Smyrna Tıp Dergisi ***Araştırma Makalesi***

Imaging Modalities In Recurrent Pediatric Urinary Tract Infections: When and Which To Choose?
Tekrarlayan Pediatrik İdrar Yolu Enfeksiyonlarında Görüntüleme Yöntemleri: Ne Zaman ve Hangisi Seçilmeli?

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Summary
Objectives: Urinary tract infections (UTIs) are common during childhood and imaging for pediatric UTIs is currently a heavily debated topic. In this report, the experience of a tertiary care center regarding the efficiency of imaging modalities in recurrent pediatric UTIs is presented.
Method: The study group consisted of 424 children diagnosed with pyelonephritis and recurrent UTI who were followed up in our university hospital's pediatric nephrology division. All the patients' data were collected retrospectively and the results of urinary tract ultrasonography (USG), voiding cystourethrography (VCUG), and Tc-99m dimercaptosuccinic acid scintigraphy (DMSA) were also recorded. Next, the role and efficiency of the three different imaging modalities were evaluated.
Results: The median age of the patients was 2 years (range, 1 month - 18 years). Urinary tract USG was performed in 409 of these patients and was abnormal in 176 (43%). During the VCUG examination, vesicoureteral reflux (VUR) was found in 81 (27.7%) of the 292 patients examined, whereas renal damage was demonstrated in 78 (31.1%) of the 251 patients who were additionally evaluated with DMSA. Any grade of a VUR were shown to be present in 21.3% and 34.9% of patients with normal and abnormal USG findings respectively ($p<0.0001$). With regard to DMSA findings, the percentage of renal damage was 22.4% and 40.0%, again in patients with normal and abnormal USG findings respectively ($p<0.0001$).
Conclusions: The results of this study indicated a clearly increased risk of abnormal findings in VCUG and DMSA examinations on the occasion of the presence of abnormal USG findings in pediatric patients with recurrent UTIs. Nevertheless, urinary tract USG alone was explicitly found to be insufficient to detect all the renal pathology in the same patient group.
Key words: Renal damage, urinary tract infections, vesicoureteral reflux

Özet
Amaç: Üriner sistem enfeksiyonları (İYE) çocukluk çağında yaygındır ve pediatrik İYE'lerin görüntülenmesi şu anda çok tartışılan bir konudur. Bu raporda, tekrarlayan pediatrik İYE'lerde görüntüleme yöntemlerinin etkinliğine ilişkin üçüncü basamak bir sağlık merkezinin deneyimi sunulmaktadır.
Yöntem: Çalışma grubu, üniversite hastanemiz çocuk nefroloji bölümünde takip edilen piyelonefrit ve tekrarlayan İYE tanısı almış 424 çocuktan oluşturuldu. Tüm hastaların verileri geriye dönük olarak toplandı ve üriner ultrasonografisi (USG), işeme sistoüretrografisi (VCUG) ve Tc-99m dimerkaptosüksinik asit sintigrafisi (DMSA) sonuçları da kaydedildi. Daha sonra, üç farklı görüntüleme yönteminin rolü ve etkinliği değerlendirildi.
Bulgular: Hastaların ortanca yaşı 2 yıldı (1 ay - 18 yıl). Bu hastaların 409'una üriner USG yapıldı ve 176'sında (% 43) anormaldi. VCUG incelemesi sırasında incelenen 292 hastanın 81'inde (% 27,7) vezikoüreteral reflü (VUR) saptanırken, DMSA ile ek olarak değerlendirilen 251 hastanın 78'inde (% 31,1) böbrek hasarı görüldü. Normal ve anormal USG bulguları olan hastaların sırasıyla% 21.3 ve% 34.9'unda herhangi bir derecede VUR olduğu gösterilmiştir ($p<0.0001$). DMSA bulgularına göre, böbrek hasar yüzdesi yine normal ve anormal USG bulguları olan hastalarda sırasıyla% 22.4 ve % 40.0 idi ($p<0.0001$).

Sonuç: Bu çalışmanın sonuçları, tekrarlayan İYE'si olan pediatrik hastalarda anormal USG bulgularının varlığı ile VCUG ve DMSA incelemelerinde anormal bulgu riskinin açıkça arttığını göstermiştir. Bununla birlikte, tek başına üriner USG'sinin, aynı hasta grubundaki tüm böbrek patolojisini saptamada yetersiz olduğu açıkça bulunmuştur.
Anahtar kelimeler: Böbrek hasarı, idrar yolu enfeksiyonları, vezikoüreteral reflü.

