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RESEARCH ARTICLE / *ARAŞTIRMA*

Single Center Retrospective Cohort Analysis of Children with Congenital Anomaly of Kidney and Urinary Tract

Konjenital Böbrek ve İdrar Yolu Anomalisi Olan Çocukların Tek Merkezli Retrospektif Kohort Analizi

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ABSTRACT

Objective: The objective of the study was to determine the course of the clinical and biochemical profile of children with congenital anomalies of the kidneys and urinary tracts (CAKUT).
Material and Method: The files of the patients who were followed up with the diagnosis of CAKUT in the Pediatric Nephrology Clinic between February 2016 and September 2017 in the Süleymaniye Maternity and Pediatrics Hospital were analyzed retrospectively.
Results: Sixty five of 117 patients followed up for CAKUT were included in the study. In this study, we found that of the patients, 29.2% were diagnosed antenatally, 27.7% had comorbid disease, and 32.2% had family kidney disease history. Comparing with postnatal diagnosis, the patients who had pretnatal diagnosis had lower eGFR after follow up (p=0.048). There is a statistically significant relationship between consanguineous marriage and comorbidity (p=0.047, x^2=3.94).
Conclusion: It would be better to follow up the patients with consanguinity, family kidney disease and comorbidity closely even though they have compensatory hypertrophy.

Keywords: Congenital anomalies, kidney, urinary tract

ÖZ

Amaç: Çalışmada konjenital böbrek ve idrar yolu anomalisi olan çocukların retrospektif epidemiyolojik, demografik ve klinik özelliklerinin paylaşılması amaçlanmıştır.
Gereç ve Yöntem: Süleymaniye Kadın Doğum ve Çocuk Hastalıkları Hastanesi'nde Şubat 2016-Eylül 2017 tarihleri arasında Çocuk Nefroloji Kliniği'nde konjenital böbrek ve idrar yolu anomalisi tanısı ile takip edilen hastaların dosyaları geriye dönük olarak incelendi.
Bulgular: Konjenital böbrek ve idrar yolu anomalisi nedeniyle takip edilen 117 hastadan 65'i çalışmaya dahil edildi. Bu kohortta prenatal tanı %29,2 (19), ek hastalık %27,7 (18), ailede böbrek hastalığı %32,2 (21), kompensatuvar hipertrofi %53,8 (35) ve %9,2 (6) hipertansiyon saptanmıştır.
Sonuç: Akrabalık, aile böbrek hastalığı ve komorbiditesi olan hastaların kompensatuvar hipertrofisi olsa bile daha yakın takibi daha iyi olacaktır.

Anahtar Kelimeler: Böbrek, Konjenital anomali, üriner yol

INTRODUCTION

Congenital anomalies of the kidneys and urinary tract (CAKUT) are embryonic disorders that refer to a diverse group of structural malformations in the kidneys, ureters, bladder, and urethra. The prevalence is estimated at 4–60 per 10,000 births, depending on the study consulted (1). Data from national renal registries in Turkey show that CAKUT are the leading cause of end-stage renal disease (ESRD) in children, accounting for 45.33% of renal transplantations (RRT) in children (2). A better understanding of how the disease progresses could help the clinical application of in-patient and family counselling and symptom management. The objective of the study was to determine the course of the clinical and biochemical profile of children with CAKUT.

METHODS

The files of patients who were followed-up with after a diagnosis of CAKUT in the Pediatric Nephrology Clinic between February 2016 and September 2017 in the

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Süleymaniye Maternity and Pediatrics Hospital were analyzed retrospectively. The Local Ethics Committee approved the study (number: 04.08.2017/1056). The information from clinical records included prenatal, natal, and postnatal history; malformation subtypes, additional anomalies, treatment, family history, and demographic data; and clinical and biochemical records produced during the follow-up. Renal agenesis, renal hypoplasia, horseshoe kidney, multi-cystic dysplastic kidney (MCDB), renal dysplasia, ectopic kidney, megaureter, uretero-pelvic stenosis (UPD), uretero-vesical stenosis (UVD), vesico-ureteral reflux (VUR), posterior urethral valve (PUV), and double collector system diagnoses were included in the study. Patients with transient hydronephrosis that regressed spontaneously on follow-up were excluded from the study.

