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Original Article

Clinical value of late DMSA scan in predicting vesicoureteral reflux in children with febrile urinary tract infection

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Abstract

Aim: To assess the usefulness of late dimercaptosuccinic acid (DMSA) renal scans in revealing high-grade vesicoureteral reflux (VUR).

Material and Methods: Between July 2015 and December 2016, medical records of 112 patients who were admitted with febrile urinary tract infections (fUTIs) were retrospectively reviewed. The demographic information of the patients, and follow-up imaging [ultrasonography (USG), DMSA renal scans, and voiding cystourethrography] data were reviewed.

Results: Of the 112 patients, 82 patients (73.2%) were female, 30 were male (26.8%), and the mean age was 7.04 ± 3.94 years. Recurrent fUTIs were detected in 65 patients (58%). Of the patients, 68 (60.7%) had abnormal urinary system USG, and 74 (66.1%) had abnormal DMSA renal scans. Vesicoureteral reflux (VUR) was detected in 63 patients (56.3%). VUR was present in 49 (66.2%) of 74 patients with scarring in DMSA and detected in 14 (38.8%) of 38 patients with normal DMSA scans. Significant agreement (kappa: 0.274 / p=0.003) was found between DMSA and VUR results. The sensitivity, specificity and positive predictive values of late DMSA renal scan to predict VUR were 77.8 %, 49 % and 63.2% respectively.

Conclusion: Abnormal late DMSA scans carry a higher sensitivity and positive predictive value for predicting high-grade VUR in children with recurrent fUTIs. Late DMSA imaging seems a useful option in screening for high-grade VUR in children when the acute interventions are limited.

Keywords: Urinary tract infection; vesicoureteral reflux; dimercaptosuccinic acid scintigraphy

INTRODUCTION

Urinary tract infection (UTI) is one of the leading causes of bacterial infections in childhood (1-3). Vesicoureteral reflux (VUR) is a precipitating risk factor in recurrent febrile UTIs (fUTIs) and renal scar formation. The most commonly used imaging studies include urinary system ultrasonography (USG), voiding cystourethrography (VCUG), and dimercaptosuccinic acid (DMSA) renal scintigraphy in the evaluation of children with recurrent fUTIs (4,6).

In recent years, there has been a significant decrease in the usage of VCUG as an invasive procedure due to complications such as higher radiation exposure and iatrogenic UTI. In previous studies, it was found that not all children with VUR developed renal scarring, or that some children with fUTIs and renal scars in DMSA did not have VUR (7-11). It is now important to prevent and detect permanent renal damage, to detect patients at high risk of renal scarring, and to minimize radiation exposure and complications. Therefore, instead of the bottom-up approach which focuses on VUR detection in recurrent fUTI by use of VCUG, the top-down approach emphasizes priority of renal scar formation by use of DMSA and USG. Some authors adopted a modified approach. This approach requires an acute urinary system USG and late DMSA after fUTI, reserving VCUG for patients with abnormal DMSA, USG and/or recurrent FUTI (4,9,12).

The aim of this study was to compare the findings of urinary system USG, VCUG, and late DMSA to evaluate the consistency of VUR, and also assess the usefulness of late DMSA to identify children at risk of VUR.

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MATERIAL and METHODS

This study was performed retrospectively in 112 children with recurrent fUTIs who were followed up in the Pediatric Nephrology department of Kayseri Training and Research Hospital between July 2015 and December 2016.

The inclusion criteria of the patients were as follows: (1) patients aged ≤ 18 years, (2) patients with recurrent fUTIs, (3) patients without a history of congenital and acquired renal pathology (neurogenic bladder, chronic renal failure, cystic kidney disease, renal agenesis etc.), and (4) patients in whom urinary system USG, VCUG, and DMSA renal scintigraphy had been performed. Recurrent UTI was defined as either two or more episodes of pyelonephritis or one pyelonephritis plus one or more episodes of cystitis, or three or more episodes of cystitis, as defined in the National Institute for Care and Clinical Excellence (NICE) clinical guideline (2).

Demographic data, urine analysis and culture, urinary system USG, VCUG, and DMSA results were recorded. Hydronephrosis, hydroureter, small or hypoplastic kidney (defined as a kidney length below two standard deviations for the corresponding age), and renal parenchymal changes were considered as abnormal finding of USG. DMSA scintigraphy was taken for each patient at least 4-6 months after a fUTI. In DMSA scintigraphy, below 45% of differential renal function with cortical hypoactivity, small kidney, or loss of renal contour was accepted as abnormal. VCUG was performed in all patients suspected of VUR due to findings such as parenchymal changes, upper urinary system and ureteral dilatation on USG, and renal damage in a DMSA scan. VUR was graded according to the International Reflux Study in Children (5).

The study was approved by the Ethics Committee of Erzurum University, Faculty of Medicine (Application no: 36, Approval date: 13.02.2019). The personal data of the patients were not used for other scientific purposes.

