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Original Article

Clinical characteristics of children with congenital anomalies of kidney and urinary tract and predictive factors for Chronic Kidney Disease in a tertiary hospital, Addis Ababa, Ethiopia

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Abstract

Background: *Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading causes of chronic kidney disease (CKD) in childhood. Determining the clinical course, outcome, and prognostic factors of this heterogeneous group of diseases is important to provide appropriate management and follow-up. Therefore, we aimed to identify the risk factors of CKD in CAKUT and the differences in clinical courses between subtypes of CAKUT.*

Methods*: a retrospective cross-sectional study was done in 134 patient records diagnosed with congenital kidney and urinary tract anomalies. They were categorized with subtypes of CAKUT and a chi-square test and logistic regression analysis were done to determine risk factors for CKD and the result is presented in tables.*

Results*: Among the 134 patients, males were 107 (79.9%) and the commonest subtypes of CAKUT were posterior urethral valve in 42 (31.3%), ureteropelvic junction obstruction in 28 (20.9%), multicystic dysplastic kidney in 24 (17.9%). The median age of the study population at the time of diagnosis was 2.5 yrs. Among available 50 prenatal ultrasounds, the most frequent diagnoses were hydronephrosis in 38 patients (28.4%) and MCDK in 9 patients (6.7%). A total of 21(15.7%) patients had CKD and 6 of them (4.5%) progressed to end-stage kidney disease (ESRD). The multivariate logistic regression analysis identified proteinuria on follow-up as an independent risk factor for CKD. (p=0.004)*

Conclusion: *Posterior urethral valve is the commonest congenital anomaly of the kidney and urinary tract and proteinuria is an independent risk factor for CKD.*

Keywords*: CAKUT, chronic kidney disease, proteinuria, end-stage kidney disease*

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Introduction

Congenital anomalies of the kidney and urinary tract (CAKUTs) are some of the most common birth defects in newborns. CAKUT is characterized by structural and functional abnormalities of the kidney, collecting system, bladder, and urethra (1-7). The overall prevalence of congenital anomalies of the kidney and urinary tract in live and stillborn infants is 0.3 to 1.6 per 1000 (2)

CAKUT has been identified in 20% to 50% of all fetal congenital anomalies in some populations, but the causes remain unclear. Although children with CAKUT are often asymptomatic, CAKUT is estimated to be implicated in 30% to 60% of cases of childhood-onset chronic kidney disease (CKD) in different populations. (3) The incidence is higher in offspring with a family history of CAKUT and a maternal history of either kidney disease or diabetes (3, 4).

CAKUT are the most common cause of end-stage renal disease (ESRD) in children accounting for 50–70% of those who begin renal replacement therapy (RRT) worldwide (4-6). The severity of kidney function impairment at the time of presentation, and the presence of co -morbidities at birth like pulmonary hypoplasia, infection, and associated genetic abnormalities were prognostic indicators of progression to CKD. The great majority are diagnosed prenatally or within the first months of life. Most challenging is the early management of these infants with bilateral and severe CAKUT who have significant renal compromise at birth (4-6) The natural history of severe neonatal CAKUT remains incompletely understood concerning the demographic and biological "predictors" of progression to CKD (4-13).

Most cases of CAKUT are diagnosed from antenatal ultrasound imaging, which examines the kidneys, the outflow tracts, and most importantly the amniotic fluid volume (5, 7-13). After the 18th week of gestation, amniotic fluid is primarily composed of urine produced by the fetal kidneys. Antenatal ultrasounds correctly diagnose CAKUT in 60%–85% of infants, especially if imaging is performed in the third trimester (5, 7-13). The remaining cases of CAKUT are mostly diagnosed after an infant or child presents with a urinary tract infection prompting ultrasound and other imaging studies to examine the kidneys and outflow tracts (5). Individuals born with one or two kidneys, but low nephron number, may not exhibit any signs or symptoms until adolescence or adulthood when early onset hypertension or CKD may be diagnosed (5).

