CLINICAL AND MORPHOLOGICAL SPECTRUM OF CONGENITAL ANOMALIES OF KIDNEY AND URINARY TRACT (CAKUT) - A TERTIARY CARE CENTER EXPERIENCE

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ABSTRACT

Objective: To determine the type, frequency and clinical presentation of congenital anomalies of kidney and urinary tract in children.

Study Design: Cross sectional study.

Place and Duration of Study: Pediatric Nephrology Unit of the Children's Hospital and Institute of Child Health Lahore, from Mar 2018 to Feb 2019.

Methodology: All patients from birth to 18 years of either gender with suspicion of congenital anomalies of kidney and urinary tract presenting to Pediatric Nephrology unit with different clinical manifestation were enrolled for study. All the children were subjected to detailed history and physical examination including age, gender, height, weight and associated anomalies of other systems while screening ultrasound was carried out with other radiological investigations accordingly.

Results: One hundred and forty subjects were enrolled in the study with male to female ratio = 3:1. The mean weight and height of children were 13.35 ± 9.35 kg and 89.66 ± 29.95 cm respectively.

Total 85 (60.7%) patients were product of consanguineous parents while 12 (8.6%) were premature and 31 (22.1%) were small for gestational age (SGA). There was history of birth asphyxia in 4 (2.9%) subjects while mothers of 6 (4.3%) were diabetic at the time of conception. Patients had diverse clinical presentation - the most common being urinary tract infection (UTI) seen in 67 (47.86%) while 32 (15.7%) subjects had associated anomalies of other systems. Most common primary anomaly was vesicoureteic reflux (VUR) 83 (59.3%).

Conclusion: The most common type of congenital anomalies of kidney and urinary tract seen in our patients was vesicoureteic reflux. Majority of children presented in infancy with urinary tract infection being the clinical presentation in two-thirds subjects.

Keywords: Clinical spectrum, Congenital anomalies, Kidney and urinary tract.

INTRODUCTION

Congenital anomaly or malformation is a structural defect in body due to abnormal embryonic or fetal development. Congenital Anomalies of Kidney and Urinary Tract (CAKUT) are among most common malformations occurring in 1:500 live births and are responsible for 20-30% prenatally detected anomalies[1]. The incidence of neonatal deaths is 1:2000 births[2] and 34–59% cases have led to chronic kidney disease (CKD)[3] with obstructive uropathy being the most common abnormality[4]. In most of cases CAKUT occurs in isolated form but can be a part of a genetic syndrome, a chromosomal disorder, or an inborn error of metabolism involving other systems of body. It is often asymptomatic and can be a significant cause of morbidity and mortality in children[5] as severe cases (bilateral aplasia, hypoplasia, dysplasia, obstructive and reflux uropathy) cause end-stage renal disease (ESRD) in about 50% cases[6,7]. As environmental and genetic factors contribute to majority of cases, renal abnormalities have been detected in ~10% close relatives of CAKUT patients[8]. Several human gene mutations have been identified and associated with syndromic and non-syndromic CAKUT[9].

In literature there is little description about warning signs and symptoms of urinary system impairment. The clinical presentation of CAKUT is variable. Some patients are diagnosed antenatally during anomaly scan while others remain

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asymptomatic till adolescence. Similarly there is acute versus chronic presentation. Common upper urinary tract symptoms include polyuria, nocturia, short stature/failure to thrive, systemic hypertension and urinary tract infection[10]. Lower urinary tract symptoms such as urgency, frequency, dysuria, straining, poor urinary stream, urinary retention and incontinence indicate a need for the evaluation of lower urinary tract.

As CAKUT is the most common cause of CKD in children[11], paucity of local data forms the basis of our study to determine the diverse clinical presentation and morphological spectrum of CAKUT in our center. Timely detection can help in early intervention and reduction in morbidity and delay in ESRD.

