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Article

The Diagnostic Efficacy of and Requirement for Postnatal Ultrasonography Screening for Congenital Anomalies of the Kidney and Urinary Tract

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Abstract: Background: We aimed to investigate the effectiveness of postnatal ultrasonography in determining congenital anomalies of the kidney and urinary tract in term infants with or without a history of congenital anomalies of the kidney and urinary tract in the prenatal period. Methods: In this retrospective cohort study, the records of term infants aged between six weeks and three months undergoing urinary system ultrasonography during routine child care were examined. Results: Congenital anomalies of the kidney and urinary tract was determined in 121 (4.62%) of the 2620 cases included in the study. The most common anomaly was hydronephrosis (in 69.4% of the congenital anomalies of the kidney and urinary tract cases and 3.21% of all cases). Thirty-two of the 84 (38.1%) hydronephrosis cases detected by postnatal ultrasonography, three of the nine (33.3%) renal agenesis cases, four of the seven (57.1%) horseshoe kidneys cases, one of the four (25%) multicystic dysplastic kidney cases and two of the two (100%) duplex system cases could not be detected by prenatal ultrasonography. On the other hand, hydronephrosis was not detected at postnatal ultrasonography in 29 (1.1%) cases which detected mild or moderate hydronephrosis by prenatal ultrasonography scanning. Conclusions: In our study, it was observed that approximately one-third of the cases of hydronephrosis, unilateral renal agenesis, duplex system, horseshoe kidney, and ectopic kidney could not be detected at prenatal ultrasonography screening. We therefore believe that, in addition to prenatal ultrasonography screening, postnatal ultrasonography screening of all children for urinary tract anomalies would be beneficial.

Keywords: children; congenital anomalies of the kidney and urinary tract; prenatal; postnatal; ultrasound screening

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are still the most frequent cause of chronic kidney failure [1]. Since CAKUT can be asymptomatic and lead to hypertension and end-stage kidney failure in later years, many countries endeavour to identify cases in the prenatal period [2–5]. Ultrasonography (USG) is preferred as a screening method since it is inexpensive, non-invasive, repeatable, and reliable [6,7].

The reported incidence of CAKUT at prenatal USG screening is 0.3-5% [2–5]. However, resolution is observed in a significant proportion of these cases at imaging performed within the first postnatal week [8,9]. On the other hand, it has been reported that approximately 10-20% of hydronephrosis cases determined in the postnatal period, and some collecting system anomalies, hydroureter, and pelvic kidney, cannot be detected at prenatal USG [9]. These inconsistent findings have been attributed to physiological variations between foetus and infant, and to positional variation during USG imaging. Postnatal USG is therefore reported to be more effective in determining CAKUT than prenatal USG [8–10].

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Postnatal USG screening is generally performed in order to confirm diagnosis when CAKUT is identified in the prenatal period. Since CAKUT is one of the preventable causes of end-stage renal disease, public health procedures are needed to identify CAKUT cases that cannot be detected in the prenatal period due to technical limitations. To the best of our knowledge, there have been few postnatal USG screening studies in infants with no prenatal history of CAKUT [11–15]. The purpose of this study was to investigate the efficacy of postnatal USG in determining CAKUT in term infants with or without a history of CAKUT in the prenatal period.

Methods

Study population

In this retrospective cohort study, the records of infants aged six weeks to three months presenting to the Malatya Sevgi Hospital between 1 January 2010 and 31 December 2017 for routine child care and undergoing urinary tract USG were examined. The frequency and importance of urinary system anomalies were explained to the families and the cases who accepted ultrasonographic examination were included in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (No. 2018/06) and informed consent was obtained from all parents.

Term babies born at 37-42 weeks were included in the study. Subjects with prematurity, external genital anomalies such as hypospadias, multiple congenital anomalies, familial congenital urinary anomaly, or a history of urinary tract infection were excluded.

Equipment and procedures

All USG screening procedures were performed by the same radiologist with experience in the field of paediatric urology using a TOSHIBA Aplio 400 device and a 5-MHz convex and 8-MHz linear probe. Children were well hydrated before the screening and were examined in the prone position. Renal pelvis anteroposterior diameter (APD) was measured in the transverse plane. Kidneys were evaluated in terms of shape, dimension, location, parenchymal thickness, echogenicity, cysts, and calyceal dilation. Whether or not ureters were dilated and bladder diameter and wall thickness were also evaluated.

