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Delayed diagnosis of primary vesicoureteral reflux in children with recurrent urinary tract infections: Diagnostic approach and renal outcomes

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ABSTRACT

Objective: In this study, we aimed to assess renal outcomes of delayed diagnosis of dilating primary vesicoureteral reflux (VUR) following recurrent febrile urinary tract infections (fUTIs) and its diagnostic imaging procedures.

Material and methods: The medical records of patients who underwent ultrasonography (US), non- acute dimercaptosuccinic acid (Tc-99mDMSA) scintigraphy and voiding cystourethrography (VCUG), and who were older than 2 years at the time of VUR diagnosis were retrospectively reviewed.

Results: A total of 32 children (female, n=27: 84.4%) with a mean age of 7.67±3.34 years at the time of diagnosis of VUR were included in the study. Grade III, IV, V VUR were found in 22%, 69%, and 9% of the patients, respectively. At the time of VUR diagnosis, abnormal US findings were detected in 75% of the cases. Tc-99mDMSA detected abnormalities in 83.9% (7 with a single scar, 7 with multiple lesions, 12 with reduced kidney function) of the patients. Estimated glomerular filtration rate of 3 patients with bilateral grade IV VUR was <75 mL/min/1.73 m^2. In 5 patients (16%), VUR could not be predicted by US+DMSA scintigraphy (Grade IV VUR in 3 and Grade III in 2 cases). The sensitivity in predicting VUR was 75.00% (95% CI: 56.60-88.54) and 83.87% (95% CI: 66.27-94.55), respectively, for US alone and combined US+DMSA.

Conclusion: VCUG should be performed routinely in addition to US and non-acute DMSA in all children referred with recurrent fUTIs. Awareness of childhood UTI in public and healthcare personnels should be increased in order to refer these patients at a early stage to pediatric urology and nephrology units.

Keywords: Child; primary vesicoureteral reflux; recurrent urinary tract infections; reflux nephropathy

Introduction

Renal damage associated with primary vesicoureteral reflux (VUR) consists of two distinct and sex- related groups namely groups with congenital dysplasia or acquired postinfectious scarring. While congenital dysplasia occurs mainly in males who frequently present antenatally or in infancy, the other group includes predominantly female patients who usually present in older ages, and who are predisposed to recurrent pyelonephritis and subsequent renal scarring. Over time, substantial scarring may lead to long-term complications such as hypertension, proteinuria, renal failure which is collectively known as reflux nephropathy (RN).[1,2] Although early detection and management of VUR in these patients improve renal outcomes, RN is still a common cause of childhood end- stage renal disease (ESRD) in developing countries. Low socioeconomic status of patients, their parents' and healthcare personnel's insufficient awareness of urinary tract infection (UTI) and reflux, late referral to the pediatric urology and nephrology centers are considered as potential risk factors for RN in these regions.[3]

In this retrospective cohort study, we aimed; (i) to assess demographic and clinical characteristics (ii) efficiency of their diagnostic imaging tests and (iii) to investigate renal outcomes of delayed dilating primary VUR (Grade III-V VUR) diagnosis in children referred due to recurrent febrile urinary tract infections (fUTIs).

Material and methods

Medical records of the patients with VUR diagnosis who were followed at the Pediatric Nephrology Unit of Antalya Training and Research Hospital between September 2011 and February 2017, were reviewed retrospectively. The patients with secondary VUR, primary Grade I-II VUR, congenital renal dysplasia and those who were younger than 2 years at the time of VUR diagnosis despite an anamnesis of fUTIs were excluded from the study. Thus, study population consisted of 32 children aged ≥2 years who were diagnosed with dilating primary VUR during assessment for recurrent fUTIs.

Confirmed fUTI (a body temperature of >38.5°C) was defined as the presence of both pyuria (>5 WBC/per high-power field in centrifuged urine or positive leukocyte esterase on dipstick test) and positive urine culture, which was considered as growth of $\geq 10^5$ colony-forming units/mL (CFU) in a midstream specimen or ≥50 000 CFU/mL of a single bacterium in catheterized specimen. The presence of fever accompanied by symptoms of UTI and pyuria in a patient without urine culture results, was considered as non-confirmed fUTI. The diagnosis of recurrent fUTIs was based on previous culture-confirmed UTIs in addition to a detailed history provided by their parents, however, it was unclear whether some UTIs were febrile.