Statistical Evaluation

Statistical analyses were performed using the IBM SPSS for Windows Version 21.0 package program. Numerical variables are summarized as mean ± standard deviation (SD), and median [minimum - maximum] values. Categorical variables are represented as numbers and percentages. The differences between independent groups in terms of categorical variables were investigated using the Chi-square test or Fisher's exact test. The normality of distribution of numerical variables was examined using the Shapiro-Wilk test and homogeneity of variance using the Levene test. VUR risk factors were determined using multivariate logistic regression analysis. The level of significance was taken as $p<0.05$.

RESULTS

A total of 112 patients were enrolled in the study. There were 30 (26.8%) boys and 82 (73.2%) girls, with a mean age of 7.04±3.94 years. Sixtyfive patients had recurrent fUTIs. Abnormal urinary system USG was determined in 68 (60.7%) children. Hydronephrosis was the most common abnormality detected on USG, being present in 43 (63.2%) patients. Of the 112 children, 74 (66.1%) had scar on DMSA. VUR was detected in 63 (56.3%) patients, and according to the International Reflux Study, grades I, II, III, IV and V VUR were present in four (3.6%), 16 (14.3%), 30 (26.8%), eight (7.1%), and five (4.5%) children, respectively. Severe VUR (Grade III-V) was present in 43 patients (Table 1).

Table 1. Demographic and clinical characteristics of the patients

Parameter	Number n (%)	
Number of patient	112	
Gender (male/female)	30 (26.8 %) / 82 (73.2 %)	
Age [mean ± standard deviation (SD)]	7.04 ± 3.94 year (1-18)	
Ultrasonography (n,%)	Normal	Abnormal
	44 (39.3%)	68 (60.7%)
DMSA (n,%)	Scar negative (-)	Scar positive (+)
	38 (33.9%)	74 (66.1%)
VCUG (n,%)	VUR negative (-)	VUR positive (+)
	49 (43.8%)	63 (56.3%)
VUR grade (n,%)	Grade I	4 (3.6%)
	Grade II	16 (14.3%)
	Grade III	30(26.8%)
	Grade IV	8 (7.1%)
	Grade V	5 (4.5%),

Values are presented as number
USG, Ultrasonography; DMSA, Dimercapto-succinic Acid; VCUG, Voiding Cystourethrography; VUR, vesicoureteral reflux

Of the 44 children with normal USG, 24 had VUR, nine of whom had grade I-II VUR and 15 grade III-V VUR. Abnormal USG was seen in 68 patients, 11 of whom had grade I-II VUR, and 28 had grade III-V VUR (Table 2). Thus, 40% of high-grade VUR had abnormal USG and 34% of high-grade VUR had normal USG. There was no correlation between USG findings and the presence of VUR (p= 0.715) (Table 2).

Table 2 . The correlation between image studies and the presence or absence of VUR

Study	No VUR (n)	Grade I-II VUR (n)	Grade III-V VUR(n)	Abnormal late DMSA scan (n)
USG				
Normal, n=44	20	9	15	19
Abnormal, n=68	29	11	28	55
DMSA				
Normal ,n=38	24	4	10	
Abnormal, n=74	25	16	33	
Total, n=112	49	20	43	74

Values are presented as number
USG, Ultrasonography ; DMSA, dimercapto-succinic acid; VUR, vesicoureteral reflux

Abnormal DMSA scans were seen in 74 children, 25 of whom had no VUR, 49 (66%) had VUR, and 33 (44%) had high-grade VUR. Only 38 patients (grade IV VUR, n= 2; grade III VUR, n= 8; grade I-II VUR, n= 4; no VUR, n= 24) had normal DMSA renal scintigraphy. Pathologic results of DMSA scans were significantly associated with all grades of VUR (p= 0.003) (Table 2, Table 3).

The sensitivity, specificity and positive predictive value (PPV) of late DMSA scans in the detection of VUR were 77.8%, 49% and 0.66 respectively (Table 3). The kappa coefficient (κ) which is used to test interrater reliability, for DMSA renal scans and VUR grade was 0.274. The risk of VUR was 3.36-fold higher in the scar (+) group than in the scar (–) group (p= 0.004; OR 3.36; 95% CI: 1.48-7.6). Age, sex and abnormal USG findings did not predict the presence of VUR.

Table 3 . The correlation between Late DMSA scan findings and the presence or absence of VUR

			VCUG			
			VUR(-)	VUR(+)		
DMSA	Scar (-)	Number	24	14	**Sensitivity**	% 77.8
		% within DMSA	63.2%	36.8%	**Positive predictive value**	%66.2
		%within VCUG	49.0%	22.2%	**Specifity**	%49
	Scar (+)	Number	25	49	**Negative predictive value**	%63.2
		% within DMSA	33.8%	66.2%	**Kappa value**	0.274
		%within VCUG	51.0%	77.8%	**p**	0.003

Values are presented as number
DMSA, dimercapto-succinic acid; VUR, vesicoureteral reflux; VCUG, Voiding Cystourethrography

DISCUSSION

Although it is one of the common problems of the urinary system, there is no clear consensus in the diagnosis, treatment, and follow-up protocols of VUR. Over time informations and evidence-based data on the pathophysiology of VUR, and advances in diagnostic methods have led to significant changes in the VUR algorithm (3,4,11). In children presenting with fUTIs, due to the increased risk of renal damage especially in the presence of high-grade VUR, demonstration of VUR plays an important role in the clinical evaluation (3,6,11). We assessed the correlation between different imaging studies, and the usefulness of late renal DMSA scans in revealing high-grade VUR.