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Introduction

Urinary tract infections (UTI) may result with renal damage, hypertension and even renal failure in a long time period especially when they are recurrent. Recurrent UTIs are common during childhood and are an important cause of morbidity in the pediatric population (1). It has been documented that approximately 20% of children who had an episode of UTI underwent a symptomatic recurrence (2). Prompt diagnosis and treatment of the condition, and proper follow-up of these children are vital to avoid permanent renal damage (3). It is currently strongly recommended that screening with imaging modalities should be applied in the pediatric cases of pyelonephritis and/or recurrent UTIs (3,4). Nevertheless, there are diverse and somewhat incompatible comments in the literature, on the efficiency and safety of the imaging modalities available for this indication.

Urinary ultrasonography (USG) is a noninvasive, easily available and cost-effective modality for the evaluation of the urinary system. It describes the size, shape, position and echogenicity of the kidneys and may be helpful in the diagnosis of vesicoureteral reflux (VUR) and pyelonephritis (5). While urinary USG is definitely the initially preferred imaging modality, voiding cystourethrography (VCUG) and Tc-99m dimercaptosuccinic acid scintigraphy (DMSA) are the two other additional radiological investigations commonly employed in pediatric cases of recurrent UTIs. Whether which one of these imaging methods is more sensitive in the prediction of permanent renal damage or is useful in the follow-up is still controversial. Also, there is no consensus regarding which additional imaging modality to choose, as VCUG and DMSA are invasive methods involving radiation; and are also discomfortable and expensive. In this report, our experience in a tertiary care center regarding the efficiency of imaging modalities in recurrent pediatric UTIs was presented and discussed with the current literature.

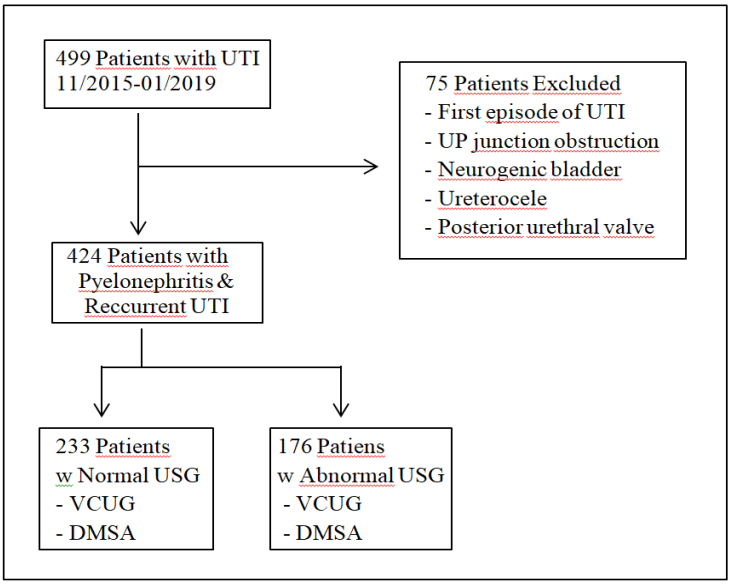
Method

Pediatric patients aged 1 month to 18 years who had been admitted to an university hospital with a diagnosis of pyelonephritis and recurrent UTI were recruited for the study. The study period extended from November 2015 to January 2019. This study was approved by Baskent University Institutional Review Board (Project no:KA20/152). All the relevant data were retrieved from the hospital's electronic medical records database. Epidemiological and clinical parameters including urine culture results, urinary USG, VCUG, and DMSA findings, including the existence of any scars, and the presence and extent of VUR were meticulously recorded. Patients with ureteropelvic junction obstruction, neurogenic bladder, ureterocele, bladder neck obstruction, and other types of congenital and/or neurological urinary tract abnormalities were excluded from the study. Also, patients presenting with their first UTI episode were excluded likewise. The study flow diagram is presented in Figure 1.