METHODOLOGY

This one year cross sectional observational study was conducted at Pediatric Nephrology Department of The Children's Hospital & the Institute of Child Health Lahore, Pakistan from 1st March 2018 to 28th February 2019 after approval from the Institutional Review Board following tenets laid down in Declaration of Helsinki 2011 (ref#16789). Informed written consent was obtained from parents of the patients. All patients from birth to 18 years of either gender with suspicion of CAKUT presenting to Pediatric Nephrology unit with different clinical manifestations were recruited for study. The sample size of 140 cases was calculated with 90% confidence level, 6% margin of error and taking expected percentage of CAKUT 25%[1] in patients presenting to pediatric nephrology unit of the Children's Hospital and Institute of Child Health, Lahore using raosoft sample size calculator. Sampling technique was non probability consecutive sampling. All the children were subjected to detailed history and physical examination including age, gender, height, weight and associated anomalies of other systems while screening ultrasound was carried out with other radiological investigations accordingly. The indices measured by renal ultrasonogram (USG) included 1) number, size and location of kidneys 2) renal cysts 3) dilatation of urinary tract and 4) morphology of urinary bladder. Other diagnostic imaging studies like Voiding Cystourethrogram (VCUG), intravenous urogram (IVU), Dimercaptosuccinic Acid (DMSA) scan, Diethylenetriamine Pentaacetic acid (DTPA) scan, mercaptoacetyltriglycine - 3 (MAG-3) scan, Computerized Tomography (CT) scan and Magnetic Resonance Imaging (MRI) were applied in subjects with suspected Vesicoureteic Reflux (VUR), Uretero-Pelvic Junction Obstruction (UPJO) and other structural defects accordingly. Children having renal cysts with primary diagnosis of nephronophthisis and neurogenic bladder with spinal dysraphism were excluded from the study. Diagnosis of CAKUT was based upon detailed history and clinical examination and confirmed by radiological investigations.

CAKUT were classified into renal, upper urinary tract and lower urinary tract anomalies. Renal anomalies were further classified into renal mass, cystic and positional anomalies. Upper urinary tract anomalies were divided into VUR, megaureter and UPJO. Lower urinary tract anomalies were divided into anomalies of urinary bladder, urethra, urinary tract fistulae and urogenital sinus[12].

a) Renal anomalies of mass and position such as renal aplasia/hypoplasia, ectopic kidney, horseshoe kidney, duplex-collecting system were diagnosed on renal ultrasonogram (USG).

b) Multicystic dysplastic kidney (MCDK) was diagnosed by USG with presence of multiple non-communicating cysts, minimal or absent renal parenchyma and the absence of a central large cyst (unilateral kidney) and confirmed by DMSA renal scan showing minimal/no function.

c) Autosomal recessive polycystic kidney disease (ARPKD) was diagnosed by the presence of enlarged kidneys with multiple bilateral renal cysts on USG with parental consanguinity (absence of cystic disease in parents) and/or hepatic involvement and/or previously affected sibling.

d) Ureteropelvic junction obstruction was defined by an obstructive pattern on MAG-3 diuretic renography i.e., a curve that rises continuously over 20 minutes or plateaus, despite furosemide administration and post-micturition.

e) Vesicoureteic reflux (VUR) was classified into 5 grades by VCUG findings. Classification of primary and secondary VUR was based on associated urinary bladder anomalies. Primary VUR was defined as absence of evidence of bladder outlet obstruction and neurogenic bladder while secondary VUR was associated with obstructive uropathy.

f) Megaureter was diagnosed by USG as ureteric dilation and confirmed by IVU which showed the pathognomonic configuration of a dilated distal ureteric spindle, a less dilated proximal ureter and a dilated or relatively normal appearing renal pelvis.

g) Anomalies of urinary bladder including diverticula and hypoplasia were diagnosed on USG and confirmed by VCUG and cystoscopy.

h) Urogenital sinus was diagnosed on clinical examination of female child by the presence of two perineal orifices (one anal and other urogenital sinus) and confirmed by genitography.

i) Urinary tract fistulae and urethral stenosis were diagnosed on clinical examination and cystography.

j) Diagnosis of PUVs was established by VCUG showing dilation/elongation of posterior urethra with trabeculation of urinary bladder and confirmed by cystoscopy.

k) Urethral diverticulum was diagnosed by VCUG.