Definitions

Hydronephrosis, renal agenesis, renal hypoplasia, horseshoe kidney, ectopic kidney, multicystic dysplastic kidney (MCDK), duplex system, posterior urethral valve (PUV), ureteropelvic junction obstruction (UPJO) and vesicoureteral reflux (VUR) were classified as CAKUT. Ureterocele, duplex kidney, PUV, VUR and UPJO were defined as “major urological pathology” in cases of hydronephrosis.

Hydronephrosis was defined based on APD measurement (7-9 mm mild, 9-15 mm moderate, and >15 mm severe) [6]. APD <7 mm at two consecutive USG imaging sessions, and renal parenchyma, calyces, ureters, and bladder being evaluated as normal was defined as resolution.

Voiding cystourethrography (VCUG) and 99mTc-dimercaptosuccinic acid scintigraphy (DMSA) were performed on subjects with unilateral or bilateral APD >15 mm or with ureteral dilatation, with febrile urinary tract infection during follow-up, or with pelvic dilatation persisting for longer than 12 months and/or increased dilatation. Diethylenetriamine pentaacetic acid (DTPA) scintigraphy was performed in all cases with severe hydronephrosis or ureteral dilatation without VUR [7].

VUR was staged in line with the International Reflux Study Committee Classification [16]. UPJO was defined as the absence of dilatation in the ureters despite the renal pelvis exceeding 10-15 mm accompanied by calyceal dilatation and an abnormal diuretic renogram pattern. In DTPA imaging, the diuretic was administered at the twentieth minute when the collector system activity is highest. The time elapsed until the collector system activity decreases by 50% after the diuretic is administered is called the T1/2 time. T1/2 time >20 minutes was considered as abnormal diuretic renogram pattern [17]. MCDK was defined as the presence of multiple, variable-sized, non-communicating cysts in the

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absence of normal renal parenchyma, and the duplex system as a single renal unit drained by two collecting systems [6].

Growth of a single pathogen at >100,000 CFU/ml in specimens collected with sterile urine bags together with fever (>38^0 C), presence of urinary symptoms and/or leukocyturia was defined as urinary tract infection (UTI) [18].

Follow-up

CAKUT cases were followed-up for 6-36 months, during which time USG, urine culture, blood pressure measurement, and growth measurement were performed once every three months. Proteinuria and estimated glomerular filtration rate (eGFR) were evaluated in patients with persistent anomalies, eGFR calculated from plasma creatinine by the Schwartz formula. Impaired renal function was defined as eGFR <90 ml/min per 1.73 m^2 according to the KDIGO guidelines stage 2–5. End-stage renal failure (ESRF) was defined as undergoing renal replacement therapy [19]. Prophylactic antibiotic therapy was initiated until VCUG was performed in the case of patients with severe unilateral or bilateral hydronephrosis (APD>15 mm) or dilated ureter, of patients developing febrile UTI during follow-up, and of patients with VUR or MCDK.

Surgical interventions were performed in the case of patients with persisting grade IV-V VUR after the age of one year, patients developing febrile UTI despite prophylaxis or with new scar formation in the renal parenchyma, patients with scintigraphic functions less than 40% in the ipsilateral kidney, of UPJO patients with impairment of kidney functions exceeding 10% at follow-up or decreased parenchymal thickness, and of duplex system patients with accompanying unilateral obstruction (ureterocele or ectopic ureter).

Data collection

Demographic data such as sex, birth week, prenatal USG imaging, history of UTI and family history of CAKUT, laboratory results such as USG, DMSA, DTPA, VCUG, complete urine analysis, and urine culture, together with the final diagnosis, whether or not UTI developed, time to resolution, and surgical procedures performed were recorded.

Statistical analysis

Data were analysed on SPSS 23.0 software (SPSS, Inc., Chicago, IL). Descriptive statistics were analysed. The chi-square test was used in the analysis of categorical variables. P values <0.05 were regarded as statistically significant.

Results

Total anomalies

CAKUT was determined in 121 (4.62%) of the 2629 cases meeting the inclusion criteria, 1218 (46.5%) girls and 1402 (53.5%) boys. Eighty-five (70.2%) of the CAKUT cases were boys and 36 (29.8%) were girls, giving a male: female ratio of 2.4:1 (p<0.001). Anomalies were on the left in 78 cases (64.5%), on the right in 17 (14%), and bilateral in 26 (21.5%).

The most common anomaly was hydronephrosis (84 cases, representing 69.4% of CAKUT cases, and 3.21% of all cases). Hydronephrosis was more common in boys, with a male:female ratio of 2.7:1. Mild dilatation was present in 47 (56%) hydronephrosis cases, moderate dilatation in 22, and severe dilatation in 15. Additionally, renal agenesis was determined in nine cases, horseshoe kidney in seven, echogenic kidney in seven, MCDK in four, ectopic kidney in four, simple cyst in three, the duplex system in two, and polycystic kidney in one (Table 1).