Clinical and laboratory parameters of fever or hypothermia, vomiting, poor feeding, nutritional problems, dehydration, irritability, flank pain, leukocytosis, elevated C-reactive protein (CRP) levels and erythrocyte sedimentation rates (ESR) were accepted to be consistent with acute pyelonephritis (1,2,3,6). Urine samples of the patients were obtained as midstream samples in older children, whereas catheter or sterile bag samples were used in younger children. All urine samples were inoculated into appropriate agar plates within half an hour of sampling. In the case of midstream and sterile bag samples, bacteriuria of 10^5 colony/μL and above, and in the case of catheter samples, bacteriuria of 10^4 colony/μL were considered indicative for the presence of infection. Although not routinely preferred, urine samples were collected by suprapubic aspiration, especially in children under 1 years of age. In suprapubic aspirates any organism growth was significant. The results of the urine analysis were also evaluated for the presence and confirmation of UTI. Pyuria was

defined as the presence of more than 5 neutrophils per high-power field of centrifuged urine. Nitrite and leukocyte esterase positivity were also considered significant for the presence of an UTI. While the results of the culture and antibiotic susceptibility testing dictated the treatment protocols, trimethoprim-sulfamethoxazole (2 mg per kg/10 mg per kg once per day) or nitrofurantoin (1-2 mg per kg once per day) was used for UTI prophylaxis during the follow-up (7).

Figure 1. *Study flow diagram*



DMSA, dimercaptosuccinic acid scan; UP, ureteropelvic; USG, urinary tract ultrasonography; UT, urinary tract; UTI, urinary tract infection; VCUG, voiding cystourethrography.

The patients were divided into 2 groups with respect to their USG findings. Patients with urinary USG abnormalities including hydronephrosis, hydroureteronephrosis, significant differences between renal sizes, hypoplasia, atrophy, or irregularities in renal contours were classified as the "Abnormal USG" group. The patients without such abnormal USG findings were classified as the "Normal USG" group. Taking the VCUG findings into account, VUR severity was graded as grade I to grade V in accordance with the international system of radiographic grading of VUR (8). Grades I and II VUR were classified as "low grade" and grade III and above VUR as "high grade". The findings of renal cortical defects with 1 or more scarred areas and/or diffuse reduced uptake (45% or less) with small renal size were accepted as abnormal DMSA scans (9). The correlation between USG findings and the results of VCUG and DMSA scans were evaluated.

The statistical analyses were performed using IBM SPSS Statistics for Windows (IBM Corp. Released 2011, Version 20.0. Armonk, NY: IBM Corp.). All numerical variables with normal distribution were expressed as the mean±SD, whereas numerical variables not demonstrating normal distribution were given as the median together with the minimum and the maximum values. Categorical or ordinal variables were expressed as total counts and their percentages. Chi-square test was used in the intergroup comparison. Pearson or Spearman analyses were used for the correlation measurements, where appropriate. A p value of <0.05 was considered statistically significant.

Results

Four hundred and twenty-four children [280 (66%) girls and 144 (34%) boys] with a median age of 24 months (range 1-216 months) who were diagnosed as pyelonephritis and recurrent UTI were enrolled for the study. Urine analysis and culture were obtained unexceptionally and the most common pathogen documented was *Escherichia coli* (65%) (Table 1).

Urinary USG was performed in 409 patients (96.5%) and an ultrasonographic abnormality was detected in 176 (43.0%). An abnormal USG was more prevalent among boys than girls (51.8% and 38.5% respectively). Among the 292 patients (68.9%) screened by VCUG, any grade of a VUR was documented in 81 (27.7%). Sixty-nine (85.2%) of these 81 patients had a "high grade" reflux (grade III-V VUR). The percentage of those with a grade IV or grade V VUR was 37% (Table 2). While a "high grade" VUR was more common among boys (79.2%), a "low grade" reflux (grade I-II VUR) was more commonly documented among girls (54.4%). With respect to DMSA scanning, 251 examinations (59.2%) were performed and renal damage was shown in 78 (31.1%).

Table 1. *Pathogenic microorganisms according to urine culture results.*

Pathogenic Microorganism	**n (%)**
Escherichia coli	276 (65)
Klebsiella spp.	67 (15.8)
Proteus spp.	35 (8.3)
Enterococci	28 (6.6)
Staphylococcus aureus	15 (3.5)
Pseudomonas spp.	3 (0.7)
Total	424 (99.9)

Table 2. *Voiding cystourethrogram findings among patients with vesicoureteral reflux.*

Grade of Vesicoureteral Reflux	**n (%)**
Grades I-II	12 (14.8%)
Grade III	39 (48.2%)
Grades IV-V	30 (37.0%)
Total	81 (100.0%)

When any potential relationships between the USG, VCUG, and DMSA scan findings were examined, VUR of any grade was shown to be present in 21.3% and 34.9% of the patients in the "Normal USG" and "Abnormal USG" groups respectively (OR=1.98, p<0.0001, 95% CI: 1.62 - 2.42) (Table 3). With respect to DMSA scan results, the percentages of abnormal findings indicating any degree of renal damage were found to be 22.4% and 40%, again in the "Normal USG" and "Abnormal USG" groups respectively (OR=2.31, p<0.0001, 95% CI: 1.90 - 2.80) (Table 3).