Urinary tract ultrasonography (US), voiding cystourethrography (VCUG), non-acute dimercaptosuccinic acid (Tc-99m DMSA) scintigraphy - except for one patient with stage IIIB chronic kidney disease (CKD)- were obtained from all patients at the time of their presentation. Age at the time of VUR diagnosis was defined as patient age at the first VCUG. Renal scintigraphy, US, and VCUG results were recorded. Abnormal US findings related to VUR were considered as hydronephrosis and/or hydroureteronephrosis, pelvic or ureteral wall thickening, absence of corticomedullary differentiation, and cortical abnormalities such as cortical thinning, irregularity or hyperechoic cortex. Acquired renal scarring on DMSA scintigraphy was defined as one or more focal areas of diminished uptake of DMSA associated with contour deformation. Additionally, ≤44% loss of differential function was considered as reduced kidney function.[4] The patients with abnormal DMSA scintigraphy were divided into 3 groups: group 1 consisted of the patients with a single scar, group 2 with multiple scars, and group 3 with reduced kidney function. The accuracy of US, DMSA scintigraphy and combined US+DMSA studies to predict VUR (test positivity) was assessed. Vesicoureteral reflux was graded by using the system of the International Reflux Study in Children.[5] If VCUG showed bilateral VUR, the highest VUR grade was utilized for analysis. Estimated glomerular filtration rate (eGFR) was calculated by the Schwartz formula[6] and CKD was classified according to the Kidney Disease Outcomes Quality Initiative Guideline.[7] Children with dysfunctional voiding were evaluated by uroflow/electromyogram. All children received continuously antibiotic prophylaxis until surgical repair of VUR , and if neccessary, anticholinergic medications.

Statistical analysis

All statistical analysis were performed using IBM Statistical Packages for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) for Windows 21.0. Continuous variables were expressed as mean ± standard deviation for normally distributed data and as median and interquartile range (IQR) for non-normally distributed data. Sensitivity value and positive likelihood ratio (LR+) of US and DMSA scintigraphy for predicting VUR were calculated. Kruskal –Wallis test was performed for comparison among groups and a p value <0.05 was considered statistically significant.

Results

A total of 32 patients (including 27 (84.4%) female) with a mean age of 10.49±3.42 years and a median follow-up period of 1.70 (IQR; 1.3-4.1) years were included in the study. Mean age at VUR diagnosis was 7.67±3.34 years. The reflux was unilateral in 15 (46.8%) and bilateral in 17 (53.2%) patients. Grade III, IV, V VUR were found in 22%, 69%, and 9% of the children, respectively. Additional urological abnormalities included horseshoe kidney, contralateral ectopic kidney, duplication of collecting system, and bladder diverticulum in one patient each. Demographic and clinical characteristics of patients were given in Table 1. All of the boys in the study were circumcised.

Each patient had experienced at least 3 confirmed fUTIs and many of them had also non-confirmed fUTIs. Elapsed time after the last documented UTI varied from 1 month to 6 months. Ten patients (31%) reported symptoms of bladder and/or bowel dysfunction, such as constipation, daytime wetting, withholding maneuvers, frequency, infrequency, and urgency. Abnormal US and renal scintigraphy findings were found in 24/32 (75%) and 26/31 (83.9%) children, respectively. There were 7 patients (26.9%) in group 1, 7 (26.9%) in group 2, and 12 (46.2%) in group 3 as assessed according to the presence of DMSA anomalies. Although not statistically significant, present age and age at VUR diagnosis tended to be higher in patients with reduced kidney function when compared with the other two groups (Table 2, p>0.05). Three children with normal US had renal damage

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as detected on DMSA. In 5 (16%) children, VUR could not be predicted by the combined US and DMSA scintigraphy (Grade IV VUR in 3 and Grade III in 2 patients). The sensitivity and LR (+) in predicting VUR were 75.00% (95%CI: 56.60-88.54), and 0.75, respectively, for US alone and 83.87% (95% CI: 66.27-94.55), and 0.84, respectively, for both DMSA alone and combined US+DMSA (Table 3).