Table 1. Incidence and characteristics of congenital anomalies of the kidney and urinary tract

	Number	Percent	Affected side

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	(n)		(%)		Gender (F/M)	Right (n)	Left (n)	Bilateral (n)
	Pre-Natal#	Post-Natal§	Pre-Natal#	Post-Natal§				
Total CAKUT (n=121)	75	46	62.0	38.0	36/85	17(14)	78(64.5)	26(21.5)
Renal agenesis (n=9)	6	3	66.7	33.3	1/8	4	5	-
Horseshoe kidney (n=7)	3	4	42.9	57.1	3/4	-	-	7
Echogenic kidney (n=7)	5	2	71.4	28.6	5/2	2	1	4
Multicystic dysplastic kidney (n=4)	3	1	75.0	25.0	2/2	1	3	-
Ectopic kidney (n=4)	3	1	75.0	25.0	0/4	2	2	-
Simple cyst (n=3)	2	1	66.7	33.3	1/2	2	1	-
Duplex system (n=2)	0	2	0	100	0/2	1	1	-
Polycystic kidney (n=1)	1	0	100	0	1/0	-	-	1
Hydronephrosis (n=84)	52	32	61.9	38.1	23/61	5(5.9)	65(77.4)	14(16.7)
Mild (7-9.9 mm) (n=47)	25	22	53.2	46.8	12/35	2(4.3)	42(89.4)	3(6.4)
Moderate (10-15 mm) (n=22)	15	7	68.2	31.8	7/15	2(9.1)	14(63.6)	6(27.3)
Severe (> 15 mm) (n=15)	12	3	80.0	20.0	4/11	1(6.7)	9(60.0)	5(33.3)

Anomalies that detectable only at postnatal USG

Thirty-two of the 84 (38.1%) hydronephrosis cases detected by postnatal USG, three of the nine (33.3%) renal agenesis cases, four of the seven (57.1%) horseshoe kidneys cases, one of the four (25%) MCDK cases and two of the two (100%) duplex system cases could not be detected by prenatal USG (Table 1). Twenty-two (46.8%) of the 47 mild hydronephrosis cases detected by postnatal USG, 7 (31.8%) of the 22 moderate hydronephrosis cases and 3 (20%) of the 15 severe hydronephrosis cases could not be detected by prenatal USG. On the other hand, hydronephrosis was not detected at postnatal USG in 29 (1.1%) cases which detected mild or moderate hydronephrosis by prenatal US scanning.

Outcomes of the cases that detectable at prenatal USG

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Spontaneous resolution was observed in 34 (65.4%) hydronephrosis cases that detectable at prenatal USG. Degree of hydronephrosis not changed at renal USG during follow-up in the four moderate hydronephrosis cases and an increase was determined in the one mild, and two moderate cases. Two of the cases in the group with no change in degree of hydronephrosis were diagnosed with VUR, while UPJO was determined in three cases in the increased hydronephrosis group. UTI was diagnosed in 19 (36.5%) cases during follow-up. VCUG imaging was performed in 29 cases and DTPA in 20 cases. Major urological pathology was determined totally in 18 (34.6%) cases, 10 of them were VUR and eight were UPJO. One of the VUR cases was grade 1, two were grade II, two were grade III, three were grade IV, and two were grade V. Surgery was performed in 10 patients, including six of them were VUR and four were UPJO cases (Table 2).

Table 2. Comparison of clinical course and abnormal findings according to degree of hydronephrosis

	VUR n(%)		**UPJO n(%)**		**Spontaneous Resolution n(%)**		**UTI n(%)**		**Surgery n(%)**	
	Pre-Natal #	Post-Natal §	Pre-Natal #	Post-Natal §	Pre-Natal#	Post-Natal §	Pre-Natal #	Post-Natal §	Pre-Natal #	Post-Natal §
Mild (7-9.9 mm)	2	1	0	1	22	18	4	3	0	0
Unilateral	1	0	0	1	21	18	3	2	0	0
Bilateral	1	1	0	0	1	0	1	1	0	0
Moderate (10-15 mm)	3	1	3	0	10	4	6	1	3	1
Unilateral	1	1	3	0	8	3	3	1	2	1
Bilateral	2	0	0	0	2	1	3	0	1	0
Severe (>15 mm)	5	2	5	0	2	1	9	2	7	2
Unilateral	1	1	5	0	2	1	5	1	4	1
Bilateral	4	1	0	0	0	0	4	1	3	1
Totally	10	4	8	1	34	23	19	6	10	3

UTI developed in one patient diagnosed with horseshoe kidney. Grade III VUR was determined in one MCDK case with unilateral hydronephrosis, and grade II in one case of horseshoe kidney developing UTI. Antihypertensive therapy was initiated in one case of unilateral renal agenesis developing hypertension during follow-up. No impairment of kidney functions (eGFR <90 ml/min per 1.73 m^2), ESRF or proteinuria occurred in any cases that CAKUT detectable at prenatal USG during the 6 to 36-month follow-up period.