A diagnosis of antenatal hydronephrosis was made when the maximum diameter of the renal pelvis was ≥4mm at second trimester and ≥7mm at third trimester on a prenatal ultrasound scan (US). (All newborns with a history of antenatal hydronephrosis are evaluated by ultrasonography scan in the first week and at 4-6 weeks of life.) In cases of febrile urinary tract infection during the follow-up, a vesicoureteral reflux study was performed. Patients with a pelvis anterior-posterior diameter >10 mm and Society of Fetal Urology (SFU) stage 3-4 without VUR, and patients with a dilated ureter regardless of its grade and without VUR were evaluated by ^{99m}Tc- mercaptoacetyltriglycine (MAG3) diuretic renography. Ultrasonography (US) and dimercaptosuccinic acid (DMSA) scintigraphy were used in the diagnosis of renal agenesis, hypodysplasia, horseshoe kidney, MCDK, and ectopic kidney. Renal hypodysplasia was accepted as a kidney size <2 standard deviation (SD)for age in a urinary US and differential renal function <40% without scaring in DMSA. The diagnosis of acquired renal damage was made by the presence of scarring on DMSA scintigraphy.

The patients were followed-up every three months with physical examination, urine analysis, and US; serum creatinine was checked every six months. Hypertension was confirmed by 24-hour ambulatory blood pressure monitoring (ABPM) (3). The glomerular filtration rate (eGFR) was calculated by using the Schwartz equation (4). Patients with a follow-up time of less than six months were excluded.

Statistical analysis

SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. In the evaluation of numerical data, mean±SD was used for parameters with normal distribution, and median with interquartile range was used for parameters not showing normal distribution. Differences between subgroups were calculated using the Mann-Whitney, Kruskal Wallis, and Wilcoxon tests. The values of P<0.05 were considered statistically significant. The Chi-square test was used to determine whether there was a relationship between the two classification variables.

RESULTS

Sixty-five of 117 patients followed-up with for CAKUT were included in the study. CAKUT were detected while 24 (36.9%) of the patients were being scanned for another health problem. None of them had microalbuminuria.

Eighteen (27.7%) of the patients had an additional disease, including asthma (n=4, 6.2%), inguinal hernia (n=3, 4,6%), undescended testicle (n=2, 3.1%), hypospadias (n=2, 3.1%), urolithiasis (n=1, 1.5%), bladder carcinoma (n=1, 1.5%), anal agenesis (n=1, 1.5%), epilepsy (n=1, 1.5%), mental-motor retardation (n=1, 1.5%), mitral insufficiency (n=1, 1.5%), and atrial septal defect (n=1, 1.5%). There is a statistically significant relationship between consanguineous marriage and comorbidity (p=0.047, x^2=3.94). A similar situation was not detected in the presence of kidney disease in the family (p=0,95, x^2=0.04).

Nine (13.9%) of the patients had medical treatments which included anti-hypertensive (angiotensin converting enzyme inhibitors), anti-epileptic, and anti-asthmatic drugs.

Demographic information of the patients is presented in Table 1. The CAKUT type is presented in Table 2. The average age

Table 1: Demographic data of study population.

Parameter	Mean (±SD) or n(%)
Age (year)	6.74 (±5.2)
Gender (M)	29 (44.6%)
Weight z score	-0.18 (±5.2)
Height z score	-0.19 (±1.31)
BMI z score	-0.12 (±1.3)
Follow-up time (month)	9.53 (±2.2)
Prenatal diagnosis	19 (29.2%)
UTI History	22 (33.8%)
Preterm birth	11 (16.9%)
C/S	24 (36.9%)
Consanguineous marriage	12 (18.5%)
G1P1	46 (70.8%)
G2P1	1 (1.5%)
G2P2	14 (21.5%)
G3P2	1 (1.5%)
G3P3	1 (1.5%)
G4P1	2 (3.1%)
Family kidney disease history	21 (32.2%)
Chronic kidney disease	11 (16.9%)
Hypertension	5 (7.7%)
Urolithiasis	3 (4.6%)
UPJO	1 (1.5%)
Renal cell carcinoma	1 (1.5%)
Additional disease	18 (27.7%)
Medical treatment	9 (13.9%)
Compensatory hypertrophy	35 (53.8%)
Renal agenesis	17 (48.6%)
Renal hypoplasia	8 (22.9%)
VUR	4 (11.4%)
Ectopia	2 (5.7%)
UPJO	2 (5.7%)
MCDK	2 (5.7%)
Hypertension	6 (9.2%)
First eGFR (ml/dk/1.73m^2)	111.4±29.9
Last eGFR (ml/dk/1.73m^2)	109 (95.52-130.93)