Table 1. Demographic and clinical characteristics of patients

Female /male (n)	27/5
Mean age (year)	10.49±3.42
Mean age at VUR diagnosis (year)	7.67±3.34
Median follow-up period (year) (IQR)	1.70 (1.3-4.1)
VUR grade (n,%)*	
Grade III	7 (22)
Grade IV	22 (69)
Grade V	3 (9)
Type of additional urinary anomaly (n, %)	
Contralateral ectopic kidney+ Grade IV VUR	1 (3.1)
Unilateral urethral diverticulum + Grade IV VUR	1 (3.1)
Horseshoe kidney + Grade IV VUR	1 (3.1)
Duplication of collection system + grade IV VUR	1 (3.1)
Abnormalities detected on DMSA scintigraphy (n=31, %)	
Absence of scar	5 (15.6)
Single scar	7 (21.9)
Multiple scars	7 (21.9)
Reduced kidney function	12 (37.3)
Renal failure (n, %)	**3 (9.4)**

*If VUR was bilateral, maximum degree of reflux was taken into consideration.
VUR: vesicoureteral reflux; DMSA: dimercaptosuccinic acid

Table 2. Patient characteristics according to abnormal DMSA results

Parameters	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=12)	p
Current age (year)	9.25±3.43	9.17±2.44	11.95±3.39	0.126
Age at VUR diagnosis (year)	6.85±2.74	5.91±1.34	8.57±3.67	0.370

P values for comparison across all groups were obtained from Kruskal–Wallis.
VUR: vesicoureteral reflux; DMSA: dimercaptosuccinic acid

Table 3. Diagnostic value of US, DMSA scan, and combined US+DMSA for predicting VUR sensitivity (%) (95% CI) positive likelihood ratio

US alone	75.00% (56.60-88.54)	0.75
DMSA alone	83.87% (66.27-94.55)	0.84
Combined (US+DMSA)	83.87% (66.27-94.55)	0.84

US: ultrasonography; DMSA: dimercaptosuccinic acid

At the time of presentation, eGFR was determined as <75 mL/min/1.73m^2 in 3 (9.3%) patients with bilateral Grade IV VUR (stage II CKD in 2 and stage IIIB in 1 patient). A total of 2 patients developed hypertension (1 patient with stage II CKD and 1 with bilateral multiple scars). Proteinuria was not detected during follow-up period.

Discussion

In the studies conducted in our country before 2000, RN was reported as the most common cause of pediatric CKD. Since then, the data reflecting the current morbidity of RN are limited.[3] In the present study, the renal outcomes of 32 patients (mean age at VUR diagnosis; 7.67±3.34 years) with dilating primary VUR and recurrent UTIs were assessed. In accordance with the literature, there was a predominance of female patients (84%) in our cohort. Multiple scars and reduced kidney function on non-acute DMSA scintigraphy were detected in 26.9% and 46.2% of the patients, respectively, and 4 (13%) patients had late sequelae of reflux such as hypertension and/or renal failure at presentation. In a multi-center study from Turkey in 2005, Bek et al.[3] investigated epidemiology of childhood CKD. In their study (n=282), primary VUR accounted for 18.5% of the cases, which was the leading cause of CKD. The mean age at VUR diagnosis was 8.3±4.9 years. The patients with RN were not examined in a separate diagnostic category, however, the authors speculated that the cause of CKD was more likely to be primary VUR with recurrent UTIs rather than congenital dysplasia, because of the old age at the time of diagnosis and a slight female predominance. In another study from Turkey in 2011, Alparslan et al.[8] examined 242 children with pre-dialysis CKD, with a mean age of 8.5±4.7 years at the time of diagnosis. Similarly, the main cause of CKD was urologic diseases, mostly primary VUR.