Patients with CAKUT had diverse clinical manifestations depending upon underlying pathology. We categorized clinical presentation into end stage renal disease[13], acute kidney injury[14], UTI[15], recurrent abdominal pain[16], urinary incontinence[17], failure to thrive[18], polyuria[19] and poor urinary stream[20].

Data was collected on a specially designed proforma and was analyzed using SPSS version 20.0. Mean and standard deviation (SD) were calculated for quantitative variables and categorical variables were summarized through frequencies and percentages.

RESULTS

The study group consisted of 140 children who were postnatally diagnosed as having CAKUT - 105 (75%) males and 35 (25%) females (male to female ratio=3:1). All patients were divided into 4 groups according to age ranging from birth to 18 years, 44 (31.4%) participants presented in infancy, 48 (34.3%) subjects were between 1-5 years of age, 40 (28.2%) children were 6-12 years of age at presentation and only 8 (5.7%) patients were adolescents (13-18 years). The mean ± SD height and weight of the subjects was 89.66 ± 29.95 cm and 13.35 ± 9.35 kg respectively. Frequencies of various antenatal and perinatal risk factors are described in table.

Screening ultrasound was carried out in all patients and various imaging modalities were used for diagnosis of CAKUT. VCUG was performed in 119 (84.4%), DTPA renal scan carried out in 41 (29.1%) and DMSA renal scan was used for detection of renal parenchymal focal defects in 30 (21.3%) participants. Other radiological investigations included MAG-3 renal scan in 15 (10.6%), CT scan in 8 (5.7%), MRI in 10 (7.1%) and IVP in 10 (7.1%) subjects while 26 (18.4%) children underwent cystoscopy.

Table: Frequency of antenatal and perinatal risk factors in CAKUT.

Antenatal factors	Frequency (n=140) Percentage (%)
Consanguinity	85 (60.7%)
Prematurity	12 (8.6%)
Birth asphyxia	4 (2.9%)
Oligohydramnios	23 (16.4%)
Small for gestational age	31 (22.1%)
Maternal diabetes mellitus	6 (4.3%)

The clinical presentation in 67 (47.86%) children was urinary tract infection followed by recurrent abdominal pain in 15 (10.71%) (fig-1).

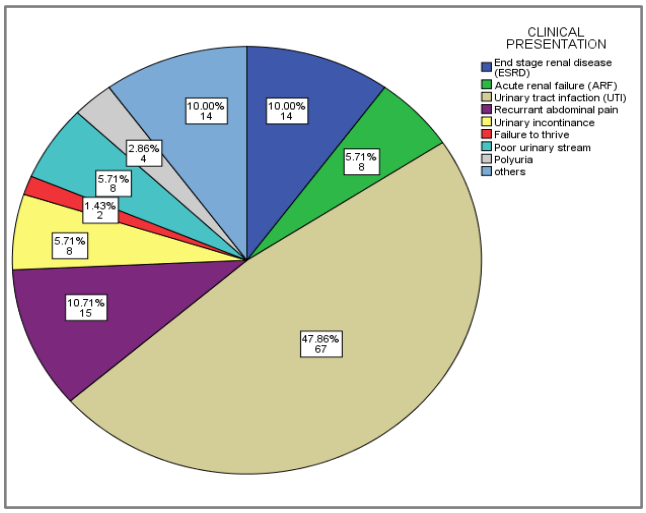

Figure-1: Clinical presentation of congenital anomalies of the kidney and urinary tract.

Associated malformations of other systems were observed in 32 (15.7%) patients (fig-2).

The most common urinary tract anomaly seen in our series was VUR 83 (59.3%). Secondary VUR was more common 50 (35.7%) than primary VUR 33 (23.5%). Secondary VUR was found to be

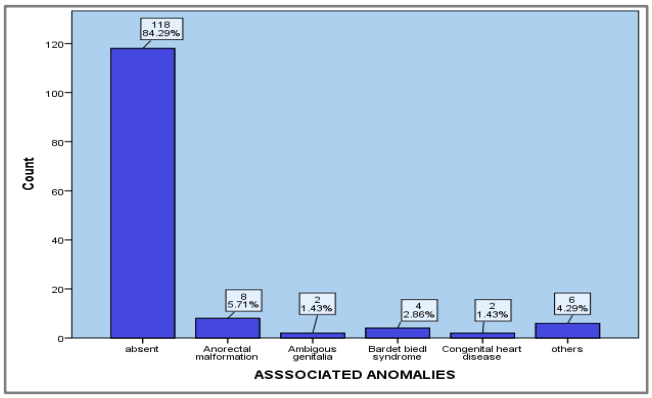

Figure-2: Association of CAKUT with other congenital anomalies.