BMI: body mass index, C/S: cesarean section, eGFR: estimated glomerular filtration rate, F: female, G: gravidity, M: male, MCDK: multicystic dysplastic kidney, P: parity, SD: standard deviation, UTI: urinary tract infection, UPJO: Ureteropelvic junction obstruction, VUR: vesicouretheral reflux

Table 2: Type of CAKUT.

Type of CAKUT	n (%)
Renal agenesis	23 (35.4%)
Renal hypoplasia	24 (36.9%)
Renal ectopia	4 (6.2%)
VUR	8 (12.3%)
UPJO	2 (3.1%)
Horseshoe kidney	1 (1.5%)
MCDK	3 (4.6%)

CAKUT : congenital anomalies of the kidneys and urinary tracts, MCDK: multicystic dysplastic kidney, UPJO: ureteropelvic junction obstruction, VUR: vesicouretheral reflux

of patients according to diagnosis reasons are presented in Table 3 and the characteristics hypertensive of patients are presented in Table 4.

Between patients with and those without compensatory hypertrophy, there were no differences for age, gender, weight, height, BMI, birth week, consanguinity, additional disease, hypertension, and prenatal diagnosis.

DISCUSSION

In this study, we found that of the patients, 29.2% were diagnosed antenatally, 27.7% had comorbid disease, 32.2% had family kidney disease history, 53.8% had compensatory hypertrophy and 9.2% had hypertension Due to the widespread use and sensitivity of fetal ultrasonography, most kidney anomalies are detected in the antenatal period. In this study, postnatal diagnosis due to the UTI or other disease screening was more prevalent than prenatal diagnosis. Transient hydronephrosis being the most common cause of antenatal hydronephrosis may have contributed to this result.

Table 4: Hypertensive patients' characteristics.

Parameter	% (n)
Gender (F)	100 (6)
Age (year)	10.4 (5.09-14.36)
Height z score	0.41 [(-1.18)-1.19]
BMI z score	0.55 [(-0.84)-1.69]
Consanguinity	33.3%(2)
Family kidney history	33.3%(2)
Diagnosed after UTI	50%(3)
Diagnosed coincidence	50%(3)
Comorbidity	66.7%(4)
Compensatory hypertrophy	33.3% (2)
Type of CAKUT	
Renal hypoplasia	50%(3)
VUR	33.2%(2)
MCDK	16.7% (1)

BMI: body mass index, CAKUT: congenital anomalies of kidney and urinary tract, F: female, MCDK: multicystic dysplastic kidney, UTI: urinary tract infection, VUR: vesicouretheral reflux

Table 3: Patients according to diagnosis reasons.

Parameter	Prenatal diagnosis (n=19)	Postnatal Diagnosis (n=46)		p
		Diagnosis After UTI (n=19)	Coincidence (n=27)	
Age (year)	1.06 (±3.35)	6.52 (±6.98)	8.1 (±4.98)	0.000
M/F (M%)	12/7 (63.27%)	6/13 (31.6%)	11/16 (40.7%)	0.132
Type of CAKUT				
Renal agenesis	10 (52.6%)	5 (26.3%)	8 (29.6%)	
Renal Hypolasia	4 (21%)	5 (26.3%)	15 (55.6%)	
VUR	2 (10.5%)	5 (26.3%)	1 (3.7%)	
UPJO	1 (5.3%)	1 (5.3%)		
Horseshoe kidney	1 (5.3%)			
MCDK	1 (5.3%)			
Renal ectopia		2 (10.5%)	3 (11.1%)	
		1 (5.3%)		
Preterm	6 (31.6%)	5 (10.8%)		0.069 (x^2:4.102)
Term	13 (68.4%)	41 (89.2%)		
NVD	8 (42.1%)	33 (71.7%)		0.046 x^2:5.07
C/S	11 (57.9%)	13 (28.3%)		
First creatinine (mg/dl)	0.4 (0.28-0.48)	0.46 (0.33-0.54)		0.035
First eGFR	96.8 (84.2-128)	112 (95.5-133.7)		0.024
Last creatinine(mg/dl)	0.31 (0.27-0.51)	0.47 (0.42-0.55)		0.027
Last eGFR	95.52 (78-110)	115 (103.6-134.8)		0.048