Malformed kidneys that are small by length measurements on ultrasound are classified as hypoplastic kidneys; whereas those that are small, hyperechoic, and with/without cysts are described as dysplastic kidneys (5). Although renal hypoplasia/dysplasia refers to the histologic appearance of the kidney, this type of CAKUT is rarely diagnosed by kidney biopsy partly because the small kidney size and/or the

coexistence of a dilated ureter may increase complications from the biopsy(5).

The genetic diagnosis is complex due to the numerous genes involved and the variable genotype-phenotype-correlation. More than 20 genes are currently known in which mutations can cause monogenic CAKUT. Nevertheless, in most cases, genetic defects responsible for the abnormalities cannot be identified. There is still a lack of knowledge about how to assess different patient's aspects because the phenotypes and genotypes of patients with CAKUT are so diverse (6).

The prognosis of the patients varies considerably as in some patients the ultrasound findings return to normal after some time. On the other hand, CAKUT accounts for about 40% of causes of ESRD in childhood and adolescence. Up to now, little is known about which factors influence the outcome of children and adolescents with CAKUT (6, 7). Hence, the objective of this study is to identify the subtypes of CAKUT and risk factors of CKD in CAKUT.

Methods and materials

Study area

Tikur Anbessa Specialized Hospital (TASH) is the largest referral hospital in the country, with more than 700 beds. TASH is now the main teaching hospital for clinical and preclinical training in most disciplines. It is also an institution where specialized clinical services not available in other public or private institutions are rendered to the whole nation. The Department of Pediatrics and Child Health runs 9 subspecialty clinics, including the renal clinic. The clinic delivers outpatient follow-up services twice weekly and there are 25-30 attendees per clinic day.

Study period

This study was conducted from May 2022 up to September 2022 and records of patients who were on follow-up and treatment for the years 2021-22 were reviewed

Study design: Hospital-based retrospective cross-sectional study design was applied.

Population

Source population: The source population was all patients seen at TASH and renal clinics in the pediatric unit during the study period.

Study population: The study population was all pediatric patients diagnosed with congenital kidney and urinary tract anomalies in the study period.

Inclusion criteria: All pediatric patients up to 18 years old who had confirmed congenital anomalies of the kidney and urinary tract treated at TASH and were on follow-up during the study period for a minimum of 1 year and had complete records were included.

Exclusion criteria: All incomplete records and without definitive diagnosis were excluded.

Sample size and sampling technique

For the infinite population, taking a 95% confidence interval our "z" value will be 1.96, according to local data, CAKUT contributes to 26.8% of all kidney patients (8), making a p-value of 0.268, the margin of error 5%, and

the sample size will be 121. The sample size adjusted to account for 10% of the missing data will be 133.

Operational definition

Chronic kidney disease: is defined as an e-GFR <60 ml/mn/1.73m^2

Data collection

A structured questionnaire in the English language was prepared to collect data. All records of patients obtained from the kidney follow-up registry of patients treated for congenital kidney and urinary tract anomalies during the study period, at TASH and the renal clinic were reviewed and trained interns and residents filled out questionnaires. The first author closely supervised data collection.

Data analysis

Statistical Package for the Social Science (SPSS) version 25 was used for data analysis. A chi-square test was applied to assess the patients' demographic features. Mean values, medians, interquartile ranges (IQR), and standard deviations (SD) were calculated based on the clinical and laboratory results. Factors with a P-value less than 0.05 on univariate analysis were considered in multivariate analysis to determine the independent predictors of CKD.