Table 3. *Demographic data and complementary imaging modalities' results with respect to urinary ultrasonography findings*

	Normal USG n: 233	**Abnormal USG n: 176**	**p**
Gender (F/M)	166/67	104/72	>0.05
Median age as months (min-max)	22.5 (1-228)	24 (1-216)	>0.05
VCUG Vesicoureteral Reflux (+)	21.3%	34.9%	<0.0001
DMSA Renal Scar (+)	22.4%	40.0%	<0.0001

DMSA: Dimercaptosuccinic acid scan, USG: Ultrasonography, VCUG: Voiding cystourethrogram

No significant correlations were observed among gender, age, the causative agent of the UTI, and the presence of any degree of renal scarring (p>0.05 for all). In the present study, 56.4% of the children were under 3 years of age and 43.6% were over 3 years of age. There was no

difference between the rates of scar positivity in DMSA, VUR positivity and USG abnormalities in these children (p> 0.05 for all). There was a significant and moderate degree of positive correlation among the presence of a scar in DMSA and a "high grade" VUR (r=0.39, p=0.003). While DMSA revealed renal scarring in 50.8% of the patients with any grade of a VUR, scarring was detected in only 25.0% of the patients without any VUR (OR=3.09, p<0.0001, 95% CI:2.56-3.74). When patients with both VUR and renal scarring were examined specifically, 73.3% of these patients proved to be suffering from a "high grade" VUR. It is important to notice that, only 4.3% of the same patients had normal urinary USG findings.

Discussion

While imagings in UTIs help with the diagnosis of acute pyelonephritis, identification of the children at risk of developing renal damage, and documentation of any renal scarring, the correct approach for imaging in pediatric recurrent UTIs is still a debated topic (10,11). In this report which analyzed pediatric recurrent UTI cases, it was shown that while an abnormal urinary USG increased the likelihood of subsequent abnormal VCUG and DMSA findings; an abnormal VCUG also increased the probability of abnormal DMSA findings and to a higher extent. Nevertheless; it was also among our findings that none of these three imaging modalities (i.e., USG, VCUG, and DMSA) on their own was efficacious to document all the present abnormalities. Accordingly, following a meticulously performed urinary USG, careful identification of high-risk children with an increased risk for renal and/or urinary tract abnormalities and further implementation of selected additional imaging modalities in this patient group, appear to be effective, safe, and appropriate. A similar approach has already been suggested in the literature by Marks and Dacher and their colleagues (10,12).

Among the 424 children enrolled in the study, 66% were girls and 34% were boys. As it is repeatedly stated in the relevant literature, the epidemiology of pediatric UTIs varies based on age and gender. According to the published data, while during the initial year of life, boys are exhibiting a higher incidence of UTIs, and in other age groups, girls are more predisposed to developing UTIs (13). The present study included children aged 1-216 months with a median age of 24 months, and therefore produced the above gender ratio of 66 to 34 (girls to boys respectively).

In accordance with the literature, the most common infectious agent isolated in our cases of pediatric recurrent UTIs was Escherichia coli (Table 1) (13,14). Albeit UTIs may be caused by any microorganism which can colonize the urinary tract, most causative pathogens are enteric bacteria and E. coli is the most frequently identified pathogenic microorganism (15). Otherwise, the causative pathogen in cases of pediatric UTIs varies based on the concurrent comorbidities and the age of the patients. In the study, 96.3% of the isolated causative pathogens were members of the enteric flora (Table 1). The exclusion criteria which strictly left out patients with any type of congenital and/or neurological urinary tract abnormalities surely was one of the determinants for this uropathogen spectrum observed.