Outcomes of the cases that detectable only at postnatal USG

Spontaneous resolution was observed in 23 (71.9%) hydronephrosis cases that detectable at only postnatal USG. Degree of hydronephrosis not changed at renal USG during follow-up in the two

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moderate hydronephrosis cases and an increase was determined in the one mild case. VUR was determined in one case in the increased hydronephrosis group. UTI was diagnosed in 6 (18.8%) cases during follow-up. VCUG imaging was performed in 15 cases and DTPA in 10 cases. Major urological pathology was determined totally in five (15.6%) cases, four of them were VUR and one was UPJO. One of the VUR cases was grade 1, one was grade III, one was grade IV, and one was grade V. Surgery was performed in the three patients with VUR (Table 2).

UTI developed in one patient diagnosed with horseshoe kidney and in two patients diagnosed with the duplex system. Grade II VUR was determined in the one case of horseshoe kidney developing UTI, and grade II in one of the two duplex system patients developing UTI, while the other case was grade III. Surgery was performed in one duplex system case accompanying ureterocele. No impairment of kidney functions (eGFR <90 ml/min per 1.73 m^2), ESRF or proteinuria occurred in any cases that CAKUT detectable only at postnatal USG during the 6 to 36-month follow-up period.

Considering all the cases included in the study, VUR was determined in 5 (7.1%) of the 70 cases of unilateral hydronephrosis and UPJO in 9 (12.9%), and VUR was detected in 9 (64.3%) of the 14 cases of bilateral hydronephrosis. The incidence of major urological pathology was significantly higher in cases of bilateral hydronephrosis than in those of unilateral hydronephrosis ($p<0.001$). Determination of urological pathology ($p<0.001$) and frequency of surgery ($p<0.001$) were higher in the severe hydronephrosis group than in the mild and moderate groups.

Discussion

The most common cause of childhood end-stage renal failure is still CAKUT [1]. It has been reported that renal hypoplasia also increases the risk of end-stage renal failure in adulthood [20]. Therefore, it is important to detect CAKUT cases in early life and to treat them if possible. For this purpose, the urinary system is scanned prenatally and cases with CAKUT are followed up by postnatal ultrasonography. However, it is known that some CAKUT cases cannot be detected by prenatal USG due to technical and physiological reasons [9,13,21,22]. In the few studies that have examined screening of the urinary system with postnatal USG in randomly selected cases regardless of prenatal CAKUT history, there has been no standard screening time, screening has been performed over a wide time spectrum from three days to six months, and a prevalence of CAKUT of between 1.5% and 7.4% has been reported [11–15]. We determined a prevalence of CAKUT of 4.62% at this retrospective cohort study which we screened terms infants aged between six weeks and three months with postnatal USG regardless of the prenatal CAKUT history. We think that this wide divergence in the prevalence of CAKUT derives from subjects' physiological conditions at the time of screening, and particularly whether or not cases of transient hydronephrosis were identified.

In our study, 32 of the 84 (38.1%) hydronephrosis cases detected by postnatal USG, three of the nine (33.3%) renal agenesis cases, four of the seven (57.1%) horseshoe kidneys cases, one of the four (25%) MCDK cases and two of the two (100%) duplex system cases could not be detected by prenatal USG. Drnasin et al. [21] reported that the frequency of hydronephrosis of 7.4% in a study in which they postnatally screened 1000 healthy infants who were screened with prenatal USG and were declared as "normal". Miyakita et al. [11] reported that 39% of 92 cases of hydronephrosis were identified in the prenatal period. Hálek et al.[13] reported that only 8.5% of 234 cases of hydronephrosis were identified in the prenatal period and all cases of unilateral agenesis, and ectopic kidney were diagnosed at postnatal USG screening. Richter-Rodier et al. [15] reported that only 16.4% cases of hydronephrosis were detected at prenatal screening and although prenatal USG exhibited high effectiveness in detecting cases of renal agenesis and MCDK, its effectiveness in determining duplex system, horseshoe kidney, and dysplastic and ectopic kidney was low. Mamì et al. [22,23] reported that only 35.7% of moderate hydronephrosis cases and 73.2% of severe hydronephrosis cases were detected by prenatal USG. In our study, hydronephrosis was detected at prenatal USG screening in 53.2% of cases of mild hydronephrosis determined at postnatal USG, in 68.2% of moderate cases and in 80% of severe cases. In line with previous studies, we observed that the rate of detecting severe hydronephrosis in the prenatal period was high in our study.