In this study, VUR was found in 63 (56.3%) patients, 43 of whom had grade III-V VUR. Abnormal USG and DMSA scintigraphy results were found in 60.7% and 74% of children with recurrent fUTIs respectively. Fifteen of 44 patients with normal USG had grade III-V reflux, and VUR was not correlated with USG findings (p= 0.715), whereas pathologic results of DMSA scans were significantly associated with all grades of VUR (p= 0.003).

The findings of our study indicate that USG may be inadequate for the identification of patients at risk in the diagnosis of VUR in accordance with the literature (13-15). Nowadays, the main goal of modern radiologic tests for children presenting with fUTIs is to identify VUR that is a risk factor for recurrent fUTI and renal damage, and also to avoid unnecessary VCUG which is an invasive technique and causes high radiation exposure. In the evaluation of children with recurrent fUTI, according to the top-down approach, DMSA is obtained as a first choice to diagnose renal parenchymal involvement. Patients who demonstrate parenchymal inflammation with DMSA are investigated with VCUG to show VUR. In addition, in these patients, a late DMSA scan is obtained for the assessment of permanent renal scarring after 6 or 12 months (16-18).

Several studies have demonstrated that acute DMSA

scans were effective in the detection of high-grade VUR with high sensitivity (10,17-24). However, a systematic review questioned the usefulness of acute DMSA as a screening test for high-grade VUR. A negative DMSA study had a summary sensitivity of 0.93, the specificity was low (0.44), such that it limits its utility as a screening test for VUR (25). In the studies of Herz et al. (7) and Hansson et al. (23), it was found that 20% and 24% of patients with VUR had normal acute DMSA scans respectively. Fouzas et al. (26) found VUR in 12 of 296 children whose DMSA scintigraphy and USG findings were normal. Tekgül et al. (11) reported that the diagnosis of VUR might be missed in 5-27% of cases if VCUG is not performed in patients with normal DMSA scintigraphy. Other limitation of acute DMSA is that fUTI does not recur in a significant proportion of patients after a fUTI, and many centers cannot perform DMSA in all patients during acute infections (11,17).

Due to all these limitations, some studies have recommended the modified top-down approach in clinical use, namely late DMSA imaging, and showed the correlation between acute and late DMSA scans in detecting high-grade reflux (13,19,27,28). In our study, we found that the high-grade VUR was significantly more common in patients with a history of recurrent UTI and in patients with renal parenchymal scarring on late DMSA scans. The sensitivity of late DMSA scans in the detection of VUR was 77.8%, and the risk of VUR was 3.36-fold higher in the abnormal DMSA group. Quirino et al. (27) and Wongbencharat et al. (17) reported the sensitivity of late DMSA in predicting high-grade VUR as 83.3% and 87.5% respectively.

Novelty, the present study showed that the diagnostic accuracy of late DMSA scan for all grade reflux was a sensitivity of 77.8 % and negative predtice value of 63.2 % with 14 patients with normal scan results. In our study, according to the top-down approach, 14 (22.2%) patients with VUR but with no scarring would have been missed. Two of these patients had grade IV VUR, 8 had grade III and the other 4 had grade I-II VUR. A similar study by Snodgrass et al. (29) found that 43% of patients with grade IV-V VUR had no renal scarring on late DMSA. Also, note that in the present study, 25 of the 74 patients (33.8%) with an abnormal DMSA scan had no VUR. Hansson et al. (23) reported that 46% of patients with scarred kidney on DMSA had no VUR. These results question the value and importance of DMSA or VCUG findings in clinical decision-making. Our primary goal in managing patients with VUR should be the prevention of infection. The patient-based approach, such as an individualized risk-based dynamic approach, can help physicians in the management and treatment of VUR. Newer imaging modalities are currently being investigated in order to non-invasively diagnose VUR. Contrast-enhanced voiding urosonography, Radionuclide cystography has been proposed for the detection of VUR with an acceptable accuracy and radiation dose. More recently, magnetic resonance urography has been used for the detection of renal scarring in children with recurrent UTI. More evidence is needed before these newer imaging modalities can be recommended for routine use in clinical practice (30).

There are some limitations in our study. First, retrospective data were collected from a single center. Secondly, the variations in the number of the patient's groups prevent further generalizations on the necessity of late DMSA examination and subsequent management. Further prospective studies with larger cohorts are warranted.

CONCLUSION

Abnormal late DMSA scans carry a higher sensitivity and positive predictive value for predicting high-grade VUR in children with recurrent fUTIs. A late DMSA scan should be considered when acute DMSA scan had not been studied due to limited interventions in public health centers.

Competing interests: The authors declare that they have no competing interest.

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