Accurate and prompt diagnosis and effective treatment of children with UTIs are vital for the prevention of permanent renal damage which may have devastating long term consequences in this age group. While the timing of imaging investigations is dictated generally by the child's clinical condition and the initial response to timely therapy, in the acute setting and the first episode of a UTI, with the exception of urinary USG, imaging modalities in general are not indicated (16). Besides and regrettably, USG following the first UTI is shown to have poor sensitivity (3,17,18). In contrast, in cases of recurrent pediatric UTIs, there is a strong agreement on the implementation of relevant imaging modalities with debate over the correct protocol regarding the timing and the order of these investigations (10). While a review of the current relevant literature emphasizes the complementary roles of USG, VCUG, and DMSA, important factors affecting the timing and the choice of imaging modalities in pediatric UTIs also seem to be the opportunity and the ease of access to them (3,6,10,11,12).

In the present study the most commonly implemented imaging modality was urinary USG (in 96.5% of the patients). This practice is in accordance with the current recommendations which stress the initial preference and basic role of urinary USG. (12,16) Indeed, the 2011

American Academy of Pediatrics guidelines also stated that urinary USG should be performed after initial febrile UTI in a young child (6). Urinary USG is a widely available, noninvasive, relatively easy to implement and safe imaging procedure. Nevertheless, as its value in both the diagnosis of pyelonephritis and the detection of low grade VUR is limited, USG is accepted as a poor screening test with low sensitivity to detect patients with renal damage (3,5,17,18,19,20,21). This proved to be true also in the presented study. The percentages of patients with abnormal VCUG and abnormal DMSA findings despite normal urinary USG were 21.3% and 22.4% respectively. This data support the approach which recommends USG as the initial imaging modality and emphasize the complementary roles of USG and VCUG/DMSA (5,12,17,18,20,21, 22).

Along with urinary USG, the two complementary imaging modalities used in this study were VCUG and DMSA. According to the generally accepted current practice dictated by the 2011 American Academy of Pediatrics guidelines, on the occasion of an abnormal urinary USG performed following an initial febrile UTI in a child, a VCUG is indicated. While VCUG and DMSA could both be considered complementary to USG, as they provide additional important, DMSA has a limited application in neonates and children under 3 months of age (10,11,12,22,23). These two imaging modalities have their own benefits and limitations. While VCUG demonstrates VUR and grades its severity, DMSA is currently considered to be the most sensitive imaging modality for diagnosing pyelonephritis and documenting renal scarring (3,4). It was documented in the study that an abnormal urinary USG result clearly increased the probability of abnormal VCUG and/or DMSA findings. Additionally it was shown that, the presence of any grade of VUR clearly and considerably increased the likelihood of renal scarring with DMSA. Also, a significant and moderate degree of correlation was observed between the presence of a scar in DMSA and the presence of a "high grade" VUR. These findings are consistent with the findings of Orellana et al (24). In Orellana and colleagues' study, children with VUR were shown to have a significantly higher percentage of renal scars when compared to children without VUR ($p<0.0001$). Similar findings were also reported by Ajdinovic et al (25). Likewise, in Ajdinovic and colleagues' article, a significantly higher incidence of abnormal DMSA findings were reported in children with UTI and VUR compared to children with UTI but not VUR ($p<0.001$).

Another noteworthy finding was the significantly higher prevalence of abnormal USG findings among boys than girls (51.8% and 38.5% respectively). Also, while a "high grade" (grade III-V) VUR was more common among boys (79.2%), a "low grade" reflux (grade I-II VUR) was more prevalent among girls (54.4%). The more severe reflux observed among boys most probably also resulted in more frequent permanent renal damage and abnormal urinary USG findings among them.

Conclusion

The findings of the present study pointed the complementary roles of USG, VCUG and DMSA in pediatric patients with pyelonephritis and recurrent UTI. None of these three imaging modalities was shown to be sensitive enough to document all the urinary tract pathologies in this patient group. While an abnormal urinary USG carried an unfavorable significance for VCUG and/or DMSA, a finding of VUR, specifically a "high grade" VUR denoted a clearly and significantly increased risk for renal scarring in DMSA. Thus, imaging by urinary USG should be considered for all infants and children with pyelonephritis and/or recurrent UTIs. Further work-up for the documentation of any renal scarring and assessment of VUR should be planned keeping a high level of clinical suspicion and a low threshold for performing complementary imaging modalities. This decision should be made on an individual basis by taking into account the initial urinary USG findings and the clinical presentation, and the course of each patient. It was believed that, this approach will prove to be safe and effective, and will also help to avoid the unnecessary invasive, potentially harmful, and expensive investigations.

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