C/S: cesarean section, CAKUT: congenital abnormality of kidney and urinary tract eGFR: estimated glomerular filtration rate, F: female, M: male, MCDK: multicystic displastic kidney, NVD: normal vaginal delivery, UPJO: ureteropelvic junction obstruction, UTI: urinary tract infection, VUR: vesicouretheral reflux

As the impact of UTI on kidney health is well-known, US are often performed after UTI. However, the importance of the coincidence diagnosis of CAKUT is not clear. Comparing with prenatal diagnosis, we found that the patients who had postnatal diagnosis were older, in accordance with the literature. While renal agenesis was more frequent in those who obtained a prenatal diagnosis, renal hypoplasia was more frequent at postnatal diagnosis. However, there were no significant differences in compensatory hypertrophy, eGFRs, and hypertension between these groups. One reason for this could be the low number; the other possible explanation is that coincidence diagnosis is not as inconsequential as first thought. It would be beneficial for these types of patients to have regular follow-ups.

It was reported that 30% of CAKUT could be attributed to an additional disease other than that of the kidney (5,6). Similarly, in this study it was found that 27.7% (18) of the patients had an additional disease, some of which were associated with the urogenital system such as inguinal hernia, undescended testicle, hypospadias, urolithiasis, bladder carcinoma, and anal agenesis. However, some of the additional diseases were not of the urogenital system, such as asthma, epilepsy, mental-motor retardation, mitral insufficiency, and atrial septal defect. Moreover, a statistically significant relationship between consanguineous marriage and comorbidity was found. Multifactorial pathogenesis including genetic, environmental and epigenetic factors of congenital anomalies of the kidney and urinary system are mentioned in the literature (7). It is possible that genetic factors may contribute more to the occurrence of comorbidity. Family history for kidney disease was found to be positive in 32.2% (21 cases) of the cases with CAKUT. In three other cross-sectional analysis from Turkey, this percentage was reported at 7.5, 7.7, and 15.2% (8,9,10), respectively. These differences may stem from the study design. Most of the other studies were cross-sectional, and included patients who had follow-ups for at least six months. In cases with polycystic kidney disease and VUR, the examination of first-degree relatives is recommended. Similarly, the screening of other relatives of CAKUT patients would be useful for asymptomatic patients. In this study, 41.5% (n=27) of patients were diagnosed incidentally. Also, incidental-diagnosed patients had 7.4% consanguinity marriage and 25.9% family kidney disease history. These findings point out that screening programs would be better for CAKUT patients.

Adaptive mechanism compensatory hypertrophy was found in 73.9% (17) of patients with renal agenesis. In addition, there was no significant difference in eGFRs between patients with and those without compensatory hypertrophy. None of the hypertensive patients had renal agenesis. Interestingly, 33.3% (2) of the hypertensive patients had compensatory hypertrophy. Also, eGFRs between patients with and without hypertension were not different. The possible explanation is that we need additional clinical clues for early kidney damage before the development or diagnosis of hypertension, eGFR, or microalbuminuria. Genetic and epigenetic studies look promising for this purpose. Until the clinical use of the results found in these studies, we have to evaluate the personal and family medical history of each patient along with conducting a physical examination. It would be even better to follow up the patients with consanguinity, family kidney disease, and comorbidity more closely, even though they have compensatory hypertrophy.

In conclusion, we think that all CAKUT patients need regular follow-ups whether they are diagnosed with antenatal, urinary tract infection or by coincidence. Other systems of those with consanguineous marriage or family history of kidney disease may need to be evaluated more carefully. It does not seem like an unnecessary practice to recommend screening ultrasonography to first degree relatives of those diagnosed with CAKUT. Regardless of the type or accompanying compensatory hypertrophy, we would like to emphasize the importance of blood pressure monitoring, which is a modifiable condition, especially in patients with postnatal CAKUT.

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