Results

A total of 134 children with the diagnosis of CAKUT were included and 107 of them were males. The age of the study patients ranged from 33 days to 17 years and the mean age was 3.7 years. The majority 101/134 (75.4 %) were under five years of age and the 2 most common causes of healthcare visits were urinary symptoms and antenatal U/S abnormality in 59 (44%) and 40 (29.9%) patients respectively. The diagnosis was made with antenatal ultrasound in 50/134 (37.3%) of the patients but for 84 patients (62.7%) the diagnosis was made after birth. In 68 patients (50.7%) had at least one urological operation, 36 of which occurred in the first year of life. Fifteen patients with PUV underwent valve ablation, 14 patients vesicostomy, and 10 patients both vesicostomy and valve ablation. One patient underwent cystoscopy ablation and bilateral ureteral implantation. Two patients of PUV had not yet undergone surgical intervention during data collection. From 21 patients (15.6%) that developed CKD, 9 patients (42.9%) were stage 3 and 6 patients (28.6%) were at end-stage kidney disease. Of these CKD patients, 18 (85.7%) had a urological intervention, and 8 patients (17.4%) were under 2 years of age when surgical intervention was done (Table 1).

The most common subtypes of CAKUT were posterior urethral valve (PUV) in 42 (31.3%) of the patients, ureteropelvic junction obstruction (UPJO) in 28 (20.9%), and multicystic dysplastic kidney (MCDK) in 24 (17.9%) of the patients as shown in table 2.

The imaging modalities used for diagnosis were U/S examination, voiding cystourethrography (VCUG), intravenous pyelography, and for 2 patients diagnostic cystoscopy was done in addition to U/S examination.

Table 1: Demographic and clinical characteristics of 134 children who were diagnosed to have CAKUT, in a tertiary referral hospital, in Addis Ababa, Ethiopia

Characteristics	Number	Percent (%)
Sex		
Male	107	79.9
Female	27	20.1
Age		
<1year	35	26.1
1-5 years	66	49.3
>5-17 years	33	24.6
Time at diagnosis		
During ANC	50	37.3
After birth	80	59.7
Unknown	4	3.0
Reasons for 1st healthcare visit		
Antenatal U/S abnormality	40	29.9
Pain during urination	59	44.0
Abdominal pain	10	7.5
Abdominal pain and pain during urination	4	3.0
Other	21	15.7
Timing of proteinuria detected		
At first presentation	4	3.0
During follow up	12	9.0
No proteinuria	118	88.1
Time to CKD		
6 months to < 1 year	3	2.2
1 year to 5 years	7	5.1
After 5 years	11	8.2
No CKD	113	84.3
Stage of CKD		
Stage 2	3	2.2
Stage 3	9	6.7
Stage 4	3	2.2
Stage 5	6	4.5
Age at surgical intervention		
< 6 months	20	14.9
6-12 months	16	11.9
>12 months <24 months	13	9.7
24-36 months	9	6.7
>36 months	10	7.5
No surgery	66	49.3

Table 2: Subtypes of CAKUT and sex distribution among 134 study subjects in a tertiary referral hospital, Addis Ababa, Ethiopia

Type of CAKUT	Number (%)	Male number (%)	Female number (%)	CKD number (%)	ESKD Number (%)
PUV	42 (31.3)	42 (31.3)	-	14 (10.4)	3 (2.2)
UPJO	28 (20.9)	25 (18.7)	3 (2.2)	3 (2.2)	-
MCDK	24 (17.9)	13 (9.7)	11 (8.2)	2 (1.5)	1 (0.7)
Ectopic kidney	17 (12.7)	9 (6.7)	8 (6.0)	1 (0.7)	1 (0.7)
Horseshoe kidney	5 (3.7)	4 (3.0)	1 (0.7)	-	-
Solitary kidney	4 (3.0)	3 (2.2)	1 (0.7)	-	-
Mega ureter	2 (1.5)	2 (1.5)	-	-	-
UVJO	2 (1.5)	2 (1.5)	-	-	-
Others	10 (7.5)	7 (5.2)	3 (2.2)	1 (0.7)	1 (0.7)
Total	134 (100)	107 (79.9)	27 (20.1)	21 (15.7)	6 (4.5)