bilateral more frequently 32 (22.8%) while unilateral VUR was more common in primary cases 23 (16.4%). Among bilateral cases of VUR grade IV reflux was more common both in primary 6 (4.3%) and secondary 16 (11.4%) types while in unilateral cases grade IV was more common among secondary type 6 (4.3%) and grade V in primary type 5 (3.6%). Left sided reflux was more common than right sided reflux.

Second most common anomaly was PUVs 48 (34.3%) while bladder diverticula being 3rd most common anomaly in our series 18 (12.9%) which were commonly associated with bladder outlet obstruction (fig-3).

DISCUSSION

Congenital anomalies of the kidney and urinary tract (CAKUT) is an important cause of morbidity in children and constitute approximately 20 to 30 percent of all anomalies identified in the prenatal period during routine antenatal ultrasonography[1]. The most common causes of CKD and ESRD in children are diseases related to CAKUT accounting for 30 to 50% cases[2], followed by glomerular disease, neurogenic bladder, and other disorders, so early recognition of these anomalies with timely intervention is necessary to delay the progression to ESRD.

Small for gestational age (SGA) and prematurity were seen in 22.1% and 8.6% respectively in contrast to Frank *et al*[21] who concluded that rates of prematurity and SGA were elevated in children with congenital CKD being 39.3% and 29.2% respectively. Another cohort showed a very low incidence (7%) of SGA in children with CAKUT[22].

The male to female ratio in our subjects was 3:1 as compared to studies by Radhakrishna *et al* and Zhang *et al* which revealed higher incidence of CAKUT in males (M:F = 6.4:1 and 4.26:1) respectively[23,24].

Renal tract malformations are sporadic but can be inherited as specific mutations of renal tract developmental genes found in some affected individuals. In our study positive family history of CAKUT was present in 9 (6.4%) patients.

Clinical presentation was variable with some patients presenting just after birth because of suspicion of anomaly detected on antenatal scan while 31.4% presented in infancy. All our parti-

cipants were postnatally diagnosed as CAKUT and Gong *et al* used a three level screening model as an effective strategy for early detection of CAKUT in the postnatal period (0.02% new-born)[1]. The most common clinical presentation in our study was urinary tract infection present in 47.8% subjects while 10% participants presented systems is necessary to diagnose a syndrome. We identified Bardet Biedl syndrome (obesity, pigmentary retinopathy, polydactyly and mental retardation) in 4 (2.8%) patients while anorectal malformation was most commonly associated extra renal anomaly present in 8 (5.7%) patients.