Contrary to these results from our country, VUR diagnosis associated with CKD has been established early in life (<1 year old) in other countries, which is associated with better renal outcomes.[9-11] Especially in girls, early detection and treatment of primary VUR following UTIs may preserve renal parenchyma, or at least, prevent its progression to ESRD during childhood.[11,12]

The diagnosis and management of childhood primary VUR remains controversial. Imaging algorithms used to evaluate the children who experienced the first episode of fUTI depend on two approaches; bottom-up or top-down. The bottom-up approach recommends using urinary tract US and VCUG first to detect VUR. However, in this method, since only 30-40% of the

children who experienced first fUTI have reflux, a significant proportion of these children are subjected to unnecessary urethral catheterization and radiation exposure. Alternatively, the traditional top-down approach recommends performing US, and DMSA scintigraphy to determine whether there is an acute renal parenchymal involvement at the time of fUTI. Only those with parenchymal involvement detected on acute-phase DMSA imaging are referred for a VCUG in addition to delayed DMSA (≥6 months after fUTI) to evaluate permanent scarring.[13,14] Although the diagnosis of dilating VUR is missed in a small subgroup of children at risk of developing severe kidney damage, some studies have supported this strategy having high sensitivity, specificity, and negative predictive value for predicting clinically significant VUR.[15-17] However, conclusions from two meta-analyses have demonstrated that acute-phase DMSA scintigraphy for predicting VUR was not accurate enough in children with fUTI.[18,19] In addition, it should be emphasized that there is no certain distinction between radiologically revealed congenital renal dysplasia and parenchymal inflammatory changes associated with acute pyelonephritis in young children. Therefore, the defects resulting from congenital dysplasia may be mistakenly identified as acute pyelonephritis on initial DMSA imaging.

Similarly, in the recently published guidelines, there is no consensus on what imaging studies are indicated when assessing the children with recurrent UTIs.[20] In the current study, the patients who had been referred after an acute pyelonephritis episode was already treated by primary physicians or pediatricians, and overall imaging tests (US, VCUG, and DMSA scintigraphy) were used in all patients at presentation. A single DMSA scintigraphy was performed ≥1 month after the last documented fUTI to exclude reflux early and avoid additional UTI episodes before delayed DMSA was obtained. In accordance with this imaging strategy, some studies reported that a single DMSA study (≥3 months after the latest episode of fUTI) was used in children referred for assessment of the first or recurrent episodes of fUTI.[21,22] The recent pediatric guidelines published by The European Association of Urology and European Society for Paediatric Urology have also recommended that DMSA scanning should be performed within 1–2 months of the UTI episode, except for neonates.[23]

In line with the literature, US alone had a low diagnostic value for prediction of VUR in our study. Although US and DMSA together had a higher sensitivity rate (83.87%) for predicting VUR, it failed in 5 (16%) patients. In addition, we did not find any correlation between the severity of abnormal DMSA findings and current age, age at VUR diagnosis, however, older age and a greater initial renal impairment were reported as risk factors for progression to ESRD in children with VUR.[24] We think that this result might be attributable to wide distribution of patients' age and small sample size.

Our study has several limitations. Because of short follow-up period, small number of patients, its retrospective and single center design, multi-center prospective studies are needed to detect the prevalance, management and prognosis of RN in our country. Because the number of males was too small for statistical analysis, we did not compare demographic and clinical characteristics between male and female patients.

In conclusion, although our results do not reflect national data, primary VUR with recurrent UTIs seems to be a still important cause of renal damage in childhood. Therefore, we tried to draw attention to RN that is a preventable cause of pediatric ESRD. In our country, majority of children with recurrent UTIs have already been treated in primary and secondary health care centers before admiting to pediatric urology and nephrology units. Increasing awareness of UTIs in public and among healthcare personnels and earlier referral of these patients may decrease the incidence of reflux- induced ESRD in children. Especially in developing countries, individualized management strategies, also including patient's socioeconomic status, should be taken into consideration when evaluating a child at risk of VUR. Ultrasonography and DMSA scintigraphy together do not seem to be good enough to predict dilating VUR with recurrent fUTIs. Therefore, VCUG should be performed routinely in addition to US and non- acute DMSA scintigraphy.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was not obtained since all data analysed were collected retrospectively as part of routine diagnosis and treatment and there were no concerns regarding patient privacy.