CAKUT; congenital anomaly of the kidney and urinary tract, CKD: is chronic kidney disease, EKD: end-stage kidney disease, PUV; posterior urethral valve, UPJO: ureteropelvic junction obstruction, MCDK: multicystic dysplastic kidney, UVJO: ureterovesical junction obstruction

Others: such as solitary kidney, hypoplastic kidney, renal agenesis, megaureter

On univariate regression analysis, the age of the child at first presentation (less than 6 months), antenatal ultrasound abnormality, proteinuria, and urological operation done in less than one year of age had a statistically significant association with CKD ($p<0.05$) but on multiple regression analysis only proteinuria had a statistically significant association with CKD ($p=0.004$) (table 4).

Table 3: Predictive factors of chronic kidney disease in 134 children with CAKUT in a tertiary referral hospital, Addis Ababa, Ethiopia

Predictive factors for CKD	Univariate			Multivariate		
	OR	95 % CI	P	OR	95 % CI	P
Proteinuria in follow-up	0.66	0.18-0.247	0.000	11.959	2.160-66.218	0.004
Urological operation	7.56	2.107-27.12	0.002	30.470	0.754-1231.734	0.070
Age of operation when <6 months	21.0	3.85-114.549	0.000	0.054	0.001-3.522	0.171
Age of operation >6 mo & <1yr.	9.00	1.325-61.138	0.025	0.041	0.001-2.309	0.120
Antenatal U/S abnormality	0.234	0.65-0.840	0.026	0.178	0.023-1.394	0.10
Age of the child at 1st presentation when <6 months	0.164	0.044-0.610	0.007	11.917	0.379-375.130	0.159

Discussion

In our study, a total of 134 CAKUT patients were included. From this male predominance of 107 (79.9%) was evident with an approximate male-to-female ratio of 3.96:1. In a study done in Egypt with a cohort of 107 patients, the male-to-female ratio was 2.3:1 as reported by Soliman et.al (14). In a study done in Pakistan, in children from birth up to 18 years and out of their 140 cohorts, the male-to-female ratio was 3:1 (15). In another study done in India by Kuma Ravel et.al, out of their 81 cohorts, 70 (86%) were males (16). In a report from Turkey by Cetin Kaya et al., out of their 300 patients with CAKUT, the male-to-female ratio was 203/97 (17). In all the reported studies including ours, the male predominance is partially attributed to PUV predominance.

Our study's median age at presentation was 3.7 years but ranges between 33 days to 17 years and 75.4% were under five years of age. In a report from Turkey, the age at diagnosis ranged between 4 months to 13 years, most of which were under five years (17). In another Indian study by Radhakrishna V et.al, out of their patients, 41% presented between 1-5 years and the oldest was 12 years old (18). In our study, the oldest age at presentation was 17, indicating late presentation at diagnosis. In a study done on 160 Iraqi children with CAKUT, 48.8% of children were diagnosed under five years of age (19) but in a similar study in South Africa by N C Okoronkwo (20), the median age of presentation was 8.4 years and the age ranged between 2 weeks to 18 years. This is similar to our study.

The major cause of health facility visits in our patients 63/134 (47.0%) was symptoms of UTI, 29.9% presented with an antenatal US abnormality. In a study done in Iraq, 58.1% presented with symptoms of UTI, 48.1% presented with fever, and 25.6% with abdominal pain (19). The main cause of presentation to a health institution in many studies is also symptoms of UTI (19-23). In all children with symptoms of UTI, US examination is done for screening and the diagnosis of CAKUT is made unless an ante-natal diagnosis is made by US scanning.

In our study, the most common CAKUT subgroup was PUV in 42/134 (31.3 %), UPJO in 28/138 (20.9%), and MCDK in 24/134 (17.9%) respectively. This is similar to a study done in Ethiopia by Kebede et.al (8) and in Egypt (15) and also in South Africa (20). In other studies, by Sriram et.al in India, the prevalence of UPJO was (20.1%) and MCDK (16.6%) as the second and third most common respectively preceded by primary vesicoureteral reflux (17). Compared to a study by Kumaravel in India, the most common CAKUT subgroup was UPJO (40%) (18). Geographic differences and genetic predisposition might play a role in the formation of CAKUT.