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In agreement with previous studies, CAKUT was more common in boys and on the left side [11–15]. The most frequently determined anomaly was hydronephrosis (69.4%), and 56% of these cases were mild. Hydronephrosis was more common in boys and in the left kidney. Similarly, Hálek et al. [13] and Richter-Rodier et al. [15] also reported hydronephrosis as the most common anomaly that the majority of these cases were mild, and that hydronephrosis was more common in boys and in the left kidney.

Spontaneous resolution occurred in 65.4% cases of hydronephrosis that detectable at prenatal USG, while this rate was 71.9% in those detected only at postnatal USG. In studies investigating cases identified in the postnatal screening, Drnasin et al. [21] reported a total spontaneous resolution rate of 79.2% - in 83.1% of mild cases and 33.3% of moderate-severe cases, while Hálek et al. [13] reported of 82.1%. In studies investigating cases identified in the prenatal period, Barbosa et al. [24] reported spontaneous resolution in 90% and 75% of mild and moderate hydronephrosis, respectively, while Coelho et al. [25] reported figures of 97% and 78% of mild and moderate hydronephrosis. In agreement wıth previous postnatal screening studies, we think that spontaneous resolution rates being slightly lower compared to cases determined in the prenatal period may be attributed to greater physiological hydronephrosis being determined at the prenatal screening in line with the fetus physiology. Indeed, deGrauw et al. [5] reported that 24% of cases antenatal hydronephrosis were reported normal at first postnatal USG, while Gokce et al. [26] reported that 9.4% were normal.

VUR was determined in 16.7% of cases of hydronephrosis and UPJO in 10.7%, and surgery was performed in 15.5%. These rates were 12.5%, 3.1% and 9.4%, respectively, in the cases that hydronephrosis could only be detected by postnatal USG. Also, surgery was performed in one duplex system case accompanying ureterocele. We observed that the frequency of detection of urological pathology and surgical intervention increased with the degree of hydronephrosis. Nef et al. [27] reported that approximately one-third of the patients underwent surgery in cases identified in the prenatal period, while Miyakita et al. [11] reported the surgery rate as 3.3% in cases identified only in the postnatal screening. Bhide et al. [28] stated that 59.6% of the patients operated for CAKUT could be detected in the prenatal period. Hálek et al. [13] reported an incidence of surgery of 7.1% in cases that hydronephrosis identified only in the postnatal screening, and that rates of detection of urological pathology increased in line with APD. Richter-Rodier et al. [15] reported an incidence of surgery of 12.1%. Grazioli et al. [29] reported that prenatal USG did not predict VUR, but that APD measured at postnatal USG was correlated with the risk of VUR.

End-stage renal failure or proteinuria was not detected in any of our patients with CAKUT detected in the prenatal or postnatal period during the six to thirty-six months follow-up period. In studies investigating cases identified in the prenatal period, Nef et al. [27] found the ESRF in only two of 115 patients during the 18-year follow-up period, while Herthelius et al. [30] reported that they did not find ESRF in any of their patients during the 12-15-year follow-up period. Miyakita et al. [11] reported that they did not detect ESRF in any of the cases with CAKUT detected by postnatal USG scanning regardless of the prenatal history. Although our follow-up period is short, our data encourage that progression to end-stage renal failure can be prevented in CAKUT cases detected and treated in early life.

There are several limitations to our study, particularly the use of retrospective data and a relatively small number of cases. Also, it is not possible to know the exact number of cases with VUR in our study, since VCUG was performed not in all patients but in cases meeting the defined criteria. The ideal timing recommendation for postnatal ultrasonography to avoid false positivity and to detect serious cases is another limitation of our study.

As a conclusion, CAKUT one of the causes of preventable end-stage renal disease is an important public health problem. Postnatal USG screening is an effective method of determining cases of CAKUT. In our study, it was observed that approximately one-third of the cases of hydronephrosis, unilateral renal agenesis, duplex system, horseshoe kidney, and ectopic kidney could not be detected at prenatal US screening. We therefore recommend that in addition to prenatal USG screening, all children be screened for urinary system anomalies as a public health practice. Our data should be supported by larger patient groups, especially determining timing of the ideal USG screening.

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Informed Consent Statement: Informed consent forms were received from all participants or their parents before the study commenced.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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