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References

1. Peters C, Rushton HG. Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. J Urol 2010;184:265-73. [CrossRef]

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DOI:10.5152/tud.2018.98372

2. Blumenthal I. Vesicoureteric reflux and urinary tract infection in children. Postgrad Med J 2006;82:31-5. [CrossRef]
3. Bek K, Akman S, Bilge I, Topaloğlu R, Calişkan S, Peru H, et al. Chronic kidney disease in children in Turkey. Pediatr Nephrol 2009;24:797-806. [CrossRef]
4. Snodgrass WT, Shah A, Yang M, Kwon J, Villanueva C, Traylor J, et al. Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. J Pediatr Urol 2013;9:856-63. [CrossRef]
5. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Study in Children. Pediatr Radiol 1985;15:105-9. [CrossRef]
6. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629-37. [CrossRef]
7. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
8. Alparslan C, Yavaşcan Ö, Erdoğan H, Kara OD, Bal A, Öncel EP, et al. Decreased Rate of CKD Stage V at Admission Among Children: A Single-Center Experience from the Western Part of Turkey. Turk Neph Dial Transpl 2017;26:190-5. [CrossRef]
9. Mong Hiep TT, Ismaili K, Collart F, Van Damme-Lombaerts R, Godefroid N, Ghuysen MS, et al. Clinical characteristics and outcomes of children with stage 3-5 chronic kidney disease. Pediatr Nephrol 2010;25:935-40. [CrossRef]
10. Ardissino G, Daccò V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid Project. Pediatrics 2003;111:e382-7.
11. Marra G, Oppezzo C, Barberis V, Bianchetti MG. Age at diagnosis of vesicoureteric reflux after urinary infections: historical changes. Acta Paediatr 2003;92:734-6. [CrossRef]
12. Marra G, Oppezzo C, Ardissino G, Daccò V, Testa S, Avolio L, et al. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. J Pediatr 2004;144:677-81. [CrossRef]
13. Koyle MA, Elder JS, Skoog SJ, Mattoo TK, Poh HG, Reddy PP, et al. Febrile urinary tract infection, vesicoureteral reflux, and renal scarring: current controversies in approach to evaluation. Pediatr Surg Int 2011;27:337-46. [CrossRef]
14. Prasad MM, Cheng EY. Radiographic evaluation of children with febrile urinary tract infection: bottom-up, top-down, or none of the above? Adv Urol 2012;2012:716739.
15. Lee MD, Lin CC, Huang FY, Tsai TC, Huang CT, Tsai JD. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercaptosuccinic acid scanning. J Pediatr 2009;154:797-802. [CrossRef]
16. Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. J Pediatr 2007;151:581-4. [CrossRef]
17. Sheu JN, Wu KH, Chen SM, Tsai JD, Chao YH, Lue KH. Acute 99mTc DMSA scan predicts dilating vesicoureteral reflux in young children with a first febrile urinary tract infection: a population-based cohort study. Clin Nucl Med 2013;38:163-8. [CrossRef]
18. Mantadakis E, Vouloumanou EK, Georgantzi GG, Tsalkidis A, Chatzimichael A, Falagas ME. Acute Tc-99m DMSA scan for identifying dilating vesicoureteral reflux in children: a meta-analysis. Pediatrics 2011;128:e169-79.
19. Shaikh N, Spingarn RB, Hum SW. Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. Cochrane Database Syst Rev 2016;5;7:CD010657.
20. Okarska-Napierała M, Wasilewska A, Kuchar E. Urinary tract infection in children: Diagnosis, treatment, imaging - Comparison of current guidelines. J Pediatr Urol 2017;13:567-73. [CrossRef]
21. Snodgrass WT, Shah A, Yang M, Kwon J, Villanueva C, Traylor J, et al. Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. J Pediatr Urol 2013;9:856-63. [CrossRef]
22. Bush NC, Keays M, Adams C, Mizener K, Pritzker K, Smith W, et al. Renal damage detected by DMSA, despite normal renal ultrasound, in children with febrile UTI. J Pediatr Urol 2015;11:126.e1-7.
23. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, et al. European Association of Urology; European Society for Pediatric Urology. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol 2015;67:546-58. [CrossRef]
24. Novak TE, Mathews R, Martz K, Neu A. Progression of chronic kidney disease in children with vesicoureteral reflux: the North American Pediatric Renal Trials Collaborative Studies Database. J Urol 2009;182:1678-81. [CrossRef]