Abdominal ultrasound was the most common imaging modality used for diagnosis in our patients followed by VCUG in 39.5 % of cases. In many of the studies US examination is the

preferred initial imaging modality either during ANC or the first urinary tract infection (17-23).

In this study 50/134 patients (37.3%) diagnoses was made during ANC which is lower than compared to a study done in India when 80.4% were diagnosed during ANC as reported by Sriram (17), while in Iraq ANC diagnosis was made in only 13/160 (9.4%) of cases (19).

In our study, all patients do not have a family history of similar illness and only one patient had a consanguineous marriage which is much lower than studies reported in Egypt (15) and Iraq (20). This could be because of religious reasons as Christianity does not allow consanguineous marriage in Ethiopia and the majority of the study population are Christians.

In 68 patients (50.7%) had urological operations; cystoscopy ablation being the most common procedure done in 26 patients (19.4%). This is slightly higher than studies done in Turkey as reported by Renda (14.5 %) and another report by Cetinkaya (21.3%) respectively (17, 23). This is because PUV is the most common urological abnormality in our patients and the treatment modality is cystoscopic ablation.

Proteinuria on follow-up, urological operation, age of operation when age less than 1-year-old, antenatal ultrasound abnormality, and age of the child at first presentation when less than 6 months showed statistically significant association in univariate logistic regression analysis to develop CKD, but in multiple regression analysis, only proteinuria was found statistically significant predictor of CKD (p=0.004 (2.160-66.218). This is also consistent with a study in Turkey in 2020 as reported by Cetinkaya (17). In our study diagnosis of PUV and oligohydramnios were not statistically significant associations in multivariate analysis. as compared to the survey reported by Cetinkaya (17). Different studies have compared different parameters to predict the progression to CKD and have come up with different results (14,16,17,19). This could be because of the objectives and methodology differences in these studies as well as geographic differences.

Among the study participants, 21 patients had progressed to CKD in our study (16.15%) which is higher than studies done in Turkey as reported by Renda (7.5 % of patients developed CKD) (23) and Cetinkaya (8% of patients developed CKD) (17). Of those 21 patients who developed CKD, 6 patients had progressed to end-stage renal disease. This could be because of late diagnosis and recurrent urinary tract infections in our patients before diagnosis.

Of 16 patients who had proteinuria, 11 patients progressed to CKD (68.75%). Proteinuria is considered an important predictor of CKD in CAKUT. Proteinuria has also been shown as an unfavorable factor in renal survival in patients with CAKUT. In agreement with existing literature data, we demonstrated that proteinuria on the follow-up was an independent predictor for CKD, and therefore should be

Conclusion

The current study gives a general perspective in children with the diagnosis of CAKUT who applied to a tertiary clinical center in Ethiopia. Proteinuria on follow-up was found to be an independent predictor of CKD on multivariate logistic regression analysis. Surgical intervention did not prevent the development of CKD in this study. Future studies with large sample sizes and prospective studies should be done to better delineate associations and to act accordingly.

Limitations of the study: as this is a retrospective chart review, documentation might be incomplete and some variables like time of the surgical intervention have been missed.

Declarations

Data availability

The datasets used or analyzed for the current study are available upon reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest.

Authors contribution

MA: proposal development, data collection, and analysis and write-up, DS: proposal development and proposal review, final write-up, HL proposal review, data analysis, BA: proposal review, AM: proposal review and review of the final write-up

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Ethical clearance

The research was conducted after obtaining approval from the ethical review board of the Department of Pediatrics and Child Health, Addis Ababa University. Patient consent was not needed as this is a retrospective study but patient information confidentiality was maintained.

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