bud and metanephric mesoderm may result in CAKUT.[3] Although developmental errors in many areas can result in CAKUT, the most implicated processes are induction of metanephric kidney, establishment of urinary conduit, and maturation of pyeloureteral peristaltic mechanisms.[4] Anomalies in metanephric kidney induction may result in renal hypoplasia, renal agenesis, ectopic and supernumerary ureters and a range of other defects. Glial-derived neurotrophic factor (GDNF) is one of the most important proteins expressed in the metanephric mesenchyme. This along with another receptor GDNF-family receptor α1 is involved in induction of ureteric bud growth. Mutations of this gene result in renal agenesis or severe dysplasia. Vitamin A-dependant Ret gene is involved in ureteric growth and its abnormality may result in upper urinary tract obstruction. The pyeloureteral persistaltic mechanisms are primarily initiated by pacemaker cells that are likely to be specialized smooth muscle cells in the renal pelvis and ureters. Abnormality of these may result in PUJO and megaureters.[4]

A number of syndromes that involve multiple organ anomalies, including that of the kidney and urinary tract, have been identified with specific inheritance patterns.

However, the genetics of isolated CAKUT are less well defined. PAX 2, a paired-box transcription factor gene, has been identified as the first specific gene associated with the occurrence of CAKUT, especially vesicoureteric reflux.[5] Abnormalities of another gene angiotensin2 receptor (Agtr2) have been recently shown to be associated with the occurrence of CAKUT.[6]

Most patients having pelviureteric junction abnormalities have a unilateral lesion. Occurrence of bilateral PUJO is rare. We came across only a single case report of siblings with pelviureteric junction abnormality.[7] The siblings in the present report had bilateral PUJO. Bilateral pyeloplasties stabilized the renal disease in both brothers.

Posterior urethral valves are the most common cause of lower urinary tract obstruction in boys. This condition is observed in 1 in 8,000-25,000 births. About one-third of all children born with PUV progress to end-stage renal disease. Ten cases of PUV in two siblings and 13 cases in twins have been identified in the literature till date, often with a variable phenotype.[8-10]

Genetic factors in PUV are poorly understood. Recessive inheritance in a subgroup of patients with PUV is supported by a higher incidence of the condition in populations with an elevated background rate of consanguinity.[11] Our patients were, however, born of a non-consanguineous marriage.

Screening of family members, especially siblings, is recommended for renal cystic diseases, vesicoureteric reflux, or a family history of renal disease. A sonography of the abdomen is often sufficient as a screening tool for identifying CAKUT. Antenatal screening is especially important if a previous child was born with CAKUT. A good level II scan in the second trimester can identify most renal and urinary tract abnormalities. Genetic counseling is recommended for all patients with familial cases of CAKUT or newly diagnosed forms of CAKUT that suggest the presence of genetic anomalies.[6] Conditions such as PUJO or PUV are less likely to recur. However, if more than one child in the family is afflicted, the others too should be screened.

To have siblings with CKD imposes a great burden of care on the family, especially in a resource-poor setting like ours. The ideal management in such a situation is aimed at preventing the progression of CKD by early surgical intervention, treatment of hypertension, and correction of anemia and acidosis. In view of the limited finances of both these families, any form of renal replacement therapy is not feasible in the near future.

To conclude, the occurrence of similar structural abnormalities in these siblings is probably a result of genetic and other modifying influences, rather than a mere coincidence.

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