The phenotypic spectrum of CAKUT is

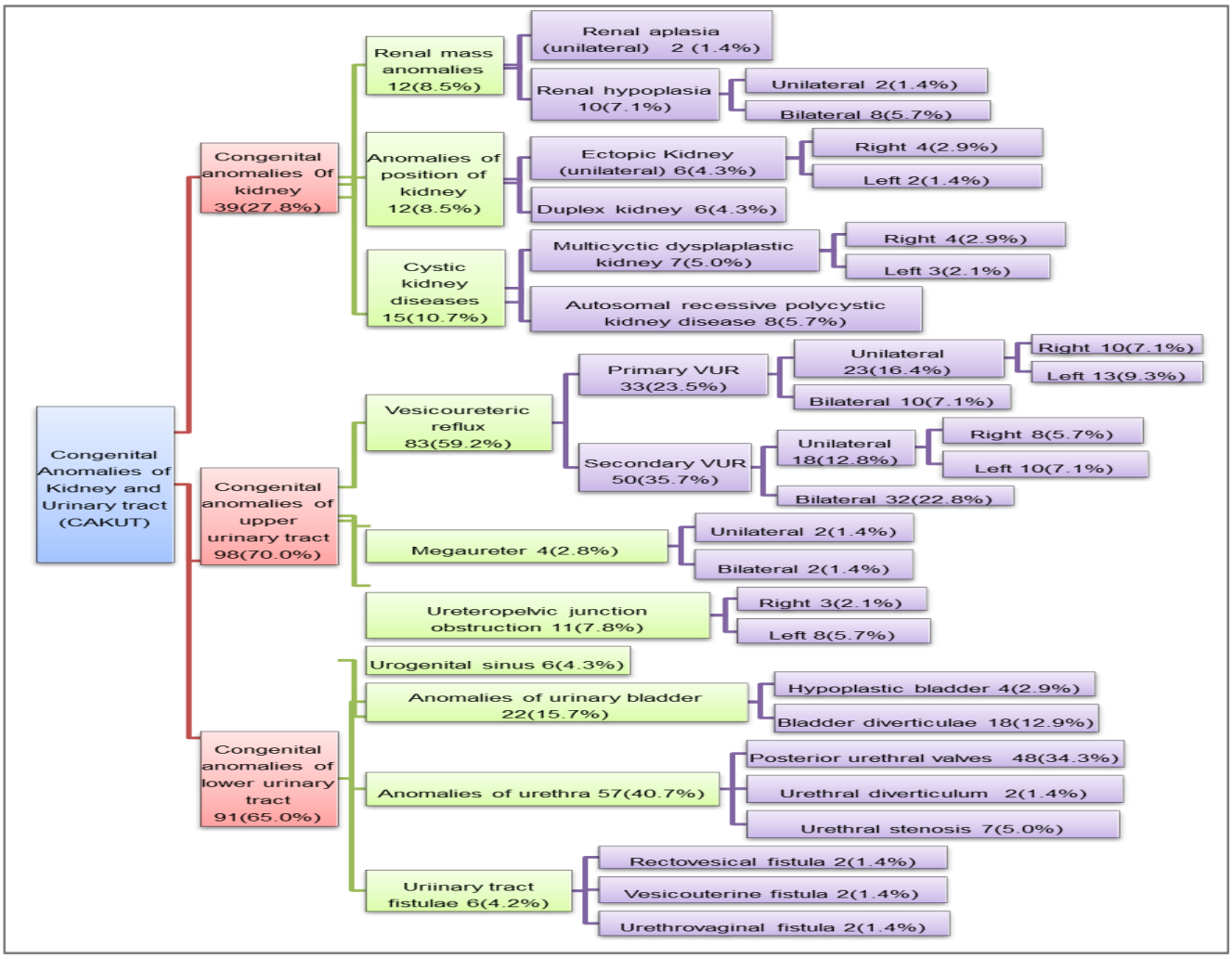

Figure-3: Distribution of congenital anomalies of the kidney and urinary tract among various patients.

with ESRD as was also observed by Ashraf *et al* who concluded that 15% children with CAKUT had CKD[25]. According to Radhakrishna *et al*, 23 (32%) children were asymptomatic as compared to our data which showed that none of the subjects were asymptomatic.

Many dysmorphic features are associated with CAKUT. So careful assessment of all organ extremely broad. Congenital abnormalities of the kidneys and urinary tract present a family of diseases of various anatomical profiles, including renal anomalies, and anomalies of the bladder and urethra. In our study we observed that the most common anomaly was VUR 83 (59.25%) while PUVs being 2nd most common anomaly 48 (34.3%). This was similar Kumar *et al* where primary VUR was most common anomaly being

present in 27.3% patients[12]. Similarly results were also comparable to conclusion drawn by Radhakrishna *et al* showing PUJO and PUVs to be the commonest types of CAKUT (40% and 32% respectively)[23].

CONCLUSION

Our study created a database of children with CAKUT and VUR was seen to be the most common anomaly. Majority of patients presented in infancy with UTI being the clinical presentation in almost two-third subjects. Multi disciplinary approach with contribution from obstetrician, general practitioner, urologist and nephrologist is need of hour for management of CAKUT. We lack long-term followup in individuals born with different types of CAKUT in this study. Identification of gene mutations involved in renal tract development can also help to predict the